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Letter to the Editor

A proposed mechanism for the possible therapeutic potential of Metformin in COVID-19

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ABSTRACT

The whole world is facing a tough time these days struggling against the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). There is not any specific effective drug for this viral infection. Thus, we are trying to treat patients with non-specific drug cocktails. Metformin, as a strong base, a potential regulator of Vacuolar ATPase (V-ATPase) and endosomal Na+/H+ exchangers (eNHEs), additionally a regenerative agent for lung fibrosis, seems to be beneficial for patients in acute, chronic and recovery phases of COVID-19.

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To the Editor

With great interest, I have read the recent article-letter entitled "Metformin in COVID-19: A possible role beyond diabetes" [1]. Respectfully, I want to make some contributions.

Researchers are hoping to find a treatment for the current viral infection Coronavirus Disease 2019 (COVID-19) caused by the SARS-CoV-2 which has spread the whole world [2].

One of the essential and effective factors for the viral membrane fusion of SARS-CoV-2 in the endocytosis phase is acidic pH [3]. Drugs which can increase the pH values of endosome and lysosome (such as chloroquine and hydroxychloroquine), can negatively alter endocytosis, maturation of endosomes, and transport of virions to the replication site [4].

Two crucial membrane compartments for the maintenance and regulation of endosomal acidic pH, are Vacuolar ATPase (V-ATPase) as proton pumping or acidifier compartment, and endosomal Na+/H+ exchangers (eNHEs) as proton leaking or alkalizing compartment on the endosomal membrane [5]. It is not crystal clear but several studies have suggested that Metformin can directly act on the eNHEs and/or the V-ATPase via its guanidine scaffold similar to Amiloride, then leads to the inhibition of viral infection through increasing the cellular pH and subsequently interfering with the endocytic cycle [5–7].

In addition, Metformin (dimethylbiguanide) is a strong base drug (pKa = 12.4) which might enhance the pH of the acidic vesicles containing viruses just like Chloroquine as a weak base drug. It is noteworthy that even in Chloroquine-resistant

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parasites, the effect of Chloroquine in pH value enhancement does not change. Therefore, increasing the pH value in vesicles loaded with viruses can be an important mechanism of Metformin against SARS-CoV-2 [8].

Furthermore, Metformin can reverse established lung fibrosis, so it has been suggested that Metformin may be an effective treatment of COVID-19-related pulmonary fibrosis [9,10]. Taken together, all these data support the opinion that Metformin can be a beneficial adjuvant therapy for patients in acute, chronic, and even recovery phases of COVID-19.

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Declaration of Competing Interest

No conflict of interest.

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