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Opinion

Harnessing the Antiviral and Anti-inflammatory Properties of Copper and Zinc Chlorophyllins: A Potential Therapeutic for COVID-19 Patients with Acute Respiratory Distress Syndrome

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Abstract

Chlorophyllins are highly soluble non-toxic derivatives of chlorophyll α, containing a centralised metal at their core, known to target and treat cancer and immune-based diseases. The antiviral and anti-inflammatory effects of sodium copper chlorophyllin (SCC) and sodium zinc chlorophyllin (SZC), though documented, are rarely considered in treatment of viral respiratory diseases. Moreover, the use of chlorophyllins to potentially treat acute respiratory distress syndrome (ARDS), triggered by infection with respiratory viruses such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has yet to be studied. The published literature suggests antiviral and anti-inflammatory effects against SARS-CoV-2 and other enveloped respiratory viruses. Treatment with chlorophyllins inhibits virus entry, as well as replication and budding of viral progeny from the host cell in cell lines infected with enveloped respiratory viruses. Furthermore, treatments with SCC *in vivo* show diminished viral loads in animals infected with respiratory viruses, suggesting clinical antiviral capacity in treating viruses that cause ARDS-like manifestations, notably coronavirus disease 2019 (COVID-19). Similarly, SZC reduces inflammatory responses, while SCC may block key pro-inflammatory markers *in vitro* and *in vivo*, producing an anti-inflammatory effect against interleukin-6 and tumour necrosis factor α, two of the main antagonists associated with poorer outcomes in viral respiratory diseases, particularly among COVID-19 patients. This indicates a possible application in treating cytokine storm and hyperinflammation. Both SCC and SZC could act as a novel therapeutic in the treatment and prevention of ARDS and related respiratory complications, especially relevant to severe COVID-19 cases.

Keywords: SARS-CoV-2, COVID-19, ARDS, respiratory virus, therapy

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1 INTRODUCTION

Clinical infections of respiratory viruses can lead to acute oxidative stress and severe disease[1]. Existing therapies for the severe clinical manifestation of acute viral respiratory distress syndrome carry significant limitations. For instance, treatment with antivirals may result in serious adverse events, including increased oxidative stress, relapse of disease, hallucinations, genotoxicity, and emergence of immunogenic variants of the viral pathogen[2-5]. Similarly, current anti-inflammatories for acute respiratory distress syndrome (ARDS) do not successfully inhibit important biomarkers linked to acute disease phases, especially those shown in clinical investigations to induce cytokine storm syndrome (CSS) and hyperinflammation, such as interleukins (IL)-6, IL-8, IL-12 and tumour necrosis factor α (TNF-α)[6,7]. Hence, single regimen antivirals and anti-inflammatory drugs are largely ineffective at reducing progression to ARDS[8], which is associated with high mortality[9]. Furthermore, available antivirals are less effective at preventing hospitalization of at-risk patients from viral lower respiratory tract infection unless taken at onset of symptoms[10]. Thus, there is a pressing need to evaluate novel therapeutics, especially to manage ARDS induced by coronavirus disease 2019 (COVID-19). It is in this context that consideration should be given to harnessing cations of copper and / or zinc. These essential trace elements play a role in normal metabolic and immune function[11], but comparatively little is known of their immunomodulatory response to respiratory virus infection[12,13].

2 KNOWLEDGE GAPS

Strong antioxidant effects of natural chlorophyll α and dose-dependent anti-inflammatory effects of sodium copper chlorophyllin (SCC) and sodium zinc chlorophyllin (SZC) have been documented[14,15]. Antiviral activities against, for instance, influenza, have been demonstrated for SCC[16]. Yet, this has not been investigated for SZC, although zinc alone has antiviral effects[17]. Despite promising activities, SCC and SZC are rarely considered in the treatment of viral respiratory diseases. Both copper and zinc inhibit human coronaviruses *in vitro*[18]. Moreover, low serum copper / zinc levels appear to correlate with poorer outcomes for COVID-19 patients[19,20]. Importantly, other derivatives of chlorophyll α (such as pheophorbide α, which lacks a central metal ion in the tetrapyrrole ring structure) have been shown to inhibit severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) *in vitro*[21,22], suggesting that SCC and SZC may likewise inhibit human coronaviruses[23-25]. Furthermore, while the anti-inflammatory capacity of SZC is only reported topically, with mechanisms unknown, in cancer studies SCC has been shown *in vivo* to block a number of pro-inflammatory markers, including IL-6 and TNF-α[26-28]. Controlled comparisons have not yet been performed between SCC, SZC and standard anti-inflammatories, especially those currently used to treat COVID-19, e.g., the immunosuppressive drug tocilizumab (sold under the brand names Actemra and RoActemra, among others). This is a humanized monoclonal antibody against the IL-6 receptor that is given intravenously to patients as a weekly injection or as an infusion once a month. Alternatives that are cheaper and simpler to administer than tocilizumab are sought as a therapeutic option to undergo clinical trials.

3 HYPOTHESIS

Despite clinical trials indicating that SZC is similar to SCC in terms of antimicrobial properties[29], and lack of toxicity[30], to date no study has investigated the antiviral effect of SZC. Given that zinc on its own has been shown to inhibit SARS-CoV[23,31], it is possible that SZC also possesses antiviral effects against this coronavirus. This suggests the potential clinical use of these compounds as antivirals in viral respiratory disease, notably COVID-19 and ARDS. It is hypothesized that if SZC behaves similarly to SCC it should downregulate pro-inflammatory biomarkers associated with CS. Hence, dietary supplementation and / or treatment with SCC and SZC could improve disease outcome in ARDS patients.

4 CONCLUSION

SCC and SZC are complexed with the divalent metals copper and zinc, respectively, which are two micronutrients responsible for immune modulation and pathogen control. Future research underpinned by the described hypothesis is expected to generate *in vitro* evidence of anti-inflammatory and antiviral action of SCC and SZC. If successful, it may be speculated that oral or other administered treatments containing SCC and / or SZC could present safe and effective co-therapeutic options for viral respiratory infections. As many as eight different respiratory viruses are implicated in the upregulated immune response that leads to CSS[32]. Pre-clinical studies could follow in order to determine the therapeutic potential of these compounds to treat specific manifestations of ARDS.

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Conflicts of Interest

The author declared no conflict of interest.

Author Contribution

The author solely contributed to draft the manuscript and

approved the final version.

Abbreviation List

ARDS, Acute respiratory distress syndrome
CSS, Cytokine storm syndrome
IL, Interleukin
SARS-CoV, Severe acute respiratory syndrome coronavirus
SCC, Sodium copper chlorophyllin
SZC, Sodium zinc chlorophyllin
TNF, Tumour necrosis factor

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