Dear Editor,

We would like to provide some novel therapeutic approaches to the COVID-19 pandemic crisis. With the global spread of COVID-19, finding novel applications for available medications could be beneficial in the current critical phenomenon. Although there is not a standard and reliable treatment for the recent COVID-19 pandemic, we decided to search for it due to its importance.

As a novel infectious disease, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2 or COVID-19) appeared in Wuhan, China, in December 2019 and broadly spread to other parts of the world (1). According to the latest global statistics, six million people in the world have been infected with this virus, with 400,000 deaths worldwide. The main symptoms of COVID-19 consist of fever, dry cough, shortness of breath, pulmonary edema, and myalgia or fatigue (2). As known, SARS-CoV-2 enters cells via angiotensin-converting enzyme 2 (ACE2) receptors. This route plays a key role in the pathogenesis of COVID-19 and the development of Acute respiratory distress syndrome (ARDS) (3, 4). It has been shown that anti-ACE2 antibodies and ACE2 inhibitors can block the SARS-CoV invasion (5, 6).

Bradykinin (BK), a linear nonapeptide, is extensively distributed in plasma and different tissues and formed by the enzymatic activity of kallikrein on kininogens. Kallikreins are divided into plasma kallikrein and tissue kallikrein (7). Various peptidases such as ACE (also known as kininase II) and carboxypeptidases (N and M) can degrade BK into inactive fragments. Bradykinin regulates plasma exudation, chronic inflammatory reactions, and nociception, and can trigger the dilatation of blood vessels through the release of prostacyclin, nitric oxide, and endothelium-derived hyperpolarizing factor; besides, it increases vascular permeability, ultimately leading to edema formation (8, 9). Kinins transduce their biologic effects through the stimulation of G protein-coupled receptors, which are divided into two groups including BK B1 and BK B2 receptors. The agonists for the BK B2 receptor are BK and Lys-bradykinin, while des-Arg-bradykinin and des-Arg-Lys-bradykinin bind to the BK B1 receptor (10).

It has been demonstrated that the SARS-CoV infection depletes ACE2 that leads to increased levels of [des-Arg (9)]-bradykinin (DABK), a bioactive metabolite of BK and a potent ligand of the BK B1 receptor in the lung that is related to lung injury and inflammation (11, 12). High levels of inflammatory cytokines upregulate the B1 receptor on endothelial cells and through the activation of the BK system, may increase the risk of capillary permeability and angioedema (13). Bradykinin-mediated angioedema consists of three angioedema types:

1) Hereditary angioedema (HAE),
2) Acquired C1-inhibitor deficiency
3) ACE inhibitor-associated angioedema.

The C1-inhibitor (C1-INH), a key protease inhibitor in the complement system, is involved in the regulation of numerous serine proteases, such as contact system protease (plasma kallikrein), early proteases of the classical and lectin complement systems (C1r/s, MASP1 and 2), coagulation factor XIa, plasminogen, and vascular permeability. As known, C1-INH dysfunction can cause inappropriate activation of the contact system with the excessive generation of kallikrein, resulting in the proteolysis of high molecular-weight kininogen and eventually the production of BK (14). Besides, HAE, an autosomal dominant disease, is caused by either a mutation in the gene encoding C1-INH or decreased C1-INH protein levels (15). In patients with acquired C1-INH deficiency, the catabolism of C1-INH increases (16). Bradykinin is inactivated by ACE, but ACE inhibitors can block the inactivation of BK by ACE, leading to an increase in its biological activity and enabling to induce angioedema (17) (Figure 1).

Possible Pharmacotherapy:

- Icatibant: Icatibant acetate (Firazyr) is a selective and competitive, synthetic inhibitor of the B2 BK receptor. Pre-
Figure 1. The schematic pathways involved in bradykinin (BK)-mediated angioedema.

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References


