




Commentary

The pathogenesis and alternative treatment of SARS-CoV2

Jun-Yong Choi  ^{a, b}, Myungsoo Joo ^{b, *, ☆}^a Department of Internal Medicine, Korean Medicine Hospital, Pusan National University, Yangsan 50612, Republic of Korea^b School of Korean Medicine, Pusan National University, Yangsan 50612, Republic of Korea

Since first reported in Wuhan, China, a mysterious respiratory illness sweeps the world. The images of patients lying unattended on the streets shock and terrorize people on the globe. The scientific community has identified the culprit of the shock wave as SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2).¹ According to the statistics updated by the Johns Hopkins University, SARS-CoV-2 shows 4% mortality worldwide. While the impact of SARS-CoV2 infection is yet to be fathomed, SARS-CoV-2 seems to infect more but kills less than its cousins: SARS-CoV-1 that infected more than 8000 people with 9.6% mortality² and MERS-CoV (Middle East Respiratory Syndrome coronavirus) did about 2500 people but killed 35% of them.³ As the WHO (World Health Organization) announced that SARS-CoV2 is pandemic, one ominous possibility is that the SARS-CoV outbreak becomes periodic, perpetually haunting humans.

Human coronavirus (hCoV) has been known to account for 5–30% of the common cold without posing a serious threat to human health.⁴ Since 2002, however, newly merged hCoV causes fever, dyspnea, and often organ failure, which bestow SARS (severe acute respiratory syndrome) to otherwise benign hCoV.⁵ Severity in hCoV infection could be related to which host receptors hCoV chooses. While hCoV 229E, which causes the common cold, binds to hAPN (human alanyl aminopeptidase), MERS-Cov and SARS-CoV do hDPP4 (human dipeptidyl peptidase 4) and hACE2 (human angiotensin-converting enzyme 2), respectively.^{6,7} Similar to SARS-CoV, SARS-CoV2 is known to use hACE2.⁸ Receptors direct where infection occurs. Unlike the common cold hCoV that infects the upper respiratory tract, SARS-CoV can travel down to the lower respiratory tract, where the receptors for SARS-CoV abound. Since SARS-CoV uses the spike protein (S) to bind to the receptors,⁹ the structure of the S protein of SARS-CoV2 was quickly elucidated.¹⁰ Discreet molecular structures of the S protein and receptors could be exploited to produce antibodies, vaccines, or small molecules, which abort the binding of SARS-CoV2 to its receptors. As yet, however, no drugs or treatments are available to prevent the infection of SARS-CoV2.

It should be noted that the dire consequence of SARS-CoV2 infection is not due to the virus per se but to entailing inflammatory response in the lung. During the MERS-CoV and SARS-CoV outbreaks, most patients died of acute lung injury (ALI) or acute respiratory distress syndrome (ARDS), a severe case of ALI.¹¹ ALI is featured by the surge of pro-inflammatory cytokines and neutrophils in the lung, which causes edema and damages capillary and lung tissue; when our system is flooded with inflammatory cytokines and chemokine, organ failure ensues, resulting in a fatal consequence.¹² As for the viruses, they simply bind to the receptors and cause the apoptotic or necrotic death of cells lining inner lung tissue. Depending on the swath of receptors, the virus infection can be limited or massive, and so do an inflammatory reaction. Fortunately, the mortality of SARS-CoV2 infection, which is related to ALI or ARDS, is lower than those of the other two outbreaks.¹³ Since ALI can be regulated by suppressing inflammation,¹⁴ various anti-inflammatory regimens had been attempted to treat patients during the last CoV outbreaks, including steroids and antibodies against cytokines.¹¹ Given the pathologic similarity among three different outbreaks of hCoV, it is highly likely that managing ALI and ARDS attentively and vigorously leads to quick recovery from SARS-CoV2 infection.

Along with the anti-inflammatory drugs, administering medicinal herbs, a pillar of traditional Asian medicine, to patients is conceivable given the long history of treating patients with various inflammatory lung diseases. For instance, Sikyungbanha-Tang (SKBHT), a concoction of 10 different herbs, is used for patients who suffer from cough and fever.¹⁵ An extract of Forsythiae Fructus is prescribed to patients with the common cold, fever, and other various infections.¹⁶ More effective formulas could be contrived from a collection of herbs showing anti-inflammatory activity.¹⁷ Mechanistic and animal studies demonstrate that these medicinal herbs suppress lung inflammation and increase the survival of mice in ALI mouse models. As yet, however, no evidence is available that, if administered to patients on the principles of traditional Asian medicine, the medicinal herbs show effectiveness against ALI caused by SARS-CoV2 infection. The pandemic situation makes scientifically unfounded attempts possible. Without scientific evidence, anti-viral drugs designed for other viral infections are allowed in clinical trials to test a possible anti-SARS-CoV2 effect. Unlike those, many medicinal herbs used in traditional Asian medicine have been used to relieve respiratory

* Corresponding author at: School of Korean Medicine, Pusan National University, Yangsan 50612, Republic of Korea.

E-mail address: mjoo@pusan.ac.kr (M. Joo).

☆ ORCID: <https://orcid.org/0000-0002-2854-3862>.

inflammation,¹⁸ which has been supported by experimental evidence from numerous laboratories. The time comes to examine whether anti-inflammatory medicinal herbs give a medical benefit to patients infected by SARS-CoV2.

Author contributions

Conception: JYC and MJ. Writing - Original Draft: JYC. Writing-Review & Editing: MJ. Supervision: JYC and MJ.

Conflict of interest

The authors declare that they have no conflicts of interest.

Funding

This study was supported by the Traditional Korean Medicine R&D program funded by the Ministry of Health & Welfare through the Korea Health Industry Development Institute (KHIDI) (HB16C0006) and by the National Research Foundation of the Korea government (NRF-2018R1A2A3075650).

Ethical statement

This article did not have any research ethical consideration as authors did not perform research with human or animal subjects.

Data availability

This article has no data openly available.

References

1. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. *Lancet* 2020;395:470–3.
2. Kuiken T, Fouchier RA, Schutten M, Rimmelzwaan GF, van Amerongen G, van Riel D, et al. Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. *Lancet* 2003;362:263–70.
3. Fehr AR, Channappanavar R, Perlman S. Middle east respiratory syndrome: emergence of a pathogenic human coronavirus. *Annu Rev Med* 2017;68:387–99.
4. Su S, Wong G, Shi W, Liu J, Lai ACK, Zhou J, et al. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. *Trends Microbiol* 2016;24:490–502.
5. Perlman S, Netland J. Coronaviruses post-SARS: update on replication and pathogenesis. *Nat Rev Microbiol* 2009;7:439–50.
6. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* 2003;426:450–4.
7. Raj VS, Mou H, Smits SL, Dekkers DH, Muller MA, Dijkman R, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. *Nature* 2013;495:251–4.
8. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020.
9. Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. *Nat Microbiol* 2020;5:562–9.
10. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science* 2020;367:1260–3.
11. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin Immunopathol* 2017;39:529–39.
12. Ware LB, Matthay MA. The acute respiratory distress syndrome 1. *N Engl J Med* 2000;342:1334–49.
13. Yao Y, Tian Y, Zhou J, Ma X, Yang M, Wang S. Epidemiological characteristics of 2019-nCoV infections in Shaanxi, China by February. *Eur Respir J* 2020;8.
14. Impellizzeri D, Bruschetta G, Esposito E, Cuzzocrea S. Emerging drugs for acute lung injury. *Expert Opin Emerg Drugs* 2015;20:75–89.
15. Lim B. Korean medicine coverage in the National Health Insurance in Korea: present situation and critical issues. *Integr Med Res* 2013;2:81–8.
16. Lee JJ, Kim KH, Kim EJ, Choi JY, Kim SJ, Jeong SI, et al. Anti-inflammatory activity of the decoction of *Forsythia suspensa* (Thunb.) Vahl is related to Nrf2 and A20. *J Ethnopharmacol* 2018;227:97–104.
17. Han JW, Kim KH, Kwun MJ, Choi JY, Kim SJ, Jeong SI, et al. Suppression of lung inflammation by the ethanol extract of Chung-Sang and the possible role of Nrf2. *BMC Complement Altern Med* 2019;19:15.
18. Xi S, Gong Y. *Essentials of Chinese material medica and medical formulas*; 2017.