

SARS-CoV-2 intervened by NSAIDs: A network pharmacology approach to decipher signaling pathway and interactive genes

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Abstract

Background: Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) *showed promising clinical efficacy toward COVID-19 patients as painkillers and anti-inflammatory agents. However, the prospective anti-COVID-19 mechanisms of NSAIDs are not evidently exposed. Therefore, we intended to decipher the most potent NSAIDs candidate(s) and its novel mechanism(s) against COVID-19 by network pharmacology.*

Method: FDA (U.S. Food & Drug Administration) approved twenty NSAIDs were used for this study. *Genes related to selected NSAIDs and COVID-19 related genes were identified by the 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. RStudio plotted the bubble chart of KEGG pathway enrichment analysis of overlapping genes. Finally, the binding affinity of NSAIDs against target genes was determined through molecular docking analysis.*

Results: *Geneset enrichment analysis exhibited 26 signaling pathways against COVID-19. Inhibition of proinflammatory stimuli of tissues and/or cells by inactivating RAS signaling pathway was identified as the key anti-COVID-19 mechanism of NSAIDs. Besides, MAPK8, MAPK10, and BAD genes were explored as the associated genes of the RAS. Among twenty NSAIDs, 6MNA, rofecoxib, and indomethacin revealed promising binding affinity with the highest docking score against three identified genes, respectively.*

Conclusions: Overall, our proposed three NSAIDs (6MNA, rofecoxib, and indomethacin) might block the RAS by inactivating its associated genes, thus may alleviate excessive inflammation induced by SARS-CoV-2.

Introduction

An initial outbreak of pneumonia caused by unknown etiology was first reported at Wuhan in Hubei Province, China, and alerted to the World Health Organization (WHO) by the Wuhan Municipal Health Commission on 31 December 2019¹. Later, the infectious disease experts detected severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can rapidly transmit from person to person through interaction or respiratory droplets². As a consequence of its tremendous spread in the world, WHO announced a changing level from epidemic to pandemic disease (COVID-19) on March 11, 2020³. Although the symptoms are identical to pneumonia, however, a considerable number of COVID-19 infected patients showed no physical sign, thus can transmit the virus to others, as silently spread⁴.

Due to the unavailability of a reliable vaccine, clinicians are utilizing anti-viral drugs and NSAIDs as a significant viable option for COVID-19 patients⁵. A recent study has reported that use of NSAIDs is safe for COVID-19 treatment without exposing specific negative side effects⁶. Though there is a lack of evidence whether combined NSAIDs treatment could worsen COVID-19 symptoms⁷, but researchers suggested that anti-inflammatory therapies might suppress the fatal cytokine storm of COVID-19 patients

⁸. Additionally, WHO announced that no evidence of unwanted side effects was reported, particularly the risk of death with the administration of NSAIDs in COVID-19 patients ⁹.

Commonly, NSAIDs are used to treat diverse anti-inflammatory symptoms due to its good therapeutic efficacy ¹⁰. However, one potential drug of interest is indomethacin which possesses both anti-inflammatory and antiviral properties. Its antiviral potentiality was first identified in 2006 during the outbreak of SARS-CoV ¹¹ and subsequent attribution was also observed against SARS-CoV-2 ¹². A study on canine coronavirus (*in vitro*) revealed that indomethacin could significantly suppress virus replication, thus protecting host cell from virus induced damage. Similar antiviral effect was also observed during *in vivo* assessment where normal anti-inflammatory dose was found very effective ^{12,13}. Although there are many NSAIDs which may have possible therapeutic interventions against COVID-19, lack of scientific evidence has limited their broad application to COVID-19 patients. Hence, we aimed to identify the most potent NSAIDs and their mechanism(s) against COVID-19 through network pharmacology.

Network pharmacology can decode the mechanism(s) of drug action with an overall viewpoint, which focuses on pattern changing from “single protein target, single drug” to “multiple protein targets, multiple drugs” ¹⁴. Currently, network pharmacology has been extensively utilized to explore multiple targets and unknown additional mechanism(s) against diverse diseases ¹⁵. In this research, network pharmacology was applied to investigate the most potent NSAIDs and their novel mechanisms of action against COVID-19. Firstly, a total of 20 approved NSAIDs was selected via using public websites. The 20 NSAIDs and COVID-19 related genes were also identified using public databases. Next, the selected overlapping genes were discovered as target genes for analyzing anti-COVID-19. Finally, pathway enrichment analysis was performed to reveal the mechanism(s) of the most potent NSAIDs against COVID-19. Figure 1 shows overall workflow.

Results

Information of NSAIDs

A total of twenty FDA approved NSAIDs was selected. Table 1 and Figure 2 display the chemical information and structure of these NSAIDs. Among the twenty NSAIDs, nineteen NSAIDs were found as active drug and one “nabumetone” was a prodrug and its metabolite form is 6-methoxy-2-naphthylacetic acid (6MNA). Figure 3 shows nabumetone oxidized into 6MNA.

NSAIDs linked to the 781 genes or COVID-19 related genes

By screening from two public databases (SEA and STP), a total of 781 NSAIDs related genes were identified (see Supplementary Table S1). The overlapping genes (228 genes) selected from the two databases were shown (see Supplementary Table S2). Figure 4 displays the result of the overlapping genes. From the PubChem database, 466 COVID-19 related genes were identified (see Supplementary

Table S3). The 26 overlapping genes were extracted between the 228 overlapped genes and 466 COVID-19 related genes (see Supplementary Table S4). Figure 5 shows the result of overlapping genes.

Pathway enrichment analysis of overlapping genes and identification of significant genes against COVID-19

Figure 6 displays the identified overlapping 26 genes were linked closely to each other through utilizing STRING. Based on the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis with “*Homo sapiens*” mode, 26 signaling pathways from the 26 genes were revealed against COVID-19. Figure 7 shows the signaling pathways were plotted in the bubble chart through Rstudio. Table 2 provides the detailed description of the 26 signaling. Figure 8 shows that both MAPK8 and MAPK10 linked to 22 out of 26 signaling pathways, were determined as hub genes of NSAIDs against COVID-19. Coincidentally, both MAPK8 and MAPK10 play major roles in all of the 22 signaling pathways by the RAS signaling pathways, suggesting that BAD (Bcl-2-associated death promoter) gene and the two hub genes (MAPK8 and MAPK10) are associated with the RAS signaling pathway against COVID-19. The interactions between NSAIDs and each gene were visualized with RStudio (see Supplementary Figure S1).

Affinity binding energy score on three genes of the most potent NSAIDs against

COVID-19

From the SEA and STP databases, it was revealed that MAPK8 gene is associated with three NSAIDs (6MNA, Mefenamic acid, and Etodolac), MAPK10 gene is related to twelve NSAIDs (Mefenamic acid, Naproxen, Tolmetin, Fenoprofen, Ketorolac, Ketoprofen, Ibuprofen, Flurbiprofen, Oxaprozin, Sulindac, Diclofenac, and Rofecoxib), BAD gene is involved with two NSAIDs (6MNA and Indomethacin).

Figure 9 displays the molecular docking was performed to evaluate the binding mode of these three genes against their associated NSAIDs, respectively, and the docking figures are depicted in Molecular docking score of M1-M3 on MAPK8 protein (PDB ID: 4YR8) was analyzed in the “*Homo Sapiens*” mode. Based on the docking score, the order of priority of binding energy is given: M1>M2>M3. The three-affinity binding energy of M1-MAPK8, M2-MAPK8, and M3-MAPK8 indicated -7.1, -6.4, and -6.3 kcal/mol, respectively. The 6MNA (M1) had the strongest affinity on MAPK8. Interaction analysis of best-docked compound namely “6MNA” resulted one hydrogen bond (Lys-218) and seven hydrophobic bonds (Gly-88, Leu-86, Met-0, Val-44, Cys-1, Gly-46, and ASP-47). Table 3 provides the detailed information of binding energy and interactions. Molecular docking score of R1-R12 on MAPK10 protein (PDB ID: 3TTJ) was demonstrated in the “*Homosapiens*” mode. Based on the docking score, the priority of affinity binding energy is as follows: R12>R10> R9= R5> R8> R3= R11> R4 =R6 >R1 >R2 >R7. The twelve affinity binding energy of R1-MAPK10, R2-MAPK10, R3-MAPK10, R4 -MAPK10, R5-MAPK10, R6-MAPK10, R7-MAPK10, R8-MAPK10, R9-MAPK10, R10-MAPK10, R11-MAPK10, and R12-MAPK10 revealed -6.4, -6.1, -6.7, -6.5, -7.1, -6.5, -7.1, -6.5, -5.6, -6.9, -7.1, -7.4, -6.7, and -7.5 kcal/mol, respectively. The rofecoxib (R12) had the strongest affinity on MAPK10. Interaction analysis of best-docked compound namely “Rofecoxib” resulted three hydrogen bonds (Asn-194, Lys-191, Ser-217) and seven hydrophobic bonds (Asp-189, Arg-

230, Thr-203, Leu-210, Gly-209, Ala-211, Arg-107). Table 4 provides the detailed information of binding energy and interactions. Molecular docking score of B1-B2 on BAD protein (PDB ID: 1G5J) was also analyzed in the “*Homo Sapiens*” mode. Based on the docking score, the order of priority of binding energy is given: B2>B1. The two-affinity binding energy of B1-BAD and B2-BAD demonstrated -6.8 and -7.1 kcal/mol, respectively. The indomethacin (B2) had the strongest affinity on BAD. Interaction analysis of best-docked compound namely “Indomethacin” resulted one hydrogen bond (Asp-180) and eight hydrophobic bonds (Arg-169, Tyr-124, Phe-127, Val-131, Glu-128, His-181, Thr-176, Trp-173). Table 5 provides the detailed information of binding energy and interactions. Figure 10 depicts that the three NSAIDs (6MNA, Rofecoxib, and Indomethacin) might be the potential anti-inflammatory agents against COVID-19

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.bkslab.org/>) and Swiss Target Prediction (STP) (<http://www.swisstargetprediction.ch/>) with the “*Homosapience*” 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://bioinfogp.cnb.csic.es/tools/venny/>)

Network construction of interactions between NSAIDs targeted genes and COVID-19 related genes

The overlapping genes interactions between NSAIDs targeted genes and COVID-19 related genes were analyzed by STRING (<https://string-db.org/>).

Signaling pathway enrichment analysis of overlapping genes

Genes-genes interaction figure was visualized by STRING (<https://string-db.org/>). RStudio plotted the bubble chart of KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway enrichment analysis of overlapping genes. Using RStudio, 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 on genes *in silico*

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

Discussion

NSAIDs-genes networking analysis demonstrated that the clinical effect of NSAIDs on COVID-19 was directly related to 26 genes. The results of KEGG pathway enrichment analysis of 26 genes suggested that 26 signaling pathways were associated with the occurrence and development of the COVID-19 symptoms. The correlations of 26 signaling pathways with COVID-19 symptoms were succinctly discussed as follows. PPAR (*Peroxisome Proliferator-Activated Receptor*) signaling pathway: A report shows that PPAR γ (*Peroxisome Proliferator-Activated Receptor-gamma*), PPAR α (*Peroxisome Proliferator-Activated Receptor-alpha*), and PPAR β/δ (*Peroxisome Proliferator-Activated Receptor-beta/delta*) agonists have anti-inflammatory and immunomodulatory functions¹⁶. MAPK (*Mitogen-Activated Protein Kinase*) signaling pathway: The mechanisms of p38 MAPK inactivation might be a significant therapy against the SARS infected cells¹⁷. Additionally, MAPK stimulates cytokine production such as IL-10 (Interleukin 10), TNF- α (Tumor Necrosis Factor-Alpha), IL-4 (Interleukin 4), and IFN- γ (Interferon gamma)¹⁸. This report shows a coincidence with our suggested strategy in this study. ErbB (Erythroblastic Leukemia Viral Oncogene Homolog) signaling pathway: ErbB signaling reduces the proinflammatory activation in cardiac cells¹⁹. RAS (Renin Angiotensin System) signaling pathway: Inactivation of RAS can reduce tissue damage in COVID-19 patients. In addition, ACE (Angiotensin Converting Enzyme) antagonists block the response of RAS system²⁰. cGMP-PKG (Cyclic GMP-Protein Kinase G) signaling pathway: The activation of cGMP-PKG signaling inhibits inflammatory response in the prostate, and also decreases CCL5 (C-C Motif Chemokine Ligand 5) release in CD8⁺ T cells (Cluster of Differentiation 8 T cells)²¹. cAMP (Cyclic Adenosine Monophosphate) signaling pathway: The elevation of cAMP leads to diverse cellular effects, such as airway smooth muscle relaxation, repressed effects on cellular inflammation, and immune responses²². NF- κ B (Nuclear Factor kappa-light-chain-enhancer of activated B cells) signaling pathway: Activation of the NF- κ B signaling pathway gives rise to the inflammation induced by the SARS-CoV infection. In contrast, NF- κ B inhibitors are the potential antivirals against SARS-CoV, and can also contribute to other pathogenic human coronaviruses²³. FOXO (Forkhead box protein O1) signaling pathway: Decrease of FOXO3 (Forkhead box protein O3) in T cells inhibits apoptosis, enhances multifunction of CD8 cells, and elevates viral control²⁴. Sphingolipid signaling pathway: Sphingolipids play a vital role to protect lung from damages, and the control of sphingolipid signaling pathways may give a good therapeutic efficacy²⁵. Wnt (Wingless/Integrated) signaling pathway: Wnt signaling involves with the prime inflammatory pathways like intestinal inflammation. Also, elucidating the mutual modes of Wnt ligands and cytokines manifest new treatment strategies for chronic colitis and other inflammatory diseases²⁶. VEGF (Vascular Endothelial Growth Factor) signaling pathway: A report suggested that VEGFA (Vascular Endothelial Growth Factor A) is inhibited by the activation of ACE2 (Angiotensin-Converting Enzyme 2). However, ACE2 is downregulated by the attack of COVID-19. Subsequently, activation of VEGFA elevates vascular permeability and severity of endothelial damage²⁷. TLR (Toll-like receptor) signaling pathway: Toll-like receptors (TLRs) play a pivotal role in the innate immune system and contribute to defend host cells by recognizing PAMPs (Pathogen-Associated Molecular Patterns) induced by various microbes²⁸. The activation of TLRs triggers an array of response resulting into expression of different cytokines and chemokines, phagocytosis, and even apoptotic case activation to induce programmed cell death²⁹. NOD-like receptor (NLR) signaling pathway: Nod-like

receptors (NLRs) have been revealed as the major microbial signals that take part in the universal immune responses to infection, and also contribute to the prevention of infections³⁰. RIG-I-like receptor (RLR) signaling pathway: RIG-I-like receptors (RLRs) play a vital role in pathogen sensor of RNA virus infection, which enhances the antiviral immunity by sensing foreign RNA³¹. IL-17 (Interleukin-17) signaling pathway: IL-17 receptor inhibitors are widely used to ameliorate the inflammatory acuteness to date. Furthermore, it is a potential target to suppress severe inflammation induced by COVID-19³². Fc epsilon RI signaling pathway: Fc epsilon RI interconnecting causes mast cell degranulation and synthesis of proinflammatory mediators³³. TNF (Tumor Necrosis Factor) signaling pathway: TNF deficit is associated with dysfunctional secretion of inflammatory cytokine, leading to lung pathology and death during respiratory poxvirus infection, and thus TNF is very significant element for regulating inflammation³⁴. Neurotrophin signaling pathway: COVID-19 causes severe brain damage and destruction of central nervous system derived from neurotrophin (Huang and Reichardt 2001). Insulin signaling pathway: Obesity-oriented insulin resistance is associated with the induction of proinflammatory macrophage, leads to inflammation of adipose tissue³⁷. GnRH (Gonadotropin-Releasing Hormone) signaling pathway: Disrupted BBB (Blood Brain Barrier) by viral infection, lymphocytes (B and T cells), monocytes, and granulocytes can penetrate in the brain parenchyma which induce inflammation, resulting in dysregulation of GnRH neurons. Additionally, the inflammation of GnRH neurons inhibits GnRH transport through proinflammatory cytokines by impairing the cytoskeleton³⁸. Prolactin signaling pathway: HIV (Human Immunodeficiency Virus) patients have greater prolactin quantity compared to others. Besides, prolactin is regarded as a cytokine to react in immune system^{39,40}. Adipocytokine signaling pathway: Adipocytokines stimulate inflammation and disrupting immune response which cause tissue damage. Adipocytokines might also induce proinflammation in RA (Rheumatoid Arthritis) patients and thus lead to the development of bone damage⁴¹. Oxytocin signaling pathway: Oxytocin interrupts the production of proinflammatory cytokines by inactivating of the eIF-2 α -ATF4 (Eukaryotic Initiation Factor -2 alpha-Activating Transcription Factor 4) pathway⁴². Relaxin signaling pathway: Relaxin inhibitors are good therapeutic targets to suppress inflammation caused by airway dysfunction⁴³. AGE-RAGE (Advanced Glycation End product -Receptor of Advanced Glycation End product) signaling pathway in diabetic complications: The binding of AGE to its receptor RAGE can trigger the cytokine production, thus, can cause tissue damages, while the blockage of AGE-RAGE can effectively curtail the inflammation⁴⁴. Epithelial cell signaling in *Helicobacter pylori* infection: *Helicobacter pylori* interrupts T and B cell signaling to set immune system. It is apparent that COVID-19 patients with *Helicobacter pylori* might be vulnerable to inflammatory responses⁴⁵.

Generally, SARS-CoV-2 invades in the lungs and throat, induces excessive inflammation, which causes the secretion of cytokines, resulting in severe complications like acute respiratory failure, pneumonia, and acute liver injury (Reyes and Peniche 2019; Nile et al. 2020). Researchers suggested that RAS is a potential route for SARS-CoV-2 induced cellular infection which may be linked to the imbalance of RAS. It was discovered that ACE-2 is the functional receptor for the SARS-CoV-2 to trigger infection in the lung alveolar epithelial cells. The internalization of virus leads to downregulate the ACE-2 on host cell surface

that could cause the elevation and demotion of the angiotensin-II (All) and angiotensin 1-7 (A₁₋₇) respectively. Such an imbalance between these angiotensins may induce deleterious effects in the lung and heart. Thus, the SARS-CoV-2 affects humans through this mechanism⁴⁹⁻⁵². Therefore, blockade of the RAS may restore the RAS balance by reducing the deleterious effects associated with angiotensin-II⁵³. Recent evidence showed that RAS inhibitors might be a promising target for relieving acute-severe pneumonia caused by the COVID-19⁵⁴.

Interestingly, our study identified that the three genes (MAPK 8, MAPK 10, and BAD) are mainly associated with the RAS signaling pathway. MAPK 8 and MAPK 10 are members of the MAPK family which are the key mediators of the inflammation, vasoconstriction, and thrombosis. Besides, overwhelming heart and lung injury in COVID-19 infection might be due to the overactivation of MAPK⁵⁵. Therefore, inactivation of these genes can also be a viable strategy for relieving COVID-19 induced organ injury. In addition, disposal of inflammatory cells by promoting the cell death can be an innovative approach to control excessive inflammation. In this regard, inhibition of the anti-apoptotic Bcl-2 gene can also be a potential target to lessen inflammation^{56,57}. Our findings also explored that MAPK8, MAPK10 and BAD genes are related to three, twelve, and two NSAIDs, respectively. During the molecular docking analysis, 6MNA, rofecoxib, and indomethacin revealed promising binding affinity along with highest docking score against MAPK8, MAPK10 and BAD genes, respectively, which indicated that the three (6MNA, Rofecoxib, and Indomethacin) NSAIDs are very potential among all others, may possibly block the RAS signaling pathway by inactivating its associated genes (MAPK8, MAPK10 and BAD), and subsequently suppress SARS-CoV-2 induced cytokine storm.

Among various NSAIDs, indomethacin is a current drug of interest to the clinicians. Primary care physicians (New York) reported that indomethacin had been prescribed to a large number of COVID-19 patients and observed quick recovery from cough, pain, and other symptoms. Such improvements and well-being benefits were not evident in the case of ibuprofen and hydroxychloroquine implementation (Vaduganathan et al. 2020b; Little 2020). Importantly, many researchers previously reported varying degrees of antiviral activity of indomethacin against herpesvirus⁶⁰, pseudorabies virus⁶¹, cytomegalovirus⁶², hepatitis B virus⁶³, vesicular stomatitis virus⁶⁴, rotavirus⁶⁵, and canine coronavirus¹¹. In contrast, 6MNA (active metabolite of nabumetone) and Rofecoxib are also the potential anti-inflammatory drugs, but studies disclosed that they are less potent compared to the indomethacin^{66,67}. Hence, such compelling outcomes indicate that indomethacin can be considered to use alone or in combination for antiviral therapy which may assist in combating human coronavirus (SARS-CoV-2).

In summary, NSAIDs-genes network suggested that the therapeutic effect of NSAIDs on COVID-19 was associated with 26 signaling pathways. This study suggests that 6MNA, rofecoxib, and indomethacin are the most potent NSAIDs against COVID-19. The basis of this research is an understanding of how these NSAIDs (which stimulates anti-inflammatory processes against COVID-19) work on COVID-19 patients. That scientific evidence informs the selection of NSAIDs, in turn, provides for clinical design against COVID-19. Our research suggests that the inhibition of BAD-Indomethacin with other two hub genes

MAPK8-6MNA, MAPK10-Rofecoxib might play cumulative actions by inactivating the 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 to relieve COVID-19 symptoms, which is in line with the many previous studies. However, further clinical trial on indomethacin should be warranted in COVID-19 patients in order to slow down the progression of SARS-CoV-2 and mitigating the severity as well.

Abbreviations

ACE: Angiotensin-Converting Enzyme;

ACE2: Angiotensin-Converting Enzyme 2;

AGE-RAGE: Advanced Glycation End product /Receptor of Advanced Glycation End product;

BAD: Bcl-2-Associated Death promoter;

BBB: Blood Brain Barrier;

cAMP: Cyclic Adenosine MonoPhosphate;

CCL5 (C-C Motif Chemokine Ligand 5);

CD8⁺ T cells: Cluster of Differentiation 8 T cells;

cGMP-PKG: cyclic Guanosine MonoPhosphate - Protein Kinase G;

COVID-19: SARS-CoV-2 virus;

eIF-2 α -ATF4 (Eukaryotic Initiation Factor -2 alpha- Activating Transcription Factor 4);

ErbB: Erythroblastic Leukemia Viral Oncogene Homolog;

FDA: U.S. Food & Drug Administration;

FOXO: Forkhead boX protein O;

GnRH: Gonadotropin-Releasing Hormone;

HIV: Human Immunodeficiency Virus;

IFN- γ : Interferon gamma;

IL-4: Interleukin 4;

IL-10: Interleukin 10;

IL-17: Interleukin 17;

KEGG: Kyoto Encyclopedia of Genes and Genomes;

MAPK: *Mitogen-Activated Protein Kinase*;

MAPK8: *Mitogen-Activated Protein Kinase 8*;

MAPK10: *Mitogen-Activated Protein Kinase 10*;

NF- κ B: Nuclear Factor Kappa-light-chain-enhancer of activated B cells;

NLR: Nod-Like Receptor;

NLRs: Nod-Like Receptors;

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs;

PPAR: *Peroxisome Proliferator-Activated Receptors*;

PPAR α : *Peroxisome Proliferator-Activated Receptor-alpha*;

PPAR γ : *Peroxisome Proliferator-Activated Receptor-gamma*;

PPAR β/δ : *Peroxisome Proliferator-Activated Receptor-beta/delta*;

PAMPs: Pathogen-Associated Molecular Patterns;

RA: Rheumatoid Arthritis;

RAS: Renin Angiotensin System;

RLR: RIG-I-Like Receptor;

RLRs: RIG-I-Like Receptors;

SARS-CoV-2: Severe Acute Respiratory Syndrome CoronaVirus 2;

SEA: Similarity Ensemble Approach;

STP: Swiss Target Prediction;

TLR: Toll-like receptor;

TLRs: Toll-like receptors;

TNF: Tumor Necrosis Factor;

TNF- α : Tumor Necrosis Factor-Alpha;

VEGF: *Vascular Endothelial Growth Factor*;

VEGFA: *Vascular Endothelial Growth Factor A*;

WHO: World Health Organization;

Wnt: Wingless/Integrated

Declarations

Data availability

All data generated or analysed during this study are included in this published article (and its Supplementary Information files).

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Author contribution

Ki Kwang Oh and Md. Adnan: Conceptualization, Methodology, Formal analysis, Investigation, Data Curation, Writing - Original Draft. **Ki Kwang Oh and Md. Adnan**: Software, Investigation, Data Curation. **Ki Kwang Oh and Md. Adnan**: Validation, Writing - Review & Editing. **Dong Ha Cho**: Supervision, Project administration

Competing interests

The authors declare no competing interests.

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Supporting Information

Supplementary Table S1

(PDF)

Supplementary Table S2

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Supplementary Table S3

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Supplementary Table S4

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Supplementary Figure S1

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Tables

Table 1. A list of 20 NSAIDs approved by FDA

No.	Drug name	PubChem CID	Mechanism of action
1	Flubiprofen	3394	Nonselective COX inhibitor
2	Ibuprofen	3672	Nonselective COX inhibitor
3	Indomethacin	3715	Nonselective COX inhibitor
4	Ketorolac	3826	Nonselective COX inhibitor
5	Mefenamic acid	4044	Nonselective COX inhibitor
6	Piroxicam	54676228	Nonselective COX inhibitor
7	Diflunisal	3059	Prostaglandin synthesis inhibitor
8	Fenoprofen	3342	Prostaglandin synthesis inhibitor
9	Naproxen	156391	Prostaglandin synthesis inhibitor
10	Sulindac	1548887	Prostaglandin synthesis inhibitor
11	Tolmetin	5509	Prostaglandin synthesis inhibitor
12	Ketoprofen	3825	Selective COX-1 inhibitor
13	Oxaprozin	4614	Selective COX-1 inhibitor
14	Celecoxib	2662	Selective COX-2 inhibitor
15	Rofecoxib	5090	Selective COX-2 inhibitor
16	Valdecoxib	119607	Selective COX-2 inhibitor
17	Diclofenac	3033	Selective COX-2 inhibitor
18	Etodolac	3308	Selective COX-2 inhibitor
19	Meloxicam	54677470	Selective COX-2 inhibitor
20*	6MNA	32176	Selective COX-2 inhibitor

* **6MNA (Active form) of Nabumetone (Prodrug)**

Table 2. Target genes in 26 signaling pathways enrichment related to COVID-19.

KEGG ID & Description	Target genes	RichFactor	False discovery rate
hsa04014: Ras signaling pathway	MAPK8,MAPK10,BAD	0.013157895	0.0071
hsa04921: Oxytocin signaling pathway	PTGS2,PPP1CA	0.013422819	0.0294
hsa04010: MAPK signaling pathway	MAPK8,MAPK10,MAPK14,CASP3	0.013651877	0.0016
hsa04310: Wnt signaling pathway	MAPK8,MAPK10	0.013986014	0.0276
hsa04022: cGMP -PKG signaling pathway	ENDRA,BAD,PPP1CA	0.01875	0.003
hsa04064: NF-kappa B signaling pathway	CXCL8,PTGS2	0.021505376	0.0136
hsa04926: Relaxin signaling pathway	MAPK8,MAPK10,MAPK14	0.023076923	0.0018
hsa04068: FoxO signaling pathway	MAPK8,MAPK10,MAPK14	0.023076923	0.0018
hsa04071: Sphingolipid signaling pathway	MAPK8,MAPK10,MAPK14	0.025862069	0.0014
hsa04910: Insulin signaling pathway	MAPK8,MAPK10,BAD,PPP1CA	0.029850746	0.00013
hsa04621: NOD-like receptor signaling pathway	MAPK8,MAPK10,MAPK14,CXCL8,CASP1	0.030120482	0.0000197
hsa04024: cAMP signaling pathway	ENDRA,MAPK8,BAD,MAPK10,PPP1CA,PPARA	0.030769231	0.00000373
hsa04912:	MAPK8,MAPK10,MAPK14	0.034090909	0.00072

GnRH signaling pathway				
hsa04722: Neurotrophin signaling pathway	MAPK8,MAPK10,MAPK14,BAD	0.034482759	0.00000853	
hsa04012: ErbB signaling pathway	MAPK8,MAPK10,BAD	0.036144578	0.00062	
hsa04620: Toll-like receptor signaling pathway	MAPK8,MAPK10,MAPK14,CXCL8	0.039215686	0.0000581	
hsa03320: PPAR signaling pathway	PPARA,PPARG,FABP2	0.041666667	0.00044	
hsa04920: Adipocytokine signaling pathway	MAPK8,MAPK10,PPARA	0.043478261	0.00041	
hsa04917: Prolactin signaling pathway	MAPK8,MAPK10,MAPK14	0.043478261	0.00041	
hsa04664: Fc epsilon RI signaling pathway	MAPK8,MAPK10,MAPK14	0.044776119	0.00039	
hsa04668: TNF signaling pathway	MAPK8,MAPK10,MAPK14,CASP3,PTGS2	0.046296296	0.00000413	
hsa04370: VEGF signaling pathway	MAPK8,MAPK10,BAD	0.050847458	0.00029	
hsa04933: AGE-RAGE signaling pathway in diabetic complications	MAPK8,MAPK10,MAPK14,CXCL8,CASP1	0.051020408	0.00000373	
hsa04622: RIG-I like receptor signaling pathway	MAPK8,MAPK10,MAPK14,CXCL8	0.057142857	0.0000197	
hsa04657: IL-17 signaling pathway	MAPK8,MAPK10,MAPK14,CXCL8,CASP3,PTGS2	0.065217391	0.000000135	

hsa05120: Epithelial cell signaling in Helicobacter pylori infection	MAPK8,MAPK10,MAPK14,CXCL8,CASP3	0.075757576	0.000000954
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Table 3. Binding energy and interactions of potential three NSAIDs on MAPK8 (PDB ID:4YR8)

Protein	Ligand	PubChem ID	Symbol	Binding energy(kcal/mol)	Hydrogen Bond Interactions	Hydrophobic Interactions
					Amino Acid Residue	Amino Acid Residue
4YR8	6MNA	32176	M1	-7.1	Lys-218	Pro-221, Gly-199
						Pro-254, Phe215
						Cys-216, Gln-253
						Pro-210, Lys-218
						Glu-217, Lys-225
Mefenamic acid	4044	M2	-6.4	Glu-217	Trp-222, Val-211	
					Arg-208, Cys-216	
					Asn-193, Lys-218	
					Pro-211	
Etodolac	3308	M3	-6.3	n/a	Tyr-202, Lys-203	
					Met-200, Gly-201	
					Pro-221, Lys-218	
					Lys-251, Ser-307	
					Ala-306	

Table 4. Binding energy and interactions of potential twelve NSAIDs on MAPK10 (PDB ID: 3TTJ)

Protein	Ligand	PubChem ID	Symbol	Binding energy(kcal/mol)	Hydrogen Bond Interactions	Hydrophobic Interactions
					Amino Acid Residue	Amino Acid Residue
3TTJ	Mefenamic acid	32176	R1	-6.4	Arg-107	Asp-207, Gln-75
						Leu-206, Lys-93
						Asn-194, Asp-207
	Naproxen	4044	R2	-6.1	Asn-194, Lys-93	Arg-107, Asp-189
						Val-225, Lys-191
						Gln-75, Gly-73
	Tolmetin	3308	R3	-6.7	Asn-194, Asp-189	Lys-106, Leu-210
						Ala-211, Arg-110
						Arg-230, Lys-191
						Arg-107, Thr-103
	Fenoprofen	3342	R4	-6.5	Lys-93, Lys-191	Ser-193, Ser-72
						Asn-194
						Val-78, Gly-73
						Gln-75, Ala-74
						Arg-107

Ketorolac	3826	R5	-7.1	Glu-111, Arg-107	Asp-207, Leu-206
				Asn-194, Lys-93	Gln-75, Ser-193
					Ser-72, Val-78
					Gly-73
Ketoprofen	3825	R6	-6.5	Lys-93, Asn-194	Val-78, Leu-206
				Ser-193	Arg-107, Gln-75
					Gly-73
Ibuprofen	3672	R7	-5.6	Lys-93, Ser-193	Leu-206, Ala-74
				Asn-194	Gly-73, Gln-75
					Val-78
Flubiprofen	3394	R8	-6.9	Lys-191, Asp-189	Lys-93, Val-78
				Asn-194	Gly-73, Arg-107
					Gln-75
Oxaprozin	4614	R9	-7.1	Asn-194, Arg-107	Asp-189, Thr-103
				Lys-191	Ser-217, Val-225
					Arg-230
Sulindac	1548887	R10	-7.4	Asn-152	Arg-107, Asn-194
					Lys-93, Ser-72

						Gly-73, Ser-193
						Ala-74
Diclofenac	3033	R11	-6.7		Asn-194	Ser-72, Gly-73
						Ser-193, Gln-75
						Arg-107, Lys-93
						Leu-206, Val-78
						Gly-71
Rofecoxib	5090	R12	-7.5		Asn-194, Lys-191	Asp-189, Arg-230
					Ser-217	Thr-203, Leu-210
						Gly-209, Ala-211
						Arg-107

Table 5. Binding energy and interactions of potential two NSAIDs on BAD (PDB ID: 1G5J)

					Hydrogen Bond Interactions	Hydrophobic Interactions
Protein	Ligand	PubChem ID	Symbol	Binding energy(kcal/mol)	Amino Acid Residue	Amino Acid Residue
1G5J	6MNA	32176	B1	-6.8	Trp-173, His-181	Arg-169, Tyr-124
						Phe-127, Tyr-177
						Thr-176
	Indomethacin	3715	B2	-7.1	Asp-180	Arg-169, Tyr-124
						Phe-127, Val-131
						Glu-128, His-181
						Thr-176, Trp-173

Figures

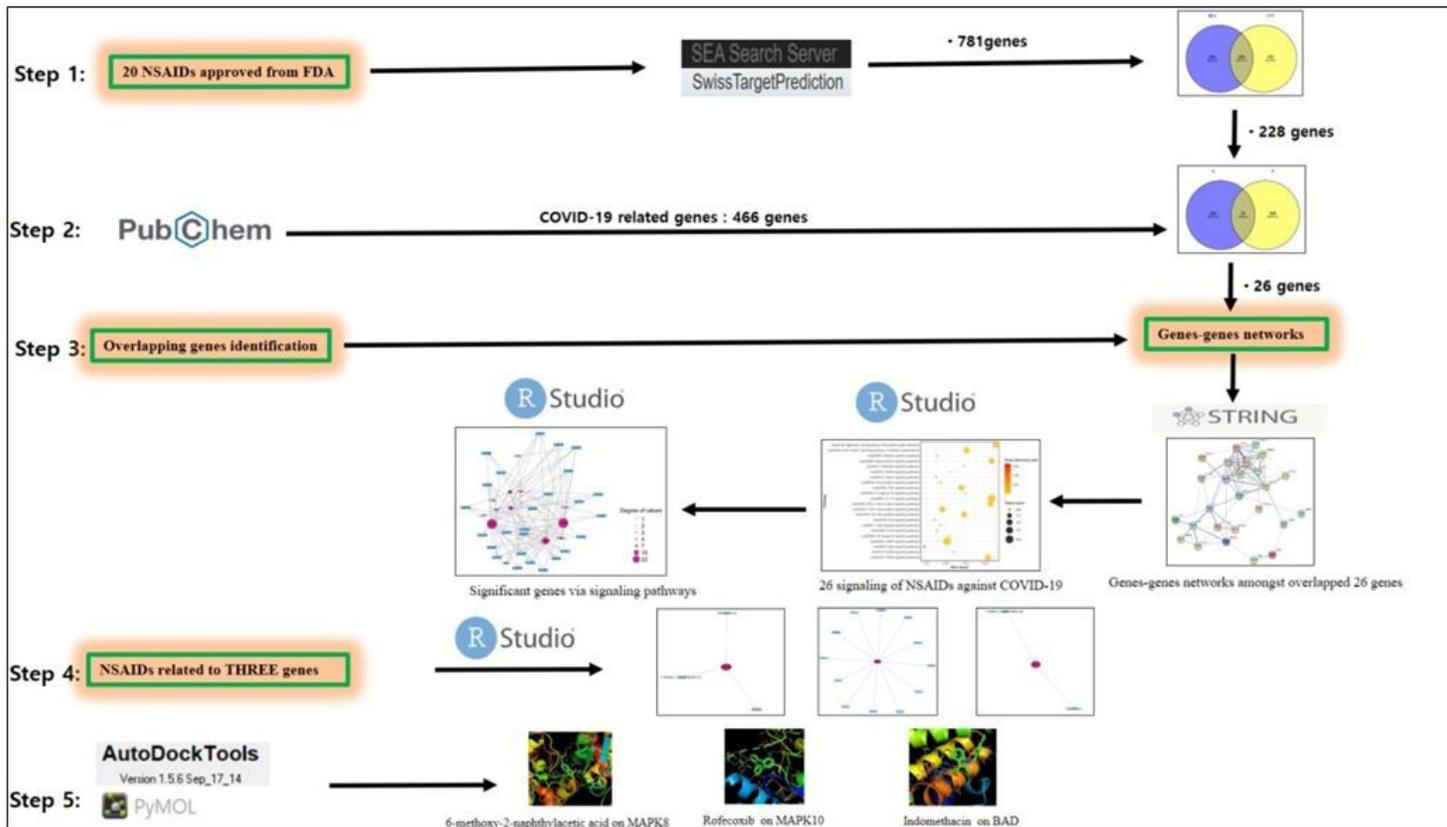


Figure 1

Workflow of network pharmacology analysis of NSAIDs against COVID-19.

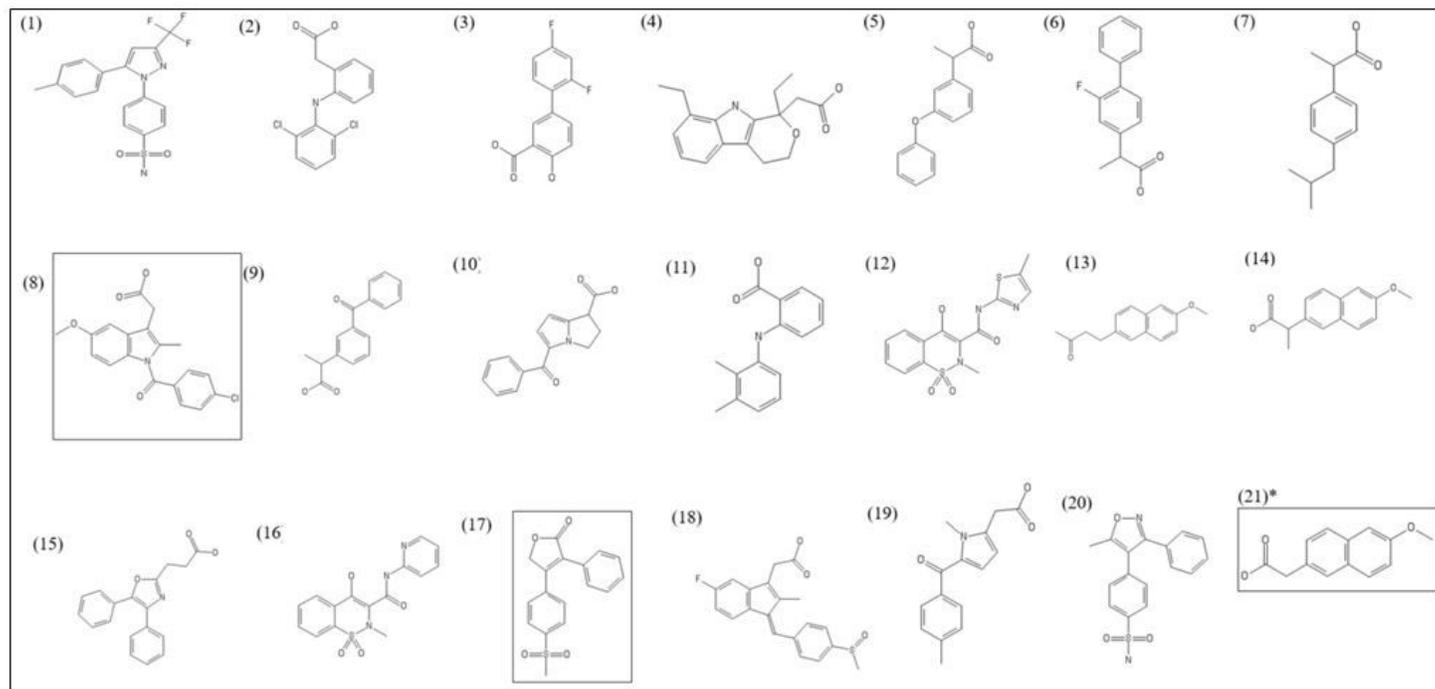


Figure 2

Structure of 20 NSAIDs and 1 prodrug (1) Celecoxib (2) Diclofenac (3) Diflunisal (4) Etodolac (5) Fenoprofen (6) Flubiprofen (7) Ibuprofen (8) Indomethacin (9) Ketoprofen (10) Ketorolac (11) Mefenamic acid (12) Meloxicam (13) Nabumetone (14) Naproxen (15) Oxaprozin (16) Piroxicam (17) Rofecoxib (18) Sulindac (19) Tolmetin (20) Valdecoxib The three NSAIDs in box line are the most potent NSAIDs candidates against COVID-19 *(21): Active form of (13) Nabumeton (Prodrug)

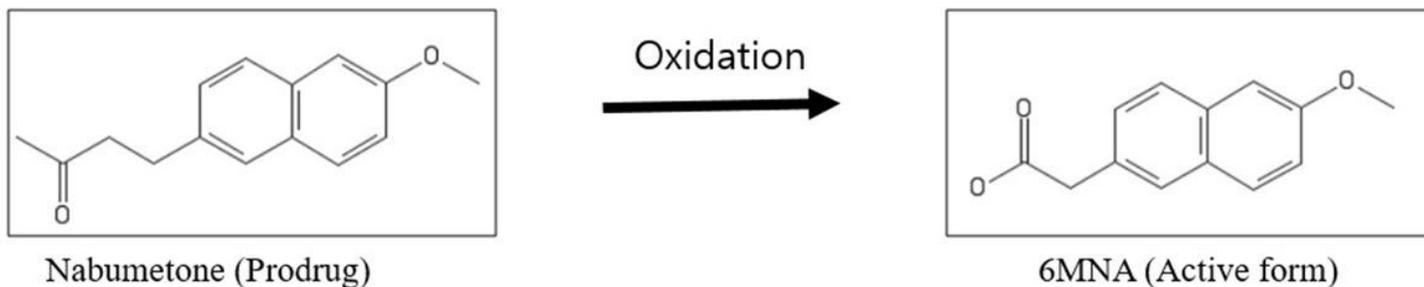


Figure 3

An active metabolite (6MNA) of Nabumetone (Prodrug).

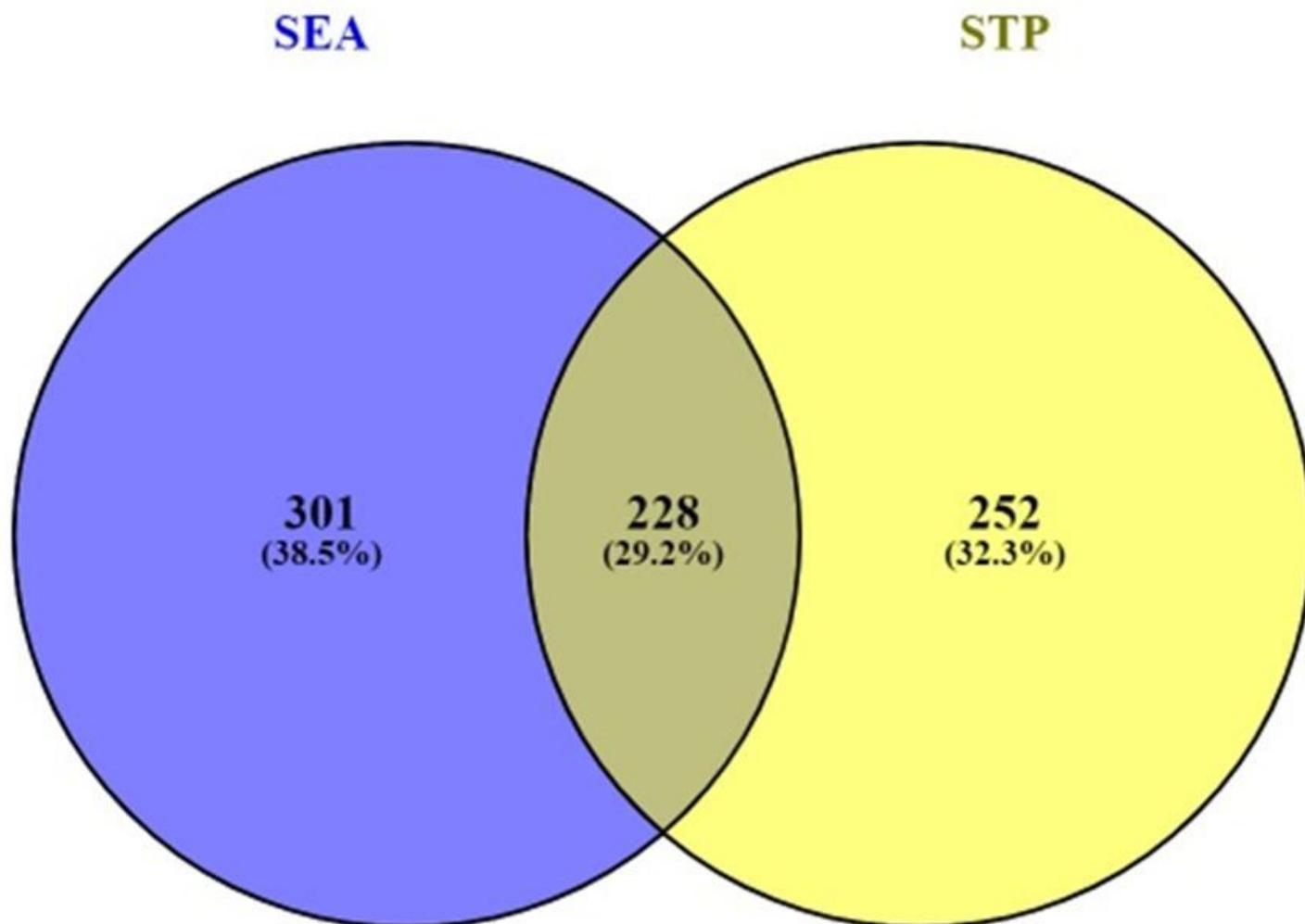


Figure 4

Overlapping genes (228 genes) of NSAIDs related genes identified from SEA (529 genes) and STP (480 genes).

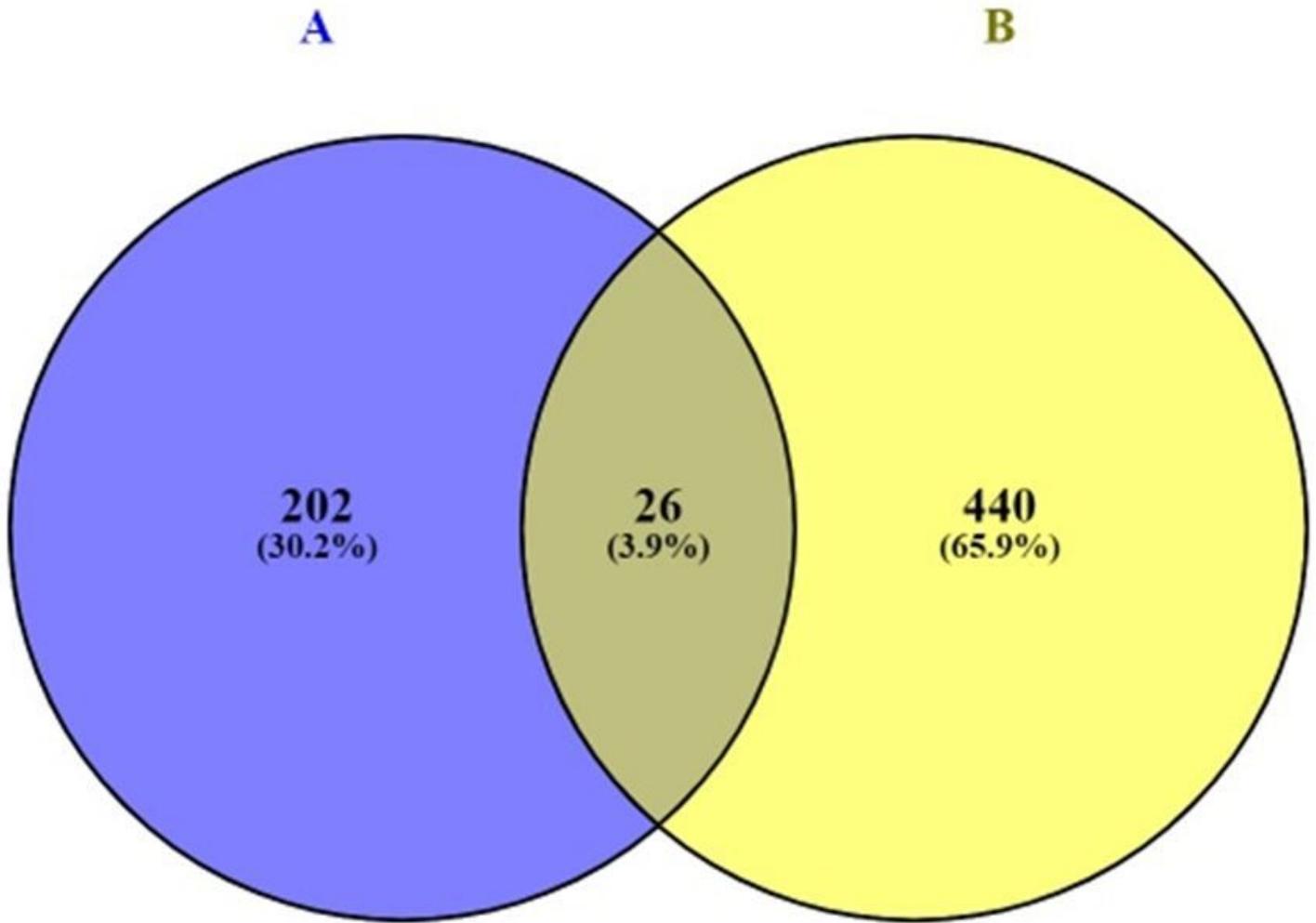


Figure 5

Overlapping genes (26 genes) between NSAIDs related 228 overlapped genes (A) and COVID-19 related 466 genes (B).

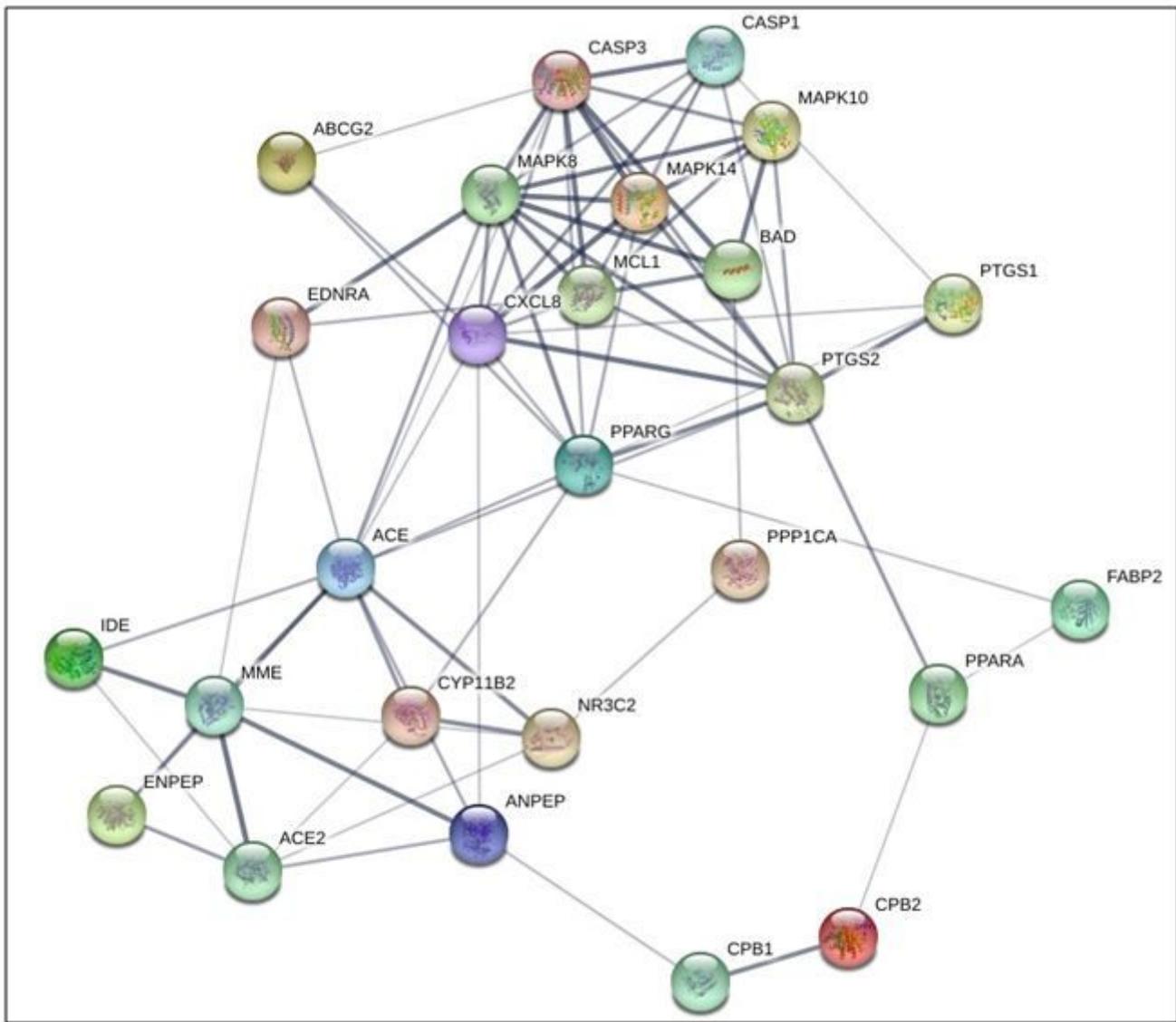


Figure 6

Gene-gene interaction with 26 nodes and 78 edges in NSAIDs against COVID-19 via STRING analysis.
 Node: The number of networks of compounds
 Edge: The number of interactions between compounds and genes

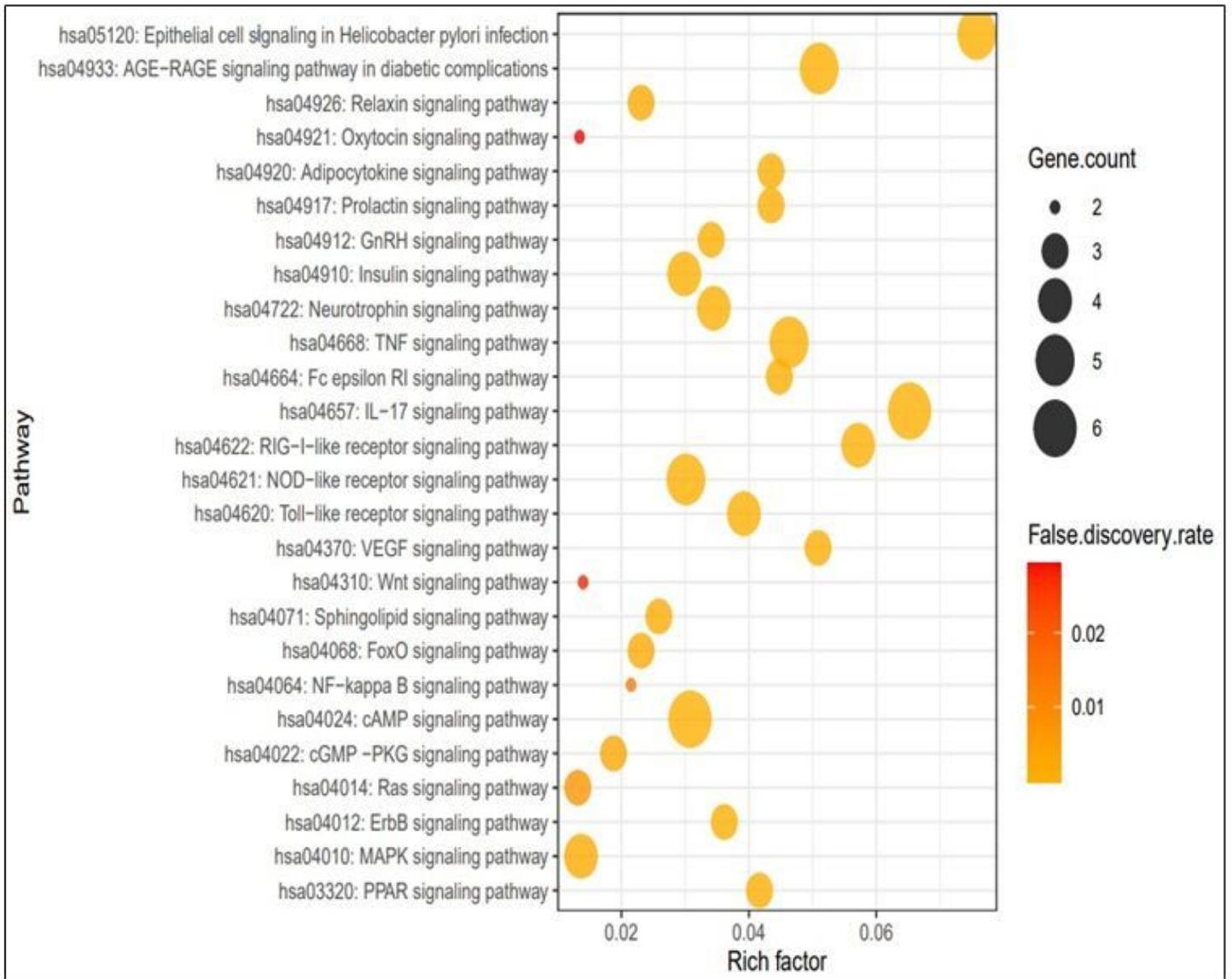


Figure 7

Bubble chart of 26 signaling pathways related to the occurrence and progression of COVID-19.

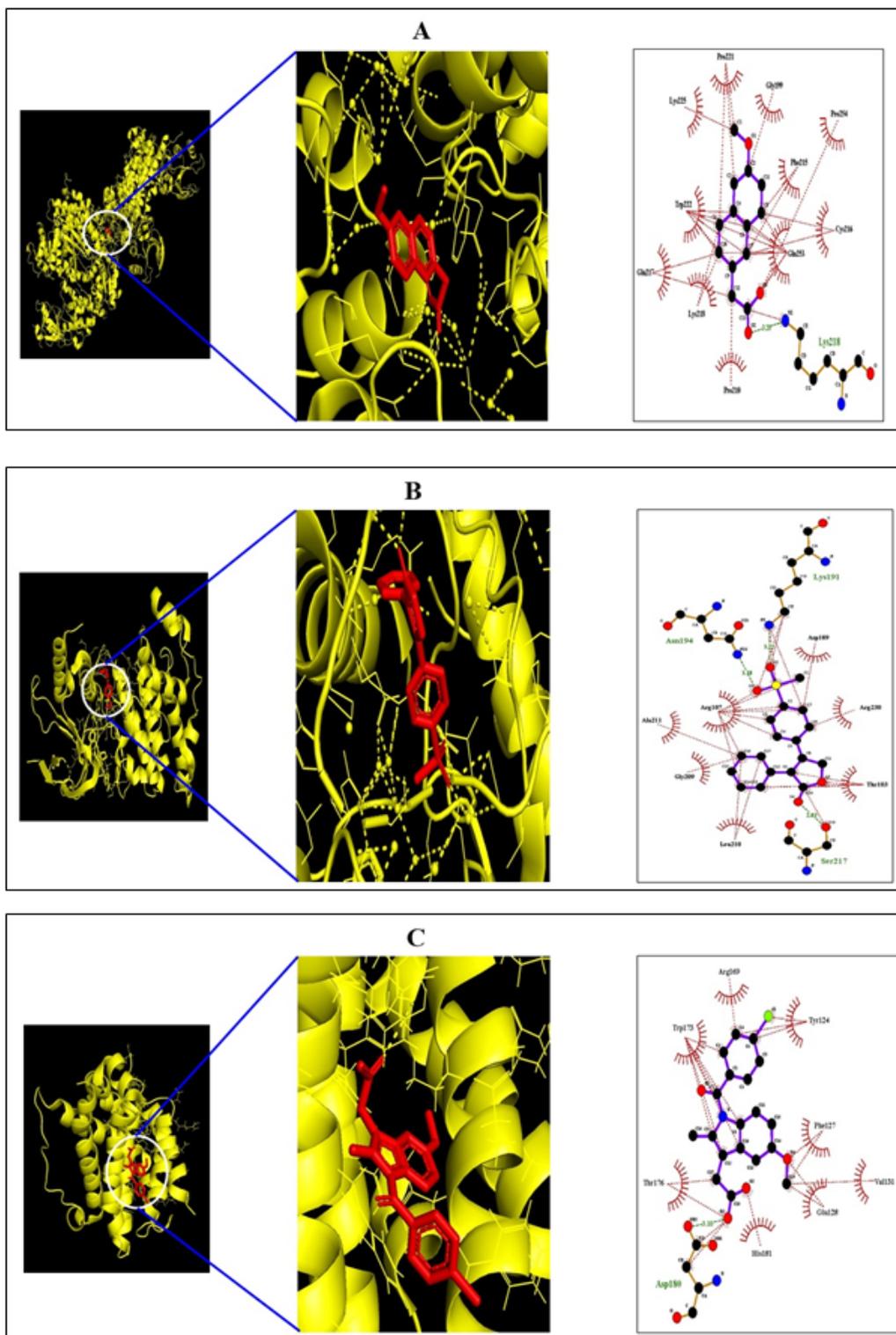


Figure 9

Molecular docking interaction between best docked NSAIDs and target proteins. (A) 6MNA on 4YR8 (B) Rofecoxib on 3TTJ (C) Indomethacin on 1G5J

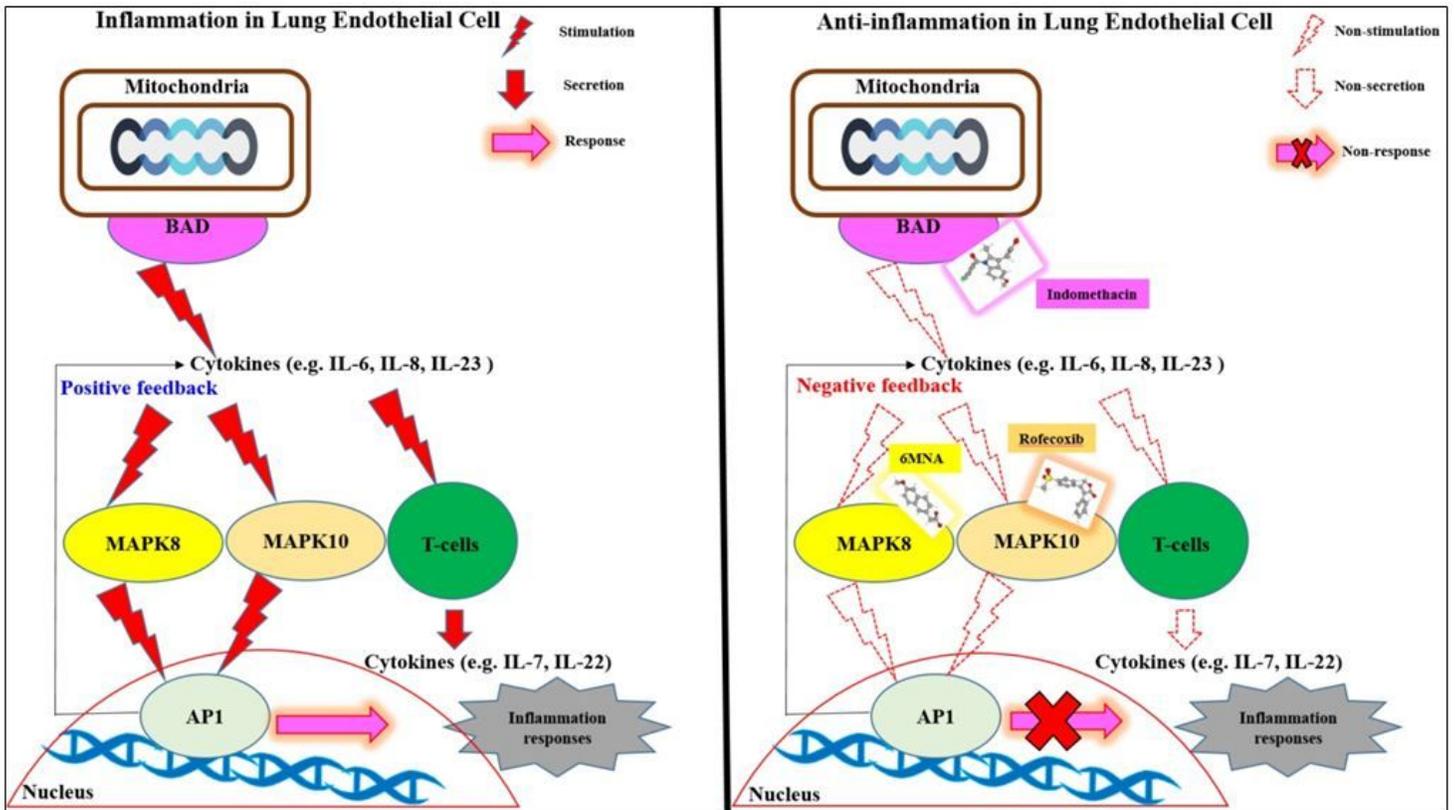


Figure 10

Anti-inflammation mechanisms of promising NSAIDs against COVID-19

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