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Sitagliptin Repositioning in SARS-CoV-2: Effects on ACE-2, CD-26, and Inflammatory Cytokine Storms in the Lung

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TO THE EDITOR

Coronavirus disease (COVID-19), a contagious and pandemic disease that leads to mortality, has become a significant global concern. The number of new cases infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is increasing daily, and so far, no effective treatment or vaccine has been confirmed. Peptidomimetic and molecular studies have shown that some critical molecules such as angiotensin-converting enzyme 2 (ACE-2)[1] and CD26/dipeptidyl peptidase-4 (DPP-4) are SARS-CoV-2 receptors[2] that enable the virus to infect cells in the lung and other tissues that express these receptors. Recent studies have demonstrated that suitable therapeutic agents can block virus receptors or downregulate their expression on host cells, thus preventing the entry of SARS-CoV-2 into host cells and reducing the risk of infection.

Furthermore, blocking the virus from entering the host cells provides an excellent opportunity for immune cells to eliminate and neutralize the virus.

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Based on these findings, we recommend sitagliptin, which is a DPP-4 inhibitor prescribed for the treatment of type 2 diabetes. It is proposed, based on molecular studies on SARS-CoV-2 receptors, that sitagliptin can either directly block or inhibit the expression of CD26/DPP-4,[3,4] one of the essential entryways of the virus. In addition, it can indirectly affect another virus receptor, ACE2, by downregulating its expression. Beraldo JI et al found that administering sitagliptin to rats reduced expression and activity of ACE2.[5]

The half-life of the virus can be reduced by the action of immune cells, which diminishes the risk of other cells being infected.

Sitagliptin has some additional properties to help control SARS-CoV-2 infection and improve patient outcomes. Several studies have shown that sitagliptin is an anti-inflammatory and anti-apoptotic medication. Sitagliptin can suppress nuclear factor kappa beta (NF-κB) activation and inflammatory cytokines expression in rat insulinoma cells.[3,4,6] Treatment of type 2 diabetic patients with sitagliptin shows it significantly decreased serum levels of inflammatory markers, such as C-Reactive Protein (CRP), and tumor necrosis factor-alpha (TNF-α) and increased anti-inflammatory cytokine as well as plasma glucagon-like peptide-1 (GLP-1) and interleukin 10 (IL-10) in serum. Besides, sitagliptin increased monocyte IL-10 expression and

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decreased monocyte TNF-α expression in diabetic patients[4] Marques C et al showed that the anti-inflammatory and antiapoptotic effect of sitagliptin can be related to the activation of the GLP-1 receptor. GLP-1 has antiapoptotic actions via the upregulation of B-cell lymphoma protein 2 (Bcl-2) and inhibition of Bcl2 associated X protein (BAX) expression.[6]According to the mentioned characteristics of sitagliptin, it may reduce an inflammatory cytokine storm in the lung, which is caused by an overactive immune response in pneumonia caused by SARS-CoV-2. Cytokine storms play an essential role in the pathophysiology of COVID-19 and could be associated with disease severity[7,8] and sitagliptin may be a good therapeutic agent to control it. On the other hand, the anti-apoptotic properties of sitagliptin may improve the survival of lung cells in COVID-19 patients. As an anti-diabetic agent, sitagliptin can also control hyperglycemia in diabetic patients with COVID-19 pneumonia and non-diabetic patients whose blood sugar levels have risen unusually.

Notably, the active pharmaceutical ingredient of sitagliptin is widely available from several pharmaceutical companies globally, and its manufacturing process such as the production of monoclonal antibodies or recombinant proteins is not complicated. In addition, this drug was approved by the Food and Drug Administration in 2006 and by the European Medicines Agency in 2007, with its side effects already been thoroughly investigated.[9]

In conclusion, sitagliptin may be an effective medication for COVID-19 by directly blocking or indirectly downregulating the expression of SARS-CoV-2 receptors (e.g. CD-26 and ACE-2), in addition to its anti-apoptotic and anti-inflammatory characteristics. (Figure 1) We have started a clinical trial to test this hypothesis and it is available in the Iranian Registry of Clinical Trials now (IRCT20200420047147N1).[10]

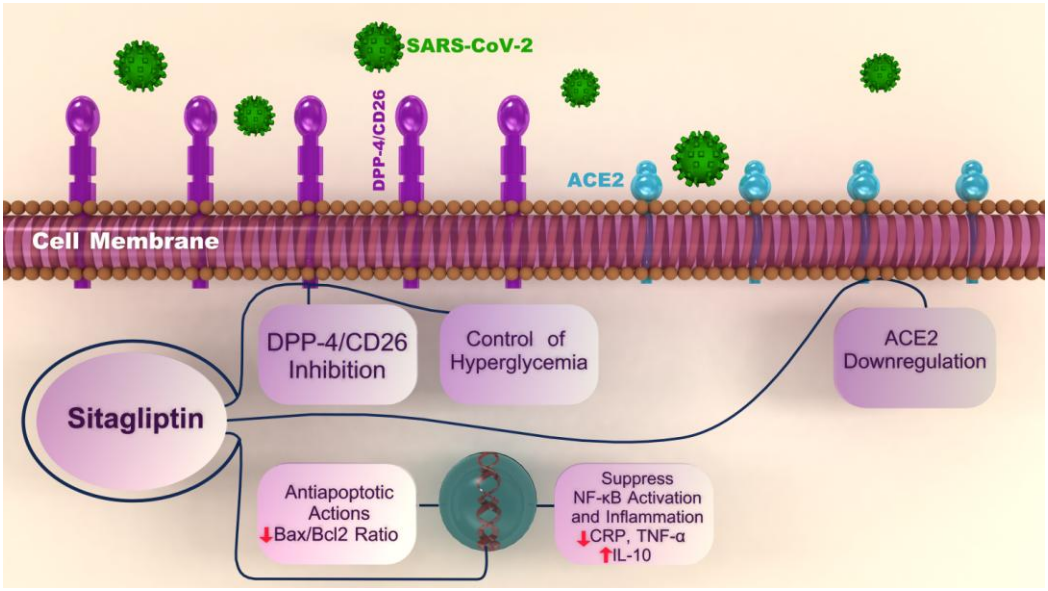

Figure 1.Schematic represents Sitagliptin mechanisms against SARS-CoV-2 and potential Effects. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, DPP-4: Dipeptidyl peptidase-4, ACE2: Angiotensin-converting enzyme 2, Bcl2: B-cell lymphoma protein 2, Bax: Bcl2-associated X protein, NF-κB: Nuclear factor kappa beta, CRP: C-reactive protein, TNF-α: Tumor necrosis factor-alpha, IL-10: Interleukin 10

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