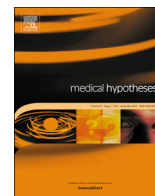




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## Aminoglycosides can be a better choice over macrolides in COVID-19 regimen: Plausible mechanism for repurposing strategy

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### ABSTRACT

In the current COVID-19 pandemic, prioritizing the immunity enhancers is equally important to anti-virals. Defensins are the forgotten molecules that enhance the innate immunity against various microbes. Although macrolides like azithromycin and clarithromycin etc., have been reported to act against respiratory infections but they lack the ability of immunity enhancement through defensins. The aminoglycosides were proved to have defensin mediated antiviral activity, that could enhance the immunity. So, Consideration of aminoglycosides can be a double edge sword *viz.*, against respiratory infection as well as Immunity enhancer (along with anti-virals) for COVID-19 regimen.

### Introduction

Although various nations throughout the globe making several strategies *viz.*, different drug combinations, proposing lock downs and herd immunity etc., to control the wide spread of COVID-19 and to tolerate its severity, the radical behaviour of virus is evident. Understanding the virus behaviour, its complete genome, identifying suitable therapeutic targets, cost and ethical issues are the bars to come with new molecule, in the current (pandemic) situation. So, drug repurposing strategy *i.e.*, application of widely and existing approved drugs for different focus, could be an ideal approach in the current pandemic situation. The current situation enlightened many people about importance of immune health which boosted up the usage of various traditional things like ashwagandha, echinacea, licorice and andrographis etc., as immune supplements, out of which andrographolides of andrographis were proved as immune builders through defensins and inhibitor of virus replication [1–3].

Immunity in the respiratory organs is one of the important aspects to consider as they are under continuous challenges with different particulates through inhalation and other contacts with nasal or oral surfaces. In the instances like current pandemic of COVID-19, where infection control becomes a great challenge, immune mediators could be a vital link. So, strengthening respiratory epithelium is also an important aspect to control lung infection [4,5].

Defensins are part of innate immunity and it is the only group of antimicrobial peptides present in both animals (vertebrates and invertebrates) and plants [6,7]. They present in cytoplasmic granules of

immune cells like neutrophils and macrophages along with other antimicrobial factors and if from epithelial cells, released into extra-cellular environment [8]. Defensins (mammalian) are classified as, the alpha, beta and theta defensins, which differ in their distribution and disulphide links (bonds) between conserved cysteine residues. The theta defensins exist as pseudo genes (cannot express) due to the presence of premature termination codon [9]. However, aminoglycosides (AGs) were proved to produce functional peptides from theta defensins (called as retrocyclins) that are active against HIV [10]. So, herewith we hypothesize addition of AGs into the therapeutic regimen of COVID-19, could be a beneficial one (See Fig. 1).

### Genesis of hypothesis and justification

Macrolides like clarithromycin and azithromycin etc., are well known for *H. Influenza* as well as upper and lower respiratory infections. And moreover, certain clinical studies supported the usage of macrolides during panbronchiolitis and cystic fibrosis [11] and also due to their possible anti-inflammatory nature [12]. These might be the reasons for the inclusion azithromycin in combination with hydroxy chloroquine. But we come with novel idea of inclusion of aminoglycosides rather than macrolides with other combinations. As mentioned below, defensins, the natural immune enhancers, could play a role in enhancing the immunity. Although widespread proved research is lacking to claim the ability of Aminoglycosides (AGs) in enhancing the defensins, it has been proved against HIV, which is also a deadly virus. As AGs were proved against deadly immune suppressing virus [10] and

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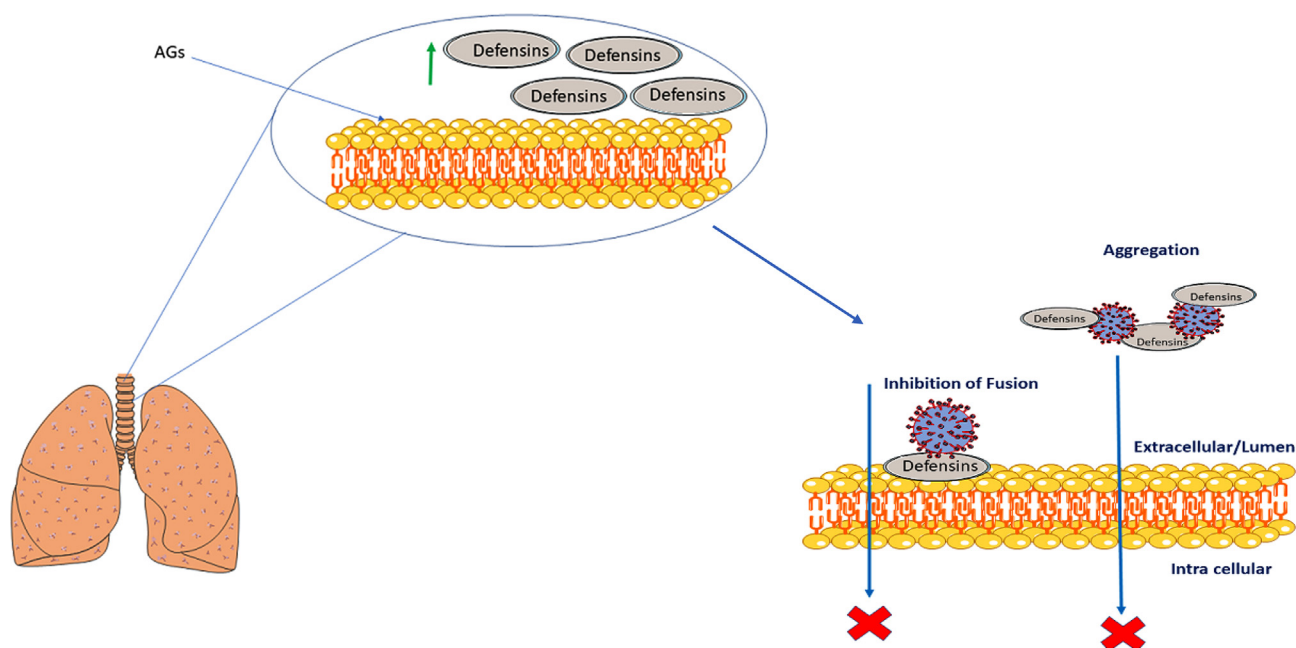


Fig. 1. Plausible mechanism of aminoglycosides in inhibiting COVID-19 through defensins.

moreover AGs are currently in use, they can be used for current situation without any regulatory or ethical restrictions.

Direct instillation of retrocyclins into mouse lung was proved to reduce the mortality from SARS corona virus infection. And moreover, various studies claimed the protective role of defensins against influenza viruses [13–16].

#### Plausible mechanism by defensins

- They promote the viral aggregation which could reduce infectious titers and finally will be cleared from airway [17].
- Defensins can block viral infection by directly acting on the virion or by affecting the target cell and thereby indirectly interfering with viral infection. So, that fusion of virion to target membrane is blocked results in the impairment of replication process [18,19].

#### Conclusion

Drug repurposing strategy is an ideal and rationale strategy to bring the therapeutic product into market in quick times. Although AGs were proved only for their enhancing/modulating capability towards theta defensins (against HIV), their role in enhancing other defensins cannot be eliminated. Since the safety profile of AGs is already established, selection of these drugs for COVID-19 therapeutic regimen could be an ideal choice.

#### 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.

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