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 cells30,31 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-1β,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
combination (e.g., FibroProtek) of luteolin (3’, 4’, 5,7-tetrahydroxyflavone) with the structurally related quercetin (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.\textsuperscript{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 ACE\textsubscript{2} receptor required for SARS-CoV-2 binding to host cells ranked the luteolin structural analogue eriodictyol (5,7,3’-tor required for SARS-CoV-2 binding to host cells ranked the enzyme G6PD. Such patients should also not be lytic anemia to Mediterranean extraction persons who peanut shells that may affect persons allergic to peanuts, sources, it is important to avoid the cheapest source of quercetin (3,3’, 5,7-tetrahydroxyflavone) with the structurally related and other flavonoid-containing dietary supplements. The author is the Scientific Director of and shareholder CONFLICT OF INTEREST The author is the Scientific Director of and shareholder in Algonot, LLC (Sarasota, FL), which markets PureLut and other flavonoid-containing dietary supplements.

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**REFERENCES**


