

HYPOTHESIS

COVID-19, pulmonary mast cells, cytokine storms, and beneficial actions of luteolin

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Dear Editor

The new coronavirus (severe acute pulmonary syndrome [SARS]-CoV-2) originated in China, where it spread rapidly,¹ and has reached pandemic proportions because of its high rate of infectivity as well as high morbidity and mortality, associated with COVID-19.² This coronavirus infects by first binding to the ectoenzyme angiotensin-converting enzyme 2 (ACE₂),^{3,4} a serine protease acting as the receptor, while another serine protease is necessary for priming the viral “S” protein required for entering the cells.⁵ Defense against the virus apparently does not involve inflammatory cytokines,⁶ but pulmonary infection and its serious sequelae result from the release of multiple chemokines and cytokines that damage the lungs.

A recent report correlated coronaviruses infection with activation of mast cells and subsequent cytokine storms in the lungs.⁷ Mast cells are known to be triggered by viruses.⁸ Mast cells are unique immune cells that are ubiquitous in the body, especially the lungs,⁹ and are critical for allergic and pulmonary diseases,¹⁰ including mastocytosis¹¹ by secreting histamine, leukotrienes, and proteases. Mast cells are also involved in the development of inflammation¹² via release of multiple pro-inflammatory cytokines and chemokines.^{13,14}

Mast cells contain the serine protease ACE₂, which can convert angiotensin I into angiotensin II.¹⁵ In addition to the bronchoconstrictive action of mast cell-derived leukotrienes, mast cells cause further bronchoconstriction via an active renin-angiotensin generating system in the lungs.¹⁶ Moreover, mast cells express a number of serine proteases,¹⁷ especially the mast cell-serine protease tryptase,¹⁸ which are necessary for infection by SARS-

CoV-2. A serine protease inhibitor, camostat mesylate, was recently shown to prevent entry of the virus into the lung cells of SARS-CoV-2-infected patients.¹⁹ It would be important to not only inhibit entry of SARS-CoV-2 but also prevent SARS associated with COVID-19.

The possible use of nonsteroidal anti-inflammatory agents has come into question for possibly aggravating pulmonary symptoms,²⁰ while broad-spectrum immune suppressors, such as corticosteroids,²¹ would not be advisable given that an intact immune system is necessary to fight the infection and it may even lead to increased plasma viral load.²²

Inhibition of mast cell-associated inflammation could be accomplished with natural molecules, especially the polyphenolic flavonoids.²³ The flavone luteolin (not lutein, which is a carotenoid) has been shown to have broad antiviral properties.²⁴⁻²⁶ Luteolin specifically binds to the surface spike protein of SARS-Cov-2 and inhibits entry of the virus into host cells.²⁷ Furthermore, luteolin inhibits serine proteases,²⁸ including the SARS-CoV 3CL protease²⁹ required for viral infectivity.

Moreover, luteolin inhibits mast cells^{30,31} and has anti-inflammatory properties.³² A novel luteolin analogue, tetramethoxyluteolin, is even more potent³² and can also inhibit secretion of the pro-inflammatory cytokines TNF and IL-1 β ,^{33,34} as well as the chemokines CCL2 and CCL5³⁵ from human mast cells.

Effective ways to administer luteolin would be those that overcome the poor oral absorption of flavones,³⁶ as in the available liposomal formulation of luteolin (e.g., PureLut), mixed in olive pomace oil that has additional anti-inflammatory actions of its own.³⁷ The

combination (e.g., FibroProtek) of luteolin (3', 4', 5,7-tetrahydroxyflavone) with the structurally related quercetin (3,3', 4',5,7-pentahydroxyflavonol) would be even more potent because both luteolin and quercetin were recently identified via molecular docking software to have the best potential to act as COVID-19 inhibitors.^{38,39} Moreover, the use of the world's most powerful supercomputer SUMMIT to carry out high-throughput screening for small molecules interacting with the human ACE₂ receptor required for SARS-CoV-2 binding to host cells ranked the luteolin structural analogue eriodictyol (5,7,3',4'-tetrahydroxyflavanone) among the best *potential* inhibitors of COVID-19.⁴⁰ A new dietary supplement to be available soon combines luteolin, quercetin, and eriodictyol (ViralProtek, proprietary formulation, patent pending) to achieve the maximal benefit of these flavonoids.

These flavonoids are generally considered safe^{41,42} and can be used together with acetaminophen,⁴³ but should not exceed a cumulative dose of 1–2 g/day because they can reduce liver metabolism.³⁶ Although these flavonoids can be obtained from different plant sources, it is important to avoid the cheapest source of peanut shells that may affect persons allergic to peanuts, or fava beans, consumption of which could cause hemolytic anemia to Mediterranean extraction persons who lack the enzyme G₆PD. Such patients should also not be administered the antimalarial drugs chloroquine and hydroxychloroquine, which have been advocated based on anecdotal reports for the treatment of COVID-19.⁴⁴

It would be important to study the effect of SARS-CoV-2 directly on human mast cells and epithelial cells, as well as the effect of these flavonoids both on infectivity and on release of pro-inflammatory molecules *in vitro* and *in vivo*.

CONFLICT OF INTEREST

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