Alpha Lipoic Acid as a Potential Treatment for COVID-19 – A Hypothesis

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SARS-CoV-2 infection has led to COVID-19 outbreak worldwide. To date, a specific antiviral drug does not exist to treat the disease and control the virus. In this paper, we have explored the potential utility of alpha lipoic acid, an anti-inflammatory and antioxidant molecule, for treatment. Alpha lipoic acid exhibits strong antioxidant properties and modulates the immune system by regulating T cell activation making it a useful therapeutic candidate for cytokine storm triggering SARS-CoV-2 infection. In the present communication, we focused on the therapeutic potential of ALA with respect to its potential role on reducing the severity of symptoms and the adverse effects of other antiviral drugs used. We consider different mechanisms by which modulating ACE2 levels after virus replication and preventing cytokine storm and also focus on a new therapeutic venue that utilizes ALA.

Keywords: ACE2, Alpha lipoic acid, COVID-19, Cytokines, SARS-CoV-2, T cell

Abbreviations Used: Angiotensin-converting enzyme 2, ACE2; Alpha lipoic acid, ALA; Alanine aminotransferase, ALT; Aspartate aminotransferase, AST; Dihydriolipoic acid, DHLA; Interferon-gamma, IFN-γ; Interleukin-6, IL-6; Monocyte chemoattractant protein-1, MCP-1; Nuclear factor kappa B, NF-κB; Severe acute respiratory syndrome coronavirus 2, SARS-CoV-2; Tumor necrosis factor-α, TNF-α

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INTRODUCTION

COVID-19 is a disease that is caused by SARS-CoV-2, which has rapidly spread and evolved into a worldwide outbreak since December 2019 leading to unsurmountable difficulties for healthcare systems globally (Contini et al., 2020). To date, no active therapeutic agent has been found to cure severe COVID-19 (Hassan et al., 2020; Padron-Regalado, 2020; Singhal, 2020; Wang et al., 2020). Besides, multiple studies on developing vaccines continue widely for prophylactic effects. To date, two vaccine candidates have successfully been established recently, thus promising prophylaxis (Walsh et al., 2020).

CORONAVIRUS INDUCED CYTOKINE STORM AND ALPHA LIPOIC ACID

CoVs have been reported to be nonsegmented RNA viruses that cause zoonotic infections and show steady mortality rate in humans (Lu et al., 2020). These viruses consist of four structural proteins which are E, M, N, and S proteins (Rota et al., 2003). The S protein is the key constituent that is responsible for invasion of CoV. It mediates cell membrane fusion (Hulswit et al., 2016). The host cell receptor for SARS-CoV-2 is the ACE2 present in numerous tissues including alveolar epithelial cells, endothelial cells of blood vessels, and smooth muscle cells (Kai et al., 2020). The invasion of SARS-CoV-2 in host cells occurs via interaction of the S protein and ACE2 (Mathewson et al., 2008). In studies, it was determined that the situation where ACE2 receptors mediate and cause virus replication during SARS-CoV-2 invasion causes a decrease in ACE2 levels, leading to an increase in ACE1-mediated angiotensin II level and thus lung and heart damage (Guo et al., 2020; Huang et al., 2020). Angiotensin II effects the formation of free oxygen radicals by influencing the metabolism of smooth muscle cells and increasing the activity of NADPH oxidase. Free oxygen radicals play an essential role in virus invasion, organ damage, and systemic inflammatory response (Zhang et al., 2007, 2020a). Therefore, increasing ACE2 levels after viral replication will provide protection (Kai et al., 2020).

Rapidly emerging literature and reports indicate that SARS-CoV-2 infection affects the CD4 and CD8 proteins on T cells, and
plays a role in inflammation due to overexpression of cytokines such as IFN-γ, IL-6, MCP-1, and TNF-α and transcription factor, NF-κB (Zhai et al., 2016). Thus, suggesting that cytokine storm may play a role in the progression of COVID-19 (Liu et al., 2020; Saghazadeh et al., 2020). Therefore, effective suppression of cytokine storm will be an important way to save the lives and help patients to fight against COVID-19 (Fu et al., 2020; Ye et al., 2020; Zhang et al., 2020b). de Queiroz et al. (2015) have shown that ALA plays a role in decreasing cytokine expression by affecting CD4 and CD8 proteins on T cells which will play a preventative role in tissue damage by increasing the ACE2 activity. Upon SARS-CoV-2 invasion in the cell, viral replication occurs and cause decrease in the ACE2 activity. This leads to increase in cytokine expression associated with cardiopulmonary damage. Therapeutic use of ALA decreases ACE2 levels after viral replication which will increase the angiotensin II level that will reduce cardiopulmonary damage. This is accomplished through angiotensin II reducing the formation of free oxygen radicals by increasing the activity of NADPH oxidase (Fig. 1). Previous studies have demonstrated that ALA and its metabolite, DHLA with two thiol groups per molecule, are more potent reductants than glutathione that inhibits reactive oxygen species such as superoxide, hydroxyl, and hypochloric acid by suppressing the

**FIGURE 1** | SARS-CoV-2 reduces ACE2 levels, increases ACE1 levels through T cell activation after replication, thereby causing cytokine expression. ALA administration after SARS-CoV-2 replication will alter ACE1 increase and ACE2 decline to prevent cytokine expression and thus cardiopulmonary damage.
NADPH oxidase activity (Dulundu et al., 2007; Cakir et al., 2015; Wang et al., 2016; Savtekin et al., 2018; Aksoy et al., 2019; Sehirli et al., 2019). Free oxygen radicals trigger the binding of cytokines such as IFN-γ, TNF-α, MCP1, and IL-6, and the transcription factor NF-κB to membrane receptors by affecting the T cells. In this case, free oxygen radicals act as a secondary messenger within the cell (Agostinis et al., 2015; Fei et al., 2016; Aksoy et al., 2019; Sehirli et al., 2019). Besides, ALA has enhancer effects also on different antioxidants such as coenzyme Q10, vitamins C and E, and increases intracellular levels of these antioxidants (Busse et al., 1992; Bharat et al., 2002). In line with these studies, ALA may decrease the ACE2 activity after replication of the SARS-CoV-2, and reduce the NADPH oxidase activity leading to suppression of the increase in cytokine expression (Fig. 1).

**ANTIVIRAL EFFECTS OF ALPHA LIPOIC ACID**

Several different treatment options that have been suggested as a COVID-19 specific treatment include antiviral treatments, immune enhancers, even some nutritional interventions, and few other compounds with potential therapeutic administration. Nutritional interventions that could have a positive effect on the host immune response against viral infections have been suggested as supportive treatment in conjunction with antiviral treatments. Administration of ALA after SARS-CoV-2 replication may diminish ACE1 increase and ACE2 decrease, thereby contributing to the prevention of cardiopulmonary damage by preventing cytokine expression. Previously, it has been shown that influenza virus (IVFujian01) increases NF-κB and caspase activities in MDCK cells. Cells with low NF-κB activity are resistant to influenza virus infection (Nimmerjahn et al., 2004). Thus, preventing NF-κB activation plays a major role in the treatment of influenza virus infection. ALA has been shown to inhibit influenza spread by blocking NF-κB activation (Bai et al., 2012). Another study has shown that ALA prevents TNF-α-mediated apoptosis caused by influenza A virus (Severa et al., 2007).

Additionally, ALA has been demonstrated to inhibit HIV replication by regulating the T cell activity such as CD4+ and CD8+ and by suppressing NF-κB and other cytokines (Jarirwalla et al., 2008). Further, ALA has been found to have a protective effect on alveolar cells against HCoV 229E infection in pulmonary cells which are under high oxidative stress due to HCoV 229E infection, and by reducing the NADPH oxidase activities and increasing GSH levels (Wu et al., 2008). In line with the above-mentioned studies, use of ALA prevents growth against the vaccinia virus by regulating the NK-kB and IFN-γ activations (Spisakova et al., 2009). In addition to human studies, ALA has also been determined to be a potent supportive agent in bovine rhinotracheitis disease in veterinary medicine (Schmidt et al., 2006).

ALA, a natural substance found in some foods and also synthesized in the body (Reed, 1951), has been shown to ameliorate heart, soft tissue, and bone damage caused by Coxsackievirus B3 (Kim et al., 2013). It has also been stated that it improves ALT and AST levels against the hepatitis C virus and shows protective effect by reducing oxidative damage and cytokine expressions (Melhem et al., 2005). ALA is also shown to be supportive in the therapy of postinfection olfactory dysfunction. ALA was further shown to significantly improve the smell sensitivity measured by “threshold, discrimination, and identification; TDI” score and lowered the rate of “parosmia”/“troposmia” (Hummel et al., 2002).

**CONCLUSION**

We suggest that ALA, used after viral replication, may alleviate the prognosis of the disease by regulating T cell activity and suppressing NF-κB. Besides, ALA being also used as an immunomodulator allows us to speculate its potential use and benefits of use in combination with antiviral agents may prove to be a more effective treatment of choice by reducing the side effect potential of those drugs. This is principally because of the fact that ALA will reduce the NADPH oxidase activity resulting in decreased cytokine expression, free oxygen radicals, and thus tissue damage. Inhibiting virus replication as well as limiting excess inflammation is very important to the treatment of COVID-19. For this purpose, the agents regulating the immune system should be considered together with antiviral treatments. ALA, having the potential of inhibiting cytokine expression, allows us to speculate on its potential benefit of use in balancing cytokine storm.

**CONFLICT OF INTEREST DECLARATION**

The authors state that there are no conflicts of interest to disclose.

**AUTHOR CONTRIBUTIONS**

SS, AO, and NS conceived the idea for the manuscript, performed literature search, and data analysis. SS and AO drafted the manuscript and NS critically revised the manuscript.

**REFERENCES**


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