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# THE FUNCTIONAL MEDICINE APPROACH TO COVID-19

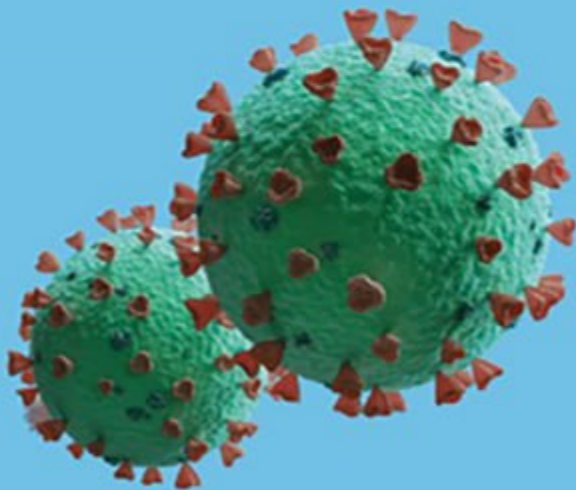
**DR. LORETTA BOLGAN**

Doctor of Pharmaceutical Chemistry and Technology

Ph.D. in Pharmaceutical Sciences

Scientific advisor

[loretta.bolgan@gmail.com](mailto:loretta.bolgan@gmail.com)



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## VIRUS-SPECIFIC NUTRACEUTICAL AND BOTANICAL AGENTS

The following discussion and attached tables are extracted from *The Institute for Functional Medicine* (IFN) website and specifically from [COVID-19: Functional Medicine Resources](#).<sup>1</sup> The recommendations given are from functional medicine experts who compiled them based on their clinical experience.<sup>2</sup>

This paper discusses the mechanisms of action of a number of different botanical agents and nutraceuticals that are considered **immunoadjuvants**, that is, as substances that act to accelerate, prolong, or enhance antigen-specific immune responses by enhancing or modulating the immune response.<sup>[1]</sup>

### Mechanism of action of nutraceutical agents

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 a cytokine storm and severe, sometimes irreversible, damage to the respiratory epithelium.<sup>[2]</sup> It has been shown in recent studies that SARS-CoV-2 virus activates the NLRP3 inflammasome.<sup>[3,4]</sup>

A 2016 review article<sup>[5]</sup> titled "*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 in more than one element of the pathways involved. However, it should be noted that these polyphenols have an even broader biological effect, as they affect a variety of signaling pathways." For example, these polyphenols modulate NF-kB upregulation, which is useful in counteracting hyperinflammation by COVID-19."<sup>[6]</sup>

A preprint published on March 23, 2020, identified the ability of plant bioactive compounds to inhibit the major protease COVID-19 (M<sup>pro</sup>),<sup>[7]</sup> required for viral replication. There is much interest around the recent identification of M<sup>pro</sup>, as a potential current drug target. Caempferol, quercetin, luteolin-7-glucoside, demethoxycurcumin, naringenin, apigenin-7-glucoside, oleuropein, curcumin, catechin, and epicatechin-gallate have been identified as the natural compounds with the best potential to act as inhibitors of COVID-19 M<sup>pro</sup>. Although further research is needed to demonstrate their efficacy, this study provides the biological plausibility and mechanistic support (SARS-CoV-2 protease inhibition) to justify their use.

For these reasons, IFN experts recommend the following compounds, at standard dosages, to prevent NLRP3 inflammasome activation, to decrease NF-kB activation, and to inhibit SARS-CoV-2 replication. There is no literature to support a regimen of a single versus multiple agents. The recommendation is to use a higher dose and/or multiple agents when patient contextual factors (e.g., patient desire, pre-existing inflammation, multiple comorbidities, higher risk, etc.) and/or therapeutic decisions warrant such use.

| Medicinal plant or active ingredient | posology  |
|--------------------------------------|---|
| Andrographis paniculata              | Standardized extract (typically 30% andrographolide) 100-600 mg daily, most often given in combination with other herbal preparations.  |
| Astragalus membranaceus              | The dosage range varies between 1 and 20 grams per day, depending on the percentage of astragalosides and other immunoactive polysaccharides. In China, it is usually in the form of dried root powder. |
| Berberine                            | 500 mg / 2-3 times a day  |

<sup>1</sup> <https://www.ifm.org/news-insights/the-functional-medicine-approach-to-covid-19-virus-specific-nutraceutical-and-botanical-agents/>

Reference literature is given at the end of the paper, and in-text citations are indicated by superscript numbers in red square brackets

<sup>2</sup> Evans JM, Luby R, Lukaczer D, et al.

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

Integr Med (Encinitas). 2020;19(Suppl 1):34-42.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7482149/>

|   |   |
|---|---|
| Beta glucans  | 250-500 mg / per day  |
| Scutellaria baicalensis   | 750-1,500 mg daily standardized in flavonoids, baicalin or baicalein.<br>Given the variability of standardization, it is suggested that dosing instructions be based on finding specific standardized extracts. |
| Curcumin  | 500-1000 mg / 2 x di  |
| Echinacea   | Given the variety of active ingredients in various species and the variability of extraction processes, it is suggested that dosing instructions be tailored based on research of specific Echinacea species.   |
| Eldeberry (Sambucus nigra)  | 500 mg per os / per day   |
| Epigallocatechin gallate (EGCG) or green tea                                  | Green tea: 4 cups per day<br>EGCG 225 mg per os/per day   |
| Medicinal mushrooms   | Given the variety of active ingredients in fungi and the variability of extraction processes, it is suggested that dosing instructions be tailored to the research of specific genera and species of fungi      |
| Licorice (Glycyrrhiza species)  | Licorice root standardized in glycyrrhizin: 200-400 mg daily in fractionated doses.<br>Short-term use: <4 weeks.  |
| Luteolin  | 100-200 mg /2-3 times a day   |
| Melatonin   | 5-20 mg / in the evening  |
| N-acetylcysteine  | 600-900 mg / 2 x di   |
| Palmitoylethanolamide (PEA)   | Prevention: 300 mg per os / 2 x di<br>Treatment: 600-900 mg / 3 per day for 2 weeks   |
| Quercitin   | 1000 mg (per os) / 2 x di<br>Phytosome * 500 mg / 2 x di  |
| Resveratrol   | 100-150 mg per os / 2 x di  |
| Vitamin A   | 10,000-25,000 IU / per day  |
| Vitamin C   | 1-3 g per os/per day  |
| Vitamin D   | 5000 IU per os / per di   |
| Zinc (acetate, citrate, picolinate, glycinate)<br>Zinc gluconate (as lozenge) | 30-60 mg per os per day divided into several doses  |

\* A phytosome is a complex consisting of a natural active ingredient and a phospholipid: it is used to improve the bioavailability of poorly bioavailable active ingredients. Active components that are too polar are unable to cross the lipid barrier of the skin or alimentary canal and be absorbed. Phytosome is used to reduce the polarity of active substances thus making them more absorbable.<sup>3</sup>

<sup>3</sup> <https://www.lerboristeria.com/glossario/fitosoma.php>

The following table summarizes the main mechanism of action of some dietary supplements: <sup>4</sup>

| INTEGRATOR              | FEATURES  |
|-------------------------|---|
| <b>VITAMIN C</b>        | <ol style="list-style-type: none"> <li>1. Collagen synthesis in connective tissue</li> <li>2. Antioxidant activity</li> <li>3. Regulation of DNA synthesis and histone methylation</li> <li>4. Immunomodulation of:                             <ul style="list-style-type: none"> <li>- Stimulatory effect on IFN formation,</li> <li>- support of lymphocyte proliferation,</li> <li>- Enhancement of the phagocytic capacity of neutrophils</li> </ul> </li> <li>5. Enhances innate immunity of alveolar epithelium type II via inhibition of lactate secretion</li> </ol>   |
| <b>VITAMIN D</b>        | <ol style="list-style-type: none"> <li>1. Immunomodulation by subregulation of proinflammatory cytokines</li> <li>2. Reduction of acute lung injury by inhibitory effects on the angiotensin-2/Tie-2 and renin-angiotensin signaling pathways (The angiotensin-Tie signaling pathway is an important vascular signaling pathway involved in angiogenesis, vascular stability, and quiescence)</li> <li>3. Modulation of the innate immune system</li> <li>4. Modulation of the adaptive immune system by:                             <ul style="list-style-type: none"> <li>- The suppression of Th1 responses</li> <li>- The induction of regulatory T cells</li> </ul> </li> <li>5. Local "respiratory homeostasis" by induction of release of certain antimicrobial peptides</li> <li>6. Preserves cell junctions</li> <li>7. Consolidation of cellular immunity</li> <li>8. Reduction of cytokine storm due to effects on TNF-<math>\alpha</math> and IFN-<math>\gamma</math> release</li> </ol> |
| <b>MELATONIN</b>        | <ol style="list-style-type: none"> <li>1. Antioxidant activity by:                             <ul style="list-style-type: none"> <li>- Intracellular neutralization of hydroxyl and peroxy radicals,</li> <li>- Indirect enhancement of antioxidant enzyme activities (including glutathione peroxidase, glutathione reductase, superoxide dismutase, and catalase)</li> </ul> </li> <li>1. Anti-inflammatory effect by preventing the release of proinflammatory cytokines</li> <li>2. Probable role in suppressing the initial cytokine storm</li> <li>3. Effect on the immune system and respiratory cells through modulation of calcium signaling pathways</li> <li>4. Effect on angiogenesis via inflammatory signaling pathways</li> <li>5. Anti-vascular properties of endothelial growth factor (anti-VEGF)</li> <li>6. Inhibition of pyroptosis</li> </ol>  |
| <b>SELENIUM</b>         | <ol style="list-style-type: none"> <li>1. Antioxidant activity through incorporation into selenoproteins</li> <li>2. Affects different types of immune responses, including expression of inflammatory proteins and cytokines</li> <li>3. Effect on virus-host cell attachment interaction</li> <li>4. Inhibition of angiotensin-converting enzyme</li> <li>5. Anti-inflammatory activity</li> <li>6. Anti-coagulation properties</li> </ol>  |
| <b>N-ACETYLCYSTEINE</b> | <ol style="list-style-type: none"> <li>1. Antioxidant potential as a limiting substrate in glutathione synthesis</li> <li>2. Role in increasing the number of immune cells</li> </ol>   |
| <b>ZINC</b>             | <ol style="list-style-type: none"> <li>1. Maintenance of adaptive and innate immunity</li> <li>2. Important cofactor for several enzymes involved in immune system function</li> </ol>  |

<sup>4</sup>Sahebnaasagh A, Saghafi F, Avan R, et al.

The prophylaxis and treatment potential of supplements for COVID-19. Eur J Pharmacol. 2020;887:173530. doi:10.1016/j.ejphar.2020.173530 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7462519/>

3. Role in the proliferation, differentiation, and maturation of lymphocytes and other leukocytes
4. Regulation and formation of inflammatory responses
5. Effect on viral biological processes including viral protein replication and translation
6. Antiviral activity stimulated by secretion of interferon  $\alpha$

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7462519/>

**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. [5] [8-17]

**CURCUMIN**



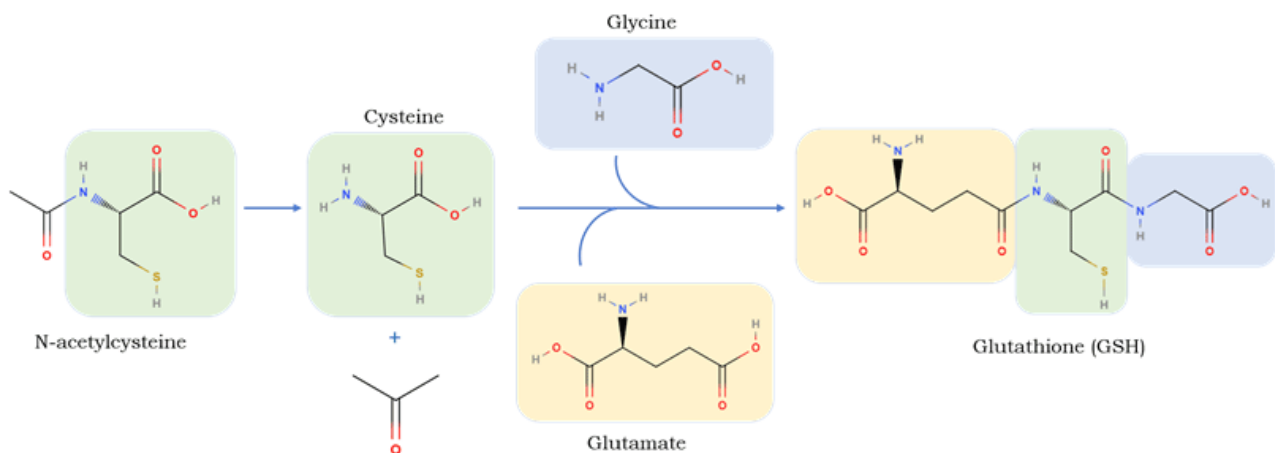
Curcumin has been shown to modulate the NLRP3 inflammasome,<sup>[5]</sup> and a preprint suggests that curcumin may target the major protease of SARS-CoV-2 to reduce viral replication.<sup>[18-27]</sup>

**EPIGALLOCATECHIN GALLATE (EGCG)**



Green tea, in addition to modulating NLRP3 inflammasome and targeting the major protease (M)<sup>pro[7]</sup> of SARS-CoV-2 to reduce viral replication, has been shown to prevent influenza in health care workers. Of note is a potential risk of hepatotoxicity<sup>[28-35]</sup>.

**N-ACETYLCYSTEINE (NAC)**



<https://www.psychiatrictimes.com/view/exploring-n-acetylcysteine-in-psychiatry>

N-acetylcysteine promotes glutathione production, which has been shown to be protective in influenza-infected rodents. In a little-noticed six-month controlled clinical trial that enrolled 262 primarily elderly subjects, those receiving 600 mg of NAC twice daily, compared with those receiving placebo, experienced significantly fewer flu-like episodes and days of bed rest.<sup>[36-41]</sup>

## RESVERATROL



Resveratrol, a naturally occurring polyphenol, shows many beneficial health effects. It has been shown to modulate the NLRP3 inflammasome.<sup>[5]</sup> and has in vitro activity against MERS-CoV.<sup>[43-51]</sup>

## VITAMIN D

| Alimento                                    | Contenuto di vitamina D in UI |
|---|-------------------------------|
| Latte                                       | 3-40/L                        |
| Burro                                       | 35/100 g                      |
| Yogurt                                      | 89/100 g                      |
| Formaggi                                    | 12-44/100 g                   |
| Funghi shiitake freschi                     | 100/100 g                     |
| Funghi shiitake secchi                      | 1660/100 g                    |
| Tuorlo d'uovo                               | 20-25/tuorlo                  |
| Gamberetti                                  | 152/100 g                     |
| Fegato di manzo                             | 15-50/100 g                   |
| Tonno, sardine, salmone, sgombro in scatola | 224-332/100 g                 |
| Salmone rosa con lisca in scatola           | 624/100 g                     |
| Salmone, sgombro cotto                      | 345-360/100 g                 |
| Sgombro dell'atlantico (crudo)              | 360/100 g                     |
| Aringa dell'atlantico (cruda)               | 1628/100 g                    |
| Aringa affumicata                           | 120/100 g                     |
| Aringa sottoaceto                           | 680/100 g                     |
| Merluzzo                                    | 44/100 g                      |
| Olio di fegato di merluzzo                  | 175/g – 1360/cucchiaino       |

Fonte Misra M et al. *Pediatrics* 2008; 122: 398-417

Activated vitamin D, 1,25(OH)<sub>2</sub>D, is a steroid hormone and acts as a modulator of the immune system by reducing the expression of inflammatory cytokines and increasing macrophage function. Vitamin D also stimulates the expression of potent antimicrobial peptides (AMPs), which are present in neutrophils, monocytes, natural killer cells, and respiratory epithelial cells.<sup>[54]</sup> Vitamin D also increases anti-pathogenic peptides through defensins and has a dual effect through suppression of superinfection. Evidence suggests that vitamin D supplementation may prevent upper respiratory tract infections.<sup>[55-72]</sup>

MELATONIN



Melatonin has been shown to have an inhibitory effect on the NLRP3 inflammasome. [94] This has not gone unnoticed by the COVID-19 research community, with two recently published articles proposing the use of melatonin as a therapeutic agent in the treatment of patients with COVID-19. [84,85] [86-94]

VITAMIN A

Alimenti ricchi di **vitamina A** (µg/100g)

|  |  |  |  |  |
|--|--|--|--|--|
|  |  |  |  | <b>Albicocca</b> 360 µg                    |
|  |  |  |  | <b>Burro</b> 930 µg                        |
|  |  |  |  | <b>Fegato</b> 16000 µg                     |
|  |  |  |  | <b>Peperoncini</b> 824 µg                  |
|  |  |  |  | <b>Olio di fegato di merluzzo</b> 18000 µg |
|  |  |  |  | <b>Pomodoro</b> 610 µg                     |
|  |  |  |  | <b>Fontina</b> 420 µg                      |
|  |  |  |  | <b>Mango</b> 533 µg                        |
|  |  |  |  | <b>Spinaci</b> 485 µg                      |
|  |  |  |  | <b>Peperoni</b> 424 µg                     |
|  |  |  |  | <b>Zucca</b> 580 µg                        |
|  |  |  |  | <b>Uova</b> 640 µg                         |
|  |  |  |  | <b>Carote</b> 1100 µg                      |
|  |  |  |  | <b>Latte</b> 75 µg                         |
|  |  |  |  | <b>Melone</b> 189 µg                       |
|  |  |  |  | <b>Prezzemolo</b> 943 µg                   |

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Vitamin A is a key micronutrient for maintaining vision, promoting growth and development, and protecting the epithelium and mucus integrity in the body. Vitamin A is known as an anti-inflammatory vitamin because of its key role in improving immune function. It is involved in immune system development and plays regulatory roles in cellular immune responses and humoral immune processes through modulation of T helper cells, sIgA, and cytokine production. Vitamin A has demonstrated a therapeutic effect in the treatment of various infectious diseases. It should be used with caution in pregnancy. [95-102]

## SAMBUCO



Elderberry (*Sambucus nigra*) is found in many medicinal preparations and has widespread historical use as an antiviral medicinal plant. <sup>[103]</sup> Based on animal research, elderberry is probably most effective in prevention and initial respiratory virus infections. <sup>[104]</sup> One in vitro study reported an increase in TNF-alpha levels related to a specific commercial elderberry preparation <sup>[105]</sup> which led some researchers to warn that its use could trigger a "cytokine storm." However, these data were not confirmed when the same group performed similar studies published in 2002. <sup>[106]</sup> Therefore, these data suggest that it is highly unlikely that consumption of properly prepared elderberry products (from berries or flowers) contributes to an adverse outcome related to cytokine overproduction or leads to an adverse response in someone infected with COVID-19. <sup>[107-114]</sup>

## PALMITOYLETHANOLAMIDE (PEA)



It is one of the most common saturated fatty acids in animals and plants and gets its name from the fact that it is found in palm oil

PEA is a natural 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 studies examining acute respiratory illness due to influenza. <sup>[115]</sup> The dosage 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, PEA is thought to act by attenuating the potentially fatal cytokine storm. <sup>[116-119]</sup>

## VITAMIN C

Vitamin C contributes to immune defense by supporting various cellular functions of both the innate and adaptive immune systems. Vitamin C accumulates in phagocytic cells, such as neutrophils, and can increase chemotaxis, phagocytosis, reactive oxygen species generation, and ultimately microbial killing. Vitamin C supplementation appears to be able to both prevent and treat respiratory and systemic infections. <sup>[120-121]</sup> Vitamin C has been used in hospital intensive care units to treat COVID-19 infection.

*For further study, we recommend reading Dr. Roberto Gava's book*



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## Alimenti ricchi di **vitamina C** - in 100 g

|   |                                    |   |  |  |                                 |
|---|------------------------------------|---|--|--|---------------------------------|
|    | <b>Acerola</b><br>1678 mg          |    | <b>Peperoni gialli</b><br>182,5 mg     |    | <b>Timo</b><br>160 mg           |
|   | <b>Peperone piccante</b><br>144 mg |   | <b>Prezzemolo</b><br>133 mg            |   | <b>Peperoni rossi</b><br>128 mg |
|  | <b>Broccoli</b><br>89 mg           |  | <b>Cavoletti di Bruxelles</b><br>85 mg |  | <b>Zafferano</b><br>81 mg       |

ZINC

LO ZINCO NEGLI ALIMENTI  
(mg/100 g)

|                   |      |                         |     |
|-------------------|------|-------------------------|-----|
| Ostriche Atlant.  | 74,7 | Carne di vitello        | 2,8 |
| Germe di grano    | 14,3 | Grano tenero            | 2,7 |
| Carne di manzo    | 6,2  | Ceci                    | 2,7 |
| Cacao in polvere  | 5,6  | Farina grano integrale  | 2,4 |
| Formaggio         | 4,0  | Pollo                   | 2,4 |
| Fiocchi di avena  | 3,4  | Pane integrale          | 1,8 |
| Fumento duro      | 3,4  | Riso integrale          | 1,8 |
| Piselli secchi    | 3,2  | Pane di segale          | 1,6 |
| Lenticchie        | 3,1  | Farina grano semintegr. | 1,5 |
| Noci (inglesi)*   | 3,1  | Uova 2 da 50 g          | 1,0 |
| Mandorle*         | 3,0  | Spinaci crudi           | 0,8 |
| Fagioli d. occhio | 2,9  | Pesce                   | 0,7 |
| Arachidi          | 2,9  | Pane bianco             | 0,6 |
| Prosciutto        | 2,8  | Pasta comune cotta      | 0,5 |
| Fagioli           | 2,8  | Pomodoro maturo         | 0,2 |

(N.Valerio, da Krause & Mahan 1984 e \*USA Dept.Agr.)



Zinc contributes to immune defense by supporting various cellular functions of both the innate and adaptive immune systems. There is also evidence that it suppresses viral binding and replication. Zinc deficiency is common, especially in populations most at risk for severe COVID-19 infection, and it is difficult to make an accurate diagnosis with laboratory measurements. Zinc supplementation is supported by evidence that it prevents viral infections and reduces their severity and duration. It has also been shown to reduce the risk of lower respiratory tract infection, which is of particular importance in the context of COVID-19.

[128]

BIBLIOGRAPHY VIRUS-SPECIFIC NUTRACEUTICAL AND BOTANICAL AGENTS

FUNCTIONAL MEDICINE

FURTHER RESEARCH ON NUTRACEUTICAL AND BOTANICAL AGENTS <sup>5</sup>

BETA GLUCAN



It is a class of **polysaccharides** (consisting of D-Glucose units) that are indigestible i.e., classifiable as dietary fiber and **present in foods such as bran, oats, yeasts, fungi, and algae**, but also in the cell walls of common **brewer's yeast** (*Saccharomyces cerevisiae*).

Beta glucans are known to modulate immune activity, mainly by triggering or enhancing innate immune responses through interactions with pattern recognition receptors (PRRs)<sup>[1,2]</sup> and by increasing anti-inflammatory cytokines such as IL-10.<sup>[3,4,5,6,7]</sup> Beta glucans induce activity against viral attack.<sup>[8,9]</sup> Numerous human studies have shown that beta

<sup>5</sup> <https://www.ifm.org/news-insights/functional-medicine-approach-covid-19-additional-research-nutraceuticals-botanicals/>

glucans reduce cold and flu symptoms<sup>[10,11,12]</sup> and upper respiratory tract infections compared with placebo.<sup>[13,14,15,16,17,18,19]</sup>

## MUSHROOMS

*Shiitake (Lentinula edodes)*, *Lion's Mane [monkey head] (Hericium erinaceus)*, *Maitake (Grifola frondosa)*, *Reishi (Ganoderma lucidum)*



Various species of fungi have been shown to possess broad immunomodulatory effects. They possess multiple mechanisms of action, including increasing the number of circulating B cells,<sup>[21]</sup> increasing intestinal immunity,<sup>[22]</sup> stimulation of host immunity,<sup>[23]</sup> activation of innate immune cells,<sup>[24]</sup> and increasing cytotoxic activity of NK cells.<sup>[25] [26-29]</sup>

## CHINESE SKULLCAP [SKULLCAP] (SCUTELLARIA BAICALENSIS)



Chinese skullcap (*Scutellaria baicalensis*) has been used for centuries in traditional Chinese medicine (TCM). In several human studies, participants taking TCM formulations containing Chinese skullcap showed statistically significant reductions in viral infection rates compared with controls.<sup>[30]</sup> It has anti-inflammatory, antioxidant, antibacterial and antiviral properties,<sup>[31,32,33]</sup> increases immune surveillance and downregulates NLRP3 inflammasomes,<sup>[34]</sup> IL-6 and TNF-alpha.<sup>[35] [36-54]</sup>

## LICORICE (GLYCYRRHIZA SPECIES)

Licorice (*Glycyrrhiza* species) has multiple mechanisms of action, including inhibition of viral replication<sup>[55,56,57]</sup> by blocking the ACE2 receptor,<sup>[58]</sup> promoting Th1 cell activity,<sup>[59]</sup> and inhibiting pro-inflammatory cytokines,<sup>[60]</sup> prostaglandins and nitric oxide production.<sup>[61]</sup> Inhibition of hydrocortisone metabolism by 11 beta-HSD has also been suggested

as a potential mechanism of licorice's anti-inflammatory action. [62] Licorice has been used in traditional Chinese medicine (TCM) formulations against SARS-CoV-1 and H1N1 and has been reviewed for its effects on SARS-CoV-2. [63,64] In particular, two positive human studies have been conducted against SARS-CoV-1 using a TCM formulation containing licorice. [65,66] [67-74]



### ANDROGRAPHIS PANICULATA

*Andrographis paniculata* leaves have been used for centuries in traditional systems of Eastern medicine for the treatment and prevention of upper respiratory tract infections (URTIs), cough and sinusitis. [73] Systematic reviews show a consistent and clinically relevant effect when used as a single herb or in combination with other herbal preparations. [74,75,76] *Andrographis* has demonstrated anti-inflammatory, antiviral, and immunostimulatory activities and to be effective in vitro against avian influenza A (H9N2 and H5N1) and human influenza A H1N1 virus. [77,78] It inhibits platelet-activating factor-mediated inflammatory responses, reduces the expression of cyclooxygenase-2, and has analgesic and antipyretic effects. [79,80,81,82,83,84,85] In addition, *Andrographis* is one of several agents that works by decreasing furin protease activity, a necessary step in the activation and insertion of the SARS-CoV-2 spike protein into mucosal epithelial cells. [86]

[87-92]



### ASTRAGALUS MEMBRANEUS

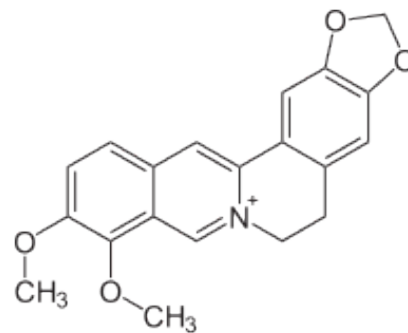
*Astragalus membranaceus* has been used in TCM for centuries. [93] Astragalus is well known for its antiviral activity, [94,95,96] for its anti-inflammatory properties, [97,98,99,100,101] to activate the innate immune system, [102,103,104] and to reduce

NLRP3-mediated inflammation.<sup>[105]</sup> In addition, the plant alkaloid swainsonine inhibits the glycosylation required for the SARS-CoV-2 spike protein to attach to human cells.<sup>[106][107-114]</sup>



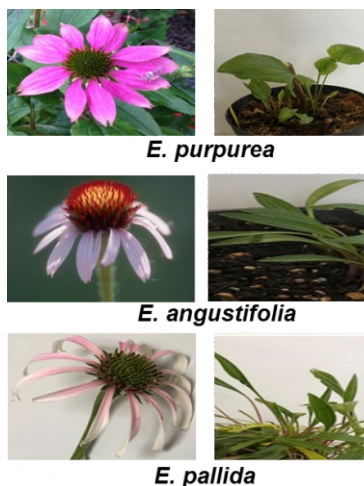
## BERBERINE

Berberine is an alkaloid found in the roots, rhizomes, and stem bark of various plants, including goldenseal, goldthread, and Oregon grape. Berberine has been shown to have antiviral activity on a wide range of viral targets.<sup>[115,116,117,118,119,120]</sup> Berberine also activates 5'AMP-activated protein kinase (AMPK),<sup>[121,122]</sup> anti-inflammatory. The anti-inflammatory effects of berberine also include suppression of I $\kappa$ B kinase inhibition and upregulation of NF $\kappa$ B, IL-1 $\beta$  and TNF $\alpha$ .<sup>[123]</sup> Berberine also acts by lowering blood glucose,<sup>[124]</sup> thus favoring with furin inhibition, as well as preserving ACE2 receptors, possibly through inhibition of aldose reductase.<sup>[125-137]</sup>



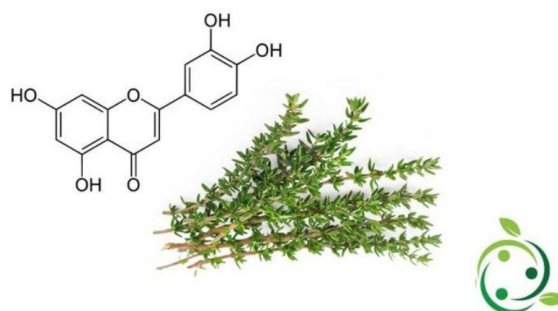
## ECHINACEA (ECHINACEA SPECIES)

The Echinacea species (*E. purpurea*, *E. angustifolia* and *E. pallida*) are all used for medicinal purposes. The immunological effects of echinacea appear to result from a combination of constituents.<sup>[138]</sup> *E. purpurea* has been shown to stimulate macrophage activation and NK cell activity in both human and animal models and may be directly linked to increased cytokine expression.<sup>[144,145]</sup> Various Echinacea preparations have shown antiviral activity,<sup>[146,147,148]</sup> also alone reduce the frequency, severity and/or duration of upper respiratory tract symptoms in several studies,<sup>[149,150,151]</sup> while various multi-herb/nutrient formulas containing Echinacea preparations are effective in reducing symptoms.<sup>[152,153,154,155]</sup> [139-163]



## LUTEOLIN

Luteolin is a flavonoid found in medicinal plants and many fruits and vegetables, including peppers, celery, radicchio, chicory, and lemons. Luteolin-rich plants have been used in traditional Chinese medicine to treat hypertension, inflammatory disorders, and cancer <sup>[164]</sup> Recent screening studies have identified luteolin as a candidate molecule to block SARS-CoV-2 entry into the cell and to modulate excessive inflammatory responses. <sup>[165-172]</sup>



## BIBLIOGRAPHY FURTHER RESEARCH ON NUTRACEUTICAL AND BOTANICAL AGENTS

## TRADITIONAL CHINESE AND AYURVEDIC MEDICINE USED IN COVID-19 PATIENTS

### Traditional Chinese Medicine

Complementing the use of phytotherapeutics in functional medicine against COVID-19, we report a number of herbs and natural compounds that have shown moderate to strong antiviral activity, used particularly in TCM. Research on many natural herbal compounds has also shown potent and significant inhibition of the different stages of viral replication of SARS-Cov-1 and SARS-Cov-2, specifically targeting 3CL<sup>PRO</sup>, PL<sup>PRO</sup>, RdRp, protein helicase, protein S, protein N, protein 3a, cathepsin L, Nsp1, Nsp3c and ORF7a and protein S/ACE-2 interaction. <sup>6</sup>

It is important to mention that in China, TCM has played an important role in the battle against COVID-19.

In late January 2020, the National Administration of Traditional Chinese Medicine (NATCM) organized an urgent study section to identify effective TCM prescriptions for the prevention and treatment of COVID-19. Based on the symptoms observed in early COVID-19 patients, several TCM formulas were developed, among which Lung Cleansing and Detoxification Decoction (LCDD) was one of the most widely used and clinically studied.

<sup>6</sup>Fuzimoto AD, Isidore C.

The antiviral and coronavirus-host protein pathways inhibiting properties of herbs and natural compounds - Additional weapons in the fight against the COVID- 19 pandemic?

J Tradit Complement Med. 2020;10(4):405-419. Published 2020 May 30. doi:10.1016/j.jtcme.2020.05.003

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7260130/>

LCDD is a combined formula developed on the basis of four classical formulas described in the Treatise on Pathogenic and Miscellaneous Diseases of Cold and contains 21 ingredients: *Ephedra sinica*, *Cinnamomum cassia* (twig), *Alisma plantago-aquatica*, *Atractylodes macrocephala*, *Bupleurum chinense*, *Scutellaria baicalensis*, *Pinellia ternate* (pretreated with ginger and potassium alum), *Aster tataricus*, *Tussilago farfara*, *Iris domestica*, *Asarum sieboldii*, *Dioscorea polystachya*, *Agastache rugosa*, *Citrus aurantium* (dried young fruit), licorice (roasted), *Prunus armeniaca* (apricot kernel), ginger, orange peel, *Wolfiporia extensa*, *Polyporus umbellatus*, and chalk ( $\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$ ).

According to a press conference held by the Chinese State Council on the Joint Prevention and Control Mechanism on April 17, the initial study indicated that LCDD was effective on 90% of the 214 COVID-19 patients enrolled. Another study with an additional 1262 patients, including 57 with severe symptoms, showed that 99.28 percent of these patients recovered and none with mild symptoms developed severe symptoms during treatment with LCDD (<http://www.gov.cn/xinwen/gwylflkjz95/index.htm> [in Chinese]).

Although these trial data have yet to be officially published, the NATCM recommended LCDD as a treatment for COVID-19. Since then LCDD has been widely used in 28 provinces and municipalities and has contributed to the relatively low mortality rate among COVID-19 patients in China. Several Chinese patented drugs (e.g., Lianhua Qingwen capsules) have also been used for the treatment of COVID-19 patients with many concomitant clinical observations currently in progress.<sup>7</sup>

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<sup>7</sup> Weng JK.

Plant Solutions for the COVID-19 Pandemic and Beyond: Historical Reflections and Future Perspectives.

Mol Plant. 2020;13(6):803-807. doi:10.1016/j.molp.2020.05.014

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7237358/>

Zhang D, Zhang B, Lv JT, Sa RN, Zhang XM, Lin ZJ.

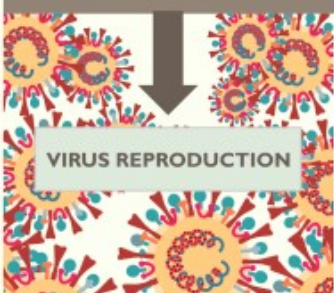
The clinical benefits of Chinese patent medicines against COVID-19 based on current evidence.

Pharmacol Res. 2020;157:104882. doi:10.1016/j.phrs.2020.104882


<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7198419/>

Dr. Loretta Bolgan


| Coronavirus-Host Target Proteins |                     | HERBS AND NATURAL COMPOUNDS  |
|----------------------------------|---------------------|--|
| A                                | S PROTEIN           | TGG (tetra-O-galloyl-β-D-glucose, from <i>Galla Chinensis</i> ) and luteolin; <i>Cimicifuga</i> rhizome, <i>Melia cortex</i> , <i>Coptidis</i> rhizome, <i>Phellodendron cortex</i> , and <i>Sophora subprostrata radix</i> ; Compounds extracted from <i>Stephania tetandra</i> : bis-benzylisoquinoline alkaloids-tetrandine (TET), fangchinoline (FAN), and cepharanthine (LEP); Dihydrotanshinone I; Licoflavonol (from <i>Glycyrrhiza uralensis</i> ), cosmosiin (from <i>Scutellaria baicalensis</i> ), neohesperidin (from <i>Citrus aurantium</i> ), mangostin (from <i>Garcinia mangostana</i> ), kouitchenside D (from <i>Swertia kouitchensis</i> ), excoecariotoxin (from <i>Excoecaria agallocha</i> ), phyllaemblicin G7 (from <i>Phyllanthus emblica</i> ), and piceatannol (from <i>Vitis vinifera</i> ).  |
|                                  | ACE-2               | Phyllaemblicin G7 (from <i>Phyllanthus emblica</i> ), xanthones (from the plants of <i>Swertiagenus</i> ), neohesperidin and hesperidin (from <i>Citrus aurantium</i> ).   |
|                                  | S/ACE2 Interaction  | Emodin <i>Rhei Radix et Rhizoma</i> , <i>Polygoni multiflora radix</i> , and <i>Polygoni multiflora Caulis</i> ; Hesperidin.   |
|                                  | TMPRSS2             | Phyllaemblicin G7, neoandrographolide, kouitchenside I, and others.  |
|                                  | CATHEPSIN L         | MOL 736 (Aurantiamide acetate from <i>Artemisia annua</i> ).   |
| B                                | 3CL <sup>PRO</sup>  | <i>Isatis Indigotica</i> , <i>sinigrin</i> , beta-sitosterol, indigo, aloe-emodin, and hesperidin; Tannic acid, 3-isothaeafavin-3-gallate (TF2B), theaflavin-3,3'-digallate (TF3); Isatin derivatives (especially 4a and 4k); 18 natural compounds from MNPD and TCMD; Isatin compound 5f; Quercetin-3-β-galactoside; Betulinic acid and savinin; <i>Houttuynia cordata</i> ; <i>Torreya nucifera</i> / amentoflavone, apigenin, luteolin and quercetin; <i>Tripterygium regelii</i> / quinone-methide triterpenes - celastrol, pristimerin, tingenone, and iguesterin; and dihydrocelastrol; CBM (dried rhizome of <i>Cibotum barometz</i> ); DBM ( <i>Dioscorea</i> rhizome); <i>Salvia Miltiorrhiza</i> and its tanshinone compounds; <i>Ecklonia cava</i> and its isolates, especially dieckol; 5-sulfonyl isatin derivatives (especially compounds 7i, 7k, 8k1 and 8k2, and others); <i>Angelica keiskei</i> and its compounds, especially xanthoangelol E (chalcone 6); <i>Broussonetia papyrifera</i> polyphenols, especially papyriflavonol A (4); Coumaroyltyramine, Cryptotanshinone, Desmethoxyreserpine, Dihomo-γ-linolenic acid, Kaempferol, Lignan, N-cis-feruloyltyramine, Quercetin, Sugiol, and Tanshinone Iia; Flavone and coumarin derivatives; Andrographolide derivatives, chrysin-7-O-β-glucuronide and cosmosiin (from <i>Scutellaria baicalensis</i> ), betulonal (from <i>Cassine xylocarpa</i> ), andrographiside and andrograpanin (from <i>Andrographis paniculata</i> ), 2β-hydroxy-3,4-seco-friedelolactone-27-oic acid, isodecortinol and cerevisterol (from <i>Viola diffusa</i> ), neohesperidin (from <i>Citrus aurantium</i> ), 2,2-Di(3-indolyl)-3-indolone (from <i>Isatis indigotica</i> ), theaflavin 3,3'-di-O-gallate (from <i>Camellia sinensis</i> ), rosmarinic acid (from <i>Salvia verticillata</i> ), kouitchenside I and oleanolic acid (from <i>Swertia</i> genus), and others. |
|                                  | PL <sup>PRO</sup>   | <i>Salvia Miltiorrhiza</i> and its tanshinone compounds; <i>Paulownia tomentosa</i> flavonoid derivative compounds; <i>Tribulus terrestris</i> and its compounds; <i>Angelica keiskei</i> and its compounds, especially xanthoangelol E (chalcone 6); <i>Broussonetia papyrifera</i> polyphenols, especially papyriflavonol A (4); <i>Trypantanthrin</i> (from <i>Strobilanthes cusia</i> ); Coumaroyltyramine, Cryptotanshinone, Kaempferol, Maoupinamide, N-cis-feruloyltyramine, Quercetin, Tanshinone Iia; Platycodin D (from <i>Platycodon grandiflorus</i> ), chrysin and baicalin (from <i>Scutellaria baicalensis</i> ), neohesperidin (from <i>Citrus aurantium</i> ), sugetriol-3,9-diacetate (from <i>Cyperus rotundus</i> ), phaitanthrin D and 2,2-di(3-indolyl)-3-indolone (from <i>Isatis indigotica</i> ), Epigallocatechin gallate (from <i>Camellia sinensis</i> ), piceatannol (from <i>Vitis vinifera</i> ), rosmarinic acid (from <i>Salvia verticillata</i> L.), magnolol (from <i>Magnolia officinalis</i> ), and others.   |
|                                  | RdRp                | <i>Houttuynia cordata</i> ; <i>Cimicifuga</i> rhizome, <i>Melia cortex</i> , <i>Coptidis</i> rhizome, <i>Phellodendron cortex</i> , and <i>Sophora subprostrata radix</i> ; <i>Trypantanthrin</i> (from <i>Strobilanthes cusia</i> ); Betulonal (from <i>Cassine xylocarpa</i> ), gnidicin and gniditrin (from <i>Gnidia lamprantha</i> ), 14-deoxy-11,12-didehydroandrographolide and andrographiside (from <i>Andrographis paniculata</i> ), theaflavin 3,3'-di-O-gallate (from <i>Camellia sinensis</i> ), baicalin (from <i>Scutellaria baicalensis</i> ), and others.   |
|                                  | N protein           | <i>Cimicifuga</i> rhizome, <i>Melia cortex</i> , <i>Coptidis</i> rhizome, <i>Phellodendron cortex</i> , and <i>Sophora subprostrata radix</i> ; <i>Sophorae radix</i> , <i>Acanthopanax cortex</i> , and <i>Torilis fructus</i> (↓ mRNA7 and N protein synthesis); <i>Sanguinobae radix</i> (only ↓ N protein synthesis); Compounds extracted from <i>Stephania tetandra</i> : bis-benzylisoquinoline alkaloids-tetrandine (TET), fangchinoline (FAN), cepharanthine (LEP).  |
|                                  | Helicase            | Myrecetin/Scutellarin (from <i>Scutellaria Baicalensis</i> ); Flavonoids from different sources (α-glucosyl hesperidin, hesperidin, rutin, quercetageitin 6-O-β-D-glucopyranoside and homovitexin), xanthones (kouitchenside H, kouitchenside A, kouitchenside D), triptexanthoside D (from <i>Swertia</i> genus), and others.   |
|                                  | Nsp1, Nsp3c & ORF7a | Platycodin D (from <i>Platycodon grandifloras</i> ), wogonoside (from <i>Scutellaria baicalensis</i> ), Vitexin (from <i>Vitex negundo</i> ), andrographolide derivatives, and xanthones (from <i>Swertia</i> genus).  |
|                                  | 3a protein          | Emodin; Kaempferol glycosides (juglanin, kaempferol, tiliroside, afzelin, kaempferol-3-O-α-rhamnopyranosyl (1→2)-[α-rhamnopyranosyl (1→6)]-β-glucopyranoside).   |



VIRUS REPRODUCTION



INHIBITION OF VIRUS REPRODUCTION



Fuzimoto & Isidoro, 2020

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7260130/>

Herbs and natural compounds that can inhibit the interaction between SARS-CoV proteins and host cell proteins.

Panel A corresponds to proteins involved in CoV internalization in host cells; panel B corresponds to additional processes involved in translation, transcription, replication, assembly, and exit from host cells.

## Ayurvedic Medicine

Since ancient times, Indian herbs have been used as a treatment and preventive strategy for various diseases, including viral respiratory infections. The benefit of using these herbs in viral respiratory infections is to develop immune-stimulating and inflammation-modulating effects to support the immune system. The holistic approach of AYUSH medicine systems focuses on prevention through improved lifestyle, diet, prophylactic interventions to boost immunity, and the use of customized herbal and homeopathic remedies.

### Preventive and prophylactic Indian medicinal plants recommended by AYUSH for COVID-19:<sup>8</sup>

AYUSH recommended medicinal plant extracts for treating COVID-19  
(Ref: AYUSH Ministry of Health Corona Advisory – D.O. No. S. 16030/18/2019 – NAM; dated: 06th March, 2020).

| Indian medicinal plant                               | Form of extract | Trade name              | Indian traditional medical practice | Preparation   | Recommended usage   | Effective against  |
|--|-----------------|-------------------------|-------------------------------------|---|---|--|
| <b>Preventive and prophylactic</b>                   |                 |                         |                                     |   |   |  |
| <i>Tinospora cordifolia</i>                          | Aqueous         | Samshamani Vati         | Ayurveda                            | Samshamani Vati 500 g with warm water                                     | Twice a day for 15 days   | Chronic fever  |
| <i>Andrographis paniculata</i>                       | Aqueous         | Nilavembu kudineer      | Siddha                              | Nilavembu kudineer 60 ml decoction  | Twice a day for 14 days   | Fever and cold   |
| <i>Cydonia oblonga</i>                               | Aqueous         | Behidana Unnab          | Unani                               | Behidana – 3 g<br>Unnab – 5 Nos   | Twice a day for 14 days   | Antioxidant, immune-modulatory, anti-allergic, smooth muscle relaxant, anti-influenza activity |
| <i>Zizyphus jujube</i>                               |                 | Sapistan                |                                     | Sapistan – 9 Nos  |   |  |
| <i>Cordia myxa</i>                                   |                 |                         |                                     | Boil these 3 in 250 ml water, boil it until it remains half and filter it |   |  |
| Arsenicum album 30                                   | Tablet          | Arsenicum album 30      | Homeopathy                          | –   | Daily once in empty stomach for 3 days (Should be repeated after 1 month till the infection persist). | Effective against SARS-CoV-2, immune-modulator.  |
| <b>Symptomatic Management for COVID-19</b>           |                 |                         |                                     |   |   |  |
| AYUSH -64  | Tablet          | –                       | Ayurveda                            | –   | 2 tablets twice a day   | Respiratory infections   |
| Agastya Haritaki                                     | Powder          | Agasthya Rasayanam      | Ayurveda                            | 5 g in warm water   | Twice a day   | Upper respiratory infections   |
| Anuthaila  | Oil             | Sesame oil              | Ayurveda                            | –   | 2 drops in each nostril daily morning   | Respiratory infections   |
| Adathodai Manapagu                                   | Aqueous         | Adathodai Manapagu      | Siddha                              | –   | 10 ml twice a day   | Fever  |
| <i>Bryonia alba</i>                                  | Tablet          | Bryonia                 | Homeopathy                          | –   | –   | Reduce lung inflammation   |
| <i>Rhus toxicodendron</i>                            | Tablet          | Rhus tox                | Homeopathy                          | –   | –   | Viral infections   |
| <i>Atropa belladonna</i>                             | Tablet          | Belladonna              | Homeopathy                          | –   | –   | Asthma and chronic lung diseases   |
| <i>Bignonia sempervirens</i>                         | Tablet          | Gelsemium               | Homeopathy                          | –   | –   | Asthma   |
| <i>Eupatorium perfoliatum</i>                        | Tablet          | Eupatorium perfoliatum  | Homeopathy                          | –   | –   | Respiratory symptoms   |
| <b>Add on interventions to the conventional care</b> |                 |                         |                                     |   |   |  |
| Vishasura kudineer                                   | Tablet          | Poly-herbal formulation | Siddha                              | Decoction 60 ml   | Twice a day   | Fever  |
| Kaba sura kudineer                                   | Tablet          | Poly-herbal formulation | Siddha                              | Decoction 60 ml   | Twice a day   | Fever, cough, sore throat, shortness of breath   |

This table depicts the Indian Medicinal plants and its usage provided by the AYUSH, Government of India as a therapeutic approach for COVID-19.

<sup>8</sup> Vellingiri B, Jayaramayya K, Iyer M, et al. COVID-19: A promising cure for the global panic. Sci Total Environ. 2020;725:138277. doi:10.1016/j.scitotenv.2020.138277  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7128376/>

## LACTOFERRIN, OVOTRANSFERRIN AND LYSOZYME

The hyperferritinemia that occurs in the complication of COVID-19 along with the cytokine storm contributes to inflammation by directly activating macrophages. Free iron in turn reacts with oxygen or hydrogen peroxide to form free radicals, thus leading to further oxidative stress and causing tissue injury.

### Lactoferrin

Bovine lactoferrin has been shown to inhibit entry of SARS-CoV and SARS-CoV-2 into cells. Lactoferrin restores iron homeostasis by sequestering free iron and modulating the levels of proteins involved in controlling blood-tissue iron balance and reduces oxidative stress and inflammation.

Oral administration of lactoferrin in animal models and human studies of viral diseases, as well as various inflammatory disease states, shows beneficial effects and safety.<sup>9</sup>

### Ovotransferrin

Ovotransferrin has antiviral peptides that are homologous with those found in human and bovine lactoferrin but ovotransferrin may have a more potent antiviral effect. It has immunomodulatory, antioxidant, anti-inflammatory and angiotensin-converting enzyme inhibitory activities.

### Lysozyme

Lysozyme shows antiviral activity via its cationic peptides and has immune-modulating, antioxidant, and angiotensin-converting enzyme inhibitory properties. Oral administration of lysozyme in animal models and human studies shows its ability to limit inflammation at the systemic level, resulting in reduced immune pathology.

### Sources, forms, and practical uses of lactoferrin, ovotransferrin, and lysozyme<sup>10</sup>

Lactoferrin is abundant in cow's milk, while ovotransferrin and lysozyme are abundant in chicken egg whites. High isolation costs have limited the widespread use of purified forms of these antimicrobials.

### Future Perspectives

These antimicrobials could be used after the presentation of symptoms to prevent noncritical cases from becoming critical cases, and lower amounts could be taken to reduce the risk of infection in those at high risk.

Lysozyme and lactoferrin can also be administered as eye drops to protect the conjunctiva from infection.

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<sup>9</sup> Chang R, Ng TB, Sun WZ.

Lactoferrin as potential preventative and adjunct treatment for COVID-19.

Int J Antimicrob Agents. 2020;56(3):106118. doi:10.1016/j.ijantimicag.2020.106118

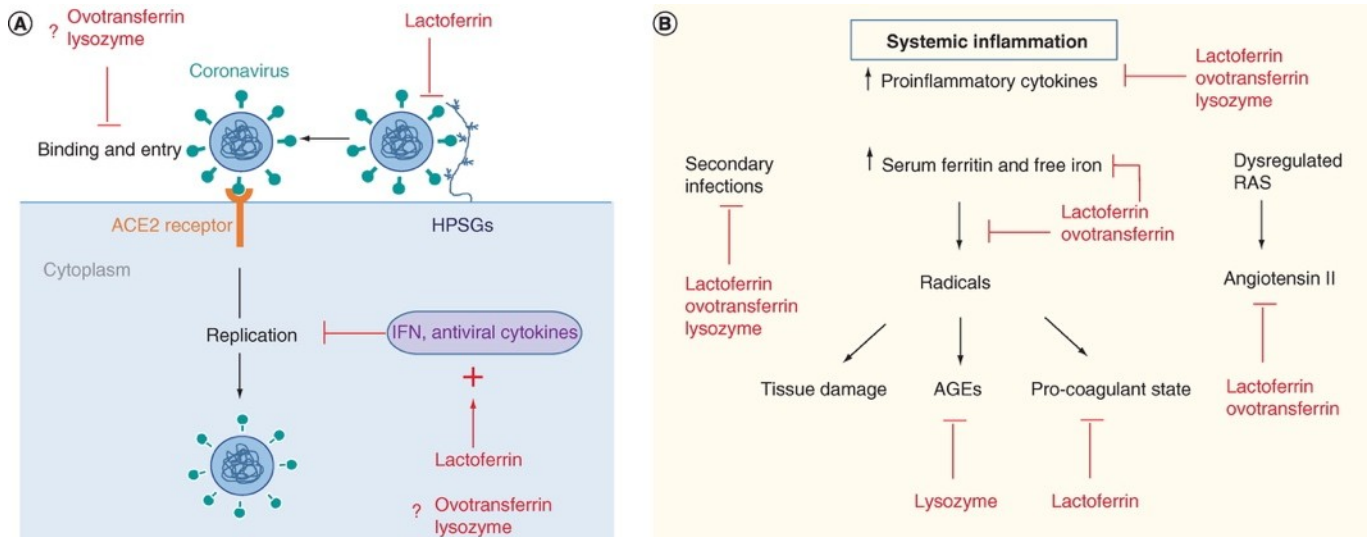
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7390755/>

<sup>10</sup> Jaclyn Kelly Mann Thumbi Ndung'u

The potential of lactoferrin, ovotransferrin and lysozyme as antiviral and immune-modulating agents in COVID-19

Future Virology 8 Oct 2020 <https://doi.org/10.2217/fvl-2020-0170>

<https://www.futuremedicine.com/doi/full/10.2217/fvl-2020-0170>



<https://www.futuremedicine.com/doi/full/10.2217/fvl-2020-0170>

### COPPER AND SELENIUM TRACE ELEMENTS <sup>11</sup>

Edited by Dr. ROBERTA CONTINI

The term trace element comes from the Greek word **oligo** meaning "little," because trace elements are minerals found in small concentrations in our bodies. Because of their low presence in our bodies, in the early 1900s some scientists thought they were **impurities** rather than fundamental elements. They are actually inorganic metals and ions that are essential for the life of the body's cells and for our well-being.

The four most important trace elements that should not be missed are **copper, chromium, manganese and zinc**. To these should be added **iodine, molybdenum, selenium and iron**. These micronutrients are involved in metabolic processes, many enzymatic activities and **immunological reactions**.

#### THE COPPER

Copper is found in organic tissues: the highest concentrations are found in the liver, heart, and brain; bones and muscles contain more than 50 percent total present in the body. Copper has been known since antiquity for its antibacterial properties and has been described as the "mineral column." As a co-factor for at least 13 enzymes, it drives a crucial series of chemical reactions that support human health and development. Once ingested, it is absorbed from the small intestine through the bloodstream. There it binds to carrier proteins, which transport it to the liver for subsequent distribution throughout the body.

- **Brain and nervous system:** copper plays a crucial function in the normal development of the brain and nervous system. It plays an important role in the production and maintenance of myelin and is also involved in the synthesis of

<sup>11</sup> Giorgini Dr. Martino "Vis Medicatrix naturae"

From the Web

Biology - Copper for Health - European Copper Institute - Miedz...

curenaturali.it; tuttogreen.it; e | l e d e c o r .com; Tuscan Health Library Network; curenaturali.it; tuttogreen.it; www.prana24.com: copper kills coronavirus

Read more:

Ministry of Health. Covid-19 - Healthy Lifestyles.

A Review of Micronutrients and the Immune System-Working in Harmony to Reduce the Risk of Infection

Gombart AF, Pierre A. Maggini S.

Nutrients. 2020 Jan 16;12(1). pii: E236. doi: 10.3390/nu12010236. Review.

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Nutrients. 2020 Sep 8;12(9). pii: E2738. doi: 10.3390/nu12092738. Review.

Dietary recommendations during the COVID-19 pandemic

de Faria Coelho-Ravagnani C, Corgosinho FC, Sanches FFZ, Prado CMM, Laviano A, Mota JF.

Nutr Rev. 2020 Jul 12. pii: nuaa067. doi: 10.1093/nutrit/nuaa067. [Epub ahead of print].

neurotransmitters that allow communication between nerve cells. In case of copper deficiency, degeneration of the nervous system occurs.

- *Immune system:* copper is necessary for maintaining a proper level of white blood cells, many of which are phagocytes that 'swallow' and destroy foreign microorganisms. In case of copper deficiency: depressed immune system, reduced level of white blood cells and increased incidence of pneumonia.
- *Blood and blood vessels:* copper acts as a co-factor for an enzyme essential for blood clotting. Blood vessels are surrounded and protected by connective tissue, and copper helps support their elasticity, particularly for the aorta and small arteries. In case of copper deficiency: low blood pressure, circulatory problems.
- *Heart:* copper is essential for the synthesis of collagen, which is found in connective tissue, i.e., the body's main supporting and connecting tissue. Copper is also needed to maintain muscle tone and function and consequently plays a vital role at the heart level. In case of copper deficiency: heart failure.
- *Iron transport:* copper plays a key role in the conversion of iron into its usable ferric form (Fe III) and also contributes to iron transport throughout the body. In case of copper deficiency: anemia, iron overload at the tissue level.
- *Bones:* collagen is the key molecule responsible for the stiffness and mechanical strength of bones. In case of copper deficiency: fractures, skeletal abnormalities, osteoporosis.
- *Skin:* Since it is the most common protein found in human skin, collagen is important for maintaining its elasticity. As a co-factor for the enzyme tyrosinase, copper participates in the synthesis of melanin, which pigments the skin. In case of copper deficiency: skin degeneration, albinism.
- *In cells:* the generation of cellular energy (ATP) within mitochondria depends on the crucial involvement of a copper-containing enzyme. A similarly vital function for copper as a co-factor is the neutralization of free radicals that would otherwise oxidize and destroy healthy cells. In case of copper deficiency: heart disease.

#### THERAPEUTIC PROPERTIES

- strengthens **the immune system**
- helps in cases of **inflammation, viral and infectious diseases**
- Acts in **metabolic processes** related to phosphorus and calcium
- Regularizes **pituitary gland** and **thyroid gland**.

Some research has shown that **copper surfaces tend to kill COVID-19** in about four hours. Encouraging the **use of copper and its alloys in public settings**, hospitals and medical facilities back in the 1980s was Phyllis J. Kuhn, who wrote "brass-an alloy typically composed of 67 percent copper and 33 percent zinc-is **bactericidal**, while stainless steel-about 88 percent iron and 12 percent chromium-does little to prevent bacterial growth."

#### DAILY COPPER REQUIREMENT

Varies between **1.5 and 5 mg**  
 0.9 mg for adults  
 1.0 mg for pregnant women  
 1.3 mg for lactating women

#### FOODS RICHEST IN COPPER



**Pearl barley; Oat bran; Wheat germ:** contain about 0.4 mg of copper

**Walnuts:** 1.6mg; **Hazelnuts:** 1.73mg copper; **Peanuts:** 100g peanuts contain 0.67mg copper. **Cocoa:** This spice if it has not undergone too extreme roasting processes contains 3.8mg of copper. **Shellfish:** Contain 1mg of copper (mussels, clams, cuttlefish, etc.).

**Avocado:** Contains 0.19mg of copper and many omega-3s that help lower cholesterol. Avocado is also rich in Vitamin E, beta-carotene and potassium

**Raisins:** Fruit that provides energy to the body while preventing insulin spikes.

## THE SELENIUM <sup>12</sup>

Chemical symbol: Se.

It is a nonmetal that is largely taken up through food and, in the case of plants, its amount depends on how much is present in the soil.

<sup>12</sup> Kieliszek M, Lipinski B.

Selenium supplementation in the prevention of coronavirus infections (COVID-19). *Med Hypotheses*. 2020;143:109878. doi:10.1016/j.mehy.2020.109878  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7246001/>

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Selenium Deficiency Is Associated with Mortality Risk from COVID-19. *Nutrients*. 2020;12(7):2098. Published 2020 Jul 16. doi:10.3390/nu12072098  
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Immune-boosting role of vitamins D, C, E, zinc, selenium and omega-3 fatty acids: Could they help against COVID-19? *Maturitas*. 2021;143:1-9. doi:10.1016/j.maturitas.2020.08.003  
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### THERAPEUTIC PROPERTIES

- Strengthens immune defenses
- Lower chance of developing cancer of the bladder, prostate, lungs and in the gastrointestinal tract.
- Antioxidant
- Enhances collagen action by preserving tissue elasticity
- Counteracts free radicals and aging
- Treats migraine, eczema, constipation, impotence.
- Useful in cases of neuralgia, prostate problems and rheumatism.
- Acts on thyroid function
- Preserves memory.
- Fluidifies the blood
- Prevents flu symptoms
- Maintains the health of hair by improving the rhythms of hair growth

### FOODS CONTAINING SELENIUM



**Cereals (rice, barley, Kamut, corn):** These are the most selenium-rich foods, especially whole grains.

**Rice** contains 15 mg of selenium per 100 grams of product. **Barley** contains selenium and phosphorus and vitamins B1, B2, B5, B6 and PP. **Kamut** is a more complete food than traditional wheat, rich in minerals, including a considerable amount of selenium, protein, amino acids, and B and E vitamins. **Corn** contains 12 mg of selenium per 100 grams.

#### **Brazil nuts**

Among plant foods they are the richest in selenium, about 19 mg per 100 grams. They also contain iron, zinc, magnesium, calcium and potassium, vitamin E and B vitamins, good fats and protein.

#### **Cashew nuts**

They contain a good dose of selenium, a high percentage of fatty acids, protein, folic acid, vitamins B1, B2, magnesium, phosphorus, calcium, potassium and zinc.

#### **Mustard seed**

They contain selenium, magnesium, calcium, phosphorus, potassium, manganese and vitamins. They are high-calorie oilseeds (469 calories per 100 grams).

#### **Eggs**

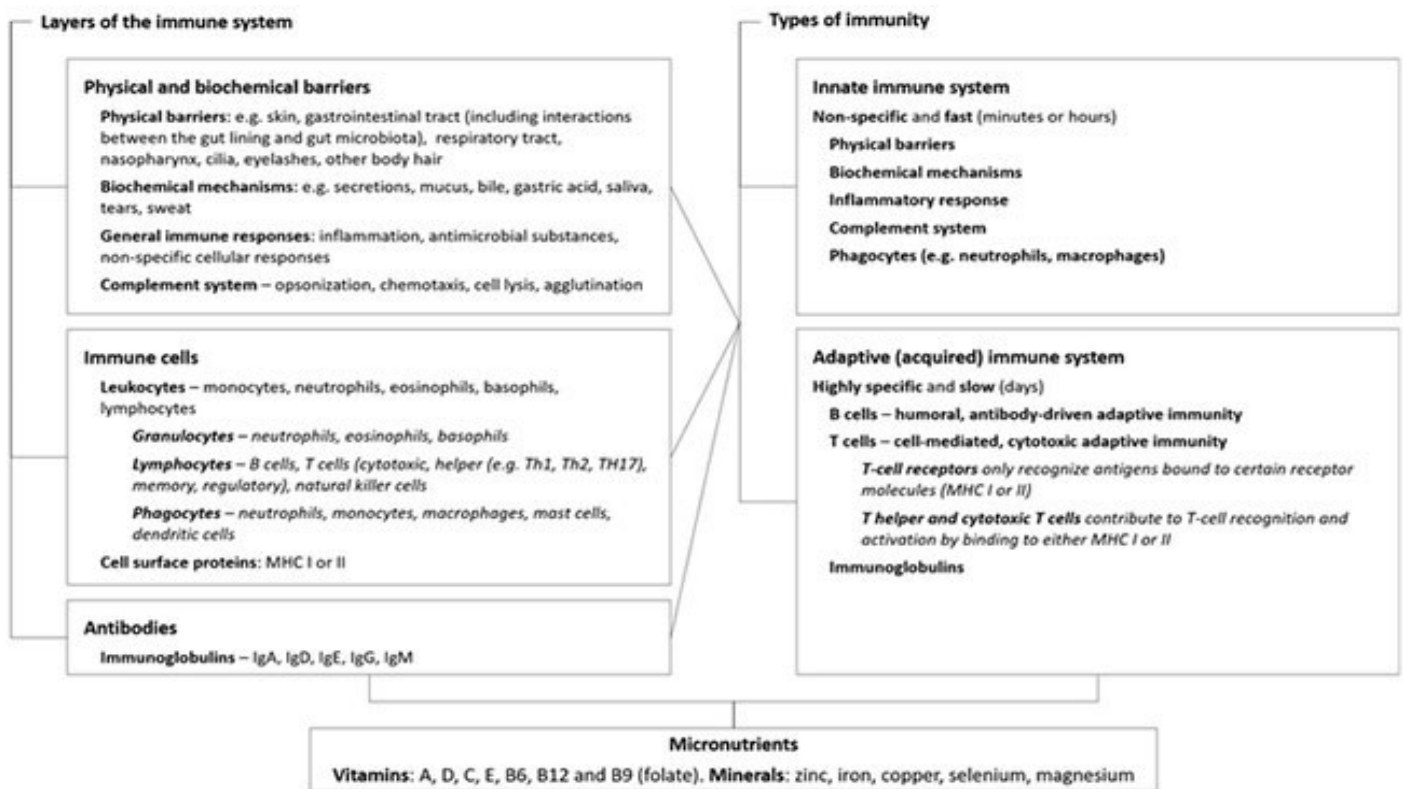
A whole egg contains about 6 mg of selenium per 100 grams of product, vitamins A, B, D, E. Egg yolk also contains noble proteins and minerals such as calcium and iron.

**Oysters, shellfish and fish in general.**

## HOW TO STRENGTHEN THE IMMUNE SYSTEM

Micronutrients are critical for boosting immunity and preventing and overcoming infections. The **European Food Safety Authority (EFSA)** has assessed that six **vitamins (D, A, C, folate, B6, B12)** and four minerals (**zinc, iron, copper, and selenium**) are critical for normal immune system function.

The article *A Review of Micronutrients and the Immune System-Working in Harmony to Reduce the Risk of Infection*-helps us with a picture to better understand the **basic components of the immune system, including the key micronutrients** that contribute to immune function. The diagram below highlights the areas of immunity and micronutrients that affect the functions that are highlighted in this review.



## RELATIONSHIP BETWEEN INTAKE OF 10 MICRONUTRIENTS AND EPIDEMIOLOGICAL DATA FOR COVID-19

In the study *Current State of Evidence: Influence of Nutritional and Nutrigenetic Factors on Immunity in the Covid-19 Pandemic Framework*, **10 nutrients essential for the proper functioning of the immune system and their use for preventive purposes against Covid-19** are discussed:

**Vitamin A, D, C, E, B6, B12, B9;**

**Minerals: zinc, iron, copper, selenium, magnesium.**

From this study it was found that the most pronounced effects of pandemic COVID-19 and in some cases mortality was found in countries with lower intakes of these trace elements and vitamins D, C, B12 and iron.

The table below shows the **effects of each micronutrient on the immune system** and their relationship of specific (sub)optimal intake to **COVID-19 epidemiological parameters**, for the 9 states considered, including Italy.

| Country     | COVID-19 Parameters |       |      |      | Vitamin Intake<br>(% vs. Requirements) |       |        |                |                 | Mineral Intake<br>(% vs. Requirements) |       |       |       |
|-------------|---------------------|-------|------|------|--|-------|--------|----------------|-----------------|--|-------|-------|-------|
|             | I                   | M     | D%   | D    | A                                      | C     | Folate | B <sub>6</sub> | B <sub>12</sub> | Zn                                     | Fe    | Cu    | Se    |
| Spain       | 595.0               | 593.0 | 10.0 | 14.1 | 77.2                                   | 109.9 | 74.9   | 112.2          | 128.1           | 81.2                                   | 110.9 | 115.4 | 108.2 |
| Belgium     | 481.6               | 786.0 | 16.3 | 25.0 | 110.0                                  | 87.8  | 63.0   | ND             | 111.3           | 112.4                                  | 94.5  | ND    | ND    |
| Italy       | 373.5               | 529.0 | 14.2 | 17.0 | 160.0                                  | 112.5 | 91.1   | 117.9          | 143.8           | 108.2                                  | 99.5  | 96.5  | 59.6  |
| UK          | 363.2               | 513.0 | 14.1 | 21.0 | 162.5                                  | 75.3  | 78.1   | 117.8          | 149.6           | 79.4                                   | 86.9  | 70.2  | 64.3  |
| Portugal    | 288.5               | 122.0 | 4.2  | 23.9 | 210.0                                  | 119.4 | 85.8   | 125.8          | 166.9           | 95.9                                   | 126.1 | ND    | ND    |
| France      | 275.7               | 433.0 | 15.7 | 15.7 | 150.0                                  | 86.9  | 84.0   | ND             | 130.8           | 101.7                                  | 93.3  | 90.8  | 71.2  |
| Netherlands | 258.3               | 334.0 | 12.9 | 27.6 | 144.9                                  | 86.6  | 68.5   | 99.7           | 119.1           | 98.2                                   | 93.9  | 77.0  | 64.2  |
| Germany     | 211.9               | 97.0  | 4.6  | 23.5 | 256.0                                  | 143.9 | 83.9   | 131.4          | 149.4           | 111.2                                  | 129.6 | 157.8 | ND    |
| Denmark     | 190.7               | 95.0  | 5.0  | 22.5 | 152.0                                  | 103.2 | 92.8   | 86.2           | 130.6           | 99.1                                   | 89.2  | ND    | 53.2  |
| Finland     | 115.5               | 54.0  | 4.7  | 62.7 | 110.0                                  | 99.8  | 72.5   | 110.3          | 160.0           | 114.3                                  | 109.5 | 95.0  | 86.4  |

Several researches have reported that available nutritional interventions can significantly improve the host immune response against RNA virus infections.

The supplementation of micronutrients in COVID-19 should not be confused with their administration in case of their deficiency, While it should be kept in mind that nutritional deficiencies weaken the immune response in many study models as well as in the human beings.

These results highlight the importance of assessing nutritional status to identify potential risk factors for viral infections.

Therefore, it is suggested that a dietary assessment of COVID-19 patients be done at the time of therapy administration, as it can help to improve the outcome, and micronutrients (minerals: Zinc, Iron, Selenium; vitamins A, B, C, D E) that have been shown to be effective remedies for MERS and SARS can also be used to manage COVID-19 during the acute phase and to help repair alveolar tissues that have been damaged as a result of the infection.<sup>13</sup>

<sup>13</sup>Junaid K, Ejaz H, Abdalla AE, et al.

Effective Immune Functions of Micronutrients against SARS-CoV-2.

Nutrients. 2020;12(10):2992. Published 2020 Sep 29. doi:10.3390/nu12102992

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7599934/>

Pecora F, Persico F, Argentiero A, Neglia C, Esposito S.

The Role of Micronutrients in Support of the Immune Response against Viral Infections.

Nutrients. 2020;12(10):3198. Published 2020 Oct 20. doi:10.3390/nu12103198

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7589163/>

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Could Vitamins Help in the Fight Against COVID-19?

Nutrients. 2020;12(9):2550. Published 2020 Aug 23. doi:10.3390/nu12092550

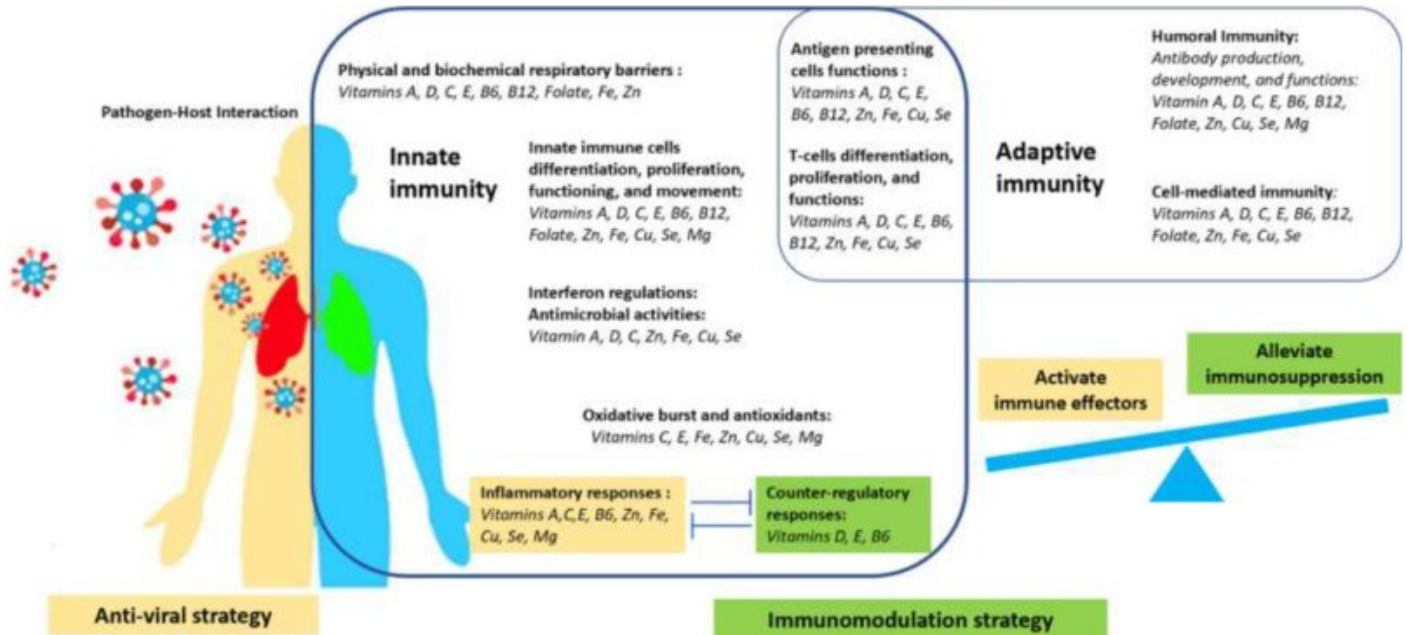
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Cytokine storm in aged people with CoV-2: possible role of vitamins as therapy or preventive strategy.

Aging Clin Exp Res. 2020;32(10):2115-2131. doi:10.1007/s40520-020-01669-y

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7456763/>



<https://www.sciencedirect.com/science/article/pii/S1521661620302825?via%3Dihub>

Certain pathological conditions cause loss of water and electrolytes in the body, especially in the gastrointestinal form of COVID-19, which is associated with diarrhea and hyponatremia. The anti-inflammatory and antioxidant properties of some vitamins and nutrients including vitamins A, B, C, D, E, folate, and trace elements including iron, zinc, magnesium, selenium, and copper have important roles in supporting the innate and adaptive immune system and may be useful for patients with COVID-19. <sup>14</sup>

| Element    | Physiologic role   | Role in COVID-19  |
|------------|--|---|
| Zinc       | It has a role in both innate and adaptive immune systems and also has an antiviral activity [16]                                 | Zinc inhibits the activity of RNA-dependent RNA polymerase (RdRp) of coronavirus [18], and compound both of zinc and CQ/HCQ is useful for COVID-19 treatment [19] |
| Selenium   | Selenium is a free radical scavenger and helps cellular immunity [24]  | High selenium intake (50–100 µg/day) causes better and more immune responses [29]   |
| Iron       | Iron is needed for some reactions and cellular functions like RNA/DNA synthesis and repairs [10]                                 | High level of iron may increase viral infections [36], although it has reported that COVID-19 patients have low serum level of iron [37]                          |
| Potassium  | It is important for cell functions and the need for membrane potential [61]  | Hypokalemia is a high prevalence condition (up to 62%) among COVID-19 patients [41]   |
| Sodium     | Sodium can modulate immune cell activities [62]  | The sodium in the serum of patients with pneumonia infected by SARS-CoV-2 is lower than non-pneumonia patients [43]   |
| Calcium    | Calcium has a role in the activation of lymphocytes [63]   | It has seen that SARS-CoV entry into some cell lines decreases when intracellular calcium decreases [49]  |
| Magnesium  | It has important roles in immune functions including immunoglobulin synthesis and immunoglobulin M (IgM) lymphocyte binding [51] | ND  |
| Folic acid | Synthesis of purines and thymidylate that they are necessary for mitochondrial producing of ATP need folic acid [65]             | Folic acid impairs the viral life cycle by creating hydrogen binds with 3CL hydrolase. In severe patients, the level of folic acid is lower [52, 64]              |
| Copper     | It is an essential trace element in body and is needed for protecting DNA from oxidative stress [53]                             | It has been reported that the human immune system response was weak when Cu is deficient. The level of serum copper in COVID-19 patients is unknown[59]           |

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7478435/>

<sup>14</sup>Taheri M, Bahrami A, Habibi P, Nouri F. A Review on the Serum Electrolytes and Trace Elements Role in the Pathophysiology of COVID-19 [published online ahead of print, 2020 Sep 8]. Biol Trace Elem Res. 2020;1-7. doi:10.1007/s12011-020-02377-4 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7478435/>

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## PROBIOTICS, PREBIOTICS AND SYMBIOTICS

**Microbial communities** (bacteria, fungi, archaeobacteria, viruses and protozoa) in the human gastrointestinal tract, lungs, skin and mouth exist in a commensal relationship with host cells, thus playing an important role in human health. Commensal bacteria ( $1 \times 10^{13}$  CFU) in the gastrointestinal tract are equivalent to the number of human cells.

This colonization begins shortly after birth, and their profile and numbers stabilize by the age of 1 year with more than 1,000 bacterial species. The gastrointestinal microbiota has the ability to interact with human cells, including specific immune cells.

These interactions produce several health benefits in the host, including regulation of gastrointestinal motility; activation and destruction of toxins, genotoxins, and mutagens; transformation of bile acids and steroids; production of vitamins; absorption of minerals; metabolism of xenobiotic substances; modification of intestinal permeability and barrier functions; modulation of mucosal and systemic immunity; and also have beneficial effects on the skin and early respiratory tract.

Recently, beneficial microbes have been reported in the upper (nasal cavity, nasopharynx, oropharynx and larynx above the vocal cords) and lower respiratory tract (larynx below the vocal cords, trachea, bronchi and bronchioles and alveoli of the lungs) of both healthy people and those with lung diseases such as cystic fibrosis and chronic obstructive pulmonary disease.

These beneficial microorganisms compete with pathogens in different organs to promote host health, and any imbalance or disruption in this system can cause dysbiosis and may allow pathogens to cause diseases such as respiratory tract infections.

Dysbiosis can also be caused by long-term antibiotic use, so probiotics are also generally recommended for patients who have recently used antibiotics to treat any disease. Other causes of dysbiosis in the human gastrointestinal tract include exposure to toxins, stress, disease, insufficient diet and advanced age.

**Probiotics** are live microorganisms that confer a beneficial physiological effect on the host when administered in appropriate amounts. Some lactic acid bacteria that can be found in various fermented foods such as yogurt, cheese, and pickles are generally recognized as safe and classified as probiotics because of their health benefits.

It has been suggested that probiotics should be consumed daily at doses of  $10^8$  to  $10^{10}$  CFUs to produce beneficial health effects in humans, which include reducing symptoms of lactose intolerance, inhibiting the onset of allergic diseases, maintaining intestinal pH, preventing or treating ischemic heart syndromes, reducing blood cholesterol levels, producing B vitamins, improving the bioavailability of dietary calcium, and stimulating immune activity.

**Prebiotics** were initially defined as "non-digestible food ingredients that positively affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria already residing in the colon." The definition of prebiotics was modified several times and finally proposed as "*substrates that are selectively utilized by host microorganisms that confer a health benefit.*" Prebiotics include fructans, oligosaccharides, arabinooligosaccharides, isomaltooligosaccharides, xylooligosaccharides, resistant starch, lactosaccharose, lactobionic acid, galactomannan, psyllium, polyphenols and polyunsaturated fatty acids. The health benefits of prebiotics for the gastrointestinal tract, including inhibition of pathogens and stimulation of the immune system, are due to their ability to modulate the composition and activity of the human microbiota.

**Synbiotics** refer to dietary supplements that combine probiotics and prebiotics in a form of synergism, that is, that enhances their isolated beneficial effects. When two nutritional ingredients or supplements are administered together, the resulting positive effect generally follows one of three patterns: potentiation, synergism, and additivity. The prebiotic in the symbiotic mixture enhances the survival of probiotic microorganisms in the intestinal tract and stimulates the activity of beneficial endogenous bacteria in the host, thereby improving its health status.<sup>15</sup>

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<sup>15</sup> Hamasalim, Hozan. (2016).

Synbiotics as Feed Additives Relating to Animal Health and Performance.

Advances in Microbiology. 06. 288-302. 10.4236/aim.2016.64028.

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Nutrients. 2017;9(9):1021. Published 2017 Sep 15. doi:10.3390/nu9091021

Examples of prebiotics and synbiotics used in human nutrition [134,145,146].

| Human Nutrition      |   |
|----------------------|---|
| Prebiotics           | Synbiotics  |
| FOS                  |   |
| GOS                  |   |
| Inulin               | <i>Lactobacillus</i> genus bacteria + inulin  |
| XOS                  | <i>Lactobacillus</i> , <i>Streptococcus</i> and <i>Bifidobacterium</i> genus bacteria + FOS |
| Lactitol             | <i>Lactobacillus</i> , <i>Bifidobacterium</i> , <i>Enterococcus</i> genus bacteria + FOS    |
| Lactosucrose         | <i>Lactobacillus</i> and <i>Bifidobacterium</i> genus bacteria + oligofructose              |
| Lactulose            | <i>Lactobacillus</i> and <i>Bifidobacterium</i> genus bacteria + inulin                     |
| Soy oligosaccharides |   |
| TOS                  |   |

Abbreviations: FOS—fructooligosaccharides; GOS—galactooligosaccharides; TOS—transgalactooligosaccharides; XOS—xylooligosaccharides.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5622781/>

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5622781/>

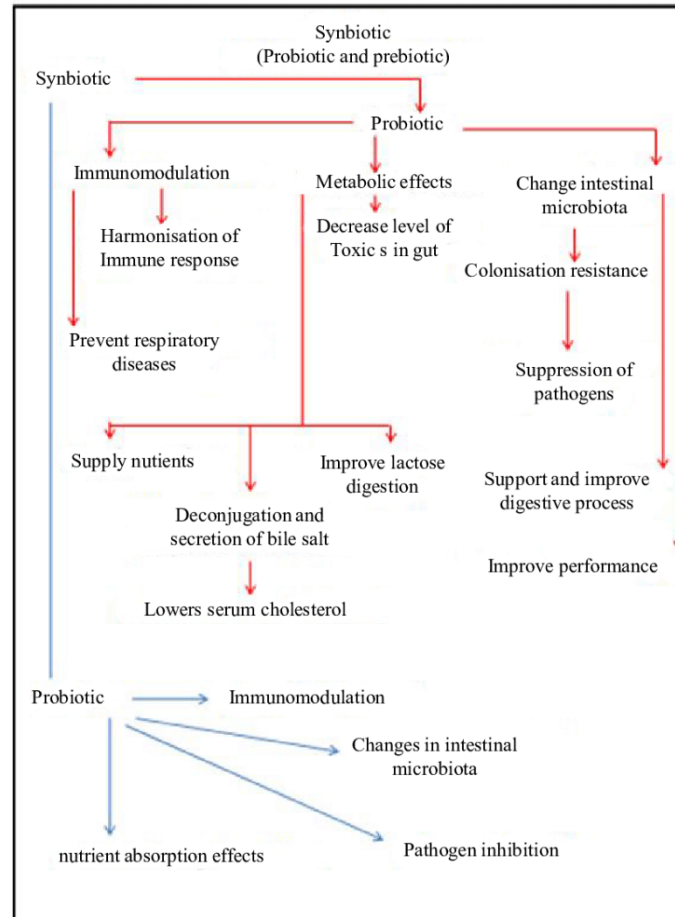
Li C, Niu Z, Zou M, Liu S, Wang M, Gu X, Lu H, Tian H, Jha R. Probiotics, prebiotics, and synbiotics regulate the intestinal microbiota differentially and restore the relative abundance of specific gut microorganisms. *J Dairy Sci.* 2020 Jul;103(7):5816-5829. doi: 10.3168/jds.2019-18003. Epub 2020 May 14. PMID: 3241868689. <https://pubmed.ncbi.nlm.nih.gov/32418689/>

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Patel R, DuPont HL. New approaches for bacteriotherapy: prebiotics, new-generation probiotics, and synbiotics. *Clin Infect Dis.* 2015;60 Suppl 2(Suppl 2):S108-S121. doi:10.1093/cid/civ177 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4490231/>

Dr. Loretta Bolgan



[https://www.researchgate.net/publication/301534912\\_Synbiotic\\_as\\_Feed\\_Additives\\_Relating\\_to\\_Animal\\_Health\\_and\\_Performance](https://www.researchgate.net/publication/301534912_Synbiotic_as_Feed_Additives_Relating_to_Animal_Health_and_Performance)

### Probiotics and COVID-19

The direct or indirect positive impact of probiotics on ACE enzymes is well established. During food fermentation, probiotics produce bioactive peptides with the ability to inhibit ACE enzymes by blocking active sites. In addition, dead probiotic cell debris has also been shown to be able to act as ACE inhibitors. These results suggest that probiotics could be potential blockers of the ACE receptor that serves as a gateway for SARS-CoV-2 to attack cells in the GI tract.

Prebiotics may also have an excellent effect against COVID-19 by enhancing the growth and survival of probiotics. In addition, prebiotics could also have a direct effect on gastrointestinal symptoms caused by COVID-19 by blocking ACE enzymes. <sup>16</sup>

<sup>16</sup> Olaimat, A.N., Aolymat, I., Al-Holy, M. et al.

The potential application of probiotics and prebiotics for the prevention and treatment of COVID-19.

npj Sci Food 4, 17 (2020). <https://doi.org/10.1038/s41538-020-00078-9>

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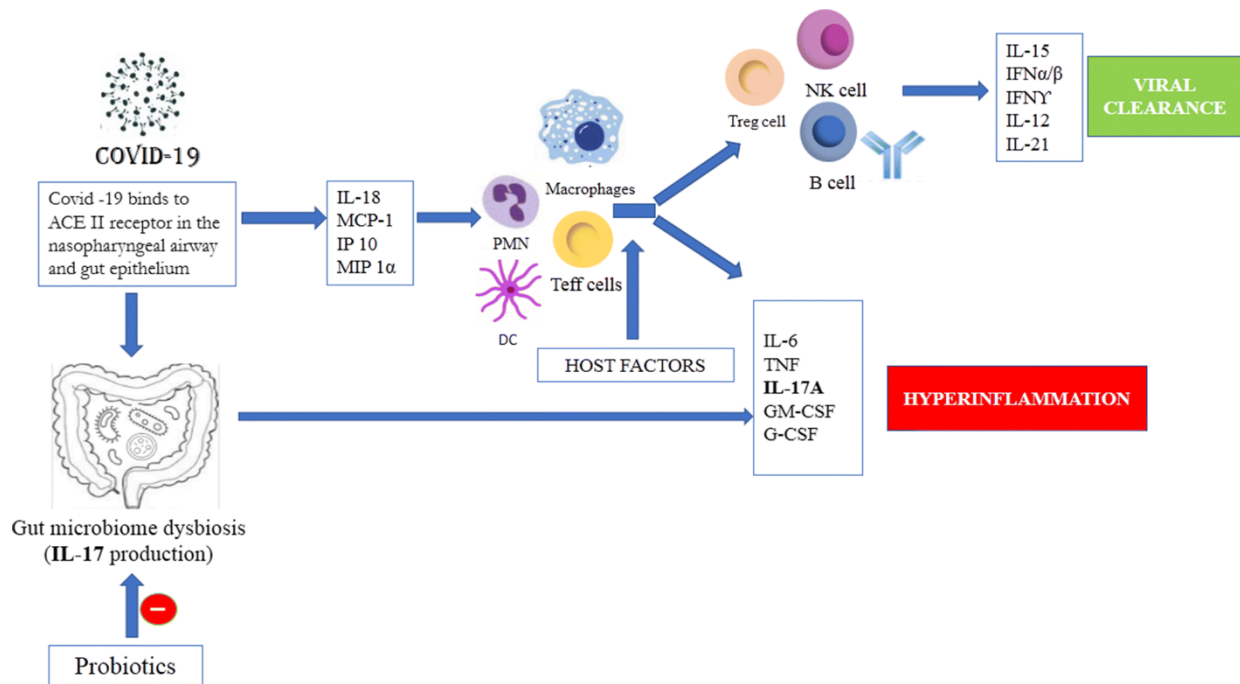
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Microorganisms. 2020;8(10):1514. Published 2020 Oct 1. doi:10.3390/microorganisms8101514

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7601735/>

Akour A.

Probiotics and COVID-19: is there any link?



<https://link.springer.com/article/10.1007/s00253-020-10832-4>

The mechanism involved in the COVID-19-infected host. Proinflammatory cytokines and interferons are released and viral cell translation is suppressed to induce viral clearance as part of the host immune response and an antiviral state in adjacent epithelial cells. Viral clearance occurs in the lung and intestinal epithelium depending on the immune status of the host. However, probiotic consumption ameliorates inflammation by regulating the immune response in the gut through various signaling pathways, helps ameliorate intestinal dysbiosis caused by SARS-CoV2, and accelerates recovery in patients. ACE II, angiotensin-converting enzyme II; PMN, polymorphonuclear granulocytes; DC, dendritic cells; TEFF cell, effector T cell; Treg cell, regulatory T cell; NK, natural killer

Because some patients with COVID-19 have shown intestinal microbial dysbiosis characterized by low numbers of different probiotic species such as Bifidobacterium and Lactobacillus, nutritional support and prebiotic or probiotic supplementation has been suggested to restore the balance of intestinal flora and reduce the risk of infection. Therefore, balanced diets, including foods containing probiotics and immunity-enhancing micronutrients such as polyphenols; vitamins A, C, and D; and minerals (mainly selenium and zinc) can alleviate the risk of COVID-19 infection. Food sources of probiotics such as fermented foods <sup>17</sup> have good potential to prevent COVID-19.

[published online ahead of print, 2020 Jun 4]. *Lett Appl Microbiol.* 2020;10.1111/lam.13334. doi:10.1111/lam.13334  
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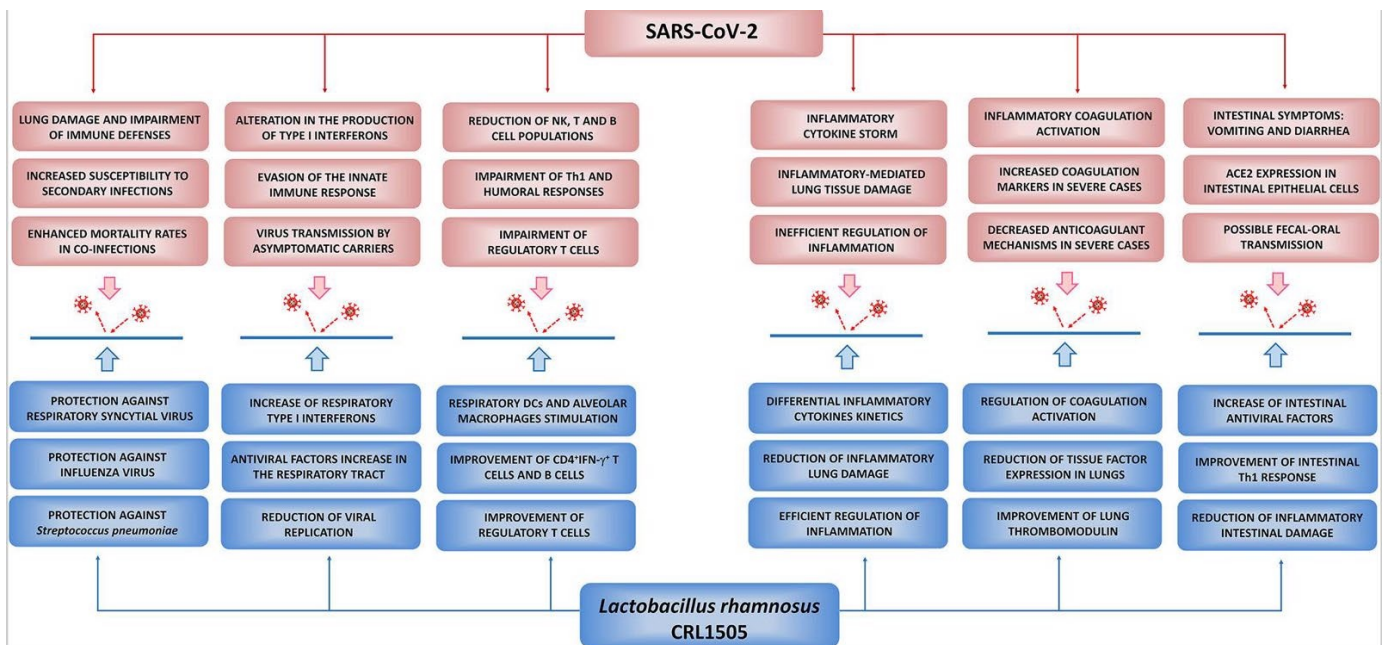
<sup>17</sup> Bousquet J, Anto JM, Czarlewski W, et al.  
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<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7436771/pdf/ALL-9999-na.pdf>

Association between consumption of fermented vegetables and COVID-19 mortality at a country level in Europe  
 Susana Fonseca, Ioar Rivas, Dora Romaguera, Marcos Quijal, Wienczysława Czarlewski, Alain Vidal, Joao Fonseca, Joan Ballester, Josep Anto, Xavier Basagana, Lui s M Cunha, Jean Bousquet  
 medRxiv 2020.07.06.20147025; doi: <https://doi.org/10.1101/2020.07.06.20147025>  
<https://www.medrxiv.org/content/10.1101/2020.07.06.20147025v1.full.pdf>

| Microbe                                | Type of infection/virus            | Mode of action                                     |
|--|------------------------------------|--|
| <i>Lb. plantarum</i> NCIMB 8826        | RSV, pneumovirus,                  | TLR-dependent inflammatory response                |
| <i>Lb. casei</i> DN-114001             | RTI, rhinopharyngitis, influenza   | Enhanced defensin expression and innate immunity   |
| <i>Lactobacillus rhamnosus</i> M21     | Pneumonia, influenza               | Increases interferon- $\gamma$ and interleukin-2   |
| <i>Bifidobacterium infantis</i> BB-12  | URTI                               | IL-17 inhibitory effect                            |
| <i>Bifidobacterium animalis</i>        | URTI                               | Prevents replication on virus, anti-interleukin-17 |
| <i>Lactobacillus plantarum</i>         | Gastroenteritis coronavirus (TGEV) | Diminishes granulocyte, reduces virus recovery     |
| <i>Lactococcus lactis</i> JCM 5805     | RTI, common infectious disease     | Activates plasmacytoid dendritic cell              |
| <i>Lactobacillus plantarum</i> CRL1506 | Gastroenteritis coronavirus (TGEV) | Diminish inflammatory-mediated tissue damage       |
| <i>Bacillus subtilis</i> OKB105        | Gastroenteritis coronavirus (TGEV) | Inhibits viral adherence by competitive inhibition |

<https://link.springer.com/article/10.1007/s00253-020-10832-4>

List of probiotics and their mode of action in stimulating the immune response against viral infections



<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7326040/>

Potential beneficial effects of *Lactobacillus rhamnosus* CRL1505 against SARS-CoV-2 infection

### Immunobiotics

More than a decade of research on the cellular and molecular mechanisms involved in the enhancement of respiratory antiviral defenses by beneficial immunobiotic microorganisms (particular strains of beneficial bacteria with immunomodulatory capabilities) clearly indicate their potential to favorably influence the immune response against SARS-CoV-2 virus.

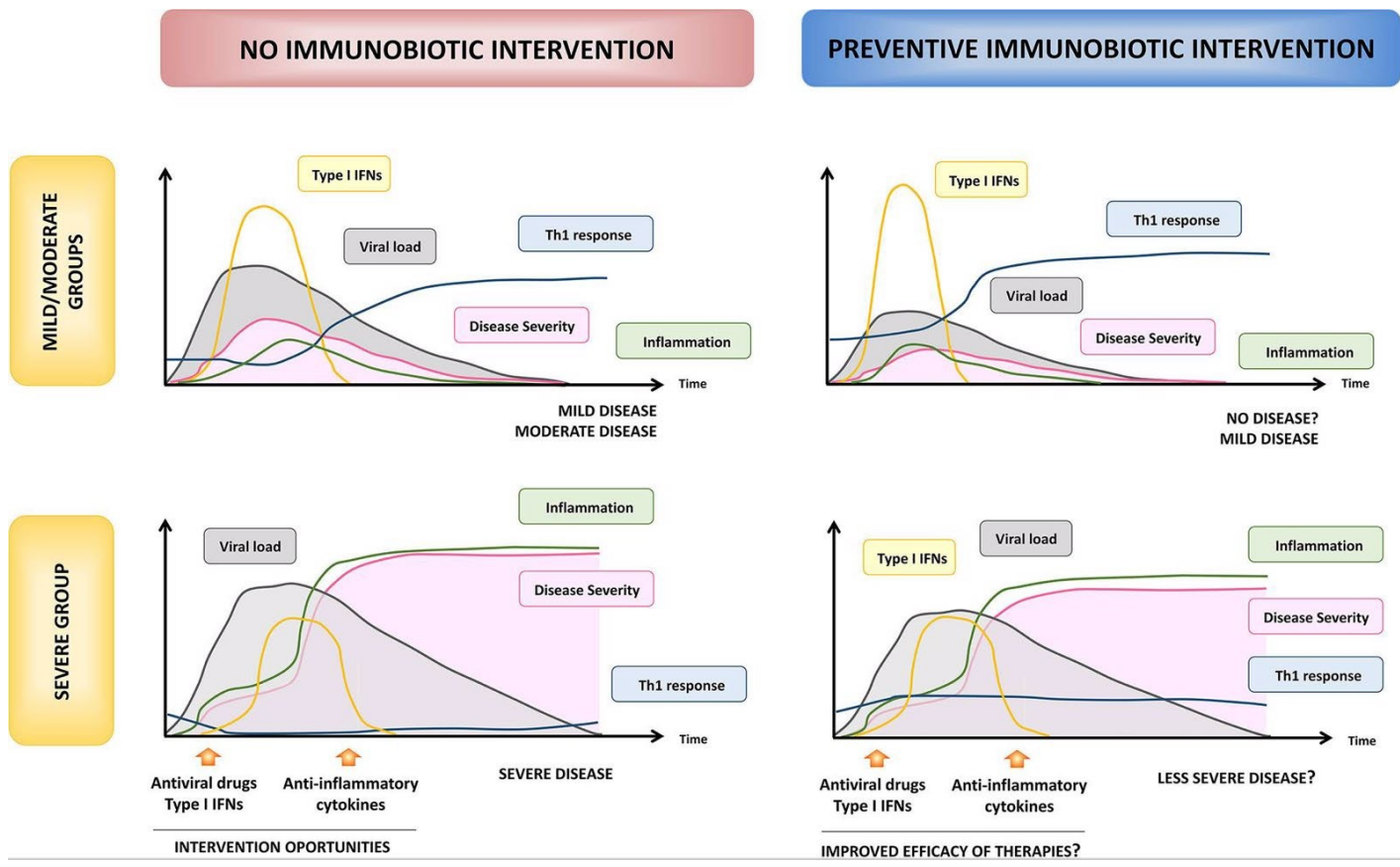
The demonstration of the ability of beneficial microorganisms to potentiate type I interferons and antiviral factors in the respiratory tract, to stimulate Th1 response and antibody production, and to regulate inflammation and coagulation activation during the course of viral infections by reducing tissue damage and functionally preserving the lungs, provides a solid scientific basis for proposing nutritional interventions with immunobiotics for strengthening the immune system and reducing the incidence and severity of COVID-19. In particular, immunobiotics such as *L. rhamnosus* CRL1505, *L. plantarum* MPL16, and *B. longum* BB536 may be considered useful, if not indispensable, adjuvant agents in the fight against COVID-19.<sup>18</sup>

<sup>18</sup> Villena J, Kitazawa H.

The Modulation of Mucosal Antiviral Immunity by Immunobiotics: Could They Offer Any Benefit in the SARS-CoV-2 Pandemic?

Front Physiol. 2020;11:699. Published 2020 Jun 16. doi:10.3389/fphys.2020.00699

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7326040/>



<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7326040/>

Hypothesis of the beneficial effects of preventive immunobiotic intervention on SARS-CoV-2 infection. The kinetics and intensity of immune players involved in the response to SARS-CoV-2, viral load and severity of COVID-19 are shown according to Jamilloux et al. <sup>19</sup> in both "mild/moderate" and "severe" susceptible hosts. Optimal timing for proposed therapeutic interventions to improve disease severity are also shown (left panels). The potential modulation of immune response kinetics and intensity, viral load, and disease severity by preventive nutritional immunobiotic interventions for low- and high-susceptible hosts is shown in the right panels.

**Zinc** <sup>20</sup>

Zinc is used as a key cofactor for metalloenzymes and is essential for membrane integrity, DNA synthesis, and cell multiplication, particularly of immune cells. It enhances the host response to numerous infections and assumes a significant role in maintaining host homeostasis. Zinc also stabilizes the cell membrane, and its deficiency destroys intestinal mucosa, reduces brush rim enzymes, and increases macrophage function, intestinal water secretion through cytokine production, intracellular killing, and phagocytosis.

In order to provide zinc in a highly bioavailable form, the probiotic strains *Lb fermentum* SR4 and *Lb rhamnosus* GG (LGG) were studied for their ability to accumulate zinc.

Effect of Lactobacillus rhamnosus HN001 and Bifidobacterium longum BB536 on the healthy gut microbiota composition at phyla and species level: A preliminary study.

World J Gastroenterol. 2017;23(15):2696-2704. doi:10.3748/wjg.v23.i15.2696

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5403748/>

<sup>19</sup> Jamilloux Y, Henry T, Belot A, et al.

Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions.

Autoimmun Rev. 2020;19(7):102567. doi:10.1016/j.autrev.2020.102567

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7196557/>

<sup>20</sup> Sundararaman, A., Ray, M., Ravindra, P.V. et al.

Role of probiotics to combat viral infections with emphasis on COVID-19.

Appl Microbiol Biotechnol 104, 8089-8104 (2020). <https://doi.org/10.1007/s00253-020-10832-4>

<https://link.springer.com/article/10.1007/s00253-020-10832-4>

The results showed that zinc in a highly bioavailable form was chelated by SR4 and LGG up to 57% and 48%, respectively, compared with commercially available inorganic forms ( $ZnSO_4$ ) and zinc gluconate.

One study showed that consumption of up to 50 mg of zinc daily suppresses SARS-Cov-2 viral replication by improving host resistance against viral infection.<sup>21</sup> In addition, zinc possesses direct antiviral characteristics through activation of innate and acquired (humoral) antiviral responses.<sup>22</sup>

### Vitamin D<sup>16,23</sup>

Vitamin D is found predominantly in the skin and is essential for calcium reabsorption in the intestines and kidneys. The active form of vitamin D hormone, 1,25-dihydroxyvitamin D (1,25OHD, also called VDR), regulates gene expression especially in immune function and inflammation and helps maintain tight junctions, gap junctions, and adherens junctions. Viral disease affects the integrity of splices thus increasing the incidence of infection in the host.

Probiotic bacteria, mostly belonging to the genera *Lactobacillus* and *Bifidobacterium*, confer a number of health benefits by protecting against vitamin deficiency. Increased dietary intakes of fat-soluble vitamins, particularly vitamin D, are associated with reduced microbial diversity of alpha-proteobacteria consisting mainly of human pathogens.

Studies have shown the importance of vitamin D directly or indirectly in combating infection caused by viruses such as rotavirus and influenza. In COVID-19, the increased incidence of mortality in the elderly may be due to reduced serum concentrations of 1,25OHD with age. Reduced vitamin D production is the result of lower levels of 7-dehydrocholesterol in the skin due to less time spent in the sun. The immunomodulatory effects of vitamin D act on both the innate and adaptive immune systems, thereby reducing the risk of infection and mortality. 1,25OHD suppresses T helper cell type 1 (Th1)-mediated responses, and the production of inflammatory cytokines IL-2 and interferon gamma (INF $\gamma$ ). In addition, 1,25OHD promotes cytokine production by type 2 (Th2) T helper cells, and induction of regulatory T cells, thus inhibiting inflammatory processes.

The peak season for acute respiratory tract infections is generally when 1,25OHD concentrations are lowest, so vitamin D supplementation can be achieved through regular intake of vitamin D-producing probiotics to increase 1,25OHD concentrations above 40-60 ng/mL.

For the treatment of patients infected with COVID-19, on the other hand, a higher dose might be useful.

<sup>21</sup> Razzaque MS.

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<sup>22</sup> Scott A Read, Stephanie Obeid, Chantelle Ahlenstiel, Golo Ahlenstiel,

The Role of Zinc in Antiviral Immunity, *Advances in Nutrition*, Volume 10, Issue 4, July 2019, Pages 696-710, <https://doi.org/10.1093/advances/nmz013> <https://academic.oup.com/advances/article/10/4/696/5476413>

<sup>23</sup> Benskin LL.

A Basic Review of the Preliminary Evidence That COVID-19 Risk and Severity Is Increased in Vitamin D Deficiency. *Front Public Health.* 2020;8:513. Published 2020 Sep 10. doi:10.3389/fpubh.2020.00513 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7513835/>

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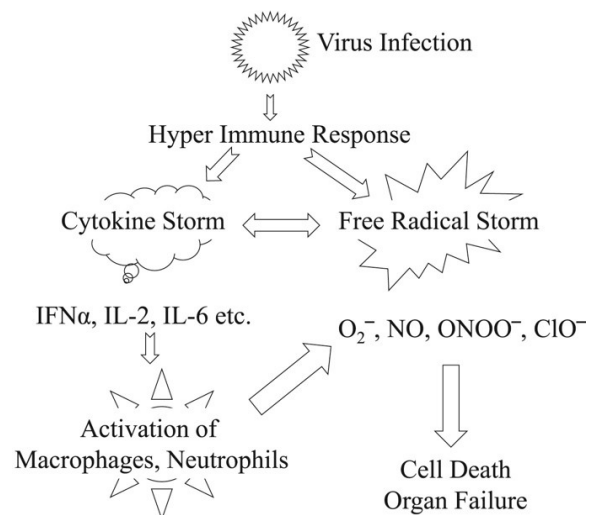
## OXIDATIVE STRESS AND ANTIOXIDANTS

### The redox system Glutathione-ascorbic acid

Oxidative stress (OS) has been defined as a disturbance of the pro-oxidant/antioxidant balance in favor of prooxidants, leading to cellular damage. However, current knowledge on redox signaling pathways has reconceptualized the definition of OS to include two main mechanisms:

- (1) macromolecular damage and
- (2) disruption of thiol redox circuits, leading to aberrant cellular signaling and dysfunctional redox control.

Disruption of redox circuits caused by specific reaction with redox-sensitive thiol elements, altered electron transfer pathways, or disruption of gating mechanisms (opening/closing of ion channels) play an important role in physiology and pathophysiology. High levels of ROS generation due to airway pollutants, toxins, and viral infections are associated with OS causing cellular damage. Several respiratory viruses induce dysregulated ROS formation as a result of increased recruitment of inflammatory cells at the site of infection. In addition, viral infections disrupt antioxidant mechanisms, leading to an unbalanced oxidative-antioxidant state and subsequent oxidative cell damage.<sup>24</sup>



<https://www.sciencedirect.com/science/article/pii/S1089860320301580?via%3Dihub>

In particular, ROS and RNS (reactive nitrogen species) are known to contribute to the development of influenza virus-induced pathogenesis and SARS-Cov-2.<sup>25</sup>

<sup>24</sup> Sahebnaasagh A, Saghafi F, Avan R, et al.

The prophylaxis and treatment potential of supplements for COVID-19. *Eur J Pharmacol.* 2020;887:173530. doi:10.1016/j.ejphar.2020.173530  
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Tackle the free radicals damage in COVID-19. *Nitric Oxide.* 2020 Sep 1;102:39-41. doi: 10.1016/j.niox.2020.06.002. Epub 2020 Jun 17. PMID: 32562746.  
<https://www.sciencedirect.com/science/article/pii/S1089860320301580?via%3Dihub>

<sup>25</sup> Saleh J, Peyssonnaux C, Singh KK, Edeas M.

Mitochondria and microbiota dysfunction in COVID-19 pathogenesis.

Physiological levels of ROS play a key role in mediating cell signaling, whereas high levels of ROS can lead to oxidative damage to cellular components and activate various cell death pathways.

An "antioxidant defense network" exists within the host cell to control ROS levels so as to enable useful functions while minimizing oxidative damage. For this reason, antioxidants represent interesting molecules that have been proposed for the treatment of viral infections.<sup>26</sup>

In vitro studies have shown that GSH is able to arrest the folding of viral hemagglutinin: this disulfide-rich glycoprotein remains in the endoplasmic reticulum (ER) as a reduced monomer, instead of undergoing oligomerization. As a result, its insertion into the cell plasma membrane is greatly reduced and virus release blocked. The mechanism underlying the antiviral effect of GSH is related to the host cell's oxidoreductase, protein disulfide isomerase. This protein acts at the level of the ER by promoting disulfide bond formation during glycoprotein maturation.<sup>27</sup>

Clinical studies show that vitamin C (VC), both intravenous and high-dose oral bolus, also provides some protection against viral infection. Neither intravenous nor oral administration of high-dose VC is associated with significant side effects. Therefore, this regimen should be included in the treatment of COVID-19 and used as a preventive measure for susceptible populations such as health care workers with higher exposure risks.<sup>28</sup>

Specifically, Hemila et al reported that high-dose intravenous infusions of VC (e.g., 200 mg/kg body weight/day, divided into 4 doses) reduced intensive care unit (ICU) stay by 7.8%, accompanied by a significant reduction in mortality rate. This experience has been replicated among patients with severe influenza. Indeed, dietary antioxidants (VC and sulforaphane) have been shown to reduce acute oxidative stress-induced inflammatory lung damage in patients undergoing mechanical ventilation. In addition, oral VC (e.g., 6 g daily) was able to reduce the risk of viral infection or improve symptoms.<sup>29</sup>

A high-dose intravenous bolus of VC was also successfully used in the treatment of 50 patients with moderate to severe COVID-19 in China. The doses used ranged from 10 to 20 g per day, administered over an 8- to 10-hour period. Additional bolus VC might have been needed for critically ill patients. The oxygenation index improved in real time, and all patients eventually recovered and were discharged.<sup>30</sup>

High-dose VC has been clinically used for several decades, and a recent NIH expert panel paper clearly states that **this regimen (1.5 g/kg body weight) is safe and without major adverse events.**<sup>31</sup>

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Mitochondrion. 2020 Sep;54:1-7. doi: 10.1016/j.mito.2020.06.008. Epub 2020 Jun 20. PMID: 32574708.  
<https://www.sciencedirect.com/science/article/pii/S1567724920301380?via%3Dihub>

<sup>26</sup> Sgarbanti R, Amatore D, Celestino I, et al.  
Intracellular redox state as target for anti-influenza therapy: are antioxidants always effective?  
Curr Top Med Chem. 2014;14(22):2529-2541. doi:10.2174/1568026614666141203125211  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4435240/>

<sup>27</sup> Sgarbanti R, Nencioni L, Amatore D, Coluccio P, Fraternali A, Sale P, Mammola CL, Carpino G, Gaudio E, Magnani M, Ciriolo MR, Garaci E, Palamara AT.  
Redox regulation of the influenza hemagglutinin maturation process: a new cell-mediated strategy for anti-influenza therapy.  
Anti.Redox Signal. 2011;15(3):593-606. doi.org/10.1089/ars.2010.3512  
<https://www.liebertpub.com/doi/full/10.1089/ars.2010.3512>

<sup>28</sup> Cheng RZ.  
Can early and high intravenous dose of vitamin C prevent and treat coronavirus disease 2019 (COVID-19)?  
Med Drug Discov. 2020;5:100028. doi:10.1016/j.medidd.2020.100028  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7167497/>

<sup>29</sup> Hemilä H, Chalker E.  
Vitamin C Can Shorten the Length of Stay in the ICU: A Meta-Analysis.  
Nutrients. 2019;11(4):708. Published 2019 Mar 27. doi:10.3390/nu11040708  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6521194/>

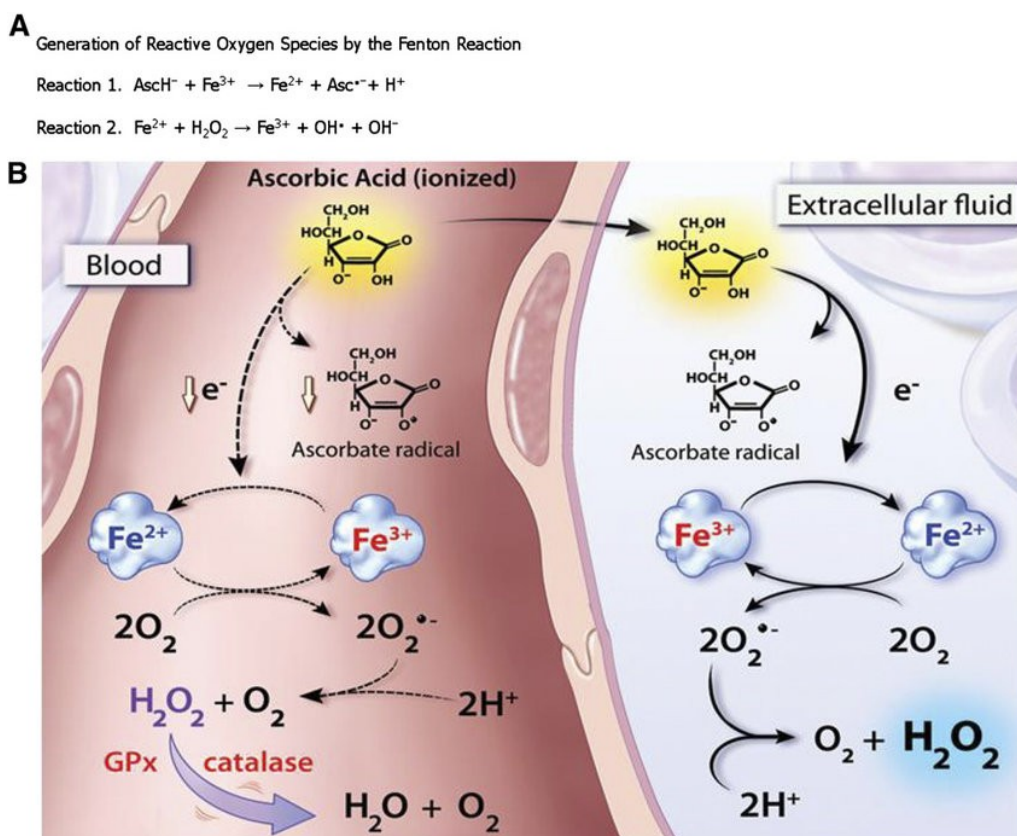
Patel V, Dial K, Wu J, et al.  
Dietary Antioxidants Significantly Attenuate Hyperoxia-Induced Acute Inflammatory Lung Injury by Enhancing Macrophage Function via Reducing the Accumulation of Airway HMGB1.  
Int J Mol Sci. 2020;21(3):977. Published 2020 Feb 1. doi:10.3390/ijms21030977  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7037000/>

<sup>30</sup> Shanghai Expert Panel, cited on Mar 23  
2020. [http://mp.weixin.qq.com/s?\\_\\_biz=MzA3Nzk5Mzc5MQ==&mid=2653620168&idx=1&sn=2352823b79a3cc42e48229a0c38f65e0&chksm=84962598b3e1ac8effb763e3ddb4858435dc7aa947a8f41790e8df2bca34c20e6ffea64cd191#rd](http://mp.weixin.qq.com/s?__biz=MzA3Nzk5Mzc5MQ==&mid=2653620168&idx=1&sn=2352823b79a3cc42e48229a0c38f65e0&chksm=84962598b3e1ac8effb763e3ddb4858435dc7aa947a8f41790e8df2bca34c20e6ffea64cd191#rd)

<sup>31</sup> High-dose vitamin C (PDQ®)-Health professional version. National Cancer Institute, cited on Feb 9 2020  
<https://www.cancer.gov/about-cancer/treatment/cam/hp/vitamin-c-pdq>

It is important to point out that VC also exhibits pro-oxidant activity that generates reactive free radicals. VC has antioxidant activity when it reduces oxidants such as hydrogen peroxide, however, it can also reduce metal ions and lead to the generation of free radicals, including the reduction reaction of Fe (III) to Fe (II), through the **Fenton reaction**.

In this reaction, iron (II) is oxidized by hydrogen peroxide to iron (III), forming a hydroxyl radical and a hydroxide ion in the process. Iron (III) is then reduced back to iron (II) by another hydrogen peroxide molecule, forming a peroxide radical and a proton. The net effect is a dismutation of hydrogen peroxide to create two different oxygen radical species, with water ( $H^+ + OH^-$ ) as a byproduct.<sup>32</sup>



<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3065766/>

(A) In reaction 1, ascorbate ( $AscH^-$ ) reacts with ferric iron ( $Fe^{3+}$ ) to produce ferrous iron ( $Fe^{2+}$ ) and the ascorbate radical ( $Asc^{\cdot-}$ ). In reaction 2, the classical Fenton reaction generates the hydroxyl radical species ( $OH^{\cdot}$ ) from  $H_2O_2$ . (B) Proposed mechanism of formation of ascorbate radical and  $H_2O_2$  in extracellular fluid versus blood. After oral and parenteral administration, ascorbic acid reaches equivalent pharmacological concentrations in blood (left side of the diagram) and extracellular fluid (right side). In extracellular fluid, an ascorbic acid molecule loses 1 electron and forms the ascorbate radical. This electron subsequently reduces a central metal on the protein, shown as the reduction of  $Fe^{3+}$  to  $Fe^{2+}$ . This complex donates an electron to molecular oxygen, forming superoxide anion ( $O_2^{\cdot-}$ ) resulting in dismutation to  $H_2O_2$ . In the blood (left side), these reactions are attenuated or inhibited (dashed lines). The appearance of ascorbate radical is inhibited by the membrane-bound reducing proteins of GRs and/or large plasma proteins that do not distribute in the extracellular space. The RBC enzymes glutathione peroxidase and catalase destroy  $H_2O_2$  so that none is detectable in the blood.

Therefore, the toxicity of free iron, similar to that of other transition metals, may result from the Fenton reaction.

It is commonly accepted that oxidant intermediates involved in Fenton reactions cause damage to biomolecules and play an important role in the aging process and in a variety of diseases such as cancer. Thus, iron and ascorbic acid form a potentially toxic cocktail. The above chemical mechanisms have been established demonstrating the potential for these compounds to interact and damage surrounding tissues.

The pro-oxidant effects of ascorbate can be significant in vivo depending on the availability of catalytic metal ions. In healthy individuals, iron is largely sequestered by iron-binding proteins such as transferrin and ferritin and iron

<sup>32</sup> Levine M, Padayatty SJ, Espey MG.

Vitamin C: a concentration-function approach yields pharmacology and therapeutic discoveries.

Adv Nutr. 2011;2(2):78-88. doi:10.3945/an.110.000109

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3065766/>

chelate is essentially redox inactive. Instead, in pathological situations, such as thalassemia or hemochromatosis, unbound transferrin iron is present. Therefore, ascorbate provided as a supplement without the administration of an iron chelator can lead to deleterious effects. Tissue damage resulting from ischemia/reperfusion is another example of increased catalytic metal availability occurring in vivo. Intravenous ascorbate before vascular surgery may increase concentrations of ascorbate radicals and lipid hydroperoxides suggesting that catalytic iron released into the circulation during the ischemic phase of surgery along with ascorbate may promote iron-induced lipid peroxidation. Elevated levels of catalytic metal ions have also been demonstrated in chronic inflammatory diseases, e.g., increased iron protein deposition in synovial membranes is found in rheumatoid arthritis. In addition, ascorbate concentrations were decreased while catalytic iron levels increased in patients with sepsis, compared with healthy subjects.<sup>33</sup>

### Ascorbic acid and its pro-oxidant activity as a therapy

Numerous observations provide insights into the mechanism by which pharmacological concentrations of ascorbate have potential in treating certain types of cancer. Indeed, ascorbate at pharmacological concentrations has been shown to act as a pro-oxidant, generating hydrogen peroxide-dependent cytotoxicity toward a variety of cancer cells in vitro without adversely affecting normal cells.

Based on these data, many in vivo studies propose that pharmacological concentrations of ascorbate are able to selectively generate Asc<sup>•</sup> in the extracellular fluid but not in the blood. Pharmacokinetics data indicate that intravenous administration of ascorbate bypasses the tight control of intestinal and renal excretion and produces very high plasma levels, resulting in high extracellular H<sub>2</sub>O<sub>2</sub> fluxes that readily diffuse into cells initiating oxidative cascades. These high H<sub>2</sub>O<sub>2</sub> fluxes appear to have little effect on normal cells, but may be detrimental to some cancer cells. Knowledge and understanding of these mechanisms brings a rationale for the use of high doses of ascorbate in cancer treatment.<sup>34</sup>

The use in therapy of the pro-oxidant action of pharmacological ascorbic acid can be applied in all conditions in which H<sub>2</sub>O<sub>2</sub> and/or ROS might be beneficial. The obvious candidates are infectious agents, including viruses, bacteria, and other human pathogens. As in cancer treatment, pharmacological ascorbate has the potential to be added to existing therapies for synergistic effect. This may be particularly useful for bacteria that have developed multiple resistances to antibiotics and for which only limited treatments are available. H<sub>2</sub>O<sub>2</sub> is the medium by which neutrophils generate ROS, and it is possible that pharmacological ascorbate may be effective against some bacteria especially in combination with antibiotics and also against various types of viruses.<sup>35</sup>

It should be emphasized that while GSH is produced by the human body, ascorbate must be taken in through the diet. In addition to being the most important and active nonenzymatic molecule with antioxidant power in the cell, which scavenges hydroxyl and superoxide radicals, GSH also has several other functions: it is a cofactor for several detoxifying enzymatic reactions and is involved in the regeneration of other important antioxidants such as vitamins C and E, with two GSH molecules oxidizing to GSSG. The reducing system resulting from the cooperation of GSH with the oxidoreductive activity of ascorbate is under normal conditions continuously regenerated through a sequence of reactions involving two enzymes: glutathione peroxidase and glutathione reductase. Regeneration is of fundamental importance in keeping the redox system in balance, because an excess of any one type of antioxidant in the absence of regeneration with the others can be counterprotective (i.e., have an oxidative effect)<sup>36</sup>

<sup>33</sup> McGregor G.

Vitamin C contributes to inflammation via radical generating mechanisms: a cautionary note. *Med Hypotheses*. 2004;62(4):641-2. doi: 10.1016/j.mehy.2003.12.013. PMID: 15050122. <https://pubmed.ncbi.nlm.nih.gov/15050122/>

<sup>34</sup> Chen Q, Espey MG, Sun AY, et al.

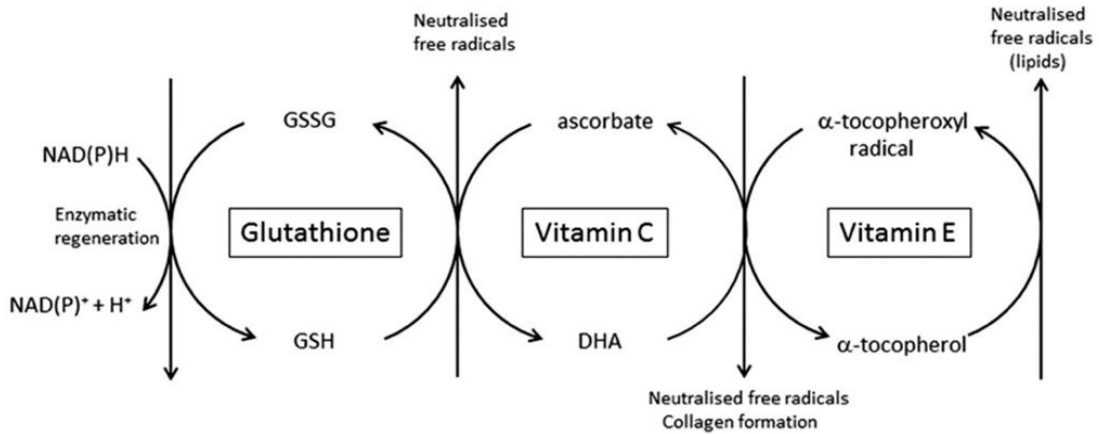
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<sup>35</sup> Hemilä H.

Vitamin C and Infections. *Nutrients*. 2017;9(4):339. Published 2017 Mar 29. doi:10.3390/nu9040339 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5409678/>

<sup>36</sup> Rietjens IM, Boersma MG, Haan Ld, Spenkelink B, Awad HM, Cnubben NH, van Zanden JJ, Woude Hv, Alink GM, Koeman JH. The pro-oxidant chemistry of the natural antioxidants vitamin C, vitamin E, carotenoids and flavonoids. *Environ Toxicol Pharmacol*. 2002 Jul;11(3-4):321-33. doi: 10.1016/s1382-6689(02)00003-0. PMID: 21782615. <https://www.sciencedirect.com/science/article/pii/S1382668902000030?via%3Dihub>

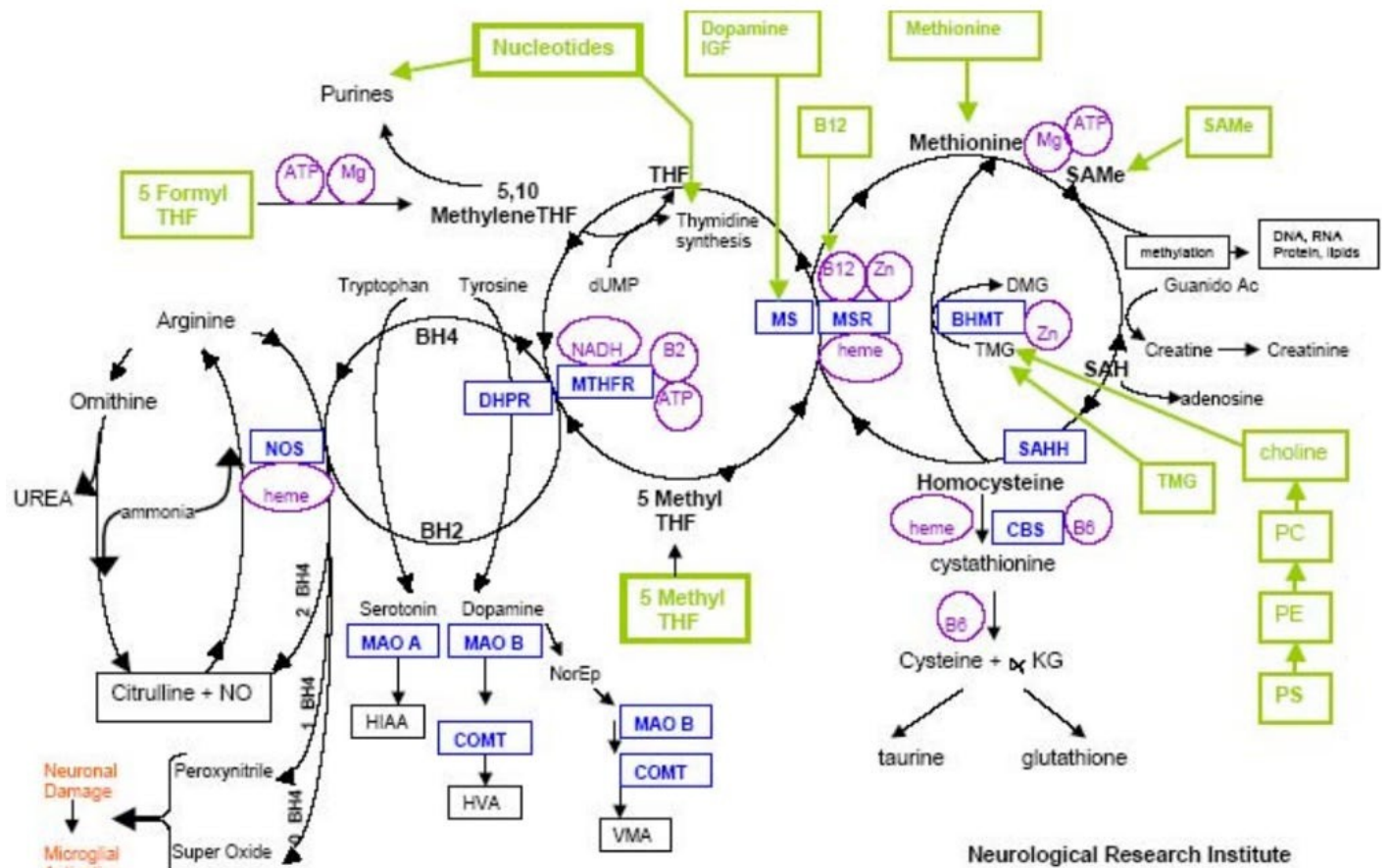
**Antioxidant cycle:**



<https://www.mdpi.com/2072-6643/9/8/866/htm>  
 GSSG: oxidized glutathione; DHA: dehydroascorbic acid

The following figure shows:

In **BLUE** boxes: major enzymes; **VIOLET** circles: enzyme cofactors; **GREEN** boxes: supplements



[https://mednat.news/cure\\_natur/metilazione-acidi-nucleici\\_Yasko.pdf](https://mednat.news/cure_natur/metilazione-acidi-nucleici_Yasko.pdf)

The following are examples of enzymatic and nonenzymatic antioxidants, tests of antioxidant capacity, and indirect antioxidant activity.<sup>37</sup>

<sup>37</sup>Bast A, Haenen GR.

| Enzymatic antioxidants                           | Antioxidant activity  | Essential groups in the active center (human origin)    |
|--|---|---|
| Superoxide dismutase (SOD) [70]                  | $2 O_2^{\cdot -} + 2 H^+ \rightarrow H_2O_2 + O_2$  | Cu and Zn (SOD1, SOD3), Mn (SOD2)                       |
| Glutathione peroxidase (GPx) [71]                | $2 GSH + ROOH \rightarrow GSSG + ROH + H_2O$  | Selenocysteine (GPx1-4, 6), cysteine (GPx5, 7, 8)       |
| Peroxiredoxin (PRDX) [72]                        | $2 R' - SH + ROOH \rightarrow R' - S - S - R' + H_2O + ROH$   | Cysteine  |
| Glutathione reductase (GR) [73]                  | $GSSG + NADPH + H^+ \rightarrow NADP^+ + 2 GSH$   | Vicinal disulfide, cofactor FAD                         |
| Catalase (Cat) [74]                              | $2 H_2O_2 \rightarrow 2 H_2O + O_2$   | Iron-containing heme group                              |
| Thioredoxin (TRX) [75]                           | Protein disulfide $\rightarrow$ protein dithiol   | Vicinal cysteine and selenocysteine                     |
| Thioredoxin reductase (TR) [76]                  | $TRX(S - Se) + NADPH + H^+ \rightarrow NADP^+ + TRX(SH SeH)$  | Vicinal disulfide, cofactor FAD                         |
| Non-enzymatic antioxidants                       | Major reactive species scavenged  | Characteristics   |
| Vitamin E [77]                                   | Lipid peroxy radical  | Lipophilic  |
| Carotenoids [78]                                 | Singlet oxygen  | Lipophilic  |
| Flavonoids [79]                                  | Superoxide radical  | Lipophilic to hydrophilic                               |
| Hydroxytyrosol [80]                              | Lipid peroxy radical  | Amphiphilic   |
| Vitamin C [81]                                   | Vitamin E radicals (regeneration)   | Hydrophilic   |
| Glutathione [82]                                 | Hydro(gen)peroxide (as cofactor)  | Hydrophilic   |
| Antioxidant capacity assay                       | Antioxidant activity  | Remarks   |
| ORAC [83]  | Prevention of lipid peroxidation induced by an artificial radical   | Well-standardized procedure required                    |
| TEAC [84]  | Amount of ABTS radicals scavenged   | A well standardized procedure has to be applied         |
| DPPH radical scavenging [85]                     | Amount of DPPH radicals scavenged   | A well standardized procedure has to be applied         |
| FRAP [86]  | Capacity to reduce iron(III) to iron(II)  | Fe(III) reduction promotes radical formation            |
| Indirect antioxidant activity                    | Antioxidant activity  | Compounds   |
| Inhibition of NADPH oxidase [87]                 | Reduced production of superoxide radicals   | Apocynin, flavonoid metabolites                         |
| Inhibition of xanthine oxidase [88]              | Reduced production of superoxide radicals   | Allopurinol   |
| Iron chelation [89]                              | Reduced production of hydroxyl radicals   | 7-mono-hydroxyethylrutoside (MonoHER)<br>Deferoxamine   |
| Inhibition of poly(ADP-ribose) polymerase-1 [90] | Increased genomic stability, mitigation of the inflammatory response  | Caffeine, theobromine, theophylline, niacin, flavonoids |
| Activation of the transcription factor Nrf2 [91] | Induction of antioxidant genes, e.g., heme oxygenase (HO-1), NAD(P)H quinone oxidoreductase 1 (NQO1), glutamate-cysteine ligase (Gcl), UDP-glucuronosyltransferase (UGT1A1, UGT1A6), glutathione transferase (GST pi) | Sulforophane, oltipraz                                  |

[https://www.cell.com/trends/pharmacological-sciences/pdf/S0165-6147\(13\)00098-9.pdf](https://www.cell.com/trends/pharmacological-sciences/pdf/S0165-6147(13)00098-9.pdf)

Ten misconceptions about antioxidants.

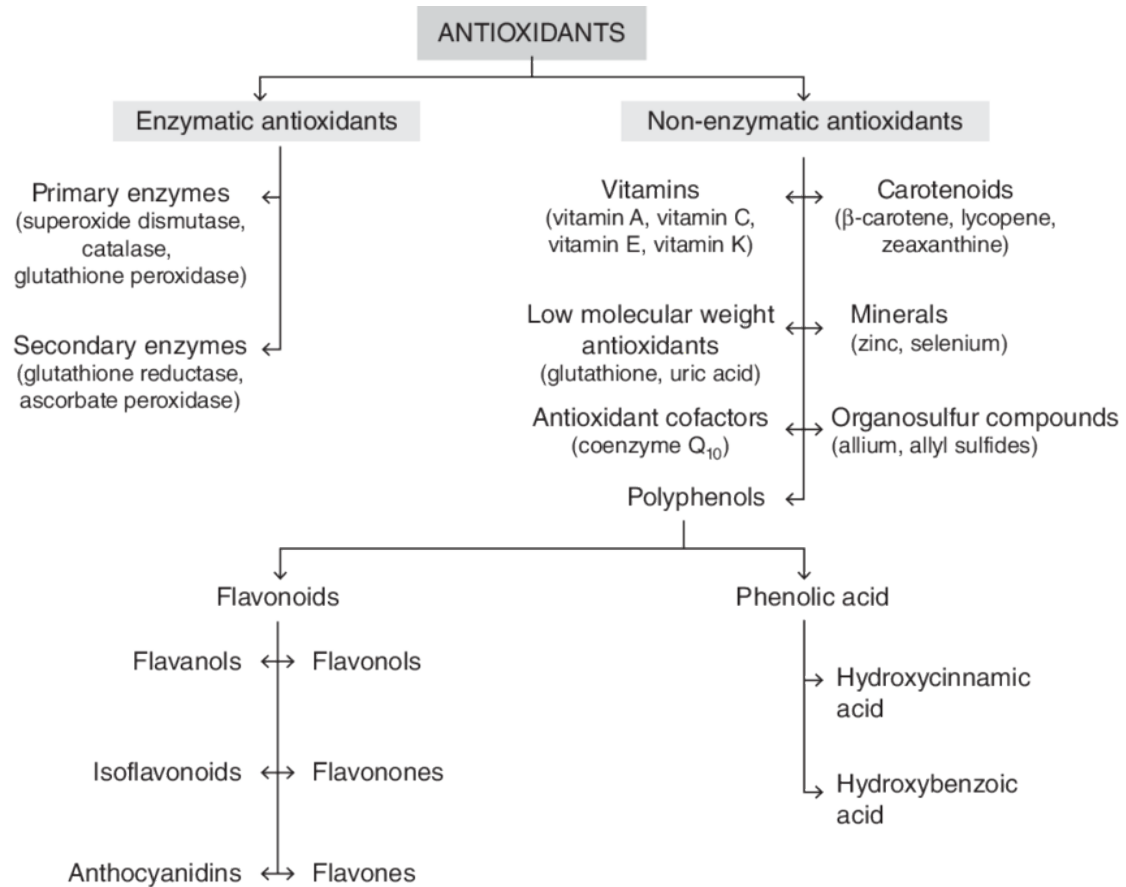
Trends Pharmacol Sci. 2013 Aug;34(8):430-6. doi: 10.1016/j.tips.2013.05.010. Epub 2013 Jun 24. PMID: 23806765.

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Pandey, Neha & Rai, Shashi Pandey. (2014). Biochemical Activity and Therapeutic Role of Antioxidants in Plants and Humans.

[https://www.researchgate.net/publication/267395391\\_Biochemical\\_Activity\\_and\\_Therapeutic\\_Role\\_of\\_Antioxidants\\_in\\_Plants\\_and\\_Humans](https://www.researchgate.net/publication/267395391_Biochemical_Activity_and_Therapeutic_Role_of_Antioxidants_in_Plants_and_Humans).

Dr. Loretta Bolgan

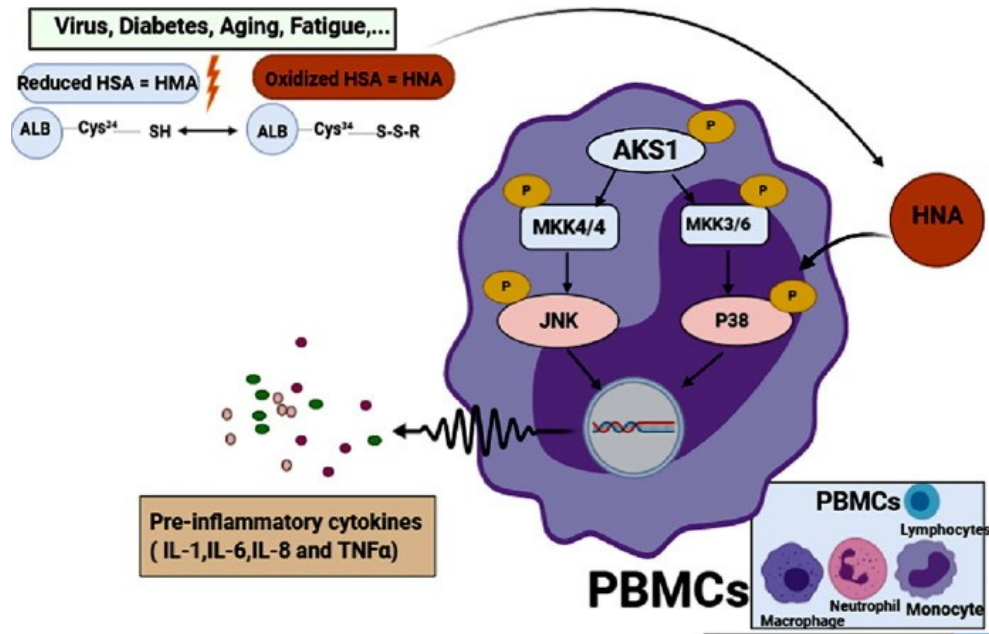


[https://www.researchgate.net/publication/267395391\\_Biochemical\\_Activity\\_and\\_Therapeutic\\_Role\\_of\\_Antioxidants\\_in\\_Plants\\_and\\_Humans](https://www.researchgate.net/publication/267395391_Biochemical_Activity_and_Therapeutic_Role_of_Antioxidants_in_Plants_and_Humans)

### Albumen

Human serum albumin (HSA), the most abundant protein in human blood plasma, is involved in maintaining colloidal osmotic pressure, transferring endogenous (hormones, bilirubin, and fatty acids)/exogenous substances, and eliminating free radicals. It can be found in two forms: reduced albumin (human mercaptalbumin (HMA)) and oxidized albumin (non-human mercaptoalbumin (HNA)). In HSA, there is a free sulfhydryl group at position 34 cysteine (cys- 34) that can act as an antioxidant by attacking free radical species. In healthy people, cys-34 on 75% of HSA is in its reduced form (HMA) and in the remaining 25% it creates a small disulfide bond with another cysteine, homocysteine or glutathione (HNA). It is important to keep in mind that human serum albumin (HSA) is an acute-phase reactant with antioxidant properties; therefore, under normal physiological conditions, plasma albumin provides an abundant source of free thiols that can eliminate reactive oxidant species (ROS). Under oxidative stress conditions, the Cys34 of HSA can undergo irreversible oxidation, which alters the antioxidant property of HSA and eventually causes cell and tissue damage. Interestingly, in this regard, albumin oxidation triggers extracellular neutrophil traps through the accumulation of ROS within neutrophils, which eventually accumulate in the lungs.<sup>38</sup>

<sup>38</sup> Inoue M, Nakashima R, Enomoto M, et al. Plasma redox imbalance caused by albumin oxidation promotes lung-predominant NETosis and pulmonary cancer metastasis. Nat Commun. 2018;9(1):5116. Published 2018 Nov 30. doi:10.1038/s41467-018-07550-x



<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7598366/>

There is a growing body of evidence suggesting that ROS are involved in the activation of platelets and coagulation, so it is plausible that in the case of albumin degradation/oxidation, both compartments are hyperactivated. Indeed, the consequence of hypoalbuminemia to oxidative stress/inflammation is associated with thrombosis tendency and poor survival.<sup>39</sup>

In a recent study, the relationship between HSA and survival was analyzed in 319 COVID-19 patients during a median follow-up of 19 days, and it was found that HSA deficiency was independently associated with mortality and could therefore be used as a predictive marker.<sup>40</sup>

It should be noted that because of the reduced HSA level of COVID-19 patients, albumin therapy may be suggested as a treatment option. However, it is necessary to say that analysis indicates that there is nearly 57% heterogeneity on the oxidized position of cys-34 in albumin preparation by firms. This change significantly reduces the antioxidant activity of albumin, decreases its ability to bind to drugs, and could be associated with the initiation of fatal inflammatory reactions demonstrated in animal models.<sup>41</sup>

## INTEGRATED MEDICINE PROTOCOLS

### PROPOSAL FOR THE PREVENTION AND TREATMENT OF COVID-19

DR. GIUSEPPE DI BELLA

Published on 13/10/2020<sup>42</sup>

<sup>39</sup> Wu CY, Hu HY, Huang N, Chou YC, Li CP, Chou YJ. Albumin levels and cause-specific mortality in community-dwelling older adults. *Prev Med.* 2018 Jul;112:145-151. doi: 10.1016/j.ypmed.2018.04.015. Epub 2018 Apr 9. PMID: 29649489. <https://pubmed.ncbi.nlm.nih.gov/29649489/>

<sup>40</sup> Violi F, et al. Is Albumin a Predictor of Mortality in COVID-19? *Antioxid Redox Signal.* 2020 Jun 22. doi: 10.1089/ars.2020.8142. Epub ahead of print. PMID: 32524832. <https://www.liebertpub.com/doi/pdf/10.1089/ars.2020.8142>

<sup>41</sup> Rahmani-Kukia N, Abbasi A, Pakravan N, Hassan ZM. Measurement of oxidized albumin: An opportunity for diagnoses or treatment of COVID-19. *Bioorg Chem.* 2020;105:104429. doi:10.1016/j.bioorg.2020.104429 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7598366/>

<sup>42</sup> <http://www.metododibella.org/it/notizie/2020-10-13/Covid-19-PREVENZIONE-ANTI-VIRALE-prescrizione-e-documentazione.html>

[Covid-19 : ANTI-VIRAL PREVENTION \(documentation and bibliographic references\).](#)

[INTERVIEW WITH B y o b l u](#)

Attachments:

[DOCUMENTATION](#) on ACTIVE PRINCIPLES and related BIBLIOGRAPHY.

**Retinoids**

40-50 thousand units per day are tolerated without any harm.

For **adults** one tablespoon in the morning on an empty stomach (contraindicated in established or presumed pregnancy or in the presence of severe liver failure).

For **babies**, administer an amount equal to 1 ml x 10 kg body weight ( ex: weight 20 kg = 2 ml, weight 30kg=3ml)

**Vit. D**

The optimal dose for children and adolescents ranges, depending also on the presence of calcium and phosphorus in the diet, from 10 to 20 gamma (corresponding to 400-800 U. I)

The average requirement of an infant is around 400 U. I. (international units) of vitamin D

For an adult also depending on weight and calcemia 20 to 30 drops per day to be added in the retinoid tablespoon

**Vit. C**

At least 4 g per day during meal, if acidity add 1\2 teaspoon baking soda in the glass

**Lysozyme**

Recommended dosage, by mouth at least 4 cps per di, to be dissolved slowly in the mouth (with ongoing disease about every 2 hours) . Also indicated is application as a nasal spray (will be available soon in some pharmacies) and by os at least 3 times a day , after nasal washes.

**Lactoferrin**

Recommended dosages cps 200 mg 3 times a day.

**Reduced glutathione C4**

By aerosol: 24 mg of reduced glutathione is diluted in 3 ml of saline and aerosolized, preferably with micronized apparatus to reach the alveolar phase. In view of the pulmonary distress typical of Coronavirus, its use, in the absence of contraindications, could probably prove useful. By mouth: reduced glutathione gastroprotectant cps 500 mg - 2 times a day

**Resveratrol**

can be used either in 400 mg gastro-resistant capsules morning and evening or by application by nasal spray after washings , and by mouth , 3 times a day.

**Alpha-lactalbumin**

Recommended dose of 500-750 mg 3 times a day, possibly together with Lactoferrin and Lysozyme

**Beta-Glucans**

start with a very thin slice to be increased very gradually over a month to about 1/3 of the package (eight to nine grams), should be diluted in 1/2 glass with water and a teaspoon of sugar, and ingested at least 15 minutes before a meal once a day.

**VITAMIN C AND MELATONIN TREATMENT PROPOSAL DR DORIS**

**LOH**

The following is a treatment scheme with vitamin C and melatonin administration proposed by Dr. Doris Loh based on the literature review. <sup>43</sup>

<sup>43</sup> Loh, Doris.

The potential of melatonin in the prevention and attenuation of oxidative hemolysis and myocardial injury from cd147 SARS-CoV-2 spike protein receptor binding. Melatonin Research. (2020). 3. 380-416. 10.32794/mr11250069. <https://www.melatonin-research.net/index.php/MR/article/view/86/569>

## VITAMIN C – ORAL ASCORBIC ACID (AA) Recommended Dosage\* for COVID-19

### ADULTS:

- take initial dose of 3 to 5 grams, depending on severity
  - ⇒ subsequent doses: 2 grams every 30 minutes
  - ⇒ if fever, breathing distress, myalgia does not improve in 3 to 4 hours, repeat this cycle with 3 to 5 grams, followed by 2 grams every 30 minutes. Repeat this cycle every 12 hours
  - ⇒ if conditions do not improve after 12 hours, increase the initial dose up to 10 grams followed by 3 to 5 grams every 30 minutes
- once your condition improves and stabilizes, go back to 2 grams every hour (instead of 30 minutes)

**SEVERE SYMPTOMS**

### ADULTS:

- take initial dose of 3 grams, followed by 1 to 2 grams every hour. You can repeat this cycle every 8 hours until symptoms subside
- once symptom-free, take 1 to 2 grams every hour – total of 8 to 12 grams daily
- make sure you take a higher level of AA than before you were infected

**INITIAL ONSET  
NO SYMPTOMS TO  
MILD SYMPTOMS**

### CHILDREN (under 12):

- take initial dose of 1 to 2 grams, depending on severity
  - ⇒ subsequent doses: 0.5 grams every 30 minutes
  - ⇒ if fever, breathing distress, myalgia does not improve in 3 to 4 hours, repeat this cycle with 1 to 2 grams, followed by 0.5 grams every 30 minutes. Repeat this cycle every 12 hours
  - ⇒ if conditions do not improve after 12 hours, increase the initial dose up to 3 to 4 grams followed by 1 gram every 30 minutes
- once your condition improves and stabilizes, go back to 0.5 grams every hour (instead of 30 minutes)

### CHILDREN (under 12):

- take initial dose of 1 gram, followed by 0.5 gram every hour. You can repeat this cycle every 8 hours until symptoms subside
- once symptom-free, take 0.5 gram every hour – total of 0.5 gram per 10 lb. body weight plus 1 gram daily, to be taken in divided doses, e.g., a 60 lb. child will be taking 4 grams in total daily, divided ideally into 8 doses, upon recovery
- infants and children under 5 years old can be given 0.5 grams per 10 lb. body weight plus 200 milligrams for each additional year of age, e.g., a 2-year-old child weighing 20 lbs. will be taking 1.4 grams total daily, divided into small even doses throughout the day
- if the child has been taking AA before infection, make sure that he/she is given a higher level of AA after infection than before if the child suffered symptoms during infection – and higher daily dose should be given after recovery from infection

*Some people have reported that as soon as their AA levels drop, shortness of breath returns immediately, if that happens, take a hammer dose of:*

**ADULTS: 3 to 5 grams of AA**

**CHILDREN: 2 to 3 grams of AA**

*During critical infections, you will essentially have an "unlimited" tolerance for AA – may increase to more than **100 grams**, and that is actually normal, because doctors in the past have used oral AA in amounts over **200 grams** to treat viral pneumonia<sup>1</sup>.*

<sup>1</sup>Cathart RF. The Method of Determining Proper Doses of Vitamin C for the Treatment of Disease by Titrating to Bowel Tolerance. *Australas Nurses J.* 1980 Mar;9(4):9-13. <http://orthomolecular.org/library/jom/1981/pdf/1981-v1i0n02-p125.pdf>

*Have you had your  
AA and MEL today?  
~ Doris Loh*

\*SHOULD NOT be regarded as MEDICAL ADVICE

## VITAMIN C - ASCORBIC ACID (AA) Recommended dose \* for COVID-19

\* Not to be construed as medical advice

## Severe symptoms

### Adults

- Take an initial dose of 3-5 g depending on severity
    - ☒ Subsequent doses: 2 g every 30 min
    - ☒ If fever, difficulty breathing, and myalgia do not improve within 3-4 h, repeat this cycle with 3-5 g, followed by 2 g every 30 min. Repeat the cycle every 12 hr.
    - ☒ If the condition does not improve after 12 h, increase the initial dose to 10 g followed by 3-5 g every 30 min.
- Once conditions improve and stabilize return to 2 g every hour (instead of every 30 min)

### Children (under 12 years old)

- Take an initial dose of 1-2 g depending on severity
  - ☒ Subsequent doses: 0.5 g every 30 min
  - ☒ If fever, difficulty breathing, and myalgia do not improve within 3-4 hours repeat this cycle with 1-2 g, followed by 0.5 g every 30 min. Repeat the cycle every 12 hr.
  - ☒ If the condition does not improve after 12 h, increase the initial dose to 3-4 g followed by 1 g every 30 min.
- Once conditions improve and stabilize return to 0.5 g every hour (instead of every 30 min)

Some people have reported that immediately after the AA level falls, breathing difficulty reappears; if this happens, take a shock dose of:

adults: 3-5 g of AA

children: 2-3 g of AA

During critical infections, you have virtually "unlimited" tolerance for AA, you can increase it up to 100 g, and this is actually normal, because doctors in the past have used oral AA in amounts up to 200 g to treat viral pneumonias <sup>1</sup>

1 <http://orthomolecular.org/library/jom/1981/pdf/1981-v10n02-p125.pdf>

## Initial symptoms - asymptomatic or mild symptoms

### Adults

- Take an initial dose of 3 g followed by 1-2 g every hour. You can repeat this cycle every 8 hours until the symptoms disappear
- once symptoms have disappeared, take 1-2 g every hour for a total of 8-12 g per day
- Make sure to take more AA than before being infected

### Children (under 12 years old)

- Take an initial dose of 1 g followed by 0.5 g every hour. You can repeat this cycle every 8 hours until the symptoms disappear
- once symptoms have disappeared, take 0.5 g every hour for a total of 0.5 g/10 lb (~ 4.5 kg) body weight plus 1 g per day to be divided into several doses; i.e., a 60 lb (~ 27 kg) child should take 4 g in total per day to be divided theoretically into 8 doses until recovery
- children under 5 years of age can take 0.5 g/10 lb (~ 4.5 kg) of body weight plus 200 g for each additional year; that is, a 2-year-old child of 20 lb (~ 9 kg) should take 1.4 g in total per day to be divided theoretically into small, equal doses throughout the day
- if the child was taking AA before the infection, ensure that he/she takes a higher amount of AA after the infection than before if the child presented symptoms during the infection and a higher daily dosage should be administered after recovery from the infection

# MELATONIN (MEL) – Maintenance and Recommended Dosage\* for COVID-19

## MAINTENANCE

### ADULTS:

- physiological dose – **0.1 to 0.5 mg**, depending on age, circadian health, night time light exposure, and endogenous melatonin production – to be taken after 8:30pm, preferably 1-2 hours before sleep

### CHILDREN:

- none required for under 8 years old. **0.025 to 0.05 mg** can be supplemented if the child has poor circadian health habits, or sleep issues – to be taken after 8:00pm, preferably 1-2 hours before sleep

## FOR COVID-19 INFECTION

### CHILDREN (0 to 7 years old) :

During first 6 months, infants rely on breastmilk for melatonin, increase mother's intake to supply melatonin to infants still breastfeeding. For all infection protocols for young children below the age of 8, follow same guidelines for children ages 8 to 14, but substitute dosage as follows:

**Day 1:** Total Melatonin = **0.1 mg**/10 lbs body weight

**Day 2:** Total Melatonin = **0.5 mg**/10 lbs body weight

**Day 3:** Total Melatonin = **1.0 mg**/10 lbs body weight

**Day 4:** Total Melatonin = **2.5 mg**/10 lbs body weight

### CHILDREN (8 to 14 years old) :

**Day 1:** upon first onset of symptoms, increase night time dosage to at least **1 mg** – also immediately commence oral Ascorbic Acid Protocols for Infection – if symptoms do not subside or improve in 24 hours, increase melatonin dose as follows:

**Day 2:** Total Dose: **5 mg** to be taken **4 mg** at night, **1 mg** during day time, divided in 2 doses – maintain this dose if there is improvement, if not, proceed to Day 3 dosage.

**Day 3:** Total Dose: **12 mg** to be taken **8 mg** at night, **4 mg** during the day, divided in 5 doses – maintain this dose if there is improvement, if not, proceed to Day 4 dosage.

**Day 4:** Total Dose: **30 mg** to be taken **24 mg** at night, **6 mg** during the day, divided in 5 doses – maintain this dose until signs of recovery, then reduce dosage every 3 days in reverse order – stay at Day 2 dosage until you are totally clear of all symptoms.

### ADULT:

**Day 1:** upon first onset of symptoms, increase night time dosage to at least **5 mg** – also immediately commence oral **Ascorbic Acid Protocols for Infection** – if symptoms do not subside or improve in 24 hours, increase melatonin dose as follows:

**Day 2:** Total Dose: **20 mg** to be taken **16 mg** at night, **4 mg** during day time, divided in 2 doses – maintain this dose if there is improvement, if not, proceed to Day 3 dosage.

**Day 3:** Total Dose: **50 mg** to be taken **40 mg** at night, **10 mg** during the day, divided in 5 doses – maintain this dose if there is improvement, if not, proceed to Day 4 dosage.

**Day 4:** Total Dose: **80 mg** to be taken **60 mg** at night, **20 mg** during the day, divided in 5 doses – maintain this dose until signs of recovery, then reduce dosage every 3 days in reverse order – stay at Day 2 dosage until you are totally clear of all symptoms.

**RECOVERY:** remain on Day 1 dosage for 1 month, if your infection is severe – half the dose if not severe

Have you had your  
AA and MEL today?  
~ Doris Loh

\*SHOULD NOT be regarded as MEDICAL ADVICE

## MELATONIN (MEL)

Maintenance and recommended dose\* for COVID-19

\* Not to be construed as medical advice

### Maintenance

#### Adults

Physiological dose: 0.1-0.5 mg depending on age, circadian rhythm status, exposure to light at night, and endogenous melatonin production. To be taken after 0.30 am and preferably 1-2 hours before bedtime.

#### Children

Not required under 8 years of age. 0.025-0.05 mg may be supplemented if the child has unhealthy circadian habits or trouble sleeping, to be taken after 8 p.m. and preferably 1-2 hours before bedtime.

### COVID-19 infection

#### Children (0-7 years)

During the first 6 months of life, infants take melatonin from breast milk. Increase intake in the mother to supplement melatonin in infants who are still breastfeeding. For all infection protocols for infants under 8 years of age, follow the same guidelines for children 8-14 years of age by substituting the dosage as below:

- Day 1: total melatonin = 0.1 mg/10 lb (~4.5 kg) body weight (bw)
- Day 2: total melatonin = 0.5 mg/10 lb (~4.5 kg) bw
- Day 3: total melatonin = 1.0 mg/10 lb (~4.5 kg) bw
- Day 4: total melatonin = 2.5 mg/10 lb (~4.5 kg) bw

#### Children (8-14 years old)

- *Day 1:* From the onset of symptoms, increase the evening dosage to at least 1 mg (also immediately start the protocol with AA for infection). If symptoms do not disappear or improve within 24 hours, increase melatonin as follows:
- *Day 2:* Total dose: 5 mg to be taken 4 mg in the evening and 1 mg during the day divided into two doses. Maintain this dosage if there is improvement, otherwise proceed to Day 3 dosage
- *Day 3:* Total dose: 12 mg to be taken 8 mg in the evening and 4 mg during the day divided into 5 doses. Maintain this dosage if there is improvement, otherwise proceed to Day 4 dosage
- *Day 4:* Total dose: 30 mg to be taken 24 mg in the evening and 6 mg during the day divided into 5 doses. Maintain this dosage until there are signs of improvement, then reduce the dosage every 3 days in reverse order and stay at Day 2 until all symptoms have disappeared

#### Adults

- *Day 1:* From the onset of symptoms, increase the evening dosage to at least 5 mg (also immediately start the protocol with AA for infection). If symptoms do not disappear or improve within 24 hours, increase melatonin as follows:
- *Day 2:* Total dose: 20 mg to be taken 16 mg in the evening and 4 mg during the day divided into two doses. Maintain this dosage if there is improvement, otherwise proceed to Day 3 dosage
- *Day 3:* Total dose: 50 mg to be taken 40 mg in the evening and 10 mg during the day divided into 5 doses. Maintain this dosage if there is improvement, otherwise proceed to Day 4 dosage
- *Day 4:* Total dose: 80 mg to be taken 60 mg in the evening and 20 mg during the day divided into 5 doses. Maintain this dosage until there are signs of improvement, then reduce the dosage every 3 days in reverse order and stay at Day 2 until all symptoms have disappeared

**Convalescence:** stay at Day 1 dosage for 1 month if infection was severe, half dose if not severe

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**PRIMARY PREVENTION DR.**  
**GIANNIANTONIO FACCHINETTI**  
facchinetti@gmail.com

- 1) **Ascorbic acid** powder: 3gr/day dissolved in a 1 1/2L bottle of water to drink throughout the day ( avoid exposure of the bottle to light).
- 2) **Vitamin D3** gtt 10,000 IU/ml : 25/30 gtt 1 time/week.
- 3) **Vitamin K 2** gtt : 5/10 gtt die ( 52.5/105 mcg/die)
- 4) **Lactoferrin** 60 mg/day fl x os: 1 fl morning fasting.
- 5) **Melatonin** 1 mg : 1cp in the evening 1/2 h before falling asleep.  
 +  
**Zinc** gluconate 8.7 mg/day or Zinc picolinate 11 mg/day with one meal  
 +  
**Selenium** : 50 mcg/day with one meal
- 6) **Copper** : 1250 mcg/day at one meal
- 7) **Vitamin A** and **Vitamin E** through intake of foods that are rich in them.

\* To be understood as supplementing and not replacing a proper lifestyle and healthy diet.

\*\*The indicated dosages should, however, always be adjusted according to the individual's age, sex, lifestyle, and clinical data.

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**PRIMARY PREVENTION AND  
TREATMENT DR. MASSIMO  
CITRO**

- 1) **Vitamin D3**: 40,000 U/day + Vitamin K2 400 mcg
- 2) **Vitamin C** 500 mg + **reduced glutathione** 200 mg + **zinc orotate** 20 mg: 1 cp after 3 meals
- 3) Possibly: 10-20 mg of **Melatonin**
- 4) If there were symptoms that may put one at risk of developing into complications (pneumonia, thromboembolism, etc., the physician will be the one to evaluate) one can also take **azithromycin** 500 mg/day on the first day and then 250 mg on the following 5 days, with possible **Hydroxychloroquine** 200 mg/two times a day for a few days (contraindicated in: favism, porphyria, myasthenia, severe renal failure, heart disease): these drugs require to be prescribed by the physician. If it is not possible to act with hydroxychloroquine, **cortisone** can be used. These are short therapies of a few days, three to a maximum of 15, so side effects or toxicity are almost absent. In addition, up to 400 mg per day, hydroxychloroquine hardly causes problems.

Protocol excerpted from the book "**HERESY! politically incorrect reflection on the pandemic**" Dr. M. Citro

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**COVID-19 PROPHYLAXIS AND TREATMENT WITH HOMEOPATHIC REMEDIES**  
**DR. STEFANO GANDUS 1 - DR. ENZA ROSASPINI AND DR. ALESSANDRA DASSORI**

<sup>1</sup> stefano.gandus@libero.it

COVID-19 PROTOCOL - OCTOBER 2020

Age groups

- 1) 0-12 Months
- 2) 1-6 years old
- 3) 6-14 years old
- 4) Adult
- 5) Elderly

**1) 0-12 months :**

Lactoferrin: BLF100gtt, Fruttdep flac- Enaflu baby D3 syrup, Fluoff, ImmunoSpecial d r o p s , Probioflor drops, Nepiros vials, Nepiros Spray (nasal, throat), Nepinar nasal fl

LISOZIMA: Notakehl

VITAMIN C : Ferment Fee, MGS 25

VITAMIN D: Olea D3 junior, Dicovit pearls, D3 Vit forte, D3 plus HOMEOPATHIC

IMMUNOSTIMULANTS: Oscillococtinum, Homeogriphi, Degrippal

SANUM MYCOTHERAPY: Sankombi (Mucor racemosus, Aspergillus niger),Fortakehl (Penicillum Roquefortii)

PROBIOTICS: Bifidi, Lactobacilli (Rhamnosus, Plantarum),Enterococcus Faecium, I-Natal ped, Erythophilus Infant, Maxiflor,Bifiselle, Citogenex, Ramnoselle, Simbiot, Flora-Mu, Diflor, Probinul, Aflugenex, AB flor, Lactodep, Osmobiotic Flora baby, Proflora

BETAGLUCAN : Linfo Immuno, Immunoped, Immunotrophin, Troca-Flu, Linfoflu

**2) 1-6 years**

Therapies as above +

HOLOIGOELEMENTS-RAME: Copper Catalitic fl, Copper Oligosol fl, Copper Gammadyn fl

PHYTOTHERAPY: Ribes nigrum, Propolis, Echinacea, Astragalus, Uncaria, Sea buckthorn, Pelargonium, Defedril, Tachi-Mu, Nepiros D3, Echinerg, Echinacea 200 plus, In-Flu 100, Kaloba, Defensol, Immunomix, Good Defense, Dicoflu, Enaflu,Biovit 3,Immunoplus , Astragen, Expando, Kerbos,Potomac 2,Phytomunil,MGS 16,Immun-up ,Influbiotic aerosol,Viral Fee

HOMEOPATHIC IMMUNOSTIMULANTS, Homeos 42, Mucozinum 200plus, Anascocinum Homeoflu, Influenzinum 15ch and 200ch,

**3) 6- 14 aa**

Therapies such as 1 and 2 +

MICOTERAPY Fomes and Coriolus ( az Antiviral), Shitake, Ganoderma Chaga (General Defenses) MTS (7,9,10,18), Pandevir, Immunosol, Linfabet Chaga, Sangam Bio

ESSENTIAL OILS: Thyme, Oregano, Myrtle, Tea tree, Lemon, Tsuga: Aborigen, Oregon, Potomac, Flora, Tim-Tim, Bacsol, Herboristeria Magentina

ELISIR lavender, Pine, Thyme: E66

SPAGYRIC TINCTURES Uncaria: TS 32

QUINTESENZE Lemon : QE 51 Oregano, Thyme, Savory, Cinnamon: Defensol GLUCOMANNAN :

AMP-Care

#### 4) ADULT

Therapies such as 1+2+3 +

ZINC AND SELENIUM: Trocaflu, Biovit 3, Bioactive Selenium+Zinc, Co-Zincum, Kappaphyt 9, Genelase

Lactoferrin: Nepiros spray (throat, nose), Kappaphyt 10

VITAMIN A , E: Haliborange, Rovigon

VITAMIN C: Immunorm C, Biovit 3 Energy, Soldatt C

OMEGA 3: Krilling-D, Immunomega, Queen Charlotte, Synerbiol, Omega3 Efa, Omega formula, Kriomega3, Krilife, Ribolio, Sea life

CURCUMA: Norflo, Pufacur, Curcusol 250, Curcumin gel

CITOCINE LOW DOSES: Citomix, 2-LEID

HOMEOPATHIC IMMUNOSTIMULANTS: Engystol, Viroti (Vincetoxicum +Sulfur), Vis-Heel, R1,R6, Vanda 1, Vanda 3, Vanda 6, Oti 6, P20

#### 5) ANCIENT

Therapies such as 1+2+3+4+

COLOSTRUM (COLOSTRUM NONI, COLOSTRUM PLUS, COLOSTRIS, EQUILAT)

GLUTATIONE and NAC (N-Acetyl-Cysteine): Troca-Flu bust

GROUP B VITAMINS: B Complex, Liquid B Solgar, B Complex ( B+C) , B-Oti complex, B Complex Long Life

MELATONIN Ponderal: Melamil gtt, Enason gtt, Fisioreve  
In homeopathic dilution : Guna-Melatonin 4CH gtt

It is always recommended to seek the advice of the physician competent in Complementary medicine, especially the Homeopathic Physician regarding specific remedies whose particular validity has been recognized in such an epidemic period according to the concept of "homeopathic genius," i.e., the collection of the totality of symptoms present in all individuals (symptoms common to all sufferers)

Fundamental then is the accurate next pathological history: collection of subjective and objective symptoms and with selection of salient, particular and rare symptoms.

Each individual epidemic has its own characteristic that is the same and common to all individuals.

**Generality of cases:** COVID-19 pathology does not have a single genius epidemicus.

Depending on virulence, characteristics in an individual's way of getting sick can be highlighted.

SYMPTOMATOLOGICAL DIAGNOSIS:

- Fever
- Asthenia

- Cough and/or Pharyngitis and/or Dyspnea and/or Chest Pain

If one of these three symptoms is missing, headache, and/or Anosmia- Ageusia may be present.

Rarely, pathology may be symptomatically presumed in the presence of anosmia and in the absence of other symptoms.

### MOST COMMONLY USED HOMEOPATHIC REMEDIES

**ARSENICUM ALBUM** prophylaxis in elderly, defecated patients, centripetal trend diseases, insomnia, desire for hot drinks; fear of suffocation from respiratory diseases, great remedy of fear of death, with great sense of loneliness.

**BELLADONNA**: fast-onset symptomatology, high fever with cold hands and feet

**BRYONIA**: Fever-related symptomatology, dry, hacking cough, aggravated coughing by talking and inhaling, holds chest and head by coughing; loss of urine by coughing deeply, thirst for large amounts of water, congestive headache, desire to be still, any movement aggravates it, irritable, cannot stand consolation.

**CHININUM SULPHURICUM**: subcontinuous fever, malaise followed by loss of much fluid, predominantly gastroenteric symptoms with nausea and diarrhea, indifference

**GELSEMIUM**: Slow manifestations, fever with great exhaustion alternating with chills, exhausting cough, tickling in larynx, profuse urination, eyelid heaviness, inability to keep eyes open. Chills down the back, headache, obnubilation, weakness with shivering. Insomnia from coughing.

**EUPATORIUM PERFOLIATUM**: Widespread joint pain, fever exhaustion, headache with cough, with fever burning pain, absence of thirst with fever, dry cough, cough improves lying on abdomen, aggravated by movement. Fever with shivering. Diffuse bone pain.

**PHOSPHORUS**: air hunger, chest tightness, desire for open air, improves in open air, loss of taste, loss of smell, lung inflammation, difficult breathing while walking, aggravated by movement,

**ANTIMONIUM TARTARICUM**: thick phlegm, wet wheezing, shortness of breath, dyspnea, difficult expectoration.

**CARBO VEGETABILIS**: In cases of acute respiratory failure **STANNUM**:

Frail individuals suffering from chronic debilitating diseases **ZINCUM and**

**AURUM**: To support stressed organisms

**SERPENT REMEDIES**: BOTHROPS LANCEOLATUS, LACHEISIS, CROTALUS HORRIDUS, NAJA for associated vascular problems Embolism and Microembolism

**HAMAMELIS, PULSATILLA**: Lack of appetite, bitter taste in mouth, need for company,

**SULPHUR** : skin diseases

**ARSENICUM ALBUM, PODOPHYLLUM, VERATRUM ALBUM** the most commonly used in cases of diarrhea

**GRINDELIA ROBUSTA**: pusses fever, weakness, occipital headache, dry cough, fear of not breathing, hypochondria, conjunctivitis, weakness in lower limbs

**CAMPHORA**: Continuous fever, cold sweating, asthenia, cough on inhalation, shallow breathing, watery rhinorrhea, diarrhea, oliguria, confusion, worry

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### COVID-19 PROPHYLAXIS AND TREATMENT WITH HOMEOPATHIC REMEDIES DR DIEGO TOMASSONE

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Based on evidence and experience since the end of 2019, it is recommended first and foremost for ALL (there are absolutely no contraindications!), to protect themselves by taking for preventive purposes (primary prevention), the remedy **EUPATORIUM PERFOLIATUM 30CH** (potency is 30CH or 30C), to be taken:

**-2 granules per week for 4 to 8 weeks (e.g., every Monday for the weeks indicated)**

On the other hand, for those experiencing Covid symptoms (especially if there is loss of taste and sense of smell!), it is recommended to start taking the homeopathic remedy **EUPATORIUM PERFOLIATUM 30CH**, as follows:

**N.B.** Prepare the remedy by diluting **5 granules** in about **250 ml. of water** (use a bottle that cannot be reused in the future for other remedies if plastic, or can be reused after washing in the dishwasher if glass!), taking one sip every hour (daytime only!), imparting **5 vigorous vertical shakes (succussions or dynamization)** to the bottle, slamming the bottle on the palm of your hand, each time before taking (when the water is about to run out simply top up with more water and impart 5 shakes, **NO** need to add more granules).

Take the remedy for 3 days then contact your doctor for evaluation.

Please remember that if you are already taking chemical drugs for flu-like syndrome, the clinical picture is "soiled," and in our experience we notice a longer recovery period, the recovery time then becomes longer (mainly because the drugs are often not prescribed in the correct way).

**N.B.** For reasons of effectiveness and quality, it is recommended that the remedy be ordered in granules from **CEMON, SODINI, HERING** or the **HELIOS** or from **REMEDIA**.

To order HELIOS remedies indicate "pills #6, 4g or 8g size"

<https://www.helios.co.uk/it/negozi/eupatorium-perfoliatum>

To order REMEDIA remedies, indicate "globules, 1g or 10g format"

<https://www.remedia-homeopathy.com/shop/Eupatorium-perfoliatum/a9004063>

If symptoms persist beyond 3 days, recommended to continue another 2 days in the same way, possibly including supplements if excessive weakness or fever persists (adults only!). The supplements proven most effective (in the absence of individualized supplementation identified by the hair mineralogram), are phytoembryo extracts and klamath algae supplements, so I personally recommend:

**IMMUNO FEE and VIRAL FEE (CEMON)** , 10 DROPS OF BOTH IN A LITTLE WATER, 3 TIMES PER DAY AT DIGIUNE, FOR 14 DAYS;

**MULTINATURAL OR NUTRIMAX (NUTRIGEA)**, 1 SCOOP OR 2 CAPSULES MORNING AND EVENING ON AN EMPTY STOMACH, FOR 14 DAYS, OR **VITAMIN D3 (SYGNUM OR VEGETAL PROGRESS)**, 3 DROPS OR 2 TABLETS IN THE MORNING ON AN EMPTY STOMACH;

**ZINC TRACE ELEMENT (CEMON-CATALITIC)**, 1 VIAL MORNING AND EVENING, ONLY FOR THE DAYS THE REMEDY IS TAKEN (ESPECIALLY IN THOSE WITH TASTE AND SMELL ALTERATIONS)

**KLAMEXTRA (NUTRIGEA)**, 1 SACHET MORNING AND EVENING FASTING FOR 14 DAYS, IN THOSE ALREADY SUFFERING FROM CHRONIC CONDITIONS.

**N.B.** Please note that these indications are good for everyone, and are given to avoid unnecessary hospitalizations (even given today's situation); however, should oxygen saturation fall below 95%, it is imperative to contact 118 and consider possible hospitalization for ventilatory assistance.

As a reminder, although this therapy is designed for everyone and has proven effectiveness (otherwise it would not be recommended it was not effective!), the best strategy always remains to be followed by a **doctor** (this very "epidemic" has made it even better understood how important it is to be followed by a good professional), who will know how to set up a possible personalized therapy and therefore more precise and recommended on the individual sufferer (especially if one already suffers from chronic diseases, takes other therapies, etc., and if the symptoms are not properly Covid).

For **children (up to 12 years of age)**, it is recommended to include in prophylaxis (especially in individuals who get sick often):

**BERRIER JUNIOR** (COLOSTRUM, DONKEY MILK AND LACTOFERRIN SUPPLEMENT), 1 VIAL PER WEEK ON AN EMPTY STOMACH FOR THE DURATION OF THE PROPHYLAXIS WITH REMEDY;

**NIMBUS DROPS OR TABLETS** (NUTRIGEA), 1 ml IF DROPS OR 1 TABLET IN THE MORNING OF A DAY, OR VITAMIN D3 (SYGNUM OR VEGETAL PROGRESS), 1 DROP OR 1 COMPRESSES EVERY MORNING AT A DAY, FOR THE DURATION OF THE PROFILASIS WITH REMEDY.

### **FURTHER STRENGTHENING PROPHYLAXIS**

Given and considering the latest evidence, which unfortunately confirms what I already indicated in the paper "**Scientific evidence of the (non)effectiveness of influenza vaccination**", that is, the presence of the "Hoskins effect" (also called "original antigenic sin"), which illustrates how flu vaccination even increases the risk of contracting respiratory infections, where the first immune response activated in response to the antigen, conditions future immune responses, making them paradoxically less effective and with less and less antibody response (so one gets vaccinated and the vaccine not only does not protect, but negatively conditions future immune responses, as was already observed in the 2009 swine flu epidemic, where those who had received the seasonal flu vaccine became more sick with swine flu itself), we recommend further "potentiating prophylaxis" with the remedy GELSEMIUM SEMPERVIRENS 30CH, again to be taken:

**- 2 granules per week for 4 to 8 weeks (to be taken on a different day from when taking Eupatorium perfoliatum)**

**N.B.** Possibly the above-mentioned supplements, i.e., **MULTINATURAL** or **NUTRIMAX** (1 scoop or 2 capsules in the morning on an empty stomach) or **VITAMIN D3**, **IMMUNO FEE** and **VIRAL FEE** (7 drops of each in a tiny bit of water), can also be included in the prophylaxis, again to be taken for the weeks of prophylaxis.

**N.B. Please** also note that if you have been in **contact with a person who has been vaccinated f o r influenza (or for those who have been vaccinated)**, it is advisable to **take 2 granules of Gelsemium sempervirens for 2 consecutive days**, this is regardless of any prophylaxis that may have been initiated.

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