Exploring Novel Therapeutic Approaches for COVID-19: Hesperidin vs. Vitamin C

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As of December 2020, over 63 million cases of COVID-19 have been reported globally, causing approximately 1.4 million deaths and a sustained strain on the healthcare system.\textsuperscript{1,2} Since the start of the pandemic, scientists have been investigating new approaches and interventions to combat SARS-CoV-2 – the virus that causes COVID-19.\textsuperscript{3,4}

Substances with a possible beneficial effect in coronavirus infection may interfere in various stages of the SARS-CoV-2 infection process:\textsuperscript{5}

- Preventing viral entry by interfering with the binding of viral S-proteins to human ACE-2 receptors or by inhibiting the function of the ACE-2 receptor
- Inhibiting viral replication by blocking RNA polymerase or proteases (i.e. 3CLpro)
- Helping the host cell resist viral attack
- Blocking the spread of the virus in the body
- Modulating the inflammation when, starting as an innate defensive mechanism, it becomes cytotoxic
The Need for Novel Approaches to SARS-CoV-2

To date, there are no SARS-CoV-2-specific antiviral agents. However, based on the early release of genomic sequence data coupled with protein structure modeling, the scientific community has been able to produce a suggested list of existing drugs with therapeutic potential for COVID-19.

Hesperidin and SARS-CoV-2

Hesperidin has recently attracted the attention of researchers, because it binds to key proteins of SARS-CoV-2. Several computational methods, independently applied by different researchers, showed that hesperidin can bind to the SARS-COV-2 Spike (S) protein and, in doing so, prevent its initial interaction with ACE-2 receptors. This may interfere with viral entry into host cells.

Wu et al (2020) used homology modeling to screen 1066 natural substances with potential antiviral effect, plus 78 antiviral drugs already known in the literature, for their binding to SARS-CoV-2 proteins. Of all these molecules, hesperidin was the only compound that could target the binding interface between viral Spike proteins and ACE-2 human receptors.

Hesperidin can also bind to 3CLpro – the main protease responsible for the cleavage of SARS-CoV-2 peptides into functional units for virus replication and packaging within the host cells. By doing so, it may help against COVID-19 viral replication. In a screening of 1500 potential molecules capable of binding to 3CLpro, hesperidin was the second most efficient for binding to chain A. In comparison, lopinavir and ritonavir showed less binding capacity.

Management of Inflammatory Mediators

Cytokine storm is a major cause of acute respiratory distress syndrome, which is the leading cause of mortality in COVID-19 patients. During a cytokine storm, the body releases various immune-active molecules, such as:
• Interferons (e.g. IFNγ)
• Interleukins (e.g. IL-1β, IL-2, IL-6)
• Chemokines
• Tumor necrosis factor-alpha (TNF-α)

While respiratory distress is the main reason for hospitalization, persistently elevated inflammatory mediators combined with a fever are the indicators for prolonged hospitalization or death. Independent of comorbidities at admission, chronic inflammation may also contribute to impaired quality of life in COVID-19 survivors.

The dysregulation of the immune response can affect the heart, kidneys, brain, and vascular system.

Hesperidin has been found to modulate inflammatory mediators, such as IL-6, IL 1β and TNF-α, in the heart, lungs, and central nervous system of multiple animal models. It may improve the host cellular immunity against infection and its anti-inflammatory activity may help in controlling cytokine storm. Hesperidin is also a potent antioxidant and scavenger of free radicals.

**Vitamin C and SARS-CoV-2**

Vitamin C is also known to be a strong antioxidant, capable of reducing the effects free radicals. However, in the abovementioned screening studies, Vitamin C did not demonstrate affinity to receptors that would interfere with SARS-CoV-2 infectivity. Furthermore, there are conflicting data on the effect of vitamin C to prevent the common cold and other respiratory diseases:

• Many studies on the efficacy of vitamin C in preventing respiratory diseases are inconclusive or negative
• Meta-analyses suggest a consistent and statistically significant benefit of vitamin C for preventing the common cold in people exposed to short periods of stress, intense exercise or in a cold environment
• Studies on animals infected with the flu virus have shown that vitamin C stimulates an antiviral immune response and reduces the lungs’ inflammatory state

In COVID-19, a complementary therapeutic effect of intravenous high doses of vitamin C has been reported and clinical trials are ongoing. However, high doses of ascorbate may also be detrimental.
Clinical Implications

The recently accumulated evidence suggests that hesperidin supplementation may be useful as a prophylactic agent against SARS-CoV-2 infection and as complementary treatment during COVID-disease. Its biological actions may counteract infection by SARS-CoV-2 and modulate the immune system’s response to the disease. Further preclinical, epidemiological, and clinical studies are needed to corroborate this hypothesis.

As new studies are published, clinicians should continue to stay abreast of new evidence for therapies that may help prevent and treat COVID-19.

References


