ALT-MED White Paper on Herbs and Supplements During Covid -19

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GOALS

- Stop virus from replicating or spreading in the body
- Prevent cytokine storm without inhibiting anti-viral immunity
- Hasten recovery

Of importance: The only integrative measures validated in human trials as effective specifically for COVID-19 is vitamin D_3. The strategies presented here are based largely on pre-clinical evidence and are supplemental to current public health measures and conventional treatments.

Overview

All medical therapies, traditional and non-traditional, involve risk vs benefit. The supplements presented here are not specific medical recommendations. This is general information. Specifics recommendations should be followed only after medical consultation weighing all of the risks and benefits.

All medical, traditional and non-traditional, involve some level of risk vs benefit. Medications for COVID-19, at this point in time, are moderate to high risk and moderate to low benefit. Hydroxychloroquine and azithromycin fall into the moderate to high risk (depending on the patient's medical history) and, you tube videos aside, minimal to no benefit. In contrast remdesivir (anti-viral) and anti-coagulant medications have moderate risk but seem to also have benefit, again depending on the patient population. Until there is a vaccine, it is unlikely that a single medication will be universally effective.

In contrast, supplements, in general, are low risk and moderate benefit depending on the supplement and medical condition (bleach is NOT a supplement). However, **NO** supplement is without risk – may interact with medications or allergic reactions –any questions about use of these or any supplements and off-label medications should be directed to a board certified integrative medical physician.

Much of the research referenced here is not new. Some of this peer-reviewed research has been known for over a decade using viruses that are COVID-19 cousins. We may already have some answers if we look.

Three Potential Ways To Affect COVID – 19

1. Block attachment of the virus to the cell
2. Prevent replication of the virus in the cell
3. Enhance immune system without over-stimulating

Covid-19 is able to attach to cells through a specific receptor termed the Angiotensin-converting enzyme 2 (ACE2) receptor. After attachment, the virus is able to enter the cell and begin its destructive process. This receptor is an enzyme on cells found in the lungs, arteries, heart, kidney, and intestines. ACE2 receptors are involved in the regulation of blood pressure.

Reducing the number of ACE-2 receptors expressed by the cell or blocking the binding of COVID-19 to the ACE-2 receptors may be an effective way to reduce the potential for a large number of viruses to enter the cell. Fortunately, there seem to be some supplements that may do exactly that.

ASTRAGALUS – Decrease the number of ACE-2 receptors

Astragalus is a large family with over 3,000 species. It is native to the northern hemisphere. It is commonly used in traditional Chinese medicine in combination with other herbs. Astragalus is employed as a therapy for many conditions, including diarrhea, fatigue, anorexia, upper respiratory infections, heart disease, hepatitis, fibromyalgia, and as an adjunctive therapy for cancer.

It is considered generally safe with rare side effects consisting primarily of diarrhea and upset stomach. Astragalus can also affect blood sugar and blood pressure. Astragalus may enhance the immune system and as such are often contra-indicated with patients taking medications that suppress the immune system, such as drugs taken by organ transplant recipients and some cancer patients.

The data for reducing ACE receptors is, truthfully, pretty weak, consisting of a single 2015 study done on mice (1). However, this study did demonstrate that regular intake of Astragalus did reduce the number of ACE receptors on kidney cells.

One important aspect of COVID-19 infection is the possibility that this virus, in some people, stimulate the immune system to over-produce specific inflammatory proteins (cytokines) leading to extensive tissue damage. This is often called a “cytokine storm”. There is the potential that supplements that stimulant the immune system may increase the risk of a cytokine storm but this is more theoretical than proven. Indeed, one study suggests that

Astragalus balances the immune system by reducing the over-production of these pro-inflammatory cytokines (2).

Side effects: Astragalus is generally considered safe for most adults. Common side effects are diarrhea. It may affect blood sugar levels and blood pressure – concern for people disorders, diabetes, or hypertension. Concern also with patient on immunosuppressant medications

Be aware pf product quality…some astragalus species, usually not found in dietary supplements, can be toxic…contain the neurotoxin swainsonine and have caused "locoweed" poisoning in animals. Other species contain potentially toxic levels of selenium.

Studies:

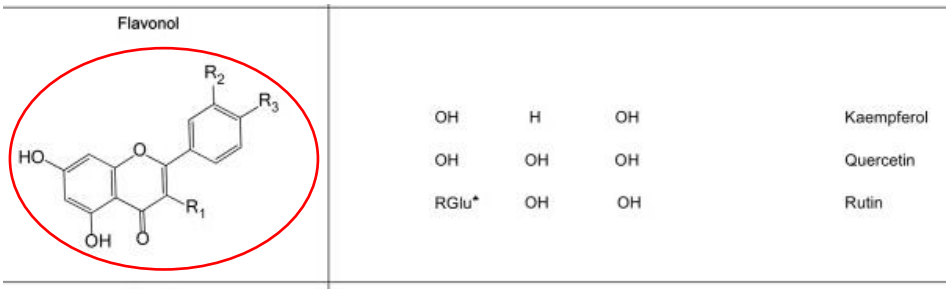
1. Wang Q-Y. *Zhongguo Zhong Yao Za Zhi*. 2015.40(21):4245
2. Astragaloside IV attenuates IL-1β secretion by enhancing autophagy in H1N1 infection. *FEMS Microbiol Lett*. 2020 Feb 1;367(4).

QUERCETIN – inhibit binding to ACE2 receptor

Compounds from plants, primarily flavonoids, can bind to the ACE receptor and potentially block the binding of the COVID-19 virus. Even tiny amounts of these compounds can have a profound effect. Two compounds, quercetin and EGCg bind aggressively to ACE receptors and may play a role in prevention of COVID-19 infections. It seems that some people have little or no symptoms of infection…might they have higher levels of flavonoids in their diets?

Flavonoids are found in many fruits, vegetables, leaves, seeds, and grains. All onions (especially red), kale, apple peals, and cilantro contain substantial amounts of quercetin. Quercetin also comes as a dietary supplement.

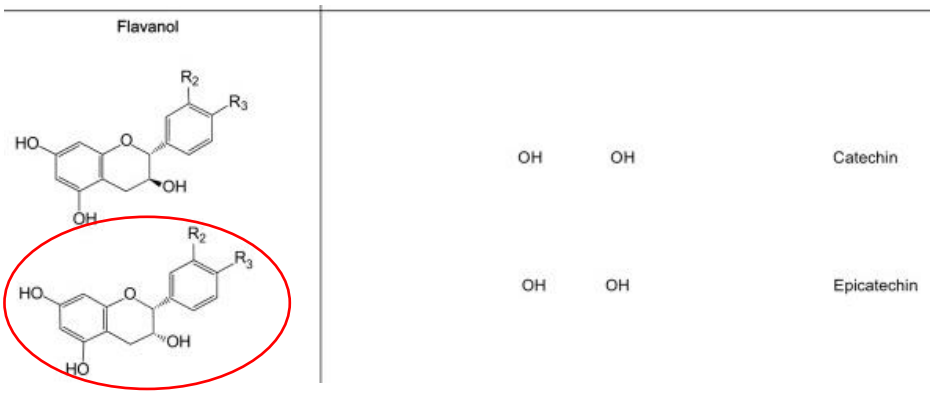
Side effects: non-specific headaches, numbness/tingling of the arms and legs – rare.

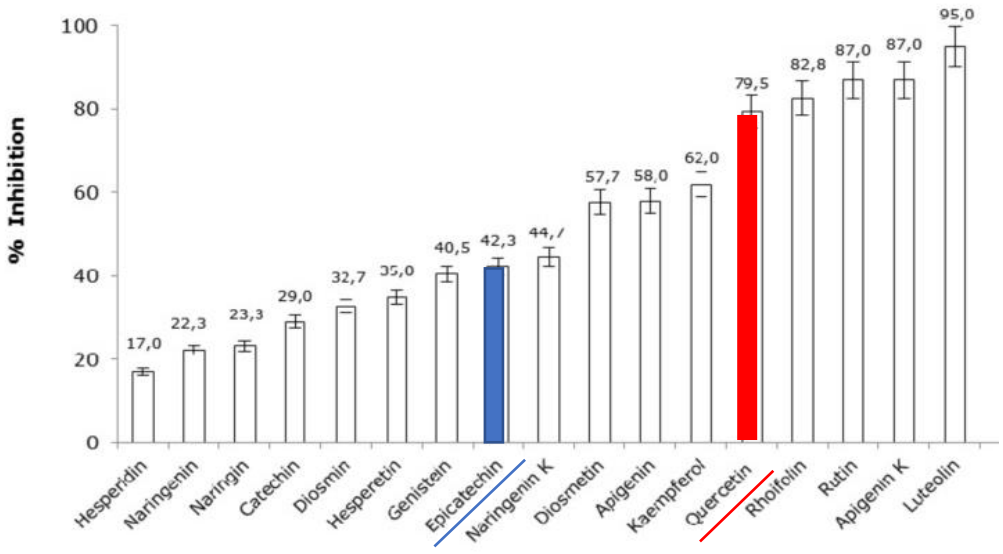


EPICATECHIN – inhibit binding to ACE2 receptor

This flavonoid is found primarily in green and black tea. A powerful co-existing catechin is epigallocatechin gallate (EGCg). Sources of catechins are tea - green, black, white and oolong; fruits - berries, kiwis, cherries, pears, peaches, apples, and avocados; nuts - pecans, pistachios, and hazelnuts all contain epicatechins that bind to the ACE receptor strongly. EGCg also comes as a dietary supplement.

Side effects: liver and kidney failure, dizziness, low blood sugar and anemia have been reported but may be due to supplement contamination



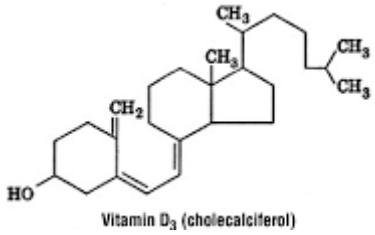


Studies:

1. Inhibition of Angiotensin-Converting Enzyme Activity by Flavonoids: Structure-Activity Relationship Studies. *PLoS One*. 2012; 7(11)

VITAMIN D – multiple roles

Vitamin D is a family of fat-soluble molecules responsible for maintaining proper the levels of calcium, magnesium, and phosphate. However, research over the past 30 years demonstrates that vitamin D is not a vitamin but a hormone that is involved with every organ system in the body.



Vitamin D_3 (cholecalciferol)

Vitamin D is critical for the functioning of the immune system and robust research indicates that people who have lower levels of vitamin D are at an increased risk from the common cold, heart disease, high blood pressure, auto-immune disease, maybe Alzheimer's disease and some cancers. For our purposes, the most biologically important form of vitamin D is D_3, (cholecalciferol).

There is a substantial amount of published medical research demonstrating the need for vitamin D in preventing and treating many viral illnesses. Most recent research has shown that vitamin D is protective against COVID-19 (1,2)

The anti-viral properties of vitamin D many operate on several levels. One medical study demonstrated that vitamin D affects the ACE2 receptors in a way that could inhibit the binding of the COVID-19 virus (2).

Vitamin D can super charge the immune system through the production of molecules termed cathelicidins and defensins through direct viral toxicity as well as mobilizing white blood cells to destroy infected cells before the virus can replicate. Interestingly, vitamin D may also help to regulate the production of cytokines involved in "cytokine storm" (1,3,4) potentially protective against severe complications, including death.

Side Effects: at very high blood levels - weakness, fatigue, sleepiness, headache, loss of appetite, dry mouth, metallic taste, nausea, vomiting

Studies:

1. The Possible Role of Vitamin D in Suppressing Cytokine Storm and Associated Mortality in COVID-19 Patients**.** *medRxiv*, Posted April 30, 2020
2. Vitamin D can prevent COVID-19 infection-induced multiple organ damage**.** Naunyn Schmiedebergs Arch Pharmacol. 2020 May 25: 1–4.
3. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. *Nutrients.* 2020 Apr 2;12(4).
4. The human cathelicidin LL-37 inhibits influenza A viruses through a mechanism distinct from that of surfactant protein D or defensins. *Journal of General Virology*. 2013 Jan; 94(Pt 1): 40–49

ELDERBERRY - multiple roles

Elderberry (Sambucus) is a flowering plant found in many parts of the world. Elderberry has historically been used as a treatment for viral infections and there are more than 50 medical studies in the traditional medical literature supporting its use. Most of the studies show benefit especially for influenza. Elderberry fruit and flowers are commonly used in the preparation of supplements and teas. Although processing for consumption is safe, the uncooked berries and other parts of elderberry can be poisonous.

One recent study in the science journal Virus Research (1) demonstrated substantial effect against the ability of the coronavirus HCoV-NL63 to replicate. This virus is a cousin to the coronavirus that causes COVID-19. This research was done in vitro (in test tubes) and not in animals or humans. Nevertheless, the results were impressive. These results are supported by other research suggesting significant effects on viral replication as well as clinical benefits for influenza infections (2-4).

According to WebMD "…It is **POSSIBLY UNSAFE** to consume the leaves, stems, unripe fruit, or uncooked fruit of elderberry. The cooked elderberry fruit seems to be safe, but raw and unripe fruit might cause nausea, vomiting, or severe diarrhea…."

Side effects: Nausea/vomiting, weakness, dizziness, numbness

Studies:

1. Antiviral activity of Sambucus Formosana Nakai ethanol extract and related phenolic acid constituents against human coronavirus NL63. *Virus Res*. 2019
2. Sambucus nigra extracts inhibit infectious bronchitis virus at an early point during replication. *BMC Vet Res*. 2014
3. Randomized study of the efficacy and safety of oral elderberry extract in the treatment of influenza A and B virus infections. *J Int Med Res*. 2004
4. Interfering with Lipid Raft Association: A Mechanism to Control Influenza Virus Infection By *Sambucus Nigra*. *Iran J Pharm Res*. 2017

ZINC – inhibit viral replication

Zinc, for decades, has been recommended as a therapy to treat or prevent viruses. Most recently zinc has been shown to disrupt the activity of the SARS-CoV PLP2, a viral enzyme critical for viral replication (1)…no enzyme activity = no new viruses. One study, all the way back to 2005, demonstrated a 70% inhibition of this specific enzyme activity by zinc (2) and then restated again in 2015 (3).

Interestingly, zinc can complex with other anti-viral compounds (in foods) like quercetin and EGCg. These complexes are more readily taken into the cell. Taken in combination, this could not only increase cellular zinc levels but also enhance the anti-viral effects beyond that of quercetin or EGCg alone (4).

Side effects: fever, stomach pain, fatigue. Long term high dose use can double risk of prostate cancer

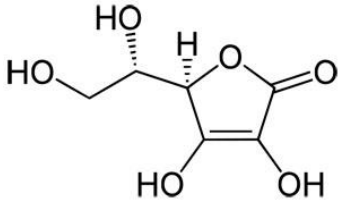
Studies:

1. Papain-like protease 2 (PLP2) from severe acute respiratory syndrome coronavirus (SARS-CoV): expression, purification, characterization, and inhibition. *Biochemistry*. 2005
2. The papain-like protease from the severe acute respiratory syndrome coronavirus is a deubiquitinating enzyme. *J. Virol.* 2005
3. The SARS-coronavirus papain-like protease: Structure, function and inhibition by designed antiviral compounds *Antiviral Res.* 2015
4. Zinc ionophore activity of quercetin and epigallocatechin-gallate: from Hepa 1-6 cells to a liposome model. J Agric Food Chem. 2014

VITAMIN C – reduces risk of "Cytokine Storm"

The debate on the benefits of vitamin C on viral colds is far from over. There seem to be equal numbers of medical studies suggesting benefit as well as no benefit at all.

Vitamin C levels in the general population are probably less than optimal. The daily dose of vitamin c recommended by the Institute of Medicine is about 60 mg. That is enough to simply prevent scurvy which is the index disease of vitamin C deficiency.



Vitamin C is crucial for the development and function of a certain set of white blood cells called T cells that are involved in fighting viral infections (1). When infected, oxidative stress increases. As a result, vitamin C levels in white blood cells can plummet and T cells may not act as aggressively towards infections. Research overall indicates that a lower level of vitamin C does not bode well for recovery. Indeed, specific groups of people with an initially lower than normal levels of vitamin C may see a reduction in duration and severity of the common cold with oral vitamin C supplementation (2). My clinical experience with patients taking intravenous vitamin C is a flu-free Fall and Winter.

One of the issues with vitamin C may be how it is delivered to the body. Research using oral vitamin C rarely shows significant benefit. This is probably related to the inability of the body

to actually absorb high doses of vitamin C. However, for oral vitamin C, the consensus is that it has low risk and a potential for benefit (3,4). For intravenous vitamin C, the results are different. One study with patients on mechanical ventilation showed a significant reduction in duration of ventilation (18.2%) (5). Indeed, several clinical trials have demonstrated a benefit of high dose vitamin C for pneumonia. Many hospitals across the country are using high dose intravenous vitamin C for ventilator-dependent COVID-19 patients.

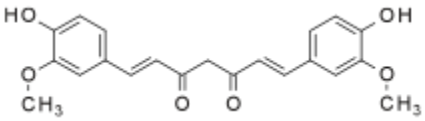
Side Effects: orally -diarrhea, abdominal pain. Intravenously – almost none except for specific medical conditions

Studies:

1. Influence of Vitamin C on Lymphocytes: An Overview. Antioxidants (Basel). 2018
2. Vitamin C and Infections *Nutrients.* 2017
3. Vitamin C for Preventing and Treating the Common Cold. *PLoS Med.* 2005
4. Vitamin C for preventing and treating the common cold. *Cochrane Database Syst Rev*. 2013
5. Vitamin C Can Shorten the Length of Stay in the ICU: A Meta-Analysis *Nutrients.* 2019

CURCUMIN – affects inflammation

It is a bright yellow compound found in turmeric. Curcumin is arguably the most researched dietary supplement with almost 15,000 publications in the medical literature. Its potential role in the treatment and prevention of COVID-19 infections is multifactorial.



Reduce risk of "cytokine storm" - curcumin exhibits an inhibitory effect on the production of a number of inflammatory cytokines (1-5) like IL-8, MIP-1alpha, MCP-1, IL-1beta, and TNF-alpha by specific white blood cells found in the lungs…alveolar monocytes and alveolar macrophages.

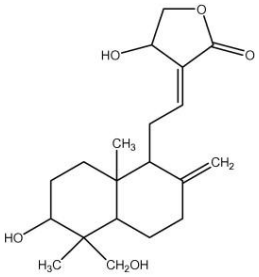
Side effects: bloating, acid reflux, flatulence, headache and nausea

Studies:

1. Suppressor of cytokine signaling 4 (SOCS4) protects against severe cytokine storm and enhances viral clearance during influenza infection *PLoS Pathog*. 2014

2. Curcumin inhibition of inflammatory cytokine production by human peripheral blood monocytes and alveolar macrophages. *Pharmacol Res*. 1999
3. Curcumin supplementation lowers TNF-alpha, IL-6, IL-8, and MCP-1 secretion in high glucose-treated cultured monocytes and blood levels of TNF-alpha, IL-6, MCP-1, glucose, and glycosylated hemoglobin in diabetic rats. *Antioxid Redox Signal*. 2009
4. Curcumin suppression of cytokine release and cytokine storm. A potential therapy for patients with Ebola and other severe viral infections. *In Vivo*. 2015
5. Curcumin Suppresses IL-1β Secretion and Prevents Inflammation through Inhibition of the NLRP3 Inflammasome J Immunol. 2018

ANDROGRAPHIS – inhibits viral replication



Grown in Southern and Southeastern Asia, Andrographis has been traditionally been used as a treatment for bacterial infections, parasites, cough, and influenza. This herb contains a compound called andrographolide, a terpenoid compound found to have antiviral effects against respiratory disease-causing viruses, including influenza N1H1 as well as herpes simplex 1, Newcastle disease, hepatitis B, HIV and cytomegalovirus (1,2,3). Recent computer models strongly suggest that Andrographis may interfere with COVID-19 enzymes crucial for viral replication (4)

Side effects: lower blood pressure and thin the blood. Taken in high doses - swollen lymph glands, allergic reactions, elevations of liver enzymes

Studies:

1. Andrographis paniculata (Chuān Xīn Lián) for symptomatic relief of acute respiratory tract infections in adults and children: A systematic review and meta-analysis". PLOS One. 2017
2. Antiviral activity of five Asian medicinal pant crude extracts against highly pathogenic H5N1 avian influenza virus. Asian Pac J Trop Med. 2017
3. Broad-spectrum antiviral properties of andrographolide. Arch Virol. 2017
4. Andrographolide as a potential inhibitor of SARS-CoV-2 main protease: an in silico approach. J Biomol Struct Dyn. 2020

SELENIUM -. Selenium is a mineral that's essential for healthy immune system

Selenium is involved with many anti-oxidant systems in the cell. Its deficiency can result in an increased level of oxidative stress in the cell. These biochemical stress reactions can actually affect the viral RNA/DNA. These changes can convert a normally benign or mildly pathogenic virus into a highly virulent virus in selenium deficient hosts. Medical research on the phenomenon has been reported in animal models for both influenza and coxsackie viruses. The exact sequence of events is not know but the end result is well documented (1, 2 3).

Even though selenium levels are easily measured with a simple blood test, we do not know the selenium status in patients who have either had a hard time or died from COVID-19. I would not be surprised if low selenium levels are associated with a grimmer clinical course.

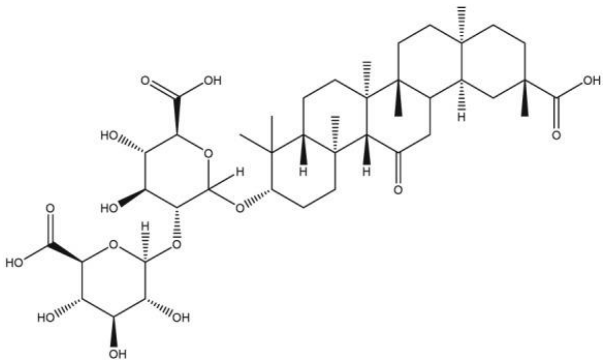
Side effects: Diarrhea, fragile nails, hair loss, skin rash, nausea/vomiting, fatigue

Studies:

1. Selenium, Selenoproteins and Viral Infection. Nutrients. 2019
2. Role of Divalent Cations in HIV-1 Replication and Pathogenicity. Viruses. 2020
3. The Role of Micronutrients in the Infection and Subsequent Response to Hepatitis C Virus Cells. 2019

LICORICE – interfere with viral replication

Glycyrrhiza glabra is a small perennial herb, commonly known as licorice, sweet wood, or mulaithi. It is found in Eurasia, northern Africa, and western Asia. Is consists of more than 30 species. Its name originated from the Grecian words glykys, which means sweet, and rhiza, which means root.



Licorice contains a plethora of anti-viral compounds especially glycyrrhizin. Glycyrrhizin has been investigated against the multiplication of various viruses, including herpes simplex, Epstein–Barr, Human cytomegalovirus, hepatitis A, B, and C, Influenza, HIV, Varicella zoster, and severe acute respiratory syndrome (SARS) coronavirus (1,3). According to test-tube research, glycyrrhizin exhibits significant antiviral activity against severe acute respiratory syndrome-related coronavirus (SARS-CoV) (2).

Side effects: high doses of licorice can lead to hypertension, hypokalemia (low potassium), or fluid retention. Other effects reflect its estrogen-like activity - Absence of a menstrual period, decreased sexual interest (libido) and erectile dysfunction.

Studies:

1. Traditional Uses, Bioactive Chemical Constituents, and Pharmacological and Toxicological Activities of *Glycyrrhiza glabra* L. (Fabaceae). *Biomolecules*. 2020
2. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. *Lancet*. 2003
3. Liquorice (Glycyrrhiza glabra): A phytochemical and pharmacological review. *Phytother Res*. 2018

Other Supplements

There is an almost limitless number of supplements that claim to have a positive effect on the immune system. Taking immune boosters does not mean that there are any clinical benefits with regards to COVID-19. Indeed, some of these supplements may increase the potential for a "cytokine storm". I do not recommend, at this time, most mushrooms, adaptogens and echinacea.

Summery

Until there is a vaccine or a medication that profoundly affects COVID-19, our best plan of action is to make the body resistant to COVID-19. There is enough reasonable research to indicate that select supplements may offer some protection. These supplements do not take the place of social distancing, wearing good quality face masks and avoiding crowds.

Even after restrictions are lifted, the history of the pandemic of 1918 teaches us that there will probably be a second and possibly even a third wave of infections and deaths. Do not be under the illusion that "all is OK" until the vaccine has been widely distributed. Flattening the curve only means there are now open beds in the intensive care unit. Be safe…be proactive..but realize that if you are on medications, even though some supplements may be beneficial, many supplements can affect your medications. If you have questions – ask.

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