MDBriefCase

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

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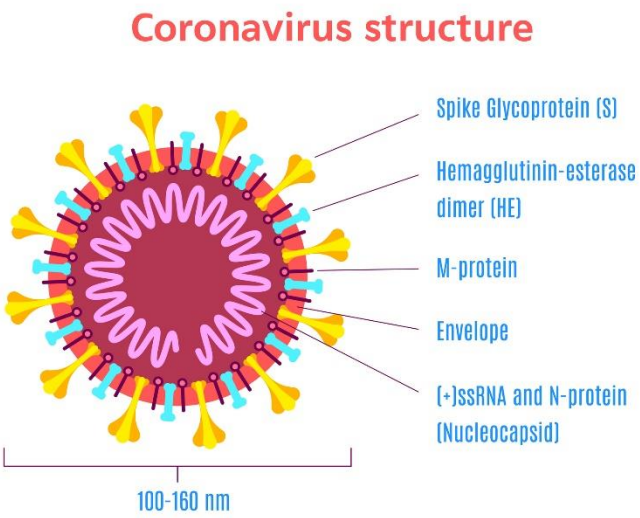
As of December 2020, over 63 million cases of COVID-19 have been reported globally, causing approximately 1.4 million deaths and a sustained strain on the healthcare system.[1,2] Since the start of the pandemic, scientists have been investigating new approaches and interventions to combat **SARS-CoV-2**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

Substances with a possible beneficial effect in coronavirus infection may interfere in various stages of the SARS-CoV-2 infection process:[5]

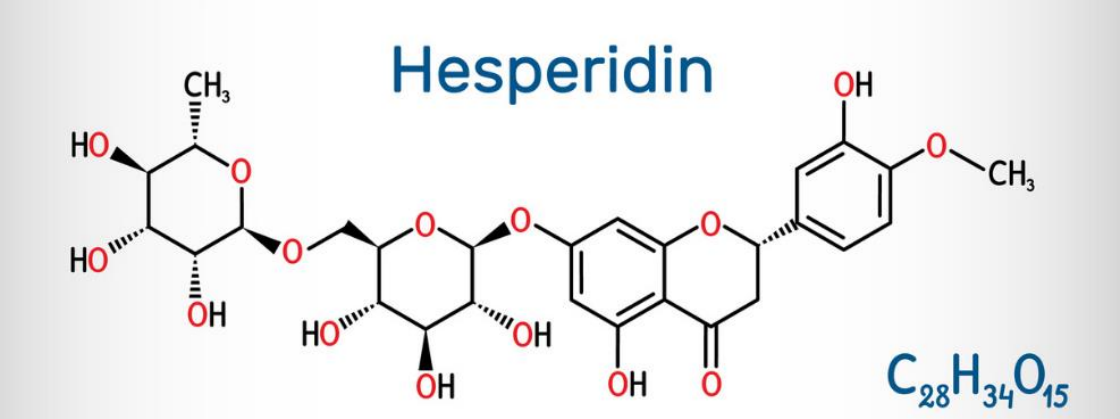
- Preventing viral entry by interfering with the binding of viral S-proteins to human ACE-2 receptors or by inhibiting the function of the ACE-2 receptor
- Inhibiting viral replication by blocking RNA polymerase or proteases (i.e. 3CLpro)
- Helping the host cell resist viral attack
- Blocking the spread 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.[6] 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.[6]

Hesperidin and SARS-CoV-2



Hesperidin has recently attracted the attention of researchers, because it binds to key proteins of SARS-CoV-2.[5] 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.[5,7,8] This may interfere with viral entry into host cells.[7]

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.[8] **Of all these molecules, hesperidin was the only compound that could target the binding interface between viral Spike proteins and ACE-2 human receptors.**[8]

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.[5,6] By doing so, it may help against COVID-19 viral replication.[7] 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.[5]

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.[9] During a cytokine storm, the body releases various immune-active molecules, such as:[7]

- 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.[10] Independent of comorbidities at admission, chronic inflammation may also contribute to impaired quality of life in COVID-19 survivors.[11]

The dysregulation of the immune response can affect the heart, kidneys, brain, and vascular system.[12–14]

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.[15–20] It may improve the host cellular immunity against infection and its anti-inflammatory activity may help in controlling cytokine storm.[7] Hesperidin is also a potent antioxidant and scavenger of free radicals.[5]

Vitamin C and SARS-CoV-2

Vitamin C is also known to be a strong antioxidant, capable of reducing the effects free radicals.[5] However, in the abovementioned screening studies, Vitamin C did not demonstrate affinity to receptors that would interfere with SARS-CoV-2 infectivity.[8] Furthermore, there are conflicting data on the effect of vitamin C to prevent the common cold and other respiratory diseases:[5]

- 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.[5] However, high doses of ascorbate may also be detrimental.[5]

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.[5] Its biological actions may counteract infection by SARS-CoV-2 and modulate the immune system's response to the disease.[5,7,8] Further preclinical, epidemiological, and clinical studies are needed to corroborate this hypothesis.[5]

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

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