Potential Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and novel mechanism insights against COVID-19 through network pharmacology

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Abstract

Background: Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) showed promising clinical efficacy toward COVID-19 patients as paracetamol and antiinflammatory agents, however, the anti-COVID-19 mechanisms of NSAIDs are not exposed. Therefore, we evaluated the most potent NSAIDs and its novel mechanism(s) against COVID-19 by network pharmacology.

Method: Genes related to selected NSAIDs and COVID-19 related genes were identified by Similarity Ensemble Approach, Swiss Target Prediction, and PubChem databases. Venn diagram identified overlapping genes between NSAIDs and COVID-19 related genes. The interactive networking between NSAIDs and overlapping genes was analyzed by STRING. RhoB plotted the bubble chart of KEGG pathway enrichment analysis of overlapping genes. Finally, binding affinity of NSAIDs against target genes was determined through molecular docking analysis.

Results: Gene enrichment analysis exhibited 26 signaling pathways against COVID-19, and inhibition of proinflammatory cytokines and cell death by inactivating RAS signaling pathway was identified as the key anti-COVID-19 mechanism of NSAIDs. MAPK8, MAPK10, and BAD genes were explored as the associated genes against COVID-19. Our study presents that indomethacin may possibly block RAS by inactivating its associated genes, thus may alleviate excessive inflammation induced by SARS-CoV-2.

Conclusion: Overall, our proposed three NSAIDs may possibly block RAS by inactivating its associated genes, thus may alleviate excessive inflammation induced by SARS-CoV-2. Currently, clinicians recommended indomethacin as a drug of interest against COVID-19. Our study presents that indomethacin is a potent therapeautic candidate among all other NSAIDs to treat COVID-19 symptoms. However, these results provide scientific evidence, plausible mechanism, target genes, and potential NSAIDs candidates against COVID-19.

Graphical abstract

Figure 1. Gene-gene interaction with 26 nodes and 78 edges in NSAIDs against COVID-19.

Table 1. Target genes in 26 signaling pathways enrichment related to COVID-19.

Table
<table>
<thead>
<tr>
<th>Signaling Pathway</th>
<th>Gene(s)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation</td>
<td>MAPK8, MAPK10, BAD</td>
<td>Inhibition of proinflammatory cytokines and cell death</td>
</tr>
<tr>
<td>MAPK8, MAPK10, BAD</td>
<td>RhoB</td>
<td>Inactivating RAS signaling pathway</td>
</tr>
</tbody>
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Materials and methods

NSAIDs linked to selected genes or COVID-19 related genes

- Based on SMILES, targeted genes of the NSAIDs approved by FDA (U.S. Food & Drug Administration) were identified utilizing Similarity Ensemble Approach (SEA) (http://sea.huatbio.com/) and Swiss Target Prediction (STP) (http://www.visiongeneproduction.com/) with the “pharm Quatro” mode. COVID-19 related genes were identified by browsing PubChem (https://pubchem.ncbi.nlm.nih.gov/). The overlapping genes between NSAIDs targeted genes and COVID-19 related genes were identified and visualized by Venny 2.1 (https://bioinformatics.cshl.edu/venny/)

Signaling pathway enrichment analysis of overlapping genes

- Genes-genes interaction figure was visualized by STRING (https://string-db.org/).
- RhoB plotted the bubble chart of KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway enrichment analysis of overlapping genes. Using RhoB, the most significant genes among signaling pathways, and correlation of NSAIDs on the most significant genes were analyzed. The results suggest a hint at the unknown molecular mechanism(s) of the most potent NSAIDs against COVID-19.

- Binding affinity energy value of the most potent NSAIDs against genes in silico

- The binding affinity energy measurement of the atomistic NSAIDs on key genes was established by Autodock (http://autodock.scripps.edu/), Vina (http://vina.scripps.edu), and Pymol (https://pymol.org/2).

Introduction

An initial outbreak of pneumonia caused by an unknown etiological virus first reported in Wuhan in Hubei Province, China, and alerted to the World Health Organizations (WHO) by the Wuhan Municipal Health Commission on 31 December 2019. Later, the disease rapidly spread across several respiratory systems in a very short period through direct or respiratory droplets. As a consequence of its tremendous spread in the world, on March 11, 2020, WHO announced a changing level from epidemic to pandemic disease COVID-19. Although the symptoms are mild to a few patients, however, a considerable number of COVID-19 affected patients died of physical signs, they can terminate the virus to receive, or to spread.

Due to the reusability of a selective sodium, decocted acini and anti-viral drugs and NSAIDs as a significant viable option for COVID-19 patients. A recent study has reported that NSAIDs are safe for COVID-19 treatment without exposing specific adverse side effects. Therefore, there is a lack of evidence whether NSAIDs treatment could reverse COVID-19 symptoms. Yet researchers suggested that anti-inflammatory therapies can support the final cytokine storms of COVID-19 patients. Additionally, WHO announced that no evidence of terminated side effects was found, particularly, the risk of death with the application of NSAIDs as COVID-19 treatment.

Currently, NSAIDs are used to treat diverse disorders and inflammatory symptoms due to its local therapeutic efficacy. However, potential drugs claimed to be anti-inflammatory drugs have both anti-inflammatory and anti-inflammatory properties. The potential mechanism was first identified in 2006 during the outbreak of SARS-CoV and the potential anti-SARS-CoV agent was also observed against SARS-CoV. A study on canine coronavirus to cover the SARS-CoV agent (https://pubmed.ncbi.nlm.nih.gov/). The overlapping genes from virus-induced damage. Similar anti-inflammatory was also observed during the process of other viral and anti-inflammatory drugs were found to be effective. Although there are many NSAIDs which may have possible therapeutic interventions against COVID-19, lack of scientific evidence has led to the broad application to COVID-19 patients. Hence, we assumed to identify the next potential NSAIDs and their mechanisms against COVID-19 through network pharmacology.

Network pharmacology, can decode the mechanism(s) of drug action with an overall viewpoint, which focuses on pattern changes from "single protein-target, single drug" to "multiple protein-target, multiple drugs". Computer network pharmacology has been successfully utilized to predict multiple targets and understand additional mechanisms against disease. In this research, network pharmacology was applied to investigate the most potent NSAIDs and novel mechanisms of action against COVID-19. Finally, a total of 21 approved NSAIDs were selected for using public website. The 21 NSAIDs and COVID-19 related genes were visualized using public databases. Next, the selected overlapping genes were dissected target genes, for analyzing anti-COVID-19.

Conclusion

In summary, NSAIDs-gene network suggested that the therapeutic effect of NSAIDs on COVID-19 was associated with 26 signaling pathways. This study suggests that SMN, relnoloids, and indomethacin are the most potent NSAIDs against COVID-19. The basis is an understanding of which anti-inflammatory pathways against COVID-19. These NSAIDs work on COVID-19 patients. This scientific evidence infers the selection of NSAIDs, which provides for clinical design against COVID-19. Our research suggests that the inhibition of RAS-Indomethacin with other two key genes MAPK8-SMN, MAPK10-Relnoids might play cumulative actions by inactivating RAS signaling pathway against COVID-19. Most recently, efficacy of indomethacin against COVID-19 has been approved clinically. Our study presents that indomethacin is a potent therapeutic candidate among all other NSAIDs to treat COVID-19 symptoms. However, these results provide scientific evidence, plausible mechanism, target genes, and potential NSAIDs candidates against COVID-19.

References