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Review

The Potential Role of Lithium as an Antiviral Agent against SARS-CoV-2 via Membrane Depolarization: Review and Hypothesis

Abdallah Barjas Qaswal [1,*], Aiman Suleiman [2,*], Hasan Guzu [3], Taima'a Harb [3] and Bashir Atiyat [3]

[1] Department of Internship Program, Jordan University Hospital, The University of Jordan, Amman 11942, Jordan
[2] Department of Anesthesia and Intensive Care, Alabdali Clemenceau Medical Center, Amman 11190, Jordan
[3] Faculty of Medicine, The University of Jordan, Amman 11942, Jordan; Hasangu91@hotmail.com (H.G.); taim.harb@gmail.com (T.H.); bashiratiyat@gmail.com (B.A.)
* Correspondence: qaswalabdullah@gmail.com (A.B.Q.); Aiman.majed@yahoo.com (A.S.)

Abstract: Studies on potential treatments of Coronavirus Disease 2019 (COVID-19) are important to improve the global situation in the face of the pandemic. This review proposes lithium as a potential drug to treat COVID-19. Our hypothesis states that lithium can suppress NOD-like receptor family pyrin domain containing-3 (NLRP3) inflammasome activity, inhibit cell death, and exhibit immunomodulation via membrane depolarization. Our hypothesis was formulated after finding consistent correlations between these actions and membrane depolarization induced by lithium. Eventually, lithium could serve to mitigate the NLRP3-mediated cytokine storm, which is allegedly reported to be the inciting event of a series of retrogressive events associated with mortality from COVID-19. It could also inhibit cell death and modulate the immune system to attenuate its release, clear the virus from the body, and interrupt the cycle of immune-system dysregulation. Therefore, these effects are presumed to improve the morbidity and mortality of COVID-19 patients. As the numbers of COVID-19 cases and deaths continue to rise exponentially without a clear consensus on potential therapeutic agents, urgent conduction of preclinical and clinical studies to prove the efficacy and safety of lithium is reasonable.

Keywords: lithium; membrane depolarization; membrane potential; cell death; NLRP3; SARS-CoV-2; COVID-19; cytokine storm

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1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a new type of coronavirus that is responsible for the COVID-19 pandemic. The first encounter with the virus was in the city of Wuhan, China, in December 2019 [1]. Since then, the pandemic has become a major threat to healthcare systems and economies worldwide. On 9 June 2020, a recent warning of the World Health Organization (WHO) stated that the COVID-19 pandemic was still worsening globally, despite an apparent reduction in infection and death rates [2]. As ominous scenarios are still possible, the scientific community should unite efforts to improve the current situation in terms of prevention, intervention, treatment, and vaccination. Therefore, urgent investigations for potential effective drugs to fight SARS-CoV-2 are crucial.

In this review, lithium is proposed as a potential drug to be used in the treatment of COVID-19 caused by SARS-CoV-2. The review provides a novel insight with reliable, reasonable, and testable mechanisms of lithium to fight the virus at different targets, and discusses the clinical efficacy and safety relevance of lithium. We aim to build a novel comprehensive hypothesis that focuses on the consistent correlations between the antiviral actions of lithium and membrane depolarization in the context of treating COVID-19. Therefore, by positing this hypothesis, we aim to encourage researchers to conduct preclinical

and clinical studies to test the efficacy of using lithium as an agent to treat COVID-19 and to prove the validity of the antiviral actions of lithium mediated by membrane depolarization.

2. SARS-CoV-2 Can Hyperpolarize the Membrane Potential to Enhance Its Own Pathogenesis and Release

SARS-CoV-2 has molecular similarities to and differences with the SARS-CoV-1 virus, which caused a previous pandemic in 2003 [3]. Both strains are enveloped, positive-sense, single-stranded RNA viruses [3]. They both encode two proteins (protein 3a and protein E) that help the virus in its pathogenesis and release from cells [4]. Both proteins possess ion channels [4–6].

Protein 3a is integrated in the membrane of the infected cell. It functions as a selective potassium channel [7] that facilitates potassium ion efflux outside the cell. In order to understand protein 3a's pathogenicity, two important effects should be explained. First, cellular hyperpolarization induced by the potassium efflux from the cell can activate apoptosis and arrest the cell cycle, leading to interruption of cellular proliferation [8–11], and hyperpolarization facilitates the influx of calcium ions to the cytoplasm in order to initiate cell death [11]. Second, potassium efflux can activate NOD-like receptor family pyrin domain containing-3 NLRP3 inflammasome, which secrets the pro-inflammatory cytokines IL-1 beta and IL-18 [12]. These cytokines contribute to the cytokine storm in COVID-19 [13]. Interestingly, SARS-CoV uses protein 3a to initiate cell death [14,15] and activate the inflammasome NLRP3 [16]. Therefore, it can be concluded that SARS-CoV uses protein 3a as a potassium-selective channel to hyperpolarize the cell membrane in order to induce cell death and activate NLRP3 inflammasome. Furthermore, there is an additional evidence that suggests potassium efflux can activate NLRP3 by membrane hyperpolarization, because the concentration range of potassium (0–5) mmol/L required to activate NLRP3 [12] causes hyperpolarization as calculated using the Goldman–Hodgkin–Katz (GHK) equation. Interestingly, the concentration range (5–45 mmol/L) needed to suppress NLRP3 [12] causes membrane depolarization as calculated using the GHK equation. Accordingly, this supports our hypothesis that protein 3a forms a potassium channel that permeates potassium ions outside the cell, not just for mere efflux, but also to cause membrane hyperpolarization, which triggers the cascade of inflammation and cell death.

Protein E is integrated in the membrane of the infected cell and in the membrane of the endoplasmic reticulum (ER) [17]. In the cell membrane, it acts as a cation-selective channel that might show preference toward potassium ions over sodium ions, resulting in potassium efflux and hyperpolarization [17,18]. In addition, it acts as a calcium channel in the membrane of ER, which facilitates the release of calcium ions into the cytoplasm, and this also can activate inflammasome NLRP3 [19] and cell death [14]. Moreover, protein E, with its ion channel activity, can induce ER stress [20], which also can hyperpolarize the cell membrane by upregulation of potassium channels [11]. The hyperpolarization effect will trigger the cascade of cell death and the activation of NLRP3. SARS-CoV can induce ER stress using other proteins, such as protein 3a and protein S, which can further exacerbate the situation [21–23].

Protein 3a of SARS-CoV-2 shares 73% of the amino-acid sequence of protein 3a with SARS-CoV-1 [15], and protein E is conserved among SARS-CoV-1 and SARS-CoV-2 viruses, with identical sequences and without significant difference in the architecture [3,24]. Hence, both proteins of SARS-CoV-2 can conduct potassium ions [25,26]. Therefore, our hypothesis of the relationship between the two proteins (3a and E) and hyperpolarization is applied to both SARS-CoV-1 and SARS-CoV-2.

How do cell death and NLRP3 contribute to the pathogenicity of SARS-CoV-2? NLRP3 inflammasome is a multi-protein complex that stimulates the process of inflammation by immune cells; this will lead to the release of pro-inflammatory cytokines such as IL-1-beta. These cytokines stimulate the release of other factors such as TNF and IL-6. Accordingly, the release of these cytokines and factors contributes to the progression into the inflammatory storm (cytokine storm) that predisposes COVID-19 patients to develop acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), which have been recognized as the

leading causes of mortality in COVID-19 patients [13,27]. Moreover, cell death induced by the virus will further maintain the immune system over activation [13,27], and cell death also causes lung parenchymal damage that negatively affects the function of the lungs, resulting in hypoxia. Additionally, the persistence of cytokine release from macrophages will encourage T-lymphocytes to undergo apoptosis, which in turn decreases the clearance of the virus [27]. This ability of the virus to induce cell death leads to the release of more copies, and these copies will infect other cells and sustain the cycle of immune-system dysregulation [13].

3. The Potential Role of Lithium in Fighting SARS-CoV-2 via Membrane Depolarization

Lithium possesses the ability to depolarize the resting membrane potential of the cell [28]. It has been proposed that lithium treats bipolar patients by membrane depolarization of neuronal cells that is triggered by quantum tunneling of lithium ions through sodium channels when lithium reaches its therapeutic concentration [29,30]. A consistent correlation between lithium actions and the effects of membrane depolarization on the cells can be constructed. Lithium and membrane depolarization have neuroprotective effects through enhancing the growth of neurons and inhibiting their death. This makes lithium very effective in treating bipolar patients [8,31–34]. Lithium and membrane depolarization can inhibit or stimulate the growth of cells in different ways according to their cell lines [8–10,35,36]. They also have immunomodulatory actions that affect the functions of immune cells [8,37–39]. Furthermore, they can effectively enhance wound healing and bone repair [8,40,41]. More interestingly, membrane depolarization is the trigger of phosphoinositide 3-kinase (PI3K) and protein kinase B(Akt) activation [42], which leads to serine phosphorylation that inhibits glycogen synthase kinase-3-beta (GSK-3-beta) [43], which is an important target that is also inhibited by lithium by the same mechanism [44]. This indicates that lithium could mediate its cellular effects via membrane depolarization.

As stated in Section 2, it is clear that membrane hyperpolarization is a fundamental trigger for the release of the virus and its pathogenesis, as well as immune-system dysregulation. On the other hand, the ability of lithium ions to depolarize the membrane can be concluded from experimental and theoretical observations and the consistent correlation between actions of lithium and membrane depolarization. Therefore, lithium has the potential to reverse the hyperpolarization through the action of depolarization. Consequently, all the pathological processes mediated by hyperpolarization will be blocked and prevented. Figure 1 illustrates how membrane depolarization by lithium interrupts the activation of NLRP3.

Lithium has an important immunomodulatory role in fighting SARS-CoV-2 by depolarizing the membrane potential when the ions are transported through the sodium channels such as TRPM4 and Nav1.5, which are present in the membranes of immune cells [45]. This role can be explained in the context of COVID-19 by the following points:

1. Macrophages, the predominant driving cells of the cytokine storm [27], are modulated by membrane potential changes. It was found that membrane depolarization inhibits the release of pro-inflammatory cytokines such as TNF and IL-6 [46,47]. Interestingly, lithium affects the polarization of macrophages and modulates their release of pro-inflammatory cytokines in a manner that favors the attenuation of the inflammatory process [37,38]. This supports the consistent correlation between the actions of lithium and the membrane potential changes.

2. In regard to lymphocytes, it was found that lithium increases the production of antibodies from B-lymphocytes by membrane depolarization, which is an early step of B-lymphocyte activation [37–39]. This step is essential in fighting SARS-CoV because these antibodies work to block the virus' entry [48]. Lithium can also augment the proliferation of T-lymphocytes [49–51] because membrane depolarization is required for T-lymphocyte activation [52,53]. On the other hand, hyperpolarization is also required to stimulate T-lymphocytes [52,53]. Hence, lithium might serve to inhibit T-lymphocyte activation and proliferation [37]. Moreover, lithium can modulate the secretion of interleukins from CD4+

and CD8+ lymphocytes. Both types of T-lymphocytes secrete IL-2 and IL-5 [54], and CD4+ cells also secrete IL-4, IL-6, IL-10, and IL-22 [54]. There is no clear consensus on the final effect of lithium on these interleukins secretions. However, we mention here the outcome obtained from the higher number of studies as the following [55]: 1. Lithium enhances the production of anti-inflammatory IL-2. 2. Lithium increases the levels of pro-inflammatory IL-4. 3. Many studies have demonstrated that lithium attenuates the production of the pro-inflammatory IL-6, but many studies also have shown that lithium enhances IL-6 secretion. 4. Lithium increases the production of the anti-inflammatory IL-10. Additionally, lithium decreases the anti-inflammatory IL-5 in co-cultured cortical cells and glial cells, but it increases its levels in co-cultured hippocampal cells and glial cells [56]. Also, lithium increased the levels of IL-22 in vitro [57], and this interleukin is implicated in pathogen defense, wound healing, and tissue reorganization [54]. Accordingly, it seems that lithium balances the regulation of the immune system in such a way that no over-activation takes place to damage the lung parenchyma, and no under-activation occurs to weaken the clearance of the virus from the body.

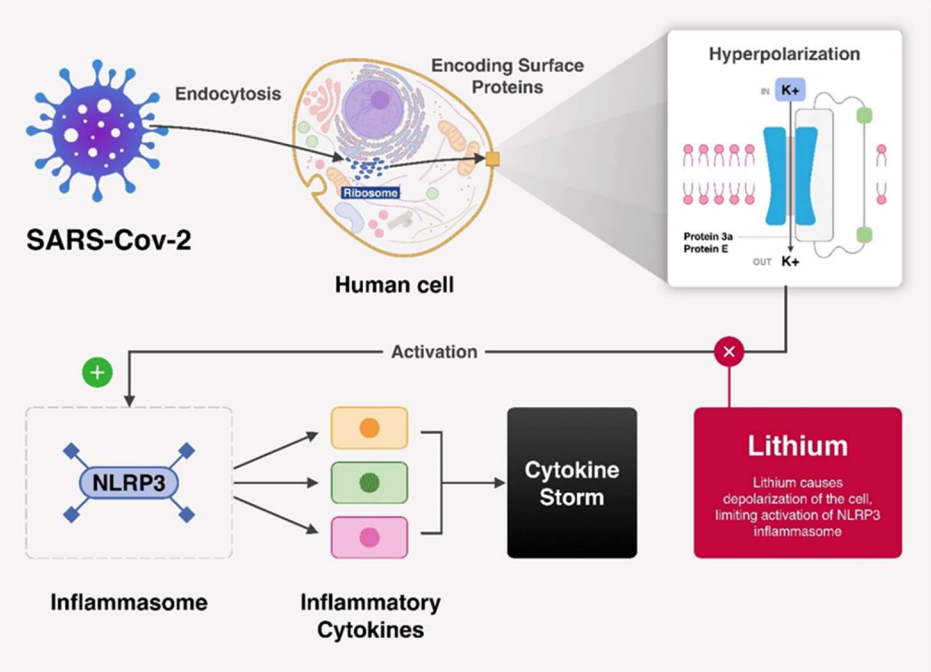

Figure 1. A theoretical scheme of how lithium depolarization interrupts the cascade that leads to NLRP3 activation.

The immunomodulatory actions of lithium are important in the context of fighting coronavirus in terms of three aspects. First, lithium can mitigate the over-activated immune response, which is predominantly driven by macrophages and is responsible for the clinical deterioration and ARDS development. Second, inhibiting the pro-inflammatory cytokines will boost the function of T-lymphocytes [27] to clear the virus from the body. Third, lithium increases the production of neutralizing antibodies from B-lymphocytes that work to block the entry of the virus, and lithium can balance the activity of T-lymphocytes in the sense that no over-activation or under-activation takes place.

Based on the collective understanding presented in Sections 2 and 3, lithium has the potential to stop the progression of COVID-19, prevent its clinical deterioration, and decrease the number of patients requiring mechanical ventilation as part of ARDS or respiratory failure treatment. Also, it is concluded that lithium has the potential to regulate the immune response in a way that mitigates the over-activation of immune reactions, but preserves the capacity of immune cells to kill the virus.

Here, in the context of membrane depolarization induced by lithium, magnesium ions should be mentioned. Interestingly, magnesium also depolarizes the membrane potential [58–60]; hence magnesium can augment the antiviral actions of lithium. However, since the effect of membrane depolarization is determined by the ion transport through the sodium channels, lithium will have a higher tendency to depolarize the membrane potential because sodium channels are more selective for lithium than magnesium [61].

4. COVID-19 Patients on Lithium: Expectations, Probabilities, and the Anti-Viral Action of Lithium

The immunomodulatory effects of lithium have been discussed [55,62]. As the number of diagnosed COVID-19 cases was approximately 96 million as of 19 January 2021 [63], one should expect that these numbers are likely to contain patients who are already on lithium due to bipolar disorder or other special indications. Nevertheless, these patients' data might not be accurate in adopting or refuting the hypothesis of lithium as a treatment for COVID-19, because long-term treatment is associated with normalization of immunomodulatory effects of lithium, or sometimes resistance to these effects [37,64].

However, what motivates testing our hypothesis and considering lithium as potential drug for COVID-19 is the documented anti-viral actions of lithium, as in the following points:

1. The possible antiviral activity of lithium was first reported in 1970, when the viral capsid of adenovirus type 7, which is a DNA virus, was disrupted by lithium iodide on laboratory bases [65]. The first in vitro inhibition of viral replication was reported in 1980, when lithium chloride inhibited the replication of type 1 and 2 herpes simplex virus (HSV), and this effect was thought to be due to the inhibition of DNA synthesis mediated by a decrease in DNA polymerase synthesis, but not its activity [66]. Moreover, the antiviral action of lithium against HSV includes the interruption of the virion-associated inhibition of host protein synthesis, and even the restoration of the protein synthesis process of the host cells [67].

2. An in vitro study on human cell lines already treated with lithium showed promising results in terms of reduction in extracellular herpes simplex virus yield [68]. Interestingly, a randomized, double-blind, placebo-controlled trial of using oral lithium carbonate on patients with a recurrent herpes simplex infection showed a decrease in the rate, duration, and severity of infections [69].

3. Moreover, it was suggested that lithium exerts antiviral activity against HSV by decreasing the intracellular potassium ions that might be required for a potassium-dependent biochemical event that occurs inside the cell [70]. Lithium showed inhibition of both DNA polymerase synthesis and activity [70]. Though this event lacked specificity, it opened the door to the overlooked electrophysiological effects of lithium and their main role in immunomodulation, as suggested in our paper.

4. Lithium showed antiviral actions against other DNA viruses. It inhibited the early stage replication of porcine parvovirus (PPV) in vitro, but it did not affect PPV entry and attachment to cells [71]. In another in vitro study, lithium decreased the viral DNA and proteins of canine parvovirus (CPV) and inhibited its entry into cells [72].

5. In RNA viruses, multiple studies have explored the antiviral effects of lithium. The first study of lithium effects on a coronavirus subtype was in 2007, in which the production of virus progeny of avian coronavirus infectious bronchitis virus (IBV) in cell culture was reduced in a dose-dependent manner [73]. However, lithium inhibitory effect on IBV, which is an RNA virus, is different from the inhibitory effect on DNA viruses such as HSV, because lithium decreased the IBV nucleocapsid (N) protein and RNA levels, and did not have a direct virucidal effect, but lithium inhibited HSV directly by inhibiting its DNA synthesis [73]. Interestingly, another in vitro study investigated the inhibitory effect on a virus that belongs to the family of coronaviruses, transmissible gastroenteritis coronavirus (TGEV) [74]. The data indicated that lithium inhibited cell apoptosis induced by TGEV, and this inhibition of apoptosis by lithium was mediated via suppressing the expression of Caspase-3, a key mediator of apoptosis in mammalian cells [74]. The inhibition of Caspase-

3-induced cell death is thought to be the action responsible for the antiviral effect of lithium against TGEV and even SARS-CoV, because the two viruses can activate Caspase-3 pathways that lead to apoptosis [74]. More interestingly, membrane depolarization originated by blocking potassium channels inhibits Caspase-3 [75]. This is very consistent with our hypothesis that lithium inhibits apoptosis via membrane depolarization.

6. Other experiments targeting respiratory RNA viruses showed promising results. An in vitro study that evaluated the effect of lithium chloride on porcine reproductive and respiratory syndrome virus (PRRSV), which is an RNA virus, showed that viral RNA and protein levels were reduced upon applying lithium chloride, which also inhibited early phases of replication by upregulating TNF-alpha [76]. Similarly, lithium chloride decreased both RNA and protein levels of the avian leucosis virus (ALV), which is an RNA virus [77]. Also, lithium chloride inhibited the early phases of ALV replication and decreased the mRNA of the pro-inflammatory cytokines such as IL-6 and IL-1-beta [77]. Additionally, in a study conducted on nine patients affected with human immunodeficiency virus-1 (HIV-1), lithium could successfully reduce viremia, HIV-1 copies, and cell-associated HIV-1 RNA transcripts, but all these effects were lost after 12 weeks of therapy [78].

7. In a large retrospective study on patients taking lithium, a preliminary report showed a statistically significant reduction in the mean yearly rates of flu-like infections [79]. Moreover, a prospective study following up with bipolar patients on lithium treatment found that the incidence rate of respiratory infections was reduced by 28% [80]. In a recent preliminary observational study, six patients with severe COVID-19 were treated with lithium carbonate. Those patients showed decreased reactive C-protein, increased lymphocyte numbers, and a decreased neutrophil-lymphocyte ratio [81]. This is consistent with the immunomodulation of lithium, and possibly with the other actions proposed in this paper.

In conclusion, theoretical and clinical evidence are in favor of clinical trials to test the acute intervention of lithium as a potential treatment for COVID-19, and to test our hypothesis that relates the anti-viral effects of lithium with membrane depolarization.

5. The Relevant Safety of Lithium and Its Administration

If lithium is considered in treating COVID-19 patients, the safety profile should be addressed to avoid any possible complications or side effects. The toxicity of lithium can be classified as acute, acute on top of chronic, and chronic. The most common type is chronic toxicity, especially in bipolar patients who use it for many years. This type of toxicity is unintentional because several associated factors can increase blood levels of lithium, such as lithium-induced diabetes insipidus, an age older than 50, drug interactions, and renal impairment [82]. The chronic toxicity develops over weeks because lithium starts to accumulate in brain and other tissues during these weeks [82]. More specifically, it has been shown that lithium accumulates in the brain tissue of rats chronically over three weeks [83]. However, in the context of treating COVID-19, which is an acute condition unlike bipolar disorder, lithium can be used for less than three weeks to decrease the chances of lithium toxicity, especially in high-risk patients. Ingestion of more than 7.5 mg/kg of elemental lithium, which corresponds to 1.4 mmol/L serum concentration and approximately 40 mg/kg of lithium carbonate, is associated with increased risk of toxicity, hence the therapeutic concentration range is 0.6–1.2 mmol/L in acute mania and 0.4–1.0 mmol/L in chronic prophylaxis therapy [82]. If lithium is considered in clinical studies for further evaluation, we suggest that lithium should be given at 450 mg twice daily for 10 days, and serum lithium must be measured 12 h after the dosing on the fourth day to ensure reaching the therapeutic concentration 0.6–1.2 mmol/L, and monitoring should be more frequent if the concentration is abnormal [84]. Additionally, every patient on lithium must have baseline for the following [84]: 1. Electrocardiogram (ECG) to detect any electrical abnormalities in the heart; 2. Kidney function tests (KFT) and urine analysis; 3. Thyroid stimulating hormone (TSH) to detect and control hypothyroidism; and 4. Electrolytes, especially calcium. All of these parameters are helpful in detecting any side effects that occur

after initiating lithium therapy. Furthermore, we suggest the following exclusion criteria in patients to avoid lithium toxicity [84]: 1. Patients with creatinine clearance less than 30 mL/minute; 2. Patients with significant cardiovascular disease; 3. Patients with acute kidney injury (AKI); 4. Patients with poor oral intake; 5. Patients who are hemodynamically unstable; 6. Elderly patients older than 75 years; 7. Pregnant women; and 8. Patients with psoriasis. In patients with a creatinine clearance of 30–89 mL/minute, lithium should be initiated with a low dose and titrated slowly with frequent monitoring [84].

Lithium can be administered orally in patients with mild and moderate disease, or even in patients with severe disease who can tolerate oral tablets to prevent the progression into ALI or ARDS. However, a challenge arises when patients are critically ill or cannot tolerate oral tablets, because the use of the injectable form of lithium is not within the routine clinical practice, and the use of forms other than the oral form in the treatment has not been addressed in the literature. Thus, if lithium is considered in COVID-19, it is important to assess the feasibility of using different routes of administration in patients who cannot tolerate the oral form. One possible way to involve oral lithium in such patients is to start with the conventional management of COVID-19 until the patients are stabilized and can take lithium orally [81].

Furthermore, our hypothesis is based on the conventional lithium salts used in bipolar patients such as lithium chloride, lithium carbonate, and others. Our hypothesis depends on the presence of positive lithium ions to depolarize the membrane [28–30], and these positive ions are found in the conventional lithium salts used in bipolar patients.

To the authors' knowledge and according to literature, there is no evidence against the ability of lithium ions to distribute to infected pneumocytes as they distribute to neurons to treat bipolar patients and to immune cells to modulate their function.

6. Summary

According to the previous sections, lithium can fight SARS-CoV-2 via three different aspects via membrane depolarization. First, lithium can suppress the NLRP3 activation mediated by protein 3a and protein E. Second, lithium can arrest the cell death cascade mediated by protein 3a and protein E. Third, lithium can modulate the immune system function to alleviate its harmful effects and to clear the virus from the body. Moreover, the relationship between the antiviral actions of lithium and membrane depolarization has not been addressed previously, and we encourage readers to test this relationship to prove its validity in the antiviral action of lithium. Table 1 summarizes the therapeutic effects of lithium for COVID-19.

Table 1. Summary of the therapeutic effects of lithium for COVID-19 via membrane depolarization.

NLRP3 Suppression	Cell Death Inhibition	Immunomodulation
Lithium prevents the activation of NLRP3 inflammasome, which is implicated in the release of pro-inflammatory cytokines in the cytokine storm.	Lithium inhibits cell death cascade, resulting in a decrease in viral release, attenuation of immune system over activation, and a decrease in lung parenchymal damage.	Lithium can balance immune system function in such a way that prevents the harmful effects of over-activation, but guarantees a level of activation that can fight and clear the virus.

In conclusion, our review proposes lithium as a potential drug to treat COVID-19 because it exhibits a strong ability to orchestrate the dysregulated immune response via the targeting of different aspects in the viral pathogenesis. We suggest that using lithium alone or along with other drugs could improve the rates of morbidity and mortality, and this should prompt the testing of lithium in pre-clinical and clinical studies to prove its validity in treating COVID-19. Additionally, shedding light on the linkage between membrane depolarization and the antiviral actions of lithium makes the present review distinct and

informative if it is compared with other studies that focused on the role of lithium in COVID-19 [85–87].

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