Received: 6 April 2020 | Accepted: 7 April 2020

DOI: 10.1002/biof.1633

Check for updates

HYPOTHESIS

Biofactors WILEY

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

Theoharis C. Theoharides[1,2,3]

[1]Laboratory of Molecular Immunopharmacology and Drug Discovery, Department of Immunology, Tufts University School of Medicine, Boston, MA

[2]School of Graduate Biomedical Sciences, Tufts University School of Medicine, Boston, Massachusetts

[3]Department of Internal Medicine, Tufts University School of Medicine and Tufts Medical Center, Boston, Massachusetts

Correspondence

Theoharis C. Theoharides, Department of Immunology, Tufts University School of Medicine, 136 Harrison Avenue, Suite 304, Boston, MA 02111.

Email: theoharis.theoharides@tufts.edu

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 (ACE_2),[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 mastocytosis[11] by secreting histamine, leukotrienes, and proteases. Mast cells are also involved in the development of inflammation[12] via release of multiple pro-inflammatory cytokines and chemokines.[13,14]

Mast cells contain the serine protease ACE_2, 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 protease[29] 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 potent[32] and can also inhibit secretion of the pro-inflammatory cytokines TNF and IL-1β,[33,34] as well as the chemokines CCL2 and CCL5[35] 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

 © 2020 International Union of Biochemistry and Molecular Biology

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 ACE_2 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 G_6PD. 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

The author is the Scientific Director of and shareholder in Algonot, LLC (Sarasota, FL), which markets PureLut and other flavonoid-containing dietary supplements.

ORCID

Theoharis C. Theoharides https://orcid.org/0000-0002-1598-460X

REFERENCES

1. Guan WJ, Ni ZY, Hu Y, et al. China medical treatment expert group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020. https://doi.org/10.1056/NEJMoa2002032.
2. Poon LLM, Peiris M. Emergence of a novel human coronavirus threatening human health. Nat Med. 2020;26(3):317–319.
3. Tai W, He L, Zhang X, et al. Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: Implication for development of RBD protein as a viral attachment inhibitor and vaccine. Cell Mol Immunol. 2020. https://doi.org/10.1038/s41423-020-0400-4.
4. Liu Z, Xiao X, Wei X, et al. Composition and divergence of coronavirus spike proteins and host ACE2 receptors predict potential intermediate hosts of SARS-CoV-2. J Med Virol. 2020;26.
5. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020.
6. Thevarajan I, Nguyen THO, Koutsakos M, et al. Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19. Nat Med. 2020. https://doi.org/10.1038/s41591-020-0819-2.
7. Kritas SK, Ronconi G, Caraffa A, et al. Mast cells contribute to coronavirus-induced inflammation: New anti-inflammatory strategy. J Biol Regul Homeost Agents. 2020;34(1).
8. Marshall JS, Portales-Cervantes L, Leong E. Mast cell responses to viruses and pathogen products. Int J Mol Sci. 2019;20(17):4241.
9. Gurish MF, Austen KF. Developmental origin and functional specialization of mast cell subsets. Immunity. 2012;37(1):25–33.
10. Olivera A, Beaven MA, Metcalfe DD. Mast cells signal their importance in health and disease. J Allergy Clin Immunol. 2018;142(2):381–393.
11. Theoharides TC, Valent P, Akin C. Mast cells, mastocytosis, and related disorders. N Engl J Med. 2015;373(2):163–172.
12. Theoharides TC, Alysandratos KD, Angelidou A, et al. Mast cells and inflammation. Biochim Biophys Acta. 2012;1822(1):21–33.
13. Mukai K, Tsai M, Saito H, Galli SJ. Mast cells as sources of cytokines, chemokines, and growth factors. Immunol Rev. 2018;282(1):121–150.
14. Gallenga CE, Pandolfi F, Caraffa AL, et al. Interleukin-1 family cytokines and mast cells: Activation and inhibition. J Biol Regul Homeost Agents. 2019;33(1):1–6.
15. Caughey GH, Raymond WW, Wolters PJ. Angiotensin II generation by mast cell alpha- and beta-chymases. Biochim Biophys Acta. 2000;1480(1–2):245–257.
16. Veerappan A, Reid AC, Estephan R, et al. Mast cell renin and a local renin-angiotensin system in the airway: Role in bronchoconstriction. Proc Natl Acad Sci U S A. 2008;105(4):1315–1320.
17. Miller HRP, Pemberton AD. Tissue-specific expression of mast cell granule serine proteinases and their role in inflammation in the lung and gut. Immunology. 2002;105(4):375–390.
18. Schwartz LB. Tryptase: A mast cell serine protease. Methods Enzymol. 1994;244:88–100.
19. Martinez MA. Compounds with therapeutic potential against novel respiratory 2019 coronavirus. Antimicrob Agents Chemother. 2020;9.
20. Day M. Covid-19: Ibuprofen should not be used for managing symptoms, say doctors and scientists. BMJ. 2020;17:368.
21. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet. 2020;395(10223):473–475.
22. Lee N, Allen Chan KC, Hui DS, et al. Effects of early corticosteroid treatment on plasma SARS-associated coronavirus RNA concentrations in adult patients. J Clin Virol. 2004;31(4):304–309.

23. Middleton E Jr, Kandaswami C, Theoharides TC. The effects of plant flavonoids on mammalian cells: Implications for inflammation, heart disease, and cancer. Pharmacol Rev. 2000;52(4): 673–751.
24. Yan H, Ma L, Wang H, et al. Luteolin decreases the yield of influenza a virus in vitro by interfering with the coat protein I complex expression. J Nat Med. 2019;73(3):487–496.
25. Fan W, Qian S, Qian P, Li X. Antiviral activity of luteolin against Japanese encephalitis virus. Virus Res. 2016;220: 112–116.
26. Xu L, Su W, Jin J, et al. Identification of luteolin as enterovirus 71 and coxsackievirus A16 inhibitors through reporter viruses and cell viability-based screening. Viruses. 2014;6(7):2778–2795.
27. Yi L, Li Z, Yuan K, et al. Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells. J Virol. 2004;78(20):11334–11339.
28. Xue G, Gong L, Yuan C, et al. A structural mechanism of flavonoids in inhibiting serine proteases. Food Funct. 2017;8(7): 2437–2443.
29. Jo S, Kim S, Shin DH, Kim MS. Inhibition of SARS-CoV 3CL protease by flavonoids. J Enzyme Inhib Med Chem. 2020;35(1): 145–151.
30. Seelinger G, Merfort I, Schempp CM. Anti-oxidant, anti-inflammatory and anti-allergic activities of luteolin. Planta Med. 2008;74(14):1667–1677.
31. Weng Z, Patel AB, Panagiotidou S, Theoharides TC. The novel flavone tetramethoxyluteolin is a potent inhibitor of human mast cells. J Allergy Clin Immunol. 2015;135(4):1044–52.e5.
32. Patel AB, Theoharides TC. Methoxyluteolin inhibits neuropeptide-stimulated proinflammatory mediator release via mTOR activation from human mast cells. J Pharmacol Exp Ther. 2017;361(3):462–471.
33. Taracanova A, Alevizos M, Karagkouni A, et al. SP and IL-33 together markedly enhance TNF synthesis and secretion from human mast cells mediated by the interaction of their receptors. Proc Natl Acad Sci U S A. 2017;114(20):E4002–E4009.
34. Taracanova A, Tsilioni I, Conti P, Norwitz ER, Leeman SE, Theoharides TC. Substance P and IL-33 administered together stimulate a marked secretion of IL-1β from human mast cells, inhibited by methoxyluteolin. Proc Natl Acad Sci U S A. 2018; 115(40):E9381–E9390.
35. Bawazeer MA, Theoharides TC. IL-33 stimulates human mast cell release of CCL5 and CCL2 via MAPK and NF-κB, inhibited by methoxyluteolin. Eur J Pharmacol. 2019;865:172760.
36. Ross JA, Kasum CM. Dietary flavonoids: Bioavailability, metabolic effects, and safety. Annu Rev Nutr. 2002;22:19–34.
37. Marquez-Martin A, de la Puerta R, Fernandez-Arche A, et al. Modulation of cytokine secretion by pentacyclic triterpenes from olive pomace oil in human mononuclear cells. Cytokine. 2006;36(5–6):211–217.
38. Khaerunnisa S, Kurniawan H, Awaluddin R, Suhartati S, Soetjipto S. Potential inhibitor of COVID-19 main protease (M^{pro}) from several medicinal plant compounds by molecular docking study. Preprints. 2020;2020030226. https://doi.org/10.20944/preprints202003.0226.v1.
39. Ton AT, Gentile F, Hsing M, Ban F, Cherkasov A. Rapid identification of potential inhibitors of SARS-CoV-2 main protease by deep docking of 1.3 billion compounds. Mol Inform. 2020. https://doi.org/10.1002/minf.202000028.
40. Smith M, Smith JC. Repurposing therapeutics for COVID-19: Supercomputer-based docking to the SARS-CoV-2 viral spike protein and viral spike protein-human ACE2 interface. ChemRxiv. 2020. https://doi.org/10.26434/chemrxiv.11871402.v3.
41. Okamoto T. Safety of quercetin for clinical application (review). Int J Mol Med. 2005;16(2):275–278.
42. Harwood M, Danielewska-Nikiel B, Borzelleca JF, Flamm GW, Williams GM, Lines TC. A critical review of the data related to the safety of quercetin and lack of evidence of in vivo toxicity, including lack of genotoxic/carcinogenic properties. Food Chem Toxicol. 2007;45 (11):2179–2205.
43. Cao L, Kwara A, Greenblatt DJ. Metabolic interactions between acetaminophen (paracetamol) and two flavonoids, luteolin and quercetin, through in-vitro inhibition studies. J Pharm Pharmacol. 2017;69(12):1762–1772.
44. Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einav S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. J Crit Care. 2020. https://doi.org/10.1016/j.jcrc.2020.03.005.

How to cite this article: Theoharides TC. COVID-19, pulmonary mast cells, cytokine storms, and beneficial actions of luteolin. *BioFactors*. 2020; 1–3. https://doi.org/10.1002/biof.1633