

# Nutraceuticals as immune-stimulating therapy to fight COVID-19. Combination of elements to improve the efficacy

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**Abstract.** – COVID-19 pandemic has underlined that unknown viral infections, which jump from animals to humans, can be extremely dangerous. In case of new viruses as SARS-CoV2, available drugs can fail to contrast the virus aggressiveness leading patients to death. Long time is necessary to create a vaccine, but immediate solutions are necessary to stop the mortality COVID-19 related. We have learned that the immune-system is the key to reduce the severity of COVID-19 and, through its modulation, it has been possible saving people's life. In this short communication, we discuss the use of nutraceuticals to modulate and stimulate the immune answer for reducing the severity of COVID-19 symptoms. The nutraceuticals are safe and can be administered to all ages. In addition, combination of natural anti-viral elements and immune-stimulating molecules already successfully tested against others upper-respiratory tract infections-could be efficient against SARS-CoV2. We believe that these natural molecules could really be a valid ally against COVID-19, especially in this moment in which a SARS-CoV2 vaccine is still not available.

*Key Words:*

COVID-19, Immune modulation, Immune stimulation, Oral supplementation.

## Introduction

Several clinical trials have shown that nutraceutical compounds can modulate and stimulate the immune-answer in patients affected by cancer<sup>1</sup>, those who have acquired immune-deficiency<sup>2</sup>, as well as in people who (despite their good health) could be at risk of viral infection<sup>3,4</sup>.

The immune-answer can be stimulated by using a single molecule<sup>5</sup> or a combination of ele-

ments, such as vitamin D, Sambucus Nigra, and tyndallized lactobacillus<sup>4</sup>. The majority of these natural compounds strengthen the immune system, improving the activity of macrophages<sup>6</sup> and leucocytes<sup>7</sup>, modulating the production of inflammatory cytokines<sup>8</sup> and reducing the byproducts of reactive oxygen species (ROS)<sup>9</sup>.

Recently, we have shown<sup>4,10</sup> the benefit of using an oral supplement including tyndallized lactocillus to reduce the severity of upper airways infection (UAI). Probiotics are beneficial for treating UAI<sup>11</sup> because by improving the health of gut microbiota<sup>12</sup> allow the correct absorption of elements in the intestinal tract<sup>13</sup>, a fundamental step for maintaining an efficient immune system<sup>3</sup>.

It has been suggested<sup>14</sup> that nutraceuticals can stimulate the immune system of patients with COVID-19 because they increase the efficiency of the immune system and reduce virus virulence<sup>15,16</sup> by limiting its replication<sup>17</sup>.

Based on our previous positive experiences with natural compounds for treating viral infection of UAI<sup>4,10</sup>, we think that oral supplementation, which improves the systemic and local immune answer, could be a valid tool for improving resistance to COVID-19 infection<sup>15,18-20</sup>.

Furthermore, as shown in previous studies<sup>4,10</sup> some specific compounds might reduce the aggressiveness of SARS-CoV-2 virus as they do with other viruses responsible for UAI.

## Immuno-Stimulating Molecules

Natural elements known as oral supplements (including complex multivitamins, multi-element boosters and probiotics) have shown a strong ability to improve the immune answer in patients suffering from cancer<sup>21</sup> and people with acqui-

red immunodeficiency<sup>22</sup>. Furthermore, vitamin D was able to modulate the immune system of patients with multiple sclerosis by reducing the severity and recurrence of a relapse<sup>23</sup>.

Recent clinical trials have shown<sup>4,24</sup> that by using a combination of these elements, it is possible to reduce the severity and recurrence of viral infection in the upper respiratory tract (URT). A combination of these molecules not only permits the modulation and stimulation of the natural immune answer, but also, thanks to the anti-viral capacity of some of these elements, reduces viral aggressiveness<sup>4,24</sup>.

Although several natural elements might effectively stimulate and modulate the immune system, some of these molecules present anti-viral capacity, which seems more appropriate for fighting COVID-19.

We will specifically describe plant extract, vitamins, trace elements and probiotics, whose properties and efficacy have been widely confirmed in literature.

*Sambucus nigra* (SN) is a plant extract already approved by FDA<sup>25</sup>, which has shown strong abilities to inhibit viral replication of chicken coronavirus at the initial stage<sup>17</sup>. Several clinical trials<sup>26</sup> have shown that SN can be a valid alternative and more appropriate than antibiotic therapy to fight viral and recurrent UAI. SN, as well as inhibiting viral replication<sup>17</sup> increases the production of pro-inflammatory cytokines (IL-1 beta, TNF-alpha, IL-6, IL-8), in particular TNF-a<sup>27,28</sup>. The latter plays a pivotal role in the regulation of inflammatory cytokine production<sup>29</sup> and improves the macrophage answer to viral infection, by explaining the reason why the administration of SN improves the immune answer against different viral infections<sup>30</sup>. SN could be useful in COVID-19 for its dual capacity of stimulating the immune system and inhibiting viral replication.

Vitamins are a strong ally of the immune system but only some of them have been confirmed as really able to improve, modulate and stimulate an efficient immune answer in humans.

Vitamin C is well known for fighting viral infection; it modulates and improves the natural immune answer during acute respiratory distress syndrome<sup>31</sup> thanks to the reduction of circulating ROS<sup>9</sup>, a waste element which at excessive levels reduces the efficiency of the immune system. This vitamin regulates cytokine production, inducing adequate but not excessive immune answer to the viral infection<sup>31</sup>; specifically, it improves chemotaxis, stimulates proliferation of leukocytes and

increases neutrophil phagocytic activity. Furthermore, Ascorbic acid increases production of  $\alpha/\beta$  interferons and downregulates the synthesis of pro-inflammatory cytokines<sup>9</sup>. Based on the qualities of vitamin C, some clinical trials have been conducted to test its efficacy on COVID-19<sup>32</sup>.

Vitamin D has shown the same ability as vitamin C to stimulate and modulate the immune answer. It also promotes differentiation of monocytes/macrophages in their active form, and at the same time, increases the chemotactic and phagocytic capacity of these cells<sup>6</sup>. In addition, cholecalciferol modulates T-cell function<sup>33</sup>, promotes the production of anti-inflammatory IL-10 and decreases the production of pro-inflammatory IL-1 $\beta$ , IL-6, TNF $\alpha$ , RANKL, COX-2, and nitric oxide<sup>34</sup>. Cholecalciferol protects the upper and lower respiratory tract from viral infection thanks to the amelioration of local immune-answer<sup>35,36</sup>; it has been shown that vitamin D deficit exposes people to high risk of developing viral airway infection<sup>37</sup>. Based on the recent evidence<sup>38</sup> on cholecalciferol effects, it has been suggested that oral supplementation with this vitamin might not only reduce the risk of COVID-19 infection, but also reduce the mortality risk in patients affected by Sars-Cov-2.

Interesting studies<sup>5,39</sup> have verified the efficacy of trace elements as supporters of immune function; two elements in particular, zinc and selenium, have been identified as valid tools for fighting viral and bacterial infection.

Zinc improves the capacity of macrophages phagocytosis, of antigen presentation and of signal transmission between these cells and others in the immune-system. In addition, this element reduces the secretion on IL-6 and TNF-a (pro-inflammatory cytokines)<sup>8</sup> which further contributes to improve the immune-answer<sup>40</sup>. The immune stimulating and immunomodulating properties of zinc have been confirmed through clinical trial on patients affected by UAI and treated with oral supplements containing this element. These patients recovered quickly and did not develop any severe form of infection<sup>5</sup>. It has been hypothesized that, based on previous studies, supplementation with zinc could also be useful against COVID-19 infection<sup>41</sup>.

Selenium is a potent immune-stimulant able to improve T-cell proliferation, NK cell activity and several innate immune cell functions<sup>42</sup>. Researchers have demonstrated that selenium implementation empowers the natural immune-answer to flu vaccine<sup>43</sup> and could modulate the inflammatory response in patients suffering from respi-

ratory distress syndrome by moderating the inflammatory responses through interleukin (IL)-1b and IL-6 levels<sup>44</sup>.

Another confirmed method for stimulating and modulating the immune system is the use of probiotics, live microorganisms which live in our gut (intestinal flora) and contribute to preserving health<sup>45</sup>. New-generation probiotic products, including heat-killed (tyndallized) strains, key components, or compounds with similar effects to living probiotic cells are being developed and are already commercialized.

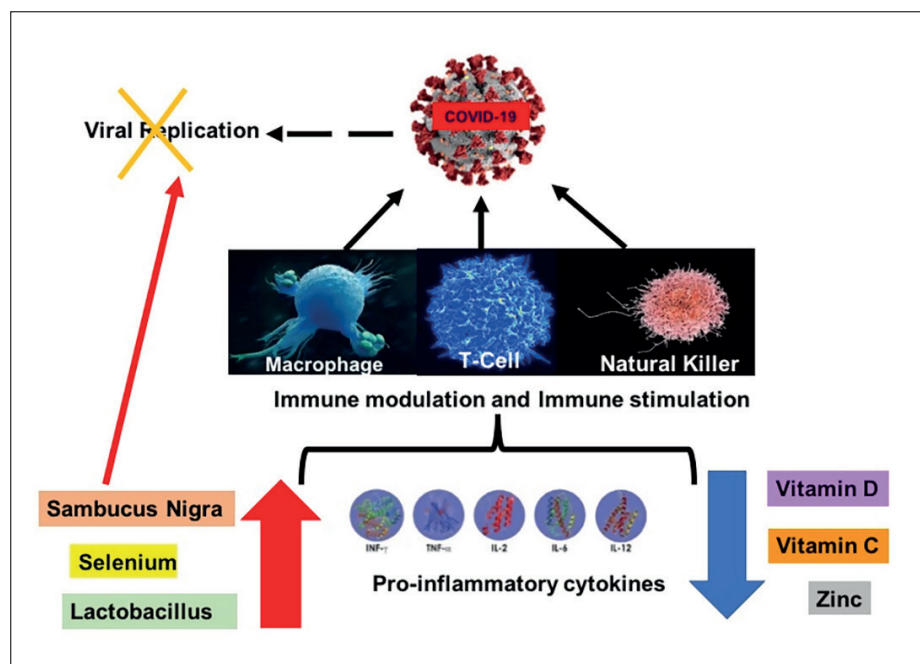
*Lactobacillus* is one of the most widely-used probiotics, because it has shown excellent capacity to enhance the immune response, especially in the case of infection of URT<sup>46</sup>. Clinical trials have shown that the use of *Lactobacillus* reduces the severity of disease and shortens the convalescent period in patients affected by URT infection<sup>46</sup>. This probiotic regulates T-cell activation by preventing an excessive immune-answer against the virus<sup>47</sup>.

Probiotics in general reduce ROS production and induce an early release of proinflammatory cytokines, such as IL-8, TNF- $\alpha$ , IL-12p70, of IL-6 and IL-1 $\beta$  but decrease their circulating levels. In addition, they increase phagocytosis and bactericidal activity of macrophages against various pathogens, such as *S. aureus*, *S. typhimurium*, and *E. coli*. Literature shows that probiotics modulate the activity of macrophages at the beginning of the infection determining an early immune-stimulating effect<sup>48</sup>.

The heat-killed (tyndallized) strains are characterized by different bacterial components and include lipoteichoic acids, peptidoglycans, and/or exopolysaccharides<sup>49</sup>. The presence of key structures in the cell or supernatant fractions confers probiotic properties, mainly through immune-modulation, protection against pathogens, and fortification of the mucosal barrier integrity<sup>13,49</sup>. Pre-treatment with heat-killed *Enterococcus faecalis* significantly reduces the neuropathogenicity induced by another RNA virus, enterovirus 71, demonstrating a reduction in the severity of viral disease and showing that the MCP-1 pathway could act as a key mediator in the best antiviral immune response<sup>17</sup>. The daily intake of heat-killed *Lactobacillus plantarum* L-137 (HK L-137) can improve inflammation and lipid metabolism in subjects at risk of inflammation<sup>50</sup>. Tyndallized *Lactobacillus acidophilus* HA122 has been used in combination with other ingredients and is effective in reducing inflammation of the URT and in improving the outcome of otitis media with effusion (OME) in children<sup>4</sup>.

Considering the positive characteristics of probiotics, the promising studies on tyndallized bacteria and the fact that current diet, stress and aging contribute to a reduction in the normal gut flora with increased risk of infection, the use of probiotics could potentially be considered as adjuvant treatment to support the immune answer against COVID-19.

**Figure 1.** The image summarizes how the different molecules modulate cytokines, white cells and how they interact to stop viral replication and fight Sars-CoV2 infection.



## Conclusions

The concept of training the cells of the immune system is innovative and interesting<sup>51</sup> and we think that oral supplements, thanks to their ability to stimulate and modulate these cells, might help the immune system to produce an appropriate adaptive answer<sup>5-7,27,28,39,47</sup> (Figure 1).

Since most natural elements act directly on immune cells, combining them could provoke a more consistent stimulation<sup>4</sup>. These natural molecules have no collateral effects and can be used for a long time without suspension<sup>4</sup>.

The efficacy of oral immune boost has been largely confirmed by clinical trials, and, as discussed above, has also been shown to be effective at cellular levels

We think that immune stimulant therapy may support the immune system in the case of COVID-19 due to its ability to stimulate the local and systemic immune system, particularly in cases where a URI is present.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

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