Letter to Editor:
COVID-19: A Hypothesis to Prevent SARS-CoV-2 From Entering Respiratory Cells

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Coronaviruses (CoVs) are a group of viruses that induce infection in the respiratory and other systems in the human body. There are two coronaviruses: Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS). They can be transmitted from animals to humans [1]. The novel coronavirus that appeared at first in Wuhan, China, in December 2019 was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or COVID-19 by the International Virus Classification Commission. This virus is a novel beta-CoV that shows 88% similarity to the sequence of two bat-derived severe acute respiratory syndromes (SARS)-like coronaviruses and about 50% similarity to the sequence MERS-CoV [2]. Thus, based on the structure of COVID-19, it can be expected that this virus will have similar effects and mechanisms to SARS and MERS. Chinese scientists showed that COVID-19, similar to SARS-CoV, requires the Angiotensin-Converting enzyme 2 (ACE2) as a receptor to enter cells. The binding of COVID-19 with host cell Angiotensin Receptor (AT) can induce pathogenesis of infection. Dipeptidyl peptidase-4 (DPP-4) enzyme has known as a functional receptor for MERS-CoV. This receptor bind with the receptor-binding S1 domain of the MERS-CoV spike protein and promotes the transmission of this virus into the cells [2].

Two distinct subtypes of angiotensin 2 receptors, termed AT1 and AT2, have been identified. The AT2 receptor is present in the mucous glands and on the brush border of the bronchial epithelial cells of the human lung. Also, the presence of AT2 receptors on small airway epithelial cells strengthens the researchers' belief about the effect of this receptor on the function of cells in this area of the lung. Stimulation of AT2 receptors causes vasodilation that dependent on Nitric Oxide (NO) and involvement of the bradykinin B2 receptor-NO-cGMP pathway. DPP-4 is more found in distal airways compared to the surface epithelium from the nasal cavity. This enzyme is found principally in alveolar type I and II cells and pleural mesothelium. The localization of AT2 and DPP4 in alveolar regions may reveal why SARS or MERS are characterized by lower respiratory tract disease [3-5].

Losartan and PD 123177 (an experimental nonpeptide antagonist) are AT1 and AT2 receptor antagonists, respectively. Angiotensin 2 and Saralasin bind equally to both subtypes. The current angiotensin 2 receptor blockers are selective for the AT1 receptor. Prolong treatment with the AT1 receptor antagonist increases circulating

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Ang II levels and increased the stimulation of AT2 receptors. This alteration leads to the activation of the AT2 receptor and vasodilation. AT2 receptor antagonists such as PD 123177 are available for research but have no clinical applications [3].

It was revealed that DPP4 inhibitors have the antiviral action that is suggested as therapeutic compounds in severe viral infections such as infection by MERS-CoV [6]. MERS-CoV S glycoprotein increases the expression of the negative regulator of Toll-Like Receptor (TLR) signaling Interleukin-1 Receptor Associated Kinase-M (IRAK-M) as well as of the transcriptional repressor Peroxisome Proliferator-Activated Receptor γ (PPARγ). Administration of DPP4 inhibitor such as sitagliptin improved the effects of MERS-CoV S glycoprotein on IRAK-M, PPARγ, and interleukin-10 (IL-10). These results indicated that this drug induces immunosuppressive effects through the DPP-4 receptor [7]. Sitagliptin, as an inhibitor of dipeptidyl peptidase-4 (DPP-4), has an oral bioavailability of over 85% and a half-life of approximately 12 hours; the dosage is 100 mg orally once daily [3].

In conclusion, given the mechanism of action of SARS and MERS viruses, it could be suggested that the use of angiotensin receptor blocking drugs, especially AT2, could be an effective preventive way to enter the COVID-19 virus into the bronchial cells at the distal airways of the lung. So, the administration of Losartan concurrently with PD 123177 is suggested to block both AT1 and AT1 receptors. On the other hand, the use of saralasin as a partial agonist of angiotensin 2 receptors is suggested to stop AT2 and decrease the presence of angiotensin 2 associates with a subsequent decline in SARS performance in the lung's airway. Also, it can be recommended that sitagliptin, as a DPP-4 inhibitor, reduces the chance of the COVID-19 being bound to this enzyme and its receptor. Because when the activity of DPP-4 decrease in alveolar regions, the exposure of the DPP-4 receptor to this enzyme reduces, and the chances of COVID-19 binding to this receptor are decreased or eliminated. Also, to achieve the best effect, it is recommended that both angiotensin 2 receptor blockers and DPP-4 inhibitors be used. Finally, because these drugs are used by patients with hypertension and diabetes, they may prevent COVID-19 infection simultaneously. However, sufficient clinical studies are needed to prove this hypothesis.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

Conceptualization, methodology, investigation, resources, writing – original draft preparation, writing – review & editing, and visualization: Hadis Ashrafizadeh and Ali Akbar Oroojan; Supervision, and project administration: Ali Akbar Oroojan.

Conflict of interest

The authors declared no conflict of interest.

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