PART B - Hesperidin is anticipated to:

III. Hesperidin anticipated interferences/inhibitions mechanisms of SARS-CoV-2

The scientific and medical rationales for the use of hesperidin in the HesperCo trial are derived from combined scientific literature reviews of reported interactions/therapeutic contributions of hesperidin. As such, hesperidin was reported to interfere with SARS-CoV/SARS-CoV-2 and their intrinsic structures such as Spike(S) protein and 3CLpro. Hesperidin was also reported to downregulate the majority of the same pro-inflammatory cytokine storm and cardiopulmonary diseases biomarkers afflicting COVID-19 patients. Furthermore, hesperidin demonstrated cognitive improvements in animal models that could lead to clinical benefits to COVID-19 patients with neurological consequences of the diseases. The extensive evidences of potential benefits in COVID-19 were compiled and lead to the development of the HesperCo clinical program.

To date there are no treatments, vaccines or effective drug that can be used to prevent the entry and replication of SARS-CoV-2 in COVID-19 patient via an understood inhibitory mechanism. Designing pharmaceutical interventions where a host is infected/immunized with a live and virulent virus can be divided into two categories: interventions that act on the human immune system/human cells or inhibition the virus itself. Hesperidin initially became a drug candidate for a clinical trial in COVID-19 patients as it was reported to directly inhibit 2 key components of the SARS-CoV family, namely Spike(S) protein and 3CLpro. While hesperidin was isolated almost 2 centuries ago[104], the hesperidin containing Chenpi, believed to regulates ch'i (气), has been used as a common ingredient in traditional Chinese medicine for more than 10 centuries[105]. Zhang Zi-he, the famous 12th century physician of the Song Dynasty has reported the properties of Chenpi as "Chen Pi is up bearing and floating, goes to the lungs and spleen, influences the upper (part) and frees the flow."[106]. To this day, Chenpi is extracted from tangerine peel and once aged, can sell up to 4500$/kg CAN for the more refined versions. As such, hesperidin and its versatile therapeutic benefits have been demonstrated through a plethora of clinical trials and animal models over the years as PubMed.gov tabulated over 2200 publications when hesperidin is the search word.

Hesper**idin** is a member of the flavonoid family and is composed of an aglycone moiety, hesper**etin** and a sugar moiety, rutinose, itself a disaccharide, made from L-rhamnosyl and D-glucose (Figure 13)[107]. Hesperidin can be isolated along with another flavonoid Naringin mainly from the albedo part that sits between the endocarp and exocarp of citrus sinensis (the fruit orange). Hesperidin is also present in significant amount in commercial orange juice[108].

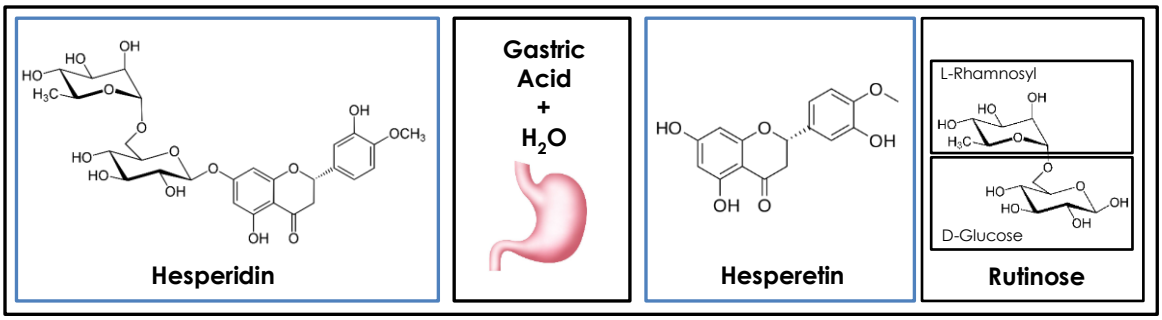

Figure 13: Structure of the flavonoid hesperidin and its aglycone hesperetin.

The scientific literature review started to focus on hesperidin as it was reported that its aglycone hesperetin directly inhibited the 3CLpro (Mpro) of SARS-CoV (2002) hence preventing possible production (replication) of virion with an IC_{50} of 8.3uM[109] and a selectivity index ~300[110].

There has been close to 300 publications with hesperidin as a key word in the last 18 months alone with over 1/3 of them published since the SARS-COV-2 outbreak in Wuhan China. Tabulation of publications regarding hesperidin cannot fully encapsulate recent literature regarding COVID-19 due to the exceptional nature of the pandemic and the speed at which publications are placed on the internet allowing scientists/medical corps to read them.

Within this massive influx of scientific/medical publications focused around SARS-COV-2 and COVID-19, computational modelling publications were the first to confirm hesperidin' potential as an inhibitor of SARS-COV-2 3CLpro[111] (Figure 13). 5 publications have now been tabulated, each confirming the replication inhibition potential[112-116]. Due to its highly conserved sequence across the SARS-CoV family, 3CLpro is an attractive therapeutic target dubbed "the Achilles' heel of coronavirus"[117].

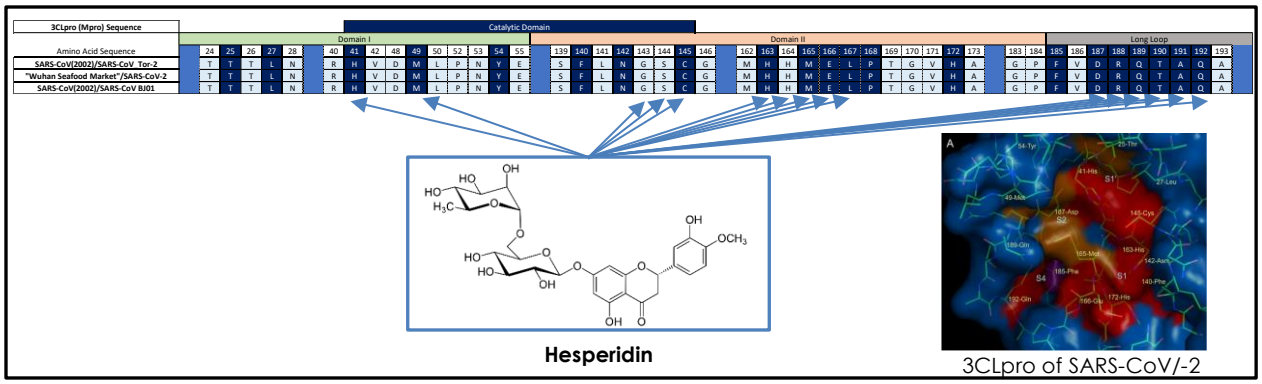

Figure 14: Representation of how hesperidin binds to SARS-CoV-2' 3CLpro catalytic site leading to prevention of viral replication

Furthermore, computational modelling publications demonstrated that hesperidin could binds the RBD of Spike(S) protein from SARS-COV-2 and, in doing so, prevent its initial interaction with ACE2 receptors ultimately leading to a prevention of entry by SARS-CoV-2[116](Figure 15).

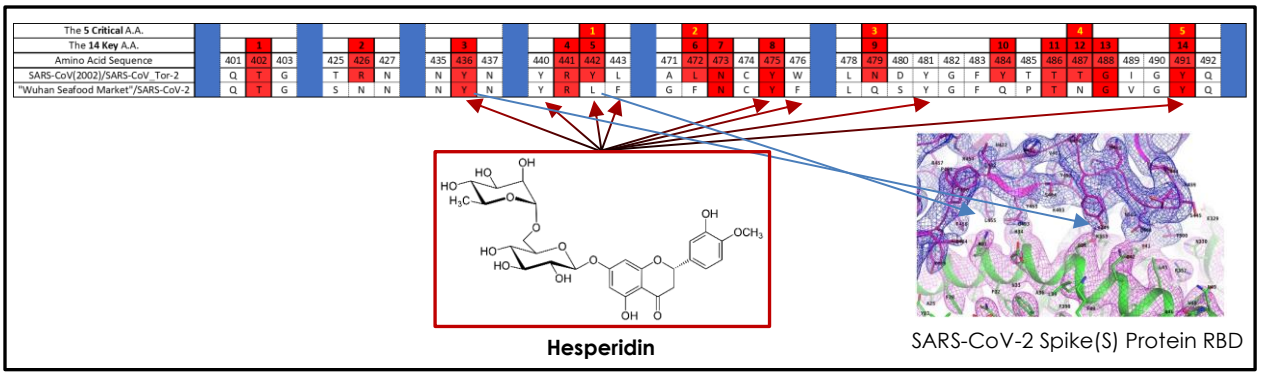

Figure15: Representation of how hesperidin binds to the region binding domain (RBD) of Spike(S) protein from SARS-CoV-2 leading to prevention of viral entry into cells expressing ACE2 receptors on their surfaces

IV. Hesperidin anticipated assistance to the immune system of COVID-19 patients

The suggested interfering/inhibiting of Spike(S) protein and 3CLpro of SARS-CoV-2 could lead to a positive decrease of its viral kinetics and *de facto* dynamics (Figure 16)[118] during the COVID-19 patient' most vulnerable period of infection/immunization, the lag time phase of the immune response. As such, hesperidin could provide the infected host a short (14 days) but key window of immunomodulation to allow development of the host natural immunity culminating with the primary immunoglobulin (IGg) response against SARS-COV-2 (Figure 17)

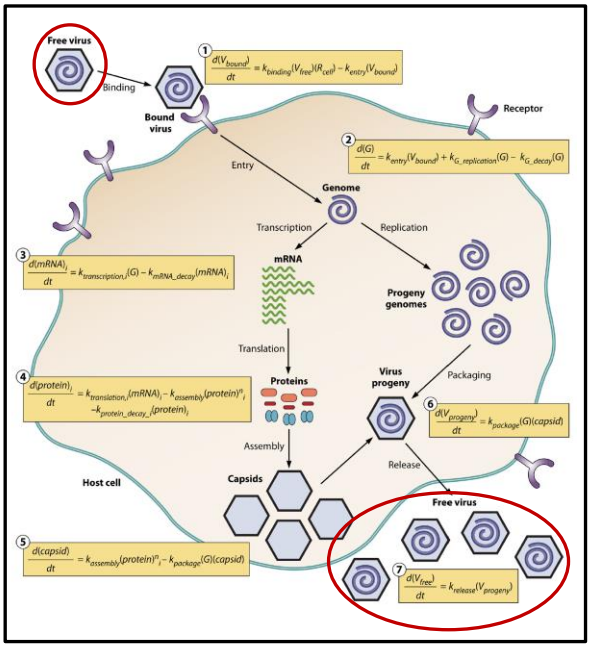

Figure 16: SARS-CoV-2 viral kinetics. Each step of reproduction can be described by a differential equation; (1) Binding, (2) Entry, (3) Transcription, (4) Translation. (5) Assembly, (6) Encapsidation and (7) Release. By interfering/inhibiting binding (Spike (S) protein) AND translation (3CLpro) hesperidin will impact or stop the kinetics leading to either a reduction or complete inhibition of the replication process.

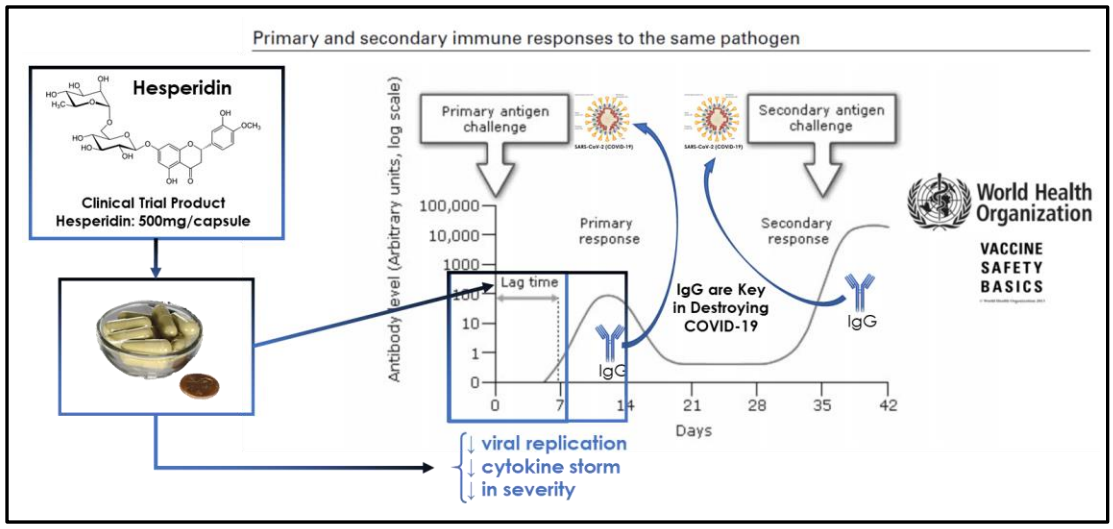

Figure17: The lag time phase of the immune response. hesperidin could provide the infected host a short (14 days) but key window of immunomodulation to allow development of the host natural immunity (primary response).

What makes hesperidin the ideal clinical candidate for the HesperCo clinical trial is its potential for not only prevent entry and replication of SARS-COV-2 but, should the immunization be already initiated, hesperidin can continues to have an active and quite substantial role by addressing the sequelae generated by SARS-COV-2.

V. Hesperidin anticipated decrease of cytokine storm, cardiopulmonary injuries and severity of COVID-19

The broad therapeutic potential of hesperidin exhibited in animal models was comprehensively reviewed recently[119]. Segments addressing hesperidin role in downregulating key pro-inflammatory cytokines such as TNFa, IL-1β, IL-6, NFκB and ERK1/2 (Map2K1), were compiled and combined to a detailed representation of the biochemical paths and processes occurring in a cytokine storm. Interestingly, the anticipated benefits of hesperidin for COVID-19 patients would be independent of disease stratification (Figure 18)[119,120].

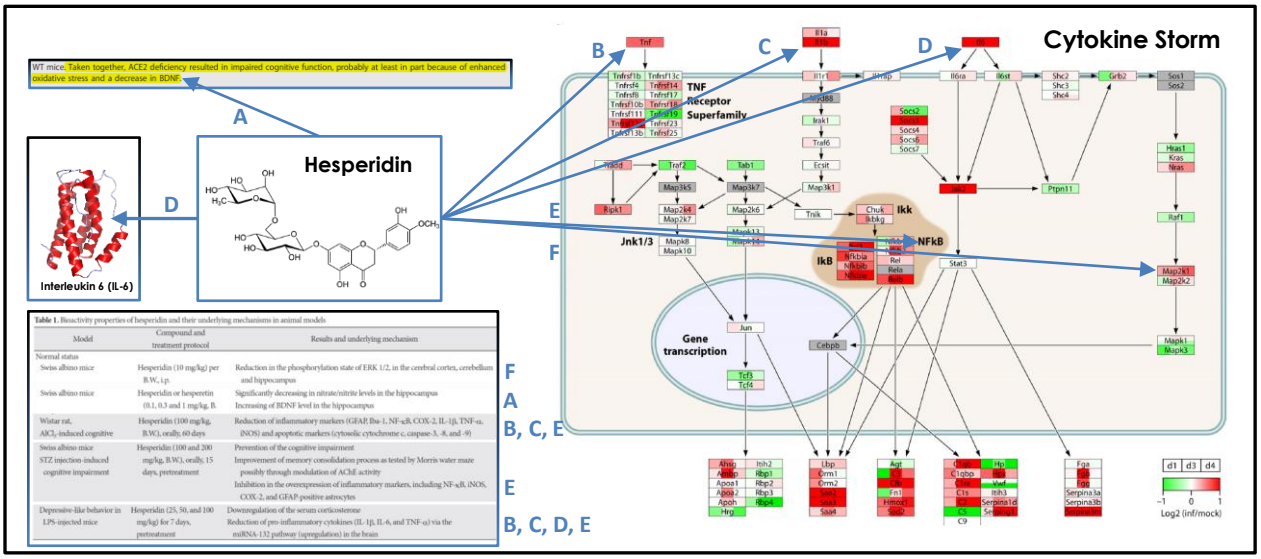

Figure18: Example of some cytokine storm biomarkers downregulated by hesperidin. The downregulation of pro-inflammatory cytokines and chemokines by hesperidin will benefit COVID-19 patients by reducing the symptoms of the infection.

As presented in section III, neurotropic and pulmonary infection by SARS-COV-2 renders the cardiopulmonary system highly susceptible to dysregulations. As a result of intense cytokine storm and severe infection, hospitalized patients with/without a history of CVD can present with dyspnea and/or acute lung injury(ALI) related to mechanical ventilator assistance or not[55,121].

Hesperidin attenuated induced lung injury in an influenza A virus (H1N1) rodent model through its anti-inflammatory effects. The pulmonary function of rats were significantly impaired, showing increased of the alveolar-arterial oxygen tension difference (P(A-a)O_2) and decreased of the oxygenation index (PaO_2/FiO_2) after a 5 day infection with H1N1. The group treated with hesperidin showed that the decreased pulmonary function was reversed in a dose-dependent manner, suggesting that, at a suitable dose, hesperidin was able to mitigate H1N1-induced lung impairment. Furthermore, Hesperidin attenuated local inflammation by inhibiting immune cell recruitment and cytokine release of pro-inflammatory cytokines including TNF-a, IFN-a, and IL-6. By decreasing the levels of those key biomarkers, Hesperidin could protect against lung injury by decreasing cytokine release from pulmonary microvascular endothelial cell (Figure 19)[122].

As presented in section II, neurotropic and potential systemic infection by SARS-COV-2 renders the cardiopulmonary system highly susceptible to dysregulations. When COVID-

19 patients require hospitalization to treat their infection, lungs and heart typically become key organs to establish severity and preferred treatment algorithm considering a *de facto* diagnosis of COVID-19. Hospitalized patients with/without a history of CVD suffer from the infection with dyspnea and ALI which result in intense cytokine storm with or without HF. Beyond the benefits vis a vis cytokine storm presented previously, hesperidin provided key benefits in an acute myocardial infarct animal model by reducing the size of the infarct in a dose dependent fashion in addition to downregulating key pro-inflammatory makers such as Il-6, CCL2 (MCP-1) and IL-1β (Figure 20)[123].

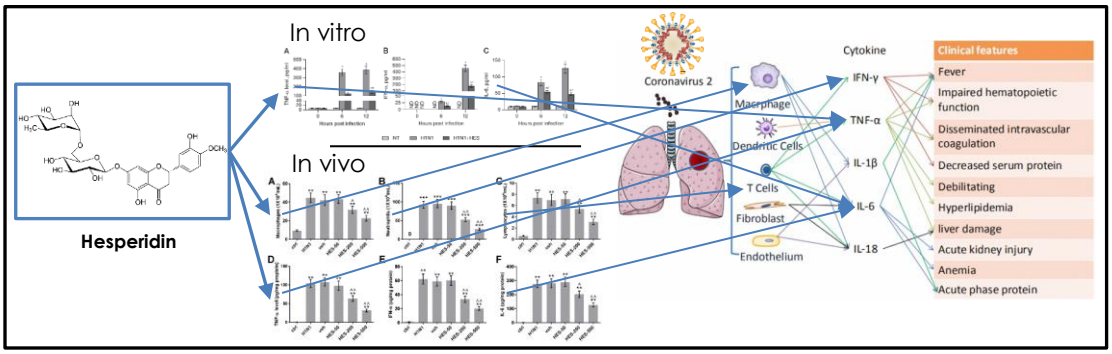

Figure 19: Hesperidin attenuated local inflammation by inhibiting immune cell recruitment and cytokine release of pro-inflammatory cytokines including TNF-a, IFN-a, and IL-6. During in vivo studies, hesperidin was reported as decreasing macrophages, neutrophils and lymphocytes.

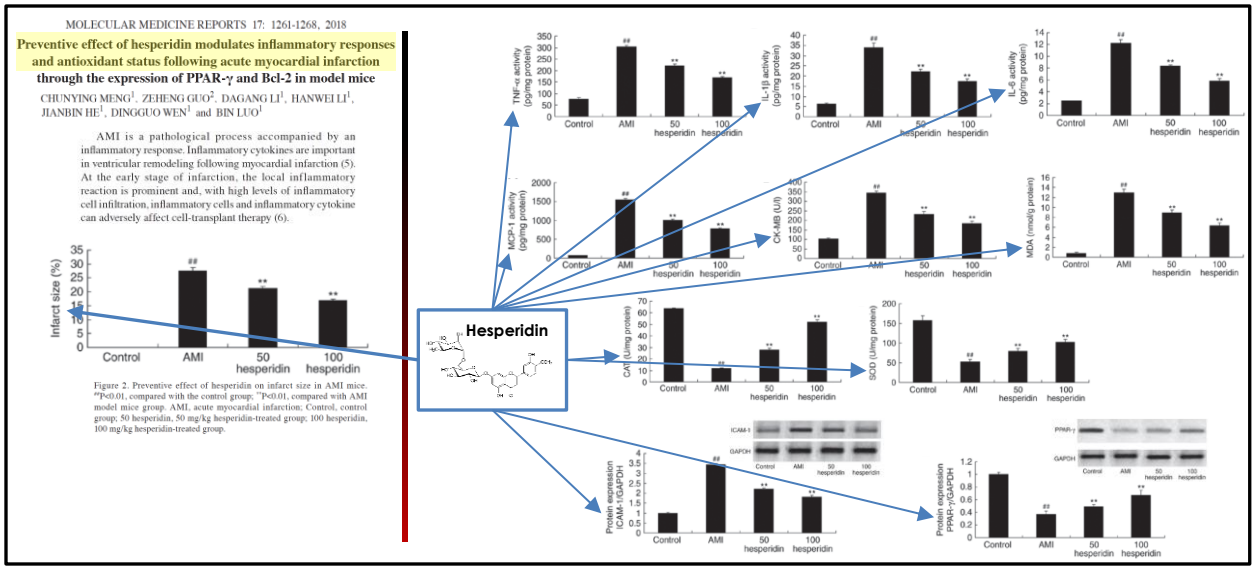

Figure20: Preventive effects of hesperidin in an AMI animal model. Hesperidin can modulate the inflammatory response created by the myocardial infarct model ultimately leading to a decrease of the infarct size.

VI. Bibliography (Additional references could be provided if requested)

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet.* 2020; 395 (10223): 497-506. https://doi.org/10.1016/s0140-6736(20)30183-5.
2. Chan JF-W, Yuan S, Kok K-H, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *The Lancet.* 2020; 395 (10223): 514-523. https://doi.org/10.1016/s0140-6736(20)30154-9.
3. Gralinski LE, Menachery VD. Return of the Coronavirus: 2019-nCoV. *Viruses.* 2020; 12 (2). https://doi.org/10.3390/v12020135. https://www.ncbi.nlm.nih.gov/pubmed/31991541.
4. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. *Nature.* 2020; 579 (7798): 265-269. https://doi.org/10.1038/s41586-020-2008-3. https://www.ncbi.nlm.nih.gov/pubmed/32015508.
5. Wu F, Zhao S, Yu B, et al. Complete genome characterisation of a novel coronavirus associated with severe human respiratory disease in Wuhan, China. 2020;10.1101/2020.01.24.919183. https://doi.org/10.1101/2020.01.24.919183.
6. WHO. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). 2020. https://www.who.int/publications-detail/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-(covid-19). https://www.who.int/publications-detail/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-(covid-19).
7. Zhao S, Lin Q, Ran J, et al. Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: A data-driven analysis in the early phase of the outbreak. *Int J Infect Dis.* 2020; 92: 214-217. https://doi.org/10.1016/j.ijid.2020.01.050. https://www.ncbi.nlm.nih.gov/pubmed/32007643.
8. Ashour HM, Elkhatib WF, Rahman MM, Elshabrawy HA. Insights into the Recent 2019 Novel Coronavirus (SARS-CoV-2) in Light of Past Human Coronavirus Outbreaks. *Pathogens.* 2020; 9 (3). https://doi.org/10.3390/pathogens9030186. https://www.ncbi.nlm.nih.gov/pubmed/32143502.
9. Chan JF, Kok KH, Zhu Z, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerg Microbes Infect.* 2020; 9 (1): 221-236. https://doi.org/10.1080/22221751.2020.1719902. https://www.ncbi.nlm.nih.gov/pubmed/31987001.
10. Naicker S, Yang CW, Hwang SJ, Liu BC, Chen JH, Jha V. The Novel Coronavirus 2019 epidemic and kidneys. *Kidney Int.* 2020; 97 (5): 824-828. https://doi.org/10.1016/j.kint.2020.03.001. https://www.ncbi.nlm.nih.gov/pubmed/32204907.
11. Perlman S, Dandekar AA. Immunopathogenesis of coronavirus infections: implications for SARS. *Nat Rev Immunol.* 2005; 5 (12): 917-927. https://doi.org/10.1038/nri1732. https://www.ncbi.nlm.nih.gov/pubmed/16322745.
12. Peiris JS YK, Osterhaus AD, Stöhr K. The Severe Acute Respiratory Syndrome. *N Engl J Med.* 2003; 349: 2431-2441. https://doi.org/10.1056/NEJMra032498. https://www.nejm.org/doi/pdf/10.1056/NEJMra032498?articleTools=true.

13. Peiris JS, Guan Y, Yuen KY. Severe acute respiratory syndrome. *Nat Med.* 2004; 10 (12 Suppl): S88-97. https://doi.org/10.1038/nm1143. https://www.ncbi.nlm.nih.gov/pubmed/15577937.
14. Huang X, Pearce R, Zhang Y. Modeling of the SARS-COV-2 Genome using I-TASSER. 2020. https://zhanglab.ccmb.med.umich.edu/COVID-19/. https://zhanglab.ccmb.med.umich.edu/COVID-19/.
15. Lan J, Ge J, Yu J, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature.* 2020;10.1038/s41586-020-2180-5. https://doi.org/10.1038/s41586-020-2180-5. https://www.ncbi.nlm.nih.gov/pubmed/32225176.
16. Shang J, Ye G, Shi K, et al. Structural basis of receptor recognition by SARS-CoV-2. *Nature.* 2020;10.1038/s41586-020-2179-y. https://doi.org/10.1038/s41586-020-2179-y. https://www.ncbi.nlm.nih.gov/pubmed/32225175.
17. Towler P, Staker B, Prasad SG, et al. ACE2 X-ray structures reveal a large hinge-bending motion important for inhibitor binding and catalysis. *J Biol Chem.* 2004; 279 (17): 17996-18007. https://doi.org/10.1074/jbc.M311191200. https://www.ncbi.nlm.nih.gov/pubmed/14754895.
18. 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; 181 (2): 271-280 e278. https://doi.org/10.1016/j.cell.2020.02.052. https://www.ncbi.nlm.nih.gov/pubmed/32142651.
19. Heurich A, Hofmann-Winkler H, Gierer S, Liepold T, Jahn O, Pohlmann S. TMPRSS2 and ADAM17 cleave ACE2 differentially and only proteolysis by TMPRSS2 augments entry driven by the severe acute respiratory syndrome coronavirus spike protein. *J Virol.* 2014; 88 (2): 1293-1307. https://doi.org/10.1128/JVI.02202-13. https://www.ncbi.nlm.nih.gov/pubmed/24227843.
20. (2014) Bcs. Medical gallery of Blausen Medical 2014. *WikiJournal of Medicine.* 2014; 1 (2). https://doi.org/10.15347/wjm/2014.010. https://commons.wikimedia.org/wiki/File:Blausen_0750_PseudostratifiedCiliatedColumnar.png.
21. Nicholls J. PL, Peiris M. Electon Microscopy of 2019 nCOV. *The University of Hong Kong; LKS Faculty of Medicine, and Electron Microscopy Unit.* 2020.
22. H. F. File_Respiratory Tract Histological Differences.png - Wikimedia Commons.pdf. 2013. https://commons.wikimedia.org/wiki/File:Respiratory_Tract_Histological_Differences.png. https://commons.wikimedia.org/wiki/File:Respiratory_Tract_Histological_Differences.png.
23. Nowak M.A. NM, May R.M.,. Virus Dynamics: Mathematical Principles of Immunology and Virology. 2000. https://books.google.ca/books?id=Kixhc3IiCy4C&dq=virus+dynamics&source=gbs_navlinks_s. 237. https://books.google.ca/books?id=Kixhc3IiCy4C&dq=virus+dynamics&source=gbs_navlinks_s.
24. Imai-Matsushima A, Martin-Sancho L, Karlas A, et al. Long-Term Culture of Distal Airway Epithelial Cells Allows Differentiation Towards Alveolar Epithelial Cells Suited for Influenza Virus Studies. *EBioMedicine.* 2018; 33: 230-241. https://doi.org/10.1016/j.ebiom.2018.05.032. https://www.ncbi.nlm.nih.gov/pubmed/29937069.

25. Mossel EC, Wang J, Jeffers S, et al. SARS-CoV replicates in primary human alveolar type II cell cultures but not in type I-like cells. *Virology*. 2008; 372 (1): 127-135. https://doi.org/10.1016/j.virol.2007.09.045. https://www.ncbi.nlm.nih.gov/pubmed/18022664.
26. Song F, Shi N, Shan F, et al. Emerging 2019 Novel Coronavirus (2019-nCoV) Pneumonia. *Radiology*. 2020; 295 (1): 210-217. https://doi.org/10.1148/radiol.2020200274. https://www.ncbi.nlm.nih.gov/pubmed/32027573.
27. Wang Y. DC, Hu Y.,. Temporal Changes of CT Findings in 90 Patients with COVID-19 Pneumonia: A Longitudinal Study. *Radiology*. 2020;doi.org/10.1148/radiol.2020200843. https://doi.org/doi.org/10.1148/radiol.2020200843. https://pubs.rsna.org/doi/full/10.1148/radiol.2020200843.
28. Marini JJ, Gattinoni L. Management of COVID-19 Respiratory Distress. *JAMA*. 2020;10.1001/jama.2020.6825. https://doi.org/10.1001/jama.2020.6825. https://www.ncbi.nlm.nih.gov/pubmed/32329799.
29. Dominguez MC, Alvares BR. Pulmonary atelectasis in newborns with clinically treatable diseases who are on mechanical ventilation: clinical and radiological aspects. *Radiol Bras.* 2018; 51 (1): 20-25. https://doi.org/10.1590/0100-3984.2016.0157. https://www.ncbi.nlm.nih.gov/pubmed/29559762.
30. Moslehi MA. Bronchoscopic surfactant administration in premature neonate with persistent lobar atelectasis: the new concept. *J Matern Fetal Neonatal Med*. 2019;10.1080/14767058.2019.1680628: 1-3. https://doi.org/10.1080/14767058.2019.1680628. https://www.ncbi.nlm.nih.gov/pubmed/31635505.
31. Lang ZW, Zhang LJ, Zhang SJ, et al. A clinicopathological study of three cases of severe acute respiratory syndrome (SARS). *Pathology*. 2003; 35 (6): 526-531. https://doi.org/10.1080/00313020310001619118. https://www.ncbi.nlm.nih.gov/pubmed/14660106.
32. Pernazza A, Mancini M, Rullo E, et al. Early histologic findings of pulmonary SARS-CoV-2 infection detected in a surgical specimen. *Virchows Arch*. 2020;10.1007/s00428-020-02829-1. https://doi.org/10.1007/s00428-020-02829-1. https://www.ncbi.nlm.nih.gov/pubmed/32356025.
33. Gralinski LE, Bankhead A, 3rd, Jeng S, et al. Mechanisms of severe acute respiratory syndrome coronavirus-induced acute lung injury. *mBio*. 2013; 4 (4). https://doi.org/10.1128/mBio.00271-13. https://www.ncbi.nlm.nih.gov/pubmed/23919993.
34. Chen Y, Chan VS, Zheng B, et al. A novel subset of putative stem/progenitor CD34+Oct-4+ cells is the major target for SARS coronavirus in human lung. *J Exp Med*. 2007; 204 (11): 2529-2536. https://doi.org/10.1084/jem.20070462. https://www.ncbi.nlm.nih.gov/pubmed/17923501.
35. Qian Z, Travanty EA, Oko L, et al. Innate immune response of human alveolar type II cells infected with severe acute respiratory syndrome-coronavirus. *Am J Respir Cell Mol Biol.* 2013; 48 (6): 742-748. https://doi.org/10.1165/rcmb.2012-0339OC. https://www.ncbi.nlm.nih.gov/pubmed/23418343.
36. Butowt R, Bilinska K. SARS-CoV-2: Olfaction, Brain Infection, and the Urgent Need for Clinical Samples Allowing Earlier Virus Detection. *ACS Chem Neurosci.* 2020; 11 (9): 1200-1203. https://doi.org/10.1021/acschemneuro.0c00172. https://www.ncbi.nlm.nih.gov/pubmed/32283006.

37. Waradon Sungnak1, Ni Huang1, Christophe Bécavin2, Marijn Berg3, 4. SARS-CoV-2 Entry Genes Are Most Highly Expressed in Nasal Goblet and Ciliated Cells within Human Airways. 2020.
38. Koyuncu OO, Hogue IB, Enquist LW. Virus infections in the nervous system. *Cell Host Microbe*. 2013; 13 (4): 379-393. https://doi.org/10.1016/j.chom.2013.03.010. https://www.ncbi.nlm.nih.gov/pubmed/23601101.
39. Patrick D.M. PM, Skowronski D.M.,. An outbreak of human coronavirus OC43 infection and serological cross-reactivity with SARS coronavirus. *Can J Infect Dis Med Microbiol*. 2006; 17: 330-336.
40. St-Jean JR, Jacomy H, Desforges M, Vabret A, Freymuth F, Talbot PJ. Human respiratory coronavirus OC43: genetic stability and neuroinvasion. *J Virol*. 2004; 78 (16): 8824-8834. https://doi.org/10.1128/JVI.78.16.8824-8834.2004. https://www.ncbi.nlm.nih.gov/pubmed/15280490.
41. Jacomy H, Talbot PJ. Vacuolating encephalitis in mice infected by human coronavirus OC43. *Virology*. 2003; 315 (1): 20-33. https://doi.org/10.1016/s0042-6822(03)00323-4.
42. Desforges M, Le Coupanec A, Dubeau P, et al. Human Coronaviruses and Other Respiratory Viruses: Underestimated Opportunistic Pathogens of the Central Nervous System? *Viruses*. 2019; 12 (1). https://doi.org/10.3390/v12010014. https://www.ncbi.nlm.nih.gov/pubmed/31861926.
43. Durrant DM, Ghosh S, Klein RS. The Olfactory Bulb: An Immunosensory Effector Organ during Neurotropic Viral Infections. *ACS Chem Neurosci*. 2016; 7 (4): 464-469. https://doi.org/10.1021/acschemneuro.6b00043. https://www.ncbi.nlm.nih.gov/pubmed/27058872.
44. Dubé M, Le Coupanec A., Wong A.H.M.,. Axonal Transport Enables Neuron-to-Neuron Propagation of Human Coronavirus OC43. *J Virol*. 2018; 92: 404-418. https://doi.org/doi.org/10.1128/JVI.
45. Chen L, Liu M, Zhang Z, et al. Ocular manifestations of a hospitalised patient with confirmed 2019 novel coronavirus disease. *Br J Ophthalmol*. 2020;10.1136/bjophthalmol-2020-316304. https://doi.org/10.1136/bjophthalmol-2020-316304. https://www.ncbi.nlm.nih.gov/pubmed/32265202.
46. Zhang X, Chen X, Chen L, et al. The evidence of SARS-CoV-2 infection on ocular surface. *Ocul Surf*. 2020;10.1016/j.jtos.2020.03.010. https://doi.org/10.1016/j.jtos.2020.03.010. https://www.ncbi.nlm.nih.gov/pubmed/32289466.
47. School DWM. Anatomy of the eye. https://www.digital-world-medical-school.net/01.%20Medical%20School/1.%201st/08.%20Regional%20Gross%20Anatomy/01.%20Head/04b.%20Orbit/02.%20Eye.html. https://www.digital-world-medical-school.net/01.%20Medical%20School/1.%201st/08.%20Regional%20Gross%20Anatomy/01.%20Head/04b.%20Orbit/02.%20Eye.html.
48. Yu AY, Tu R, Shao X, Pan A, Zhou K, Huang J. A comprehensive Chinese experience against SARS-CoV-2 in ophthalmology. *Eye Vis (Lond)*. 2020; 7: 19. https://doi.org/10.1186/s40662-020-00187-2. https://www.ncbi.nlm.nih.gov/pubmed/32289038.
49. Lu C-w, Liu X-f, Jia Z-f. 2019-nCoV transmission through the ocular surface must not be ignored. *The Lancet*. 2020; 395 (10224). https://doi.org/10.1016/s0140-6736(20)30313-5.
50. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic

Mechanisms. *ACS Chem Neurosci.* 2020; 11 (7): 995-998. https://doi.org/10.1021/acschemneuro.0c00122. https://www.ncbi.nlm.nih.gov/pubmed/32167747.
51. Bohmwald K, Galvez NMS, Rios M, Kalergis AM. Neurologic Alterations Due to Respiratory Virus Infections. *Front Cell Neurosci.* 2018; 12: 386. https://doi.org/10.3389/fncel.2018.00386. https://www.ncbi.nlm.nih.gov/pubmed/30416428.
52. Britannica TEoE. vagus nerve. 2020. https://www.britannica.com/science/vagus-nerve.(Encyclopædia Britannica, inc.). https://www.britannica.com/science/vagus-nerve.
53. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet.* 2020; 395 (10229): 1054-1062. https://doi.org/10.1016/s0140-6736(20)30566-3.
54. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *The Lancet Respiratory Medicine.* 2020; 8 (5): 475-481. https://doi.org/10.1016/s2213-2600(20)30079-5.
55. Jin YH, Cai L, Cheng ZS, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). *Mil Med Res.* 2020; 7 (1): 4. https://doi.org/10.1186/s40779-020-0233-6. https://www.ncbi.nlm.nih.gov/pubmed/32029004.
56. Verity R, Okell LC, Dorigatti I, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. *The Lancet Infectious Diseases.* 2020;10.1016/s1473-3099(20)30243-7. https://doi.org/10.1016/s1473-3099(20)30243-7.
57. Bergmann CC, Lane TE, Stohlman SA. Coronavirus infection of the central nervous system: host-virus stand-off. *Nat Rev Microbiol.* 2006; 4 (2): 121-132. https://doi.org/10.1038/nrmicro1343. https://www.ncbi.nlm.nih.gov/pubmed/16415928.
58. Janeway CA Jr TP, Walport M, et al. Immunobiology: The Immune System in Health and Disease. 2001. https://www.ncbi.nlm.nih.gov/books/NBK27090/. https://www.ncbi.nlm.nih.gov/books/NBK27090/.
59. WHO. <MODULE 1 – How the immune system works - WHO Vaccine Safety Basics.pdf>. https://vaccine-safety-training.org/how-the-immune-system-works.html. https://vaccine-safety-training.org/how-the-immune-system-works.html.
60. He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. 2020;10.1101/2020.03.15.20036707. https://doi.org/10.1101/2020.03.15.20036707.
61. Liu Y, Yan L-M, Wan L, et al. Viral dynamics in mild and severe cases of COVID-19. *The Lancet Infectious Diseases.* 2020;10.1016/s1473-3099(20)30232-2. https://doi.org/10.1016/s1473-3099(20)30232-2.
62. Schett G, Sticherling M, Neurath MF. COVID-19: risk for cytokine targeting in chronic inflammatory diseases? *Nat Rev Immunol.* 2020; 20 (5): 271-272. https://doi.org/10.1038/s41577-020-0312-7. https://www.ncbi.nlm.nih.gov/pubmed/32296135.
63. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med.* 2020;10.1007/s00134-020-05991-x.

https://doi.org/10.1007/s00134-020-05991-x.
https://www.ncbi.nlm.nih.gov/pubmed/32125452.
64. Yang Y, Shen C, Li J, et al. 2020;10.1101/2020.03.02.20029975. https://doi.org/10.1101/2020.03.02.20029975.
65. Yang Y, Shen C, Li J, et al. Plasma IP-10 and MCP-3 levels are highly associated with disease severity and predict the progression of COVID-19. *J Allergy Clin Immunol.* 2020;10.1016/j.jaci.2020.04.027. https://doi.org/10.1016/j.jaci.2020.04.027. https://www.ncbi.nlm.nih.gov/pubmed/32360286.
66. Sun X, Wang T, Cai D, et al. Cytokine storm intervention in the early stages of COVID-19 pneumonia. *Cytokine Growth Factor Rev*. 2020;10.1016/j.cytogfr.2020.04.002. https://doi.org/10.1016/j.cytogfr.2020.04.002. https://www.ncbi.nlm.nih.gov/pubmed/32360420.
67. Asadi-Pooya AA, Simani L. Central nervous system manifestations of COVID-19: A systematic review. *J Neurol Sci.* 2020; 413: 116832. https://doi.org/10.1016/j.jns.2020.116832. https://www.ncbi.nlm.nih.gov/pubmed/32299017.
68. Moriguchi T, Harii N, Goto J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis.* 2020; 94: 55-58. https://doi.org/10.1016/j.ijid.2020.03.062. https://www.ncbi.nlm.nih.gov/pubmed/32251791.
69. Kwok-Kwong Lau W-CY, * Chung-Ming Chu,† Suet-Ting Lau,* Bun Sheng* and Kwok-Yung Yuen‡. Possible Central Nervous System Infection by SARS Coronavirus. *Emerging Infectious Diseases* 2004; 10.
70. Gu J, Gong E, Zhang B, et al. Multiple organ infection and the pathogenesis of SARS. *J Exp Med*. 2005; 202 (3): 415-424. https://doi.org/10.1084/jem.20050828. https://www.ncbi.nlm.nih.gov/pubmed/16043521.
71. Mao L, Wang M, Chen S, et al. Neurological Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China: a retrospective case series study. 2020;10.1101/2020.02.22.20026500. https://doi.org/10.1101/2020.02.22.20026500.
72. Verdecchia P, Cavallini C, Spanevello A, Angeli F. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. *Eur J Intern Med*. 2020;10.1016/j.ejim.2020.04.037. https://doi.org/10.1016/j.ejim.2020.04.037. https://www.ncbi.nlm.nih.gov/pubmed/32336612.
73. Jackson L, Eldahshan W, Fagan SC, Ergul A. Within the Brain: The Renin Angiotensin System. *Int J Mol Sci.* 2018; 19 (3). https://doi.org/10.3390/ijms19030876. https://www.ncbi.nlm.nih.gov/pubmed/29543776.
74. Holappa M, Vapaatalo H, Vaajanen A. Many Faces of Renin-angiotensin System - Focus on Eye. *Open Ophthalmol J.* 2017; 11: 122-142. https://doi.org/10.2174/1874364101711010122. https://www.ncbi.nlm.nih.gov/pubmed/28761566.
75. Sama IE, Ravera A, Santema BT, et al. Circulating plasma concentrations of angiotensin-converting enzyme 2 in men and women with heart failure and effects of renin-angiotensin-aldosterone inhibitors. *Eur Heart J*. 2020;10.1093/eurheartj/ehaa373. https://doi.org/10.1093/eurheartj/ehaa373. https://www.ncbi.nlm.nih.gov/pubmed/32388565.
76. Li W. MMJ, Vasilieva N. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature*. 2003; 426: 450-454.

77. Xia H, Sriramula S, Chhabra KH, Lazartigues E. Brain angiotensin-converting enzyme type 2 shedding contributes to the development of neurogenic hypertension. *Circ Res.* 2013; 113 (9): 1087-1096. https://doi.org/10.1161/CIRCRESAHA.113.301811. https://www.ncbi.nlm.nih.gov/pubmed/24014829.
78. Xu J, Sriramula S, Xia H, et al. Clinical Relevance and Role of Neuronal AT1 Receptors in ADAM17-Mediated ACE2 Shedding in Neurogenic Hypertension. *Circ Res.* 2017; 121 (1): 43-55. https://doi.org/10.1161/CIRCRESAHA.116.310509. https://www.ncbi.nlm.nih.gov/pubmed/28512108.
79. Kang Y, Chen T, Mui D, et al. Cardiovascular manifestations and treatment considerations in covid-19. *Heart.* 2020;10.1136/heartjnl-2020-317056. https://doi.org/10.1136/heartjnl-2020-317056. https://www.ncbi.nlm.nih.gov/pubmed/32354800.
80. Epelman S, Tang WH, Chen SY, Van Lente F, Francis GS, Sen S. Detection of soluble angiotensin-converting enzyme 2 in heart failure: insights into the endogenous counter-regulatory pathway of the renin-angiotensin-aldosterone system. *J Am Coll Cardiol.* 2008; 52 (9): 750-754. https://doi.org/10.1016/j.jacc.2008.02.088. https://www.ncbi.nlm.nih.gov/pubmed/18718423.
81. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol.* 2020;10.1002/jmv.25728. https://doi.org/10.1002/jmv.25728. https://www.ncbi.nlm.nih.gov/pubmed/32104915.
82. Bonow RO, Fonarow GC, O'Gara PT, Yancy CW. Association of Coronavirus Disease 2019 (COVID-19) With Myocardial Injury and Mortality. *JAMA Cardiol.* 2020;10.1001/jamacardio.2020.1105. https://doi.org/10.1001/jamacardio.2020.1105. https://www.ncbi.nlm.nih.gov/pubmed/32219362.
83. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospitalization and critical illness among 4,103 patients with Covid-19 disease in New York City. 2020;10.1101/2020.04.08.20057794. https://doi.org/10.1101/2020.04.08.20057794.
84. Shi S, Qin M, Shen B, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol.* 2020;10.1001/jamacardio.2020.0950. https://doi.org/10.1001/jamacardio.2020.0950. https://www.ncbi.nlm.nih.gov/pubmed/32211816.
85. Cardiology ESo. ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic. 2020. https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance. https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance.
86. Guzik TJ, Mohiddin SA, Dimarco A, et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. *Cardiovasc Res.* 2020;10.1093/cvr/cvaa106. https://doi.org/10.1093/cvr/cvaa106. https://www.ncbi.nlm.nih.gov/pubmed/32352535.
87. Jiang F, Yang J, Zhang Y, et al. Angiotensin-converting enzyme 2 and angiotensin 1-7: novel therapeutic targets. *Nat Rev Cardiol.* 2014; 11 (7): 413-426. https://doi.org/10.1038/nrcardio.2014.59. https://www.ncbi.nlm.nih.gov/pubmed/24776703.

88. Cao M, Zhang D, Wang Y, et al. Clinical Features of Patients Infected with the 2019 Novel Coronavirus (COVID-19) in Shanghai, China. 2020;10.1101/2020.03.04.20030395. https://doi.org/10.1101/2020.03.04.20030395.
89. Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection-a review of immune changes in patients with viral pneumonia. *Emerg Microbes Infect.* 2020; 9 (1): 727-732. https://doi.org/10.1080/22221751.2020.1746199. https://www.ncbi.nlm.nih.gov/pubmed/32196410.
90. van der Poll T. Tissue factor as an initiator of coagulation and inflammation in the lung. *Crit Care.* 2008; 12 Suppl 6: S3. https://doi.org/10.1186/cc7026. https://www.ncbi.nlm.nih.gov/pubmed/19105796.
91. McGonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *The Lancet Rheumatology.* 2020;10.1016/s2665-9913(20)30121-1. https://doi.org/10.1016/s2665-9913(20)30121-1.
92. R.L. B. Disseminated Intravascular Coagulation: A Review of Etiology, Pathophysiology, Diagnosis, and Management: Guidelines for Care. *Clin Appl Thrombosis/Hemostasis.* 2002; 8: 1-31. https://journals.sagepub.com/doi/abs/10.1177/107602960200800103. https://journals.sagepub.com/doi/abs/10.1177/107602960200800103.
93. Asakura H. Classifying types of disseminated intravascular coagulation: clinical and animal models. *Journal of Intensive Care.* 2014; 2: 20. http://www.jintensivecare.com/content/2/1/20. http://www.jintensivecare.com/content/2/1/20.
94. Fox SE, Akmatbekov A, Harbert JL, Li G, Quincy Brown J, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. *The Lancet Respiratory Medicine.* 2020;10.1016/s2213-2600(20)30243-5. https://doi.org/10.1016/s2213-2600(20)30243-5.
95. Woelfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized cases of coronavirus disease 2019. 2020;10.1101/2020.03.05.20030502. https://doi.org/10.1101/2020.03.05.20030502.
96. Zou L. RF, Huang M.,. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *N Engl J Med.* 2020; 382: 1177-1179. https://doi.org/DOI: 10.1056/NEJMc2001737. https://www.nejm.org/doi/full/10.1056/NEJMc2001737.
97. Hu F, Chen F, Wang Y, Xu T, Tang X, Li F. Failed detection of the full-length genome of SARS-CoV-2 by ultra-deep sequencing from the recovered and discharged patients retested viral PCR positive. 2020;10.1101/2020.03.27.20043299. https://doi.org/10.1101/2020.03.27.20043299.
98. Shen C, Wang Z, Zhao F, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *JAMA.* 2020;10.1001/jama.2020.4783. https://doi.org/10.1001/jama.2020.4783. https://www.ncbi.nlm.nih.gov/pubmed/32219428.
99. Scientific TF. Basic Principles of RT-qPCR _ Thermo Fisher Scientific. https://www.thermofisher.com/ca/en/home/brands/thermo-scientific/molecular-biology/molecular-biology-learning-center/molecular-biology-resource-library/spotlight-articles/basic-principles-rt-qpcr.html.
100. Zitzmann C, Kaderali L. Mathematical Analysis of Viral Replication Dynamics and Antiviral Treatment Strategies: From Basic Models to Age-Based Multi-Scale Modeling. *Front Microbiol.* 2018; 9: 1546.

https://doi.org/10.3389/fmicb.2018.01546.
https://www.ncbi.nlm.nih.gov/pubmed/30050523.
101. Saplakoglu Y. <Recovered patients who tested positive for COVID-19 likely not reinfected _ Live Science. 2020. https://www.livescience.com/coronavirus-reinfections-were-false-positives.html.
102. Wu F, Wang A, Liu M, et al. Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. 2020;10.1101/2020.03.30.20047365. https://doi.org/10.1101/2020.03.30.20047365.
103. McDonell S. Coronavirus_ China says disease 'curbed' in Wuhan and Hubei - BBC News. 2020. https://www.bbc.com/news/world-asia-china-51813876. https://www.bbc.com/news/world-asia-china-51813876.
104. Lebreton M. Sur la matiere cristalline des orangettes, et analyse de ces fruits non encore developpes, famille des Hesperidees. *Journal de Pharmacie et de Sciences Accessories.* 1828. 377.
105. Scott J. ML, Heuertz J.,. Clinical guide to commonly used Chinese herbal formulas- 6th ed revision. 2017.
106. Sionneau P. Dui Yao_ The Art of Combining Chinese Medicinals. 1997. https://books.google.ca/books?id=IoWHP3w0sKkC&printsec=frontcover&source=gbs_ge_summary_r&cad=0#v=onepage&q&f=false.
107. Garg A, Garg S, Zaneveld LJ, Singla AK. Chemistry and pharmacology of the Citrus bioflavonoid hesperidin. *Phytother Res.* 2001; 15 (8): 655-669. https://doi.org/10.1002/ptr.1074. https://www.ncbi.nlm.nih.gov/pubmed/11746857.
108. Manach C. WG. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *Am J Clin Nutr.* 2005; 81(suppl): 230S-242S.
109. Lin CW, Tsai FJ, Tsai CH, et al. Anti-SARS coronavirus 3C-like protease effects of Isatis indigotica root and plant-derived phenolic compounds. *Antiviral Res.* 2005; 68 (1): 36-42. https://doi.org/10.1016/j.antiviral.2005.07.002. https://www.ncbi.nlm.nih.gov/pubmed/16115693.
110. De Clercq E. Potential antivirals and antiviral strategies against SARS coronavirus infections. *Expert Rev Anti Infect Ther.* 2006; 4(2): 291–302.
111. Yang H, Xie W, Xue X, et al. Design of wide-spectrum inhibitors targeting coronavirus main proteases. *PLoS Biol.* 2005; 3 (10): e324. https://doi.org/10.1371/journal.pbio.0030324. https://www.ncbi.nlm.nih.gov/pubmed/16128623.
112. Chen YW, Yiu C-PB, Wong K-Y. Prediction of the SARS-CoV-2 (2019-nCoV) 3C-like protease (3CLpro) structure: virtual screening reveals velpatasvir, ledipasvir, and other drug repurposing candidates. *F1000Research.* 2020; 9. https://doi.org/10.12688/f1000research.22457.1.
113. Vu V, Pham D-H, Le L, Pham NQA, Ngo ST. Computational Determination of Potential Inhibitors of SARS-CoV-2 Main Protease. 2020;10.26434/chemrxiv.12111297.v1. https://doi.org/10.26434/chemrxiv.12111297.v1.
114. Utomo RY, Ikawati M, Meiyanto E. Revealing the Potency of Citrus and Galangal Constituents to Halt SARS-CoV-2 Infection. 2020;10.20944/preprints202003.0214.v1. https://doi.org/10.20944/preprints202003.0214.v1.
115. Huang A. TX, Wua H.,. Virtual Screening and Molecular Dynamics Study on Blockage of Key Drug Targets as Treatment for COVID-19 caused by SARS-CoV-2. 2020. https://www.preprints.org/manuscript/202003.0239/v1. https://www.preprints.org/manuscript/202003.0239/v1.

116. Wu C, Liu Y, Yang Y, et al. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. *Acta Pharm Sin B.* 2020;10.1016/j.apsb.2020.02.008. https://doi.org/10.1016/j.apsb.2020.02.008. https://www.ncbi.nlm.nih.gov/pubmed/32292689.
117. Yang H, Bartlam M, Rao Z. Drug design targeting the main protease, the Achilles' heel of coronaviruses. *Curr Pharm Des.* 2006; 12 (35): 4573-4590. https://doi.org/10.2174/138161206779010369. https://www.ncbi.nlm.nih.gov/pubmed/17168763.
118. Yin J. RJ. Kinetic Modeling of Virus Growth in Cells. *Microbiol Mol Biol.* e00066-17: e00066-00017. https://doi.org/doi.org/10 .1128/MMBR.00066-17.
119. Kim J, Wie MB, Ahn M, Tanaka A, Matsuda H, Shin T. Benefits of hesperidin in central nervous system disorders: a review. *Anat Cell Biol.* 2019; 52 (4): 369-377. https://doi.org/10.5115/acb.19.119. https://www.ncbi.nlm.nih.gov/pubmed/31949974.
120. Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the eye of the cytokine storm. *Microbiol Mol Biol Rev.* 2012; 76 (1): 16-32. https://doi.org/10.1128/MMBR.05015-11. https://www.ncbi.nlm.nih.gov/pubmed/22390970.
121. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet.* 2020; 395 (10223): 507-513. https://doi.org/10.1016/s0140-6736(20)30211-7.
122. Ding Z, Sun G, Zhu Z. Hesperidin attenuates influenza A virus (H1N1) induced lung injury in rats through its anti-inflammatory effect. *Antivir Ther.* 2018; 23 (7): 611-615. https://doi.org/10.3851/IMP3235. https://www.ncbi.nlm.nih.gov/pubmed/29623897.
123. Meng C, Guo Z, Li D, et al. Preventive effect of hesperidin modulates inflammatory responses and antioxidant status following acute myocardial infarction through the expression of PPARgamma and Bcl2 in model mice. *Mol Med Rep.* 2018; 17 (1): 1261-1268. https://doi.org/10.3892/mmr.2017.7981. https://www.ncbi.nlm.nih.gov/pubmed/29115547.