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Pulmonary delivery of nanostructured lipid carriers for effective repurposing of salinomycin as an antiviral agent

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ABSTRACT

Coronavirus disease outbreak caused a severe public health burden all over the world. Salinomycin (SAL) is a broad-spectrum antibiotic that had drawn attention in selective targeting of cancer and viral infections. Recent drug screen identified SAL as a potent antiviral agent against SARS-CoV-2. In this hypothesis, we discuss the potential of pulmonary delivery of SAL using nanostructured lipid carriers (NLCs) against SARS-CoV-2.

Introduction

Coronaviruses (CoVs) are enveloped, single-stranded RNA viruses belonging to the family *Coronaviridae* within the order *Nidovirales*. Coronaviruses (CoV) are of four different genera, α, β, γ, and δ CoVs. Among these β CoVs like SARS-CoV, Middle East respiratory syndrome (MERS-CoV), and novel coronavirus (SARS-CoV-2) is responsible for severe and potentially fatal respiratory infections [1–3] Table 1..

It was reported that CoVs enter host cells Angiotensin-Converting Enzyme-2 (ACE-2) receptor-mediated endocytosis, which is a pH-dependent process. In this process, Spike (S) protein plays a major role in receptor binding and membrane fusion of SARS-CoV-2 for entry into host cells. It contains a large ectodomain, transmembrane anchor, and a short intracellular tail. The ectodomain of SARS-CoV-2 consists of two subunits. S1 subunit of SARS-CoV-2 is responsible for binding with the ACE-2 receptor for viral entry to host cells. Following receptor binding, the SARS-CoV-2 enter the cytosol of the host cell, by pH-dependent proteolytic cleavage of spike protein by TMPRSS2. Then the fusion of viral and host cell membranes occurs in acidified endosomes, allowing viral genomes to affect host cells with the aid of the S2 subunit [1,4,5].

Coronavirus disease 19 (COVID-19) caused by SARS-CoV-2 was the pandemic, affected nearly 1,400,000 people worldwide as on 7 April 2020, according to WHO. However, rapid spread, potential mortality, and lack of clinically approved drugs and vaccines against COVID-19 are the major challenges. There is a need, therefore, for quick discovery of drugs against this emerging infectious disease. However, the slow phase of discovery and associated costs are the major challenges in discovering drugs against SARS-CoV-2.

Drug repurposing using existing drugs is an attractive strategy to accelerate drug discovery against COVID-19. Recently researchers focused on screening of FDA approved drugs against SARS-CoV-2 [6–8]. Salinomycin (SAL) is a carboxylic polyether ionophore isolated from Streptomyces albus. Ionophores show a broad spectrum of bioactivity, like antibacterial, antifungal, antiparasitic, antiviral, and recently, they are also used as anti-tumor agents [9]. However, poor absorption, low bioavailability, and off-target effects are the potential limitations for effective repurposing of SAL as an antiviral agent against SARS-CoV-2. In the present study, we, therefore, propose the pulmonary delivery of SAL using nanostructured lipid carriers (NLCs).

Hypothesis

In the present study, we proposed to prepare NLCs for intra-pulmonary delivery of SAL to prevent SARS-CoV-2 infection (Fig. 1). The proposed drug delivery system with the following advantages:

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Table 1
FDA approved drugs used for treating SARS-CoV-2 infection.

Drug	Clinical use	Possible mechanism against SARS-CoV-2	Ref.
Arbidol	Influenza	Disruption of binding of viral envelope protein to host cells	[10]
baricitinib	Rheumatoid arthritis	JAK inhibition, anti-inflammatory effects	[11]
chloroquine	malaria	Alteration of endosomal pH	[12]
favipiravir	HIV	Inhibition of viral RNA synthesis	[13]
galidesivir	hepatitis C, Ebola and Marburg virus	Inhibition of viral nucleotide synthesis	[14]
lopinavir	HIV	Inhibition of viral protease	[15]
remdesivir	Ebola	Inhibition of viral nucleotide synthesis	[16]
ribavirin	RSV infection, hepatitis C, hemorrhagic fever	Inhibition of viral nucleotide synthesis	[14,17]

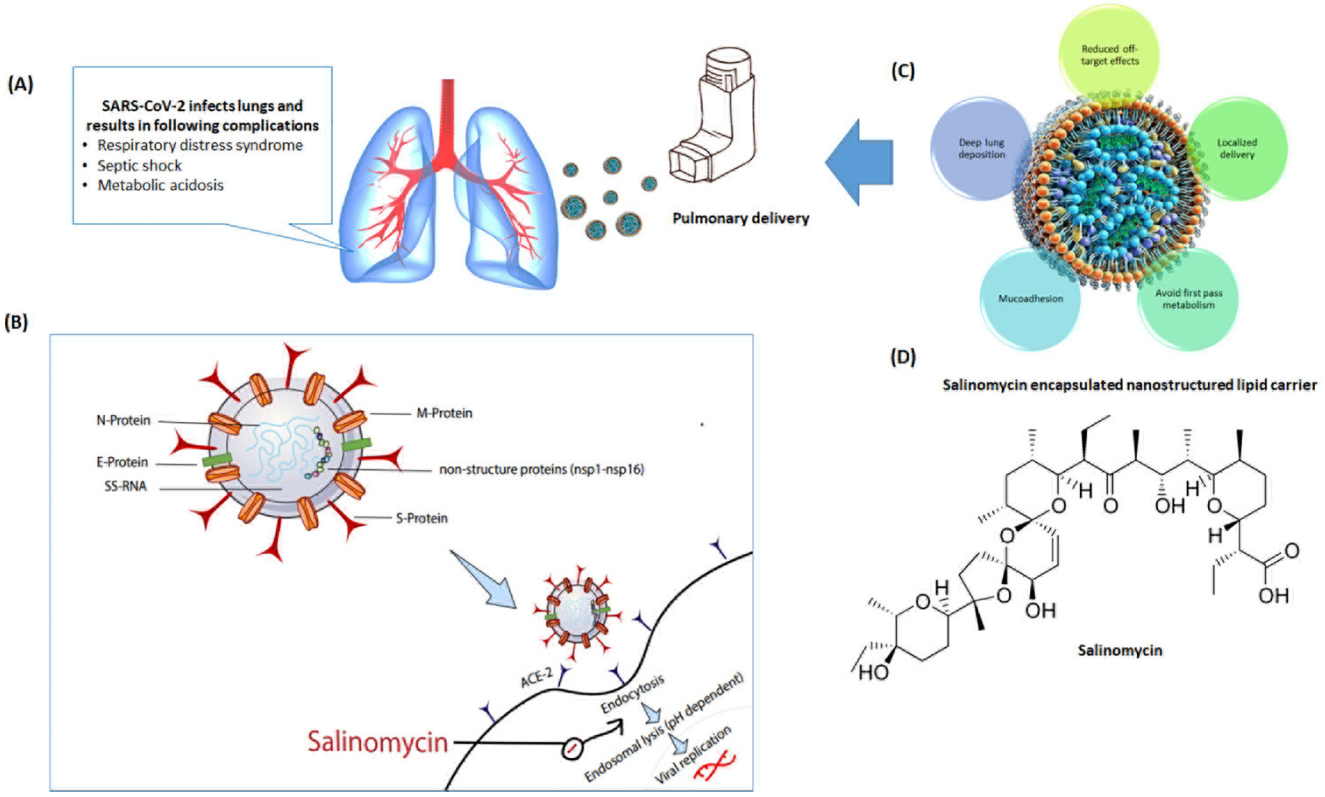

Fig. 1. A. Respiratory complications due to SARS-CoV-2; B. Mechanism of action SAL as an antiviral agent against SARS-CoV-2; C. Advantages of inhaled NLCs, D. Structure of SAL.

- Noninvasive means of administration
- Localized delivery to lung epithelium directly
- Avoid first-pass metabolism
- Reduced off-target effects
- Rapid and effective drug absorption

Justification of the proposed hypothesis

For all enveloped viruses, the significant step of entry into host cell is fusion. SARS-CoV-2 fusion occurs in low pH with a half-maximal rate of fusion at pH 5.5. A compelling body of evidence suggests, SAL inhibits replication of viral RNA in the cytoplasm by altering the pH. SAL, therefore, has the potential to prevent the entry of SARS-CoV-2 into the cytosol and prevent membrane fusion (a pH-dependent process) [18]. It was reported that SAL has antiviral propensity by preventing the migration of nuclear protein (NP) to form a viral ribonuclear complex (VNP). This fails to acidify the endosomal-lysosomal compartments due to cytoplasmic accumulation of NP in the host cells [18,19]. It was also reported that SAL could interact with S- protein, and influence ACE2 binding and prevent the release of viral RNA into the cytoplasm [20]. Besides, a recent drug screen identified SAL as a potential antiviral agent against SARS-CoV-2 (IC_{50} = 0.24 μM) [19]. However, the clinical efficacy of SAL against SARS-CoV-2 needs to be evaluated.

Pulmonary delivery is an attractive strategy for localized delivery of therapeutics to infection sites. Besides, inhaled nanoparticles overcomes the limitations of poor bioavailability and drug absorption. NLCs are biocompatible nanocarriers with good tolerability for pulmonary delivery. Due to their size in nanometers, NLCs can be easily aerosolized into droplets with suitable aero-dynamical properties. This enables deep lung deposition of an active compound. Furthermore, NLCs adhere to the mucosal surface of the lung for a more extended period compared to larger particles due to the small size. Particle adhesion, accumulation, and retention in the lung as well as prolonged-release due to NLCs results in enhanced and sustained therapeutic effects. NLCs have advantage of better patient compliance [21–25]. All these advantages of inhaled NLCs play an essential role in the treatment of respiratory infections like COVID-19.

Conclusion

There are several investigational drugs and drugs under preclinical trials for prevention/curative purposes of COVID-19, but still, there is

no current approved drug. SAL has the ability to disruption concentration across the cell membrane and prevents virus entry into the host cells by selective targeting of SAL. Encapsulation of SAL in NLC for pulmonary delivery is an attractive approach for effective repurposing of SAL as an antiviral agent by improving its absorption at the infection site.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.109858.

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