

SYSTEM DESIGN ANALYSIS OF DRUG AGAINST COVID-19

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FINAL PROJECT

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INTRODUCTION

Topic

- SARS-CoV-2, originating from bats and transmitted to humans via an intermediate host in Wuhan, China.
- Identified in December 2019; WHO declared it a Public Health Emergency in January 2020 and a pandemic in March 2020.
- Over 770 million cases and 6.9 million deaths reported globally by August 2023.

Issues

- High transmission rate via droplets and contaminated surfaces; global spread led to severe strain on healthcare systems.
- Consequences: Strain on medical facilities, delayed non-COVID care, and burnout among healthcare workers

Therapeutics

- Focus on small molecule antiviral drugs for reducing illness severity, alleviating healthcare system stress, and aiding economic recovery.
- Advantages: Effective oral drugs with global distribution potential, adaptability for combination therapies against evolving viral threats.

OBJECTIVES

- **Target Viral Proteins:** Develop small molecule compounds that effectively target key viral proteins of SARS-CoV-2, ensuring enhanced oral bioavailability and tissue penetration.
- **Accelerate Approval:** Fast-track the repurposing of existing compounds to achieve rapid regulatory approval and global accessibility, focusing on affordability and availability in low-resource settings.
- **Combination Therapies:** Explore and implement combination therapies to improve effectiveness against various viral strains and minimize the potential for drug resistance.



METHODOLOGY

1. Data Sourcing:

- Utilized the SMACC database to source 35 phytochemical dataset.

2. Gene Expression Analysis:

- Analyzed gene expression using DIGEP-Pred to predict effects based on SMILES data.
- Ranked compounds based on predicted up- or down-regulation of genes.

3. Correlation Analysis with COVID-19 Genes:

- Compared gene regulation results with 16,857 COVID-19-related genes from CTD.
- Used Venn diagrams to identify common genes between the two datasets.

4. Druglikeness Analysis:

- Evaluated druglikeness using SwissADME, Selected only SMILES entries meeting all druglikeness

5. Enrichment Analysis:

- Conducted gene enrichment analysis using Enrichr.
- Compared gene sets with KEGG pathways and GO categories.

6. Network Analysis:

- Visualized protein interaction networks using Cytoscape and STRING data.
- Identified key proteins and ranked top 10 nodes using CytoHubba.

7. Validation of Top Genes:

- Further validated top 10 genes using Enrichr for COVID-19 associations.
- Assessed interactions with viral proteins using the Virus-Host PPI P-HIPSTer 2020 database.

RESULTS & DISCUSSION

A) Overview of the Phytochemical-Likely Genes and Their Categories:

- **Immune Response:** CD86 (T-cell activation), CCL2 (immune cell recruitment), CD83, CD14 (dendritic cell response), TNFRSF1A (apoptosis induction), NOS2 (nitric oxide production), FLT1 (immune modulation).
- **Metabolism:** ADIPOQ (glucose homeostasis, fatty acid breakdown), ABCA1 (cholesterol efflux), GH1 (growth and metabolism), FNDC4, INHBE (metabolic control and reproductive growth), CAT (oxidative stress defense), SREBF2 (lipid metabolism), DHFR (DNA synthesis and repair).
- **Signal Transduction:** RARA (transcription regulation), VDR (calcium/phosphate regulation), REN (blood pressure regulation), PLAT (blood clot breakdown), RAC1 (cell skeleton organization), KRT18 (cell structure), ID1 (cell differentiation), NR3C1 (metabolism and immune regulation), MMP7 (extracellular matrix degradation).
- **Cell Cycle and DNA Repair:** CDK4, TP73 (cell-cycle regulation and apoptosis), SMN2 (RNA processing), CHEK1, TOP2A, CTNNB1 (cell cycle arrest, DNA replication, transcription).
- **Oxidative Stress Response:** NFE2L2, PRDX4, HMOX1 (oxidative stress protection), KEAP1 (reduced oxidative stress response).
- **Apoptosis and Cell Death:** SERPINA3, CLU (inflammation and apoptosis, neurodegenerative disease involvement), AR (tissue-specific apoptosis), SIVA1 (decreased role in apoptosis regulation).
- **Other Functions:** WIPI1 (autophagy), TIMP1 (cell behavior, matrix remodeling), PLAU (proteolysis, cell migration, tissue remodeling), CBR1 (drug metabolism), EPAS1 (oxygen response), TNNI3 (heart muscle contraction), IVL (epidermal cell envelope formation), SELL (lymphocyte adhesion and trafficking).

RESULTS & DISCUSSION

B) Gene Association with COVID-19

- FDNC4 (metabolic control and reproductive growth) and SMN2 (RNA processing) did not correlate with the COVID-19 gene set, suggesting they may not play a significant role in the virus's pathogenesis or host response.
- The lack of association for FDNC4 and SMN2 might indicate that these genes are either not responsive to SARS-CoV-2 or are involved in pathways irrelevant to the virus's life cycle and immediate host response.



Figure 1: The overlap of upregulated and downregulated genes with Covid-19 genes.

C) Druglikeness Analysis:

- CHEMBL1324:** Associated with 14 genes, including those related to extracellular matrix regulation (e.g., PLAT), oxidative damage protection (CAT), and metabolic pathways (ADIPOQ), suggesting broad biological activity but also a higher potential for side effects.
- CHEMBL1458891:** Primarily associated with ADIPOQ, implying a focused action on metabolic processes, potentially beneficial for treating metabolic disorders like obesity or type 2 diabetes, with possibly fewer off-target effects.
- CHEMBL3818159:** Linked to genes involved in DNA damage response (e.g., CHEK1), immune function, and metabolism, indicating therapeutic potential for conditions involving DNA damage, immune dysregulation, or metabolic disturbances.

RESULTS & DISCUSSION

D) Enrichment Analysis Summary

Key Pathways and Processes:

- Significant Pathways: "Lipid and Atherosclerosis" and "Complement and Coagulation Cascades" indicate high activity in lipid metabolism and blood clotting. Key genes include ABCA1, PLAT, and CCL2.
- Disrupted Pathways: "Fluid Shear Stress and Atherosclerosis" and "Negative Regulation of Blood Coagulation" suggest issues in cardiovascular function and immune response, involving genes like ABCA1, NPPB, ADIPOQ, and CD86.

Biological Processes:

- Upregulated: Processes like blood clotting and inflammation, with key genes ABCA1, PLAT, and CCL2.
- Downregulated: Processes such as extracellular matrix remodeling and clotting, involving genes ABCA1, NPPB, and ADIPOQ.

Cellular Components and Molecular Functions:

- Cellular Components: Upregulated components include "Collagen-Containing Extracellular Matrix" and "Platelet Alpha Granule Lumen" (genes: MMP7, PLAT). Downregulated components show reduced activity in these areas (genes: ABCA1, NPPB, ADIPOQ).
- Molecular Functions: Upregulated functions like "Serine-Type Endopeptidase Activity" and "Receptor Ligand Activity" involve genes PROC and CD86. Downregulated functions, such as "Serine-Type Peptidase Activity" and "Receptor Binding," involve genes CAT, NOS2, and RARA.

RESULTS & DISCUSSION

E) of Top Regulatory Proteins in PPI

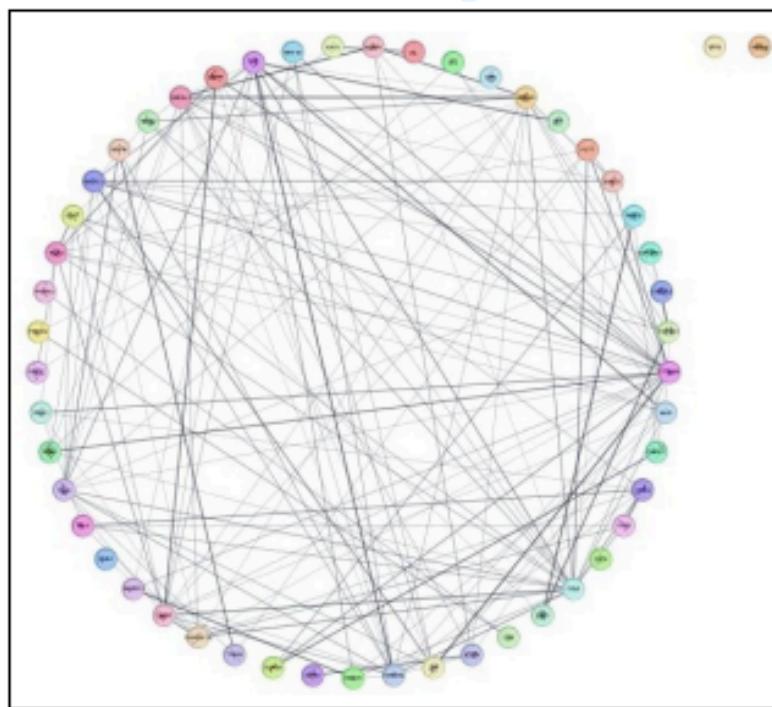


Figure 2: Protein-protein interaction network overview for upregulated and downregulated genes built using STRING in Cytoscape.

F) Association of Key Genes in Covid-19 Gene set and

PLAU (Plasminogen Activator, Urokinase):

- Frequently upregulated during SARS-CoV-2 infection and involved in inflammation and tissue remodeling. It interacts with various viral proteins, suggesting it may be a common target for viral manipulation across different viruses.

PLAT (Plasminogen Activator, Tissue):

- Less prominently represented but involved in fibrinolysis and potentially modulated by viruses like Vaccinia. Its role in coagulation could influence viral spread and survival, though its therapeutic potential is limited due to druglikeness issues.

ADIPOQ (Adiponectin):

- Contributes to glucose regulation, fatty acid breakdown, and immune modulation. Its role in metabolic responses and inflammation during viral infections, like SARS-CoV-2, could offer new therapeutic insights and targets for managing disease progression and severity.

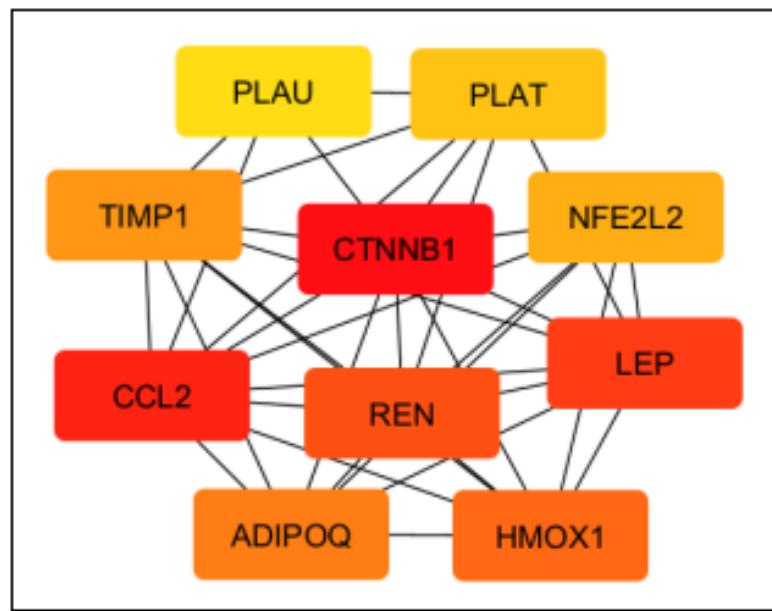
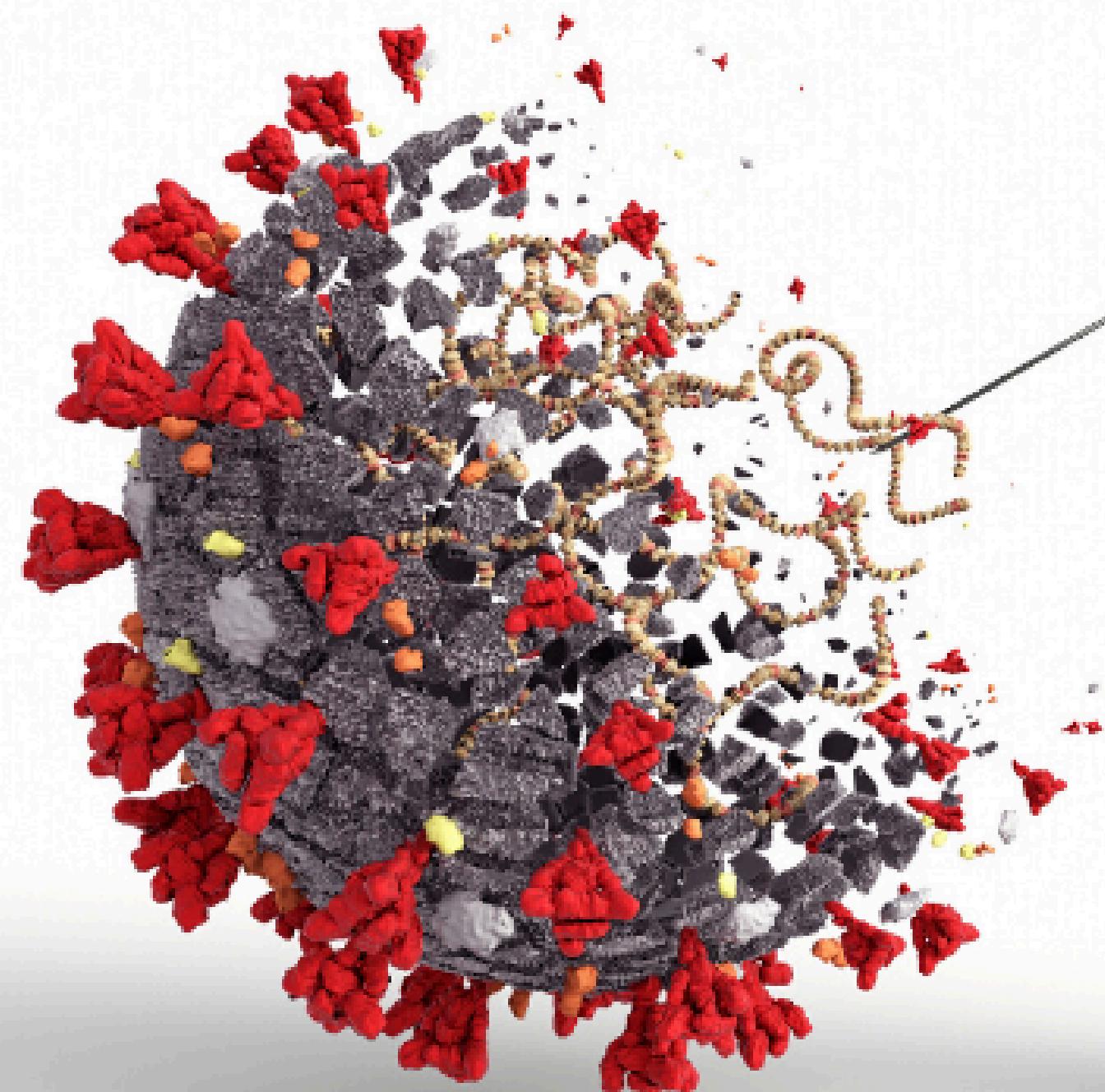


Figure 3: Ranking of the top 10 nodes based on MCC with Cytohubba plugin.

CONCLUSION

- PLAU and ADIPOQ are strong candidates for COVID-19 drug development due to their roles in immune response, inflammation, and tissue remodeling.
- Modulating PLAU and ADIPOQ can potentially prevent excessive tissue injury and manage inflammation, offering targeted intervention strategies for severe COVID-19 cases.
- Further research into PLAU and ADIPOQ inhibitors, combination therapies, and personalized treatment approaches is necessary, with a focus on long-term safety and efficacy.



REFERENCES

1. Askari, B. S., & Krajinovic, M. (2010). Dihydrofolate Reductase Gene Variations in Susceptibility to Disease and Treatment Outcomes. *Current Genomics*, 11(8), 578. <https://doi.org/10.2174/138920210793360925>
2. Baker, S. J., Poulikakos, P. I., Irie, H. Y., Parekh, S., & Reddy, E. P. (2022). CDK4: a master regulator of the cell cycle and its role in cancer. *Genes & Cancer*, 13, 21. <https://doi.org/10.18632/GENESANDCANCER.221>
3. Bloom, N., Bunn, P., Mizen, P., Smietanka, P., & Thwaites, G. (2023). The Impact of COVID-19 on Productivity. *The Review of Economics and Statistics*, 1–45. https://doi.org/10.1162/REST_A_01298
4. Bogdan, C., Röllinghoff, M., & Diefenbach, A. (2000). The role of nitric oxide in innate immunity. *Immunological Reviews*, 173, 17–26. <https://doi.org/10.1034/J.1600-065X.2000.917307.X>
5. Bydoun, M., Sterea, A., Weaver, I. C. G., Bharadwaj, A. D., & Waisman, D. M. (2018). A novel mechanism of plasminogen activation in epithelial and mesenchymal cells. *Scientific Reports* 2018 8:1, 8(1), 1–17. <https://doi.org/10.1038/s41598-018-32433-y>
6. Chiang, S. K., Chen, S. E., & Chang, L. C. (2021). The Role of HO-1 and Its Crosstalk with Oxidative Stress in Cancer Cell Survival. *Cells*, 10(9). <https://doi.org/10.3390/CELLS10092401>
7. Ciotti, M., Ciccozzi, M., Terrinoni, A., Jiang, W. C., Wang, C. Bin, & Bernardini, S. (2020). The COVID-19 pandemic. *Critical Reviews in Clinical Laboratory Sciences*, 365–388. <https://doi.org/10.1080/10408363.2020.1783198>
8. aina, A., Michelin, O., & Zoete, V. (2017). SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific Reports* 2017 7:1, 7(1), 1–13. <https://doi.org/10.1038/srep42717>
9. Davis, A. P., Wiegers, T. C., Johnson, R. J., Sciaky, D., Wiegers, J., & Mattingly, C. J. (2023). Comparative Toxicogenomics Database (CTD): update 2023. *Nucleic Acids Research*, 51(D1), D1257–D1262. <https://doi.org/10.1093/NAR/GKAC833>
10. Fang, L., Che, Y., Zhang, C., Huang, J., Lei, Y., Lu, Z., Sun, N., & He, J. (2021). PLAU directs conversion of fibroblasts to inflammatory cancer-associated fibroblasts, promoting esophageal squamous cell carcinoma progression via uPAR/Akt/NF-κB/IL8 pathway. *Cell Death Discovery* 2021 7:1, 7(1), 1–14. <https://doi.org/10.1038/s41420-021-00410-6>
11. Kanugula, A. K., Kaur, J., Batra, J., Ankireddypalli, A. R., & Velagapudi, R. (2023). Renin- Angiotensin System: Updated Understanding and Role in Physiological and Pathophysiological States. *Cureus*, 15(6). <https://doi.org/10.7759/CUREUS.40725>
12. Lagunin, A., Ivanov, S., Rudik, A., Filimonov, D., & Poroikov, V. (2013). DIGEP-Pred: web service for in silico prediction of drug-induced gene expression profiles based on structural formula. *Bioinformatics (Oxford, England)*, 29(16), 2062–2063. <https://doi.org/10.1093/BIOINFORMATICS/BTT322>

Thank You

