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Computational analysis of the phytocompounds of *Mimusops elengi* against spike protein of SARS CoV2 – An Insilico model

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ABSTRACT

The COVID-19 pandemic has been a global health crisis for over three years now, with the virus causing widespread illness and death. The urgent need for safe and effective therapeutic drugs has prompted the exploration of alternative medicine systems such as Ayurveda and Siddha. This study focuses on the potential therapeutic properties of the Ayurvedic plant, *Mimusops elengi*. In silico techniques were employed to analyze the bioactivity of the plant, including target prediction, gene ontology analysis, OMIM analysis, and molecular docking analysis. The results revealed 36 phytocompounds that interacted with 1431 receptors in the human body, and two compounds - hederagenin and quercetin - showed exceptionally high binding affinities toward their corresponding receptors, IL6 and MMP9. These results provide important insight into the potential therapeutic activity of *M. elengi* and its compounds in combating COVID-19. However, further research and clinical trials are necessary to validate these findings and develop safe and effective drugs. The study highlights the importance of combining traditional medicine with modern scientific methods to find effective treatments for global health challenges.

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of the COVID-19 pandemic, which has impacted the global population since its initial detection in late 2019. The clinical presentation of COVID-19 is heterogeneous, but common symptoms include fever, headache, fatigue, persistent coughing [1], gastrointestinal symptoms [2], and olfactory and gustatory dysfunction [3]. Individuals with pre-existing medical conditions, such as diabetes, obesity, COPD, cardiovascular disease, and autoimmune disorders [4–7], are at increased risk of severe disease progression. Severe COVID-19 can lead to pneumonia and respiratory distress, and in severe cases, the development of a cytokine storm, resulting in septic shock and death [8,9]. Despite ongoing research and the introduction of new treatments, an effective cure for COVID-19 has yet to be established.

The traditional Indian medicinal system, including Siddha and Ayurveda, incorporates the use of herbal plant combinations for the treatment of various health conditions, including digestive issues, respiratory conditions, stress, arthritis, mental health, and sleep disturbances [10]. Despite a lack of robust scientific evidence in certain aspects, recent studies have demonstrated the therapeutic properties of bioactive compounds found in herbal medicines. It is noteworthy that a significant proportion of contemporary drugs are derived from plants, and their bioactive compounds have been used as medicines for centuries [11]. Further, their purpose as modern drugs aligns with their traditional ethnomedical uses [12]. To fully understand the effects of these compounds, modern scientific approaches, such as systems pharmacology and cheminformatics, can be utilized. For instance, research on the Chinese chaste plant has revealed the presence of potent bioactive molecules with potential therapeutic benefits for COPD-related complications, such as emphysema and lung inflammation [13]. Similarly, the multi-targeted interactions of compounds found in *Ammi visnaga*

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have shown potential as a treatment for COVID-19 [14].

Mimusops elengi is an evergreen tropical plant that is widely distributed in South Asian countries and has been used for its medicinal properties in Ayurveda. This plant has been traditionally utilized as an astringent and tonic for the treatment of diarrhea and dysentery [15]. In addition to its astringent and tonic properties, recent studies have shown that *M. elengi* leaves possess antioxidant properties [16], anti-diabetic effects [17], and exhibit anti-neoplastic activity in vitro [18]. The antibacterial properties of silver nanoparticles coated with compounds from the flowers of *M. elengi* have also been reported [19]. The plant's pharmacological properties include anthelmintic, antidotal, cardiotonic, anti-inflammatory, analgesic, and antipyretic effects [20–23]. These diverse therapeutic properties make *M. elengi* a promising candidate for further research on its phytocompounds with the aim of treating symptoms associated with COVID-19.

The current study aimed to evaluate the potential of the selected plant as a therapeutic agent against COVID-19 by utilizing a series of in silico methods including gene-target identification, gene ontology analysis, OMIM analysis, compound-target-network analysis, and molecular docking analysis. The results of these computational studies provide insight into the plant's potential efficacy against COVID-19 and identify likely candidate compounds for further investigation. The ultimate goal of this research is to contribute to the development of a commercially viable formulation that can be used to treat COVID-19 following appropriate clinical testing. The results of this study represent a significant step toward understanding the therapeutic potential of this plant against COVID-19 and may provide a basis for the development of novel treatments for the disease.

2. Methods

2.1. Collation of M. elengi phytocompounds

The phytocompounds present in the plant *M. elengi* were meticulously sourced from various published literature sources. The canonical SMILES representation of these phytocompounds was obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The SMILES representation provides a standardized and unambiguous representation of the molecular structure of the compounds, which was crucial for the subsequent computational analyses.

2.2. Mining of human targets and COVID-19 virogenomic signatures

The collected canonical SMILES representation of the phytocompounds was analyzed using SwissTargetPrediction (http://www.swisstargetprediction.ch/), a state-of-the-art in silico tool for predicting protein targets of small molecules. This tool was used to identify the specific human targets of the bioactive compounds in *M. elengi*. To further enhance the relevance of the study, the signature genes associated with COVID-19 were also collected. This allowed the researchers to assess the potential of the bioactive compounds in addressing the specific biological mechanisms involved in the disease. The use of SwissTargetPrediction and the collection of signature genes helped to provide a comprehensive and scientifically rigorous analysis of the therapeutic potential of *M. elengi* against COVID-19.

2.3. Gene ontology analysis

Among the human targets identified by Swiss Target Prediction, the best targets with the highest probability were selected for further analysis. These targets were subjected to gene ontology analysis using the Panther classification system (http://www.pantherdb.org/), a widely used online tool for the functional classification of genes and proteins. This analysis aimed to identify the molecular activities associated with the genes and provided valuable insights into the underlying mechanism of action of the bioactive compounds in *M. elengi*. The gene ontology analysis was crucial in understanding the biological processes and functions that the bioactive compounds may impact, and in evaluating their potential therapeutic effects against COVID-19. The use of the Panther classification system ensured the accuracy and reliability of the results obtained in this study.

2.4. Compound-Target-Network analysis

Compound-Target-Network (CTN) analysis was performed using the Cytoscape v3.9.1 software [24]. CTN analysis helps to predict the multiple therapeutic potentialities of compounds along with their mechanism of action and provides an in-depth understanding of the interactions between the compounds and their targets. This type of network construction also allows the prediction of various interacting partners of the compounds, which is significant in the development of compound-based drugs with therapeutic effects.

2.5. Molecular docking

The interaction between the selected compounds with their respective ligands was evaluated in silico using molecular docking analysis. This type of analysis allows the study of the molecular interactions between compounds and their targets in a simulated environment and provides insight into the binding affinity and stability of these interactions. In this study, molecular docking analysis was performed using Autodock vina [25], a widely used tool for molecular docking and virtual screening. The results of the molecular docking analysis helped to determine the best compounds for further development as potential COVID-19 therapeutic candidates. PyMol visualization system (https://pymol.org/2/) and Ligplus+ tool (https://www.ebi.ac.uk/thornton-srv/software/LigPlus/) was used to visualize and analyze the receptor-compound interactions.

3. Results

3.1. Phytocompounds retrieval

The literature survey conducted in this study identified a total of 36 biologically active phytocompounds present in the *M. elengi* plant. These compounds and their corresponding PubChem IDs are listed in Table 1 for easy reference. Furthermore, the canonical SMILES of these compounds are provided in Supplementary Table 1: Canonical SMILES of the collated phytocompounds, for the purpose of predicting their specific human targets. These findings represent an important step toward understanding the potential therapeutic properties of *M. elengi* and its impact on COVID-19.

3.2. Human target receptor mining and COVID-19 virogenomic signatures

The results of the SwissTargetPrediction tool showed that 36 phytocompounds found in *M. elengi* interact with 1431 human receptors. Table 2 highlights the best targets, selected based on their probability score, for further analysis. Additionally, the COVID-19 virogenomic signature genes reported by Alsamman and Zayed (2020) [26] were compiled in supplementary Table 2: List of compounds along with their target genes, and used to support the analysis. The list of compounds targeting receptors and their respective Pubchem IDs are provided in supplementary Table 3: COVID-19 virogenomic signatures reported by Alsamman and Zayed, 2020, for reference.

3.3. Gene ontology analysis

The Gene Ontology (GO) analysis was conducted on the top-performing targets using the PANTHER online tool. The results of the GO analysis are presented in Figs. 1 and 2, which visually summarize the biological processes and molecular functions of the targeted genes. This

Table 1
List of phytocompounds in *M. elengi* identified through literature survey.

S. No	Compounds	Abbreviations	Pubchem ID
1	Benzyl alcohol	BA	244
2	Phenethyl alcohol	PA	6054
3	Styryl carbinol	SC	5,315,892
4	Methyl 4-hydroxybenzoate	MH	7456
5	Hexadecanoic acid	HEA	985
6	(Z)-9-Octadecanoic acid	OA	445,639
7	Methyl paraben	MP	7456
8	Dibutyl phthalate	DP	3026
9	Tetradecamethylcycloheptasiloxane	TDCH	7874
10	Benzoic acid	BZA	243
11	Phthalic acid	PHA	1017
12	4-Amino-2,3,5,6-tetrafluorobenzaldehyde	ATB	11,745,493
13	Tau - muurolol	TM	51,394,521
14	Alpha cadinol	AC	6,431,302
15	Di-isobutyl phthalate	DIP	6782
16	Eicosane	ES	8222
17	Oleic acid	OLA	445,639
18	Octadecadienoic acid	OCDA	5,312,457
19	Octadecanoic acid	OCA	5281
20	Spinasterol	SS	5,281,331
21	Ursolic acid	UA	64,945
22	Taraxerol	TX	92,097
23	Quercitol	QC	441,437
24	Hentriacontane	HA	12,410
25	β-carotene	BC	5,280,489
26	D-mannitol	DM	6251
27	β-sitosterol	BS	521,199
28	quercetin	QR	5,280,343
29	taraxerone	TXR	92,785
30	α-spinasterol	AS	5,315,190
31	betulinic acid	BEA	64,971
32	lupeol	LP	259,846
33	hederagenin	HG	73,299
34	Oleanolic acid	ONA	70,494
35	4-Hydroxybenzaldehyde	HB	126
36	Stigmasterol glucoside	SG	6,602,508

Table 2
List of best target receptors.

S. No.	Compounds	Receptors
1	BA	ACHE
2	PA	CA2
3	SC	HCAR2
4	MH	CA2
5	HEA	FABP4
6	OA	FABP4
7	MP	CA2
8	DP	CYP11B2
9	TDCH	MAP3K7
10	BZA	DAO
11	PHA	CA2
12	ATB	ICAM1
13	TM	CYP19A1
14	AC	CYP19A1
15	DIP	GRM5
16	ES	SHBG
17	OLA	FABP4
18	OCDA	RARB
19	OCA	PPARA
20	SS	AR
21	UA	RORC
22	TX	AR
23	QC	NPC1L1
24	HA	SHBG
25	BC	RBP4
26	DM	NPC1L1
27	BS	NPC1L1
28	QR	NOX4
29	TXR	CYP19A1
30	AS	AR
31	BEA	SAE1
32	LP	HSD11B1
33	HG	PTPN1
34	ONA	POLB
35	HB	CA2
36	SG	IL2

analysis provided insightful information on the involvement of the targeted genes in a variety of biological processes, such as the regulation of apoptosis, regulation of phosphorylation, and maintenance of homeostasis. The molecular functions of these genes were also analyzed, including multiple element binding and oxygen binding activity. Additionally, the relationship between these genes and other diseases was explored through OMIM analysis and depicted in Fig. 3. This analysis sheds light on the potential activities and benefits of the phytocompounds in reducing the risk of COVID-19 and its associated effects.

3.4. Compound-Target-Network (CTN) analysis

The Cytoscape plugin was employed to construct the CTN. The resulting network showcases the relationship between the 36 phytocompounds found in *M. elengi* and the 1431 human receptors they target (Fig. 4). The CTN analysis revealed the multiple interactions of these compounds with human receptors, solidifying their potential as promising therapeutic candidates in the fight against COVID-19.

3.5. Molecular docking analysis

The results of the comparative analysis between phytocompounds targeted receptors and COVID-19-associated signatures revealed four common genes: IL6, MMP9, ICAM1, and DPP4. To evaluate the interaction of these compounds with the selected genes, molecular docking analysis was performed using Autodock vina. The results of this analysis, including the binding energies of each compound-gene interaction, are presented in Table 3 and Table 4, respectively. The interactions between the receptors and compounds are visualized in Fig. 5.

The results of molecular docking analysis showed that compounds HG and QR had substantial binding energies against the COVID-19 associated receptors IL6 and MMP6 (Fig. 6). These findings suggest that these compounds have potential therapeutic value against COVID-19, which can be further validated through laboratory and clinical testing.

4. Discussion

The COVID-19-causing virus carries out its pathophysiology by binding to various receptors in the human body, especially through its spike proteins. Its effect is mainly on the respiratory system but also affects the cardiovascular, gastrointestinal, and nervous systems [27–29]. This is possible due to target-specific receptors present in these tissues, like ACE2, which show significant affinities toward the spike proteins [30]. In spite of various developments in medicinal sciences, a complete cure for this disease still remains a bottleneck. Hence, the search for alternative therapeutics became highly essential. Ancient Indian medicinal systems, like Siddha and Ayurveda, are still in practice because of their effective treatments for specific diseases [31]. In addition, plant-based medicines offer lesser side effects [32]. Thus, combining Indian traditional knowledge with modern technical advances can be a reliable alternative medicine for diseases like COVID-19.

Moreover, COVID-19 has manifested itself as a worldwide pandemic, through the course of which multiple variants of concern (VOCs) have shown predominance. Each variant succeeded its predecessor in various aspects of pathogenesis and infectivity, which are attributed to mutations resulting in spike proteins, binding affinity, etc. The latest variations resulted in the uprise of the Omicron variant, with a massive number of changes to spike protein genes, resulting in a 13-fold increase in viral infectivity, and being 2.8 times more infective than its previous Delta variant [33]. Allopathic formulations are hoping to alleviate the

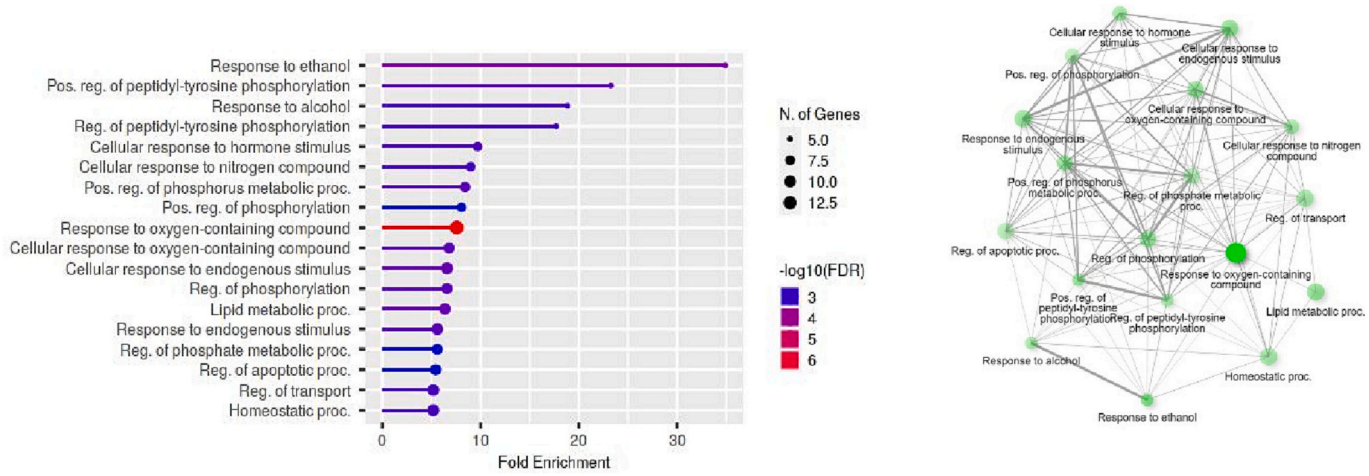


Fig. 1. Biological processes. (a) Fold enrichment of biological processes. (b) Network of biological process.

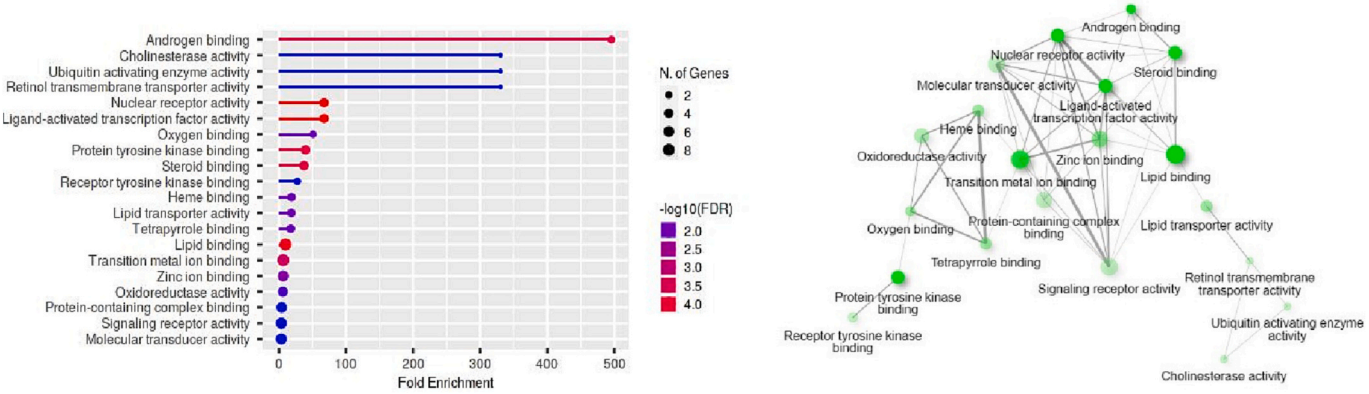


Fig. 2. Molecular functions. (a) Fold enrichment of molecular functions. (b) Network of molecular functions.

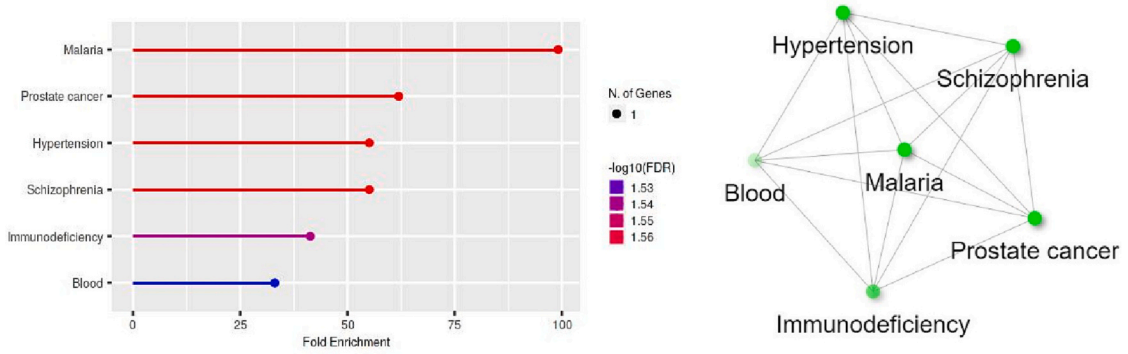


Fig. 3. Gene associated with other diseases using OMIM analysis. (a) Fold enrichment of Diseases. (b) Network of diseases.

disease, but could not achieve it, because of the unpredictable mutations. Although plant-based therapeutics seem as a promising replacement for allopathic formulations, a solid scientific basis for Ayurvedic and Siddha medicines is not yet established. *M. elengi*, also known as the Spanish cherry plant has been found to have medicinal applications in traditional Indian alternative medicines such as Ayurveda for several centuries against multiple ailments. Despite its varying properties, its specific mode of interaction with COVID-19 is unknown. Thus, this study has employed cheminformatics and systems pharmacology approaches to decipher the pharmacological potentials of *M. elengi* against COVID-19.

In this study, we have employed 36 bio-actives present in *M. elengi* (commonly present secondary metabolites such as alkaloids and tannins were excluded from the study). These 36 compounds were found to be interacting with 1431 human genes. Since various pathways are involved in COVID-19 progression, targeting multiple genes simultaneously rather than a single gene can provide desired results [34]. In addition, gene ontology analysis revealed the involvement of these receptors in several functions including oxygen-binding activity and homeostatic process. Since, these processes are significantly altered in COVID-19 conditions, targeting these receptors is highly justified. Furthermore, OMIM analysis revealed the close association of these

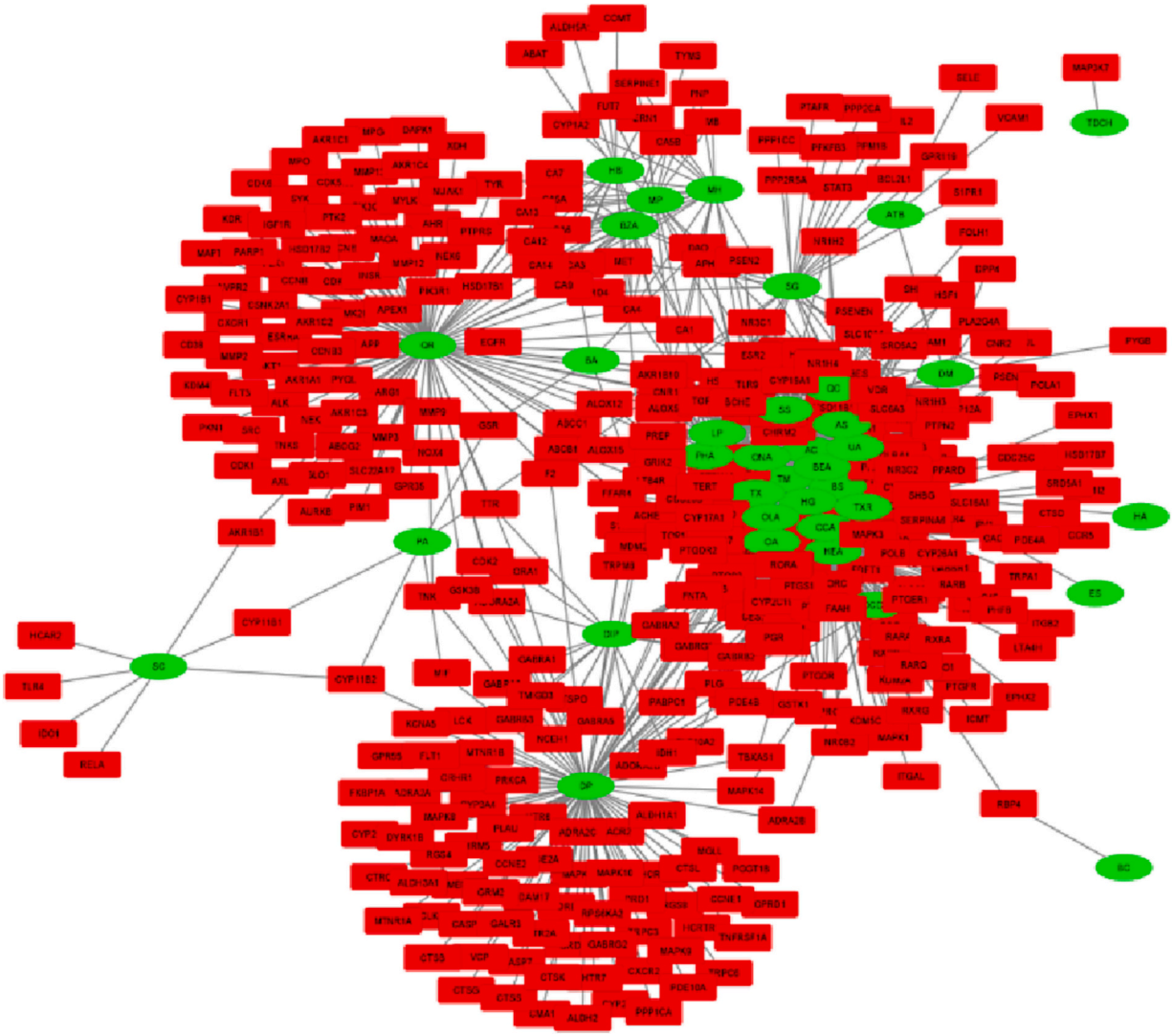


Fig. 4. Compound-Target-Network constructed using the compounds and their respective targets. The green color represents the phytocompounds and the red color represents the target genes.

Table 3
Common genes and their targeting compounds.

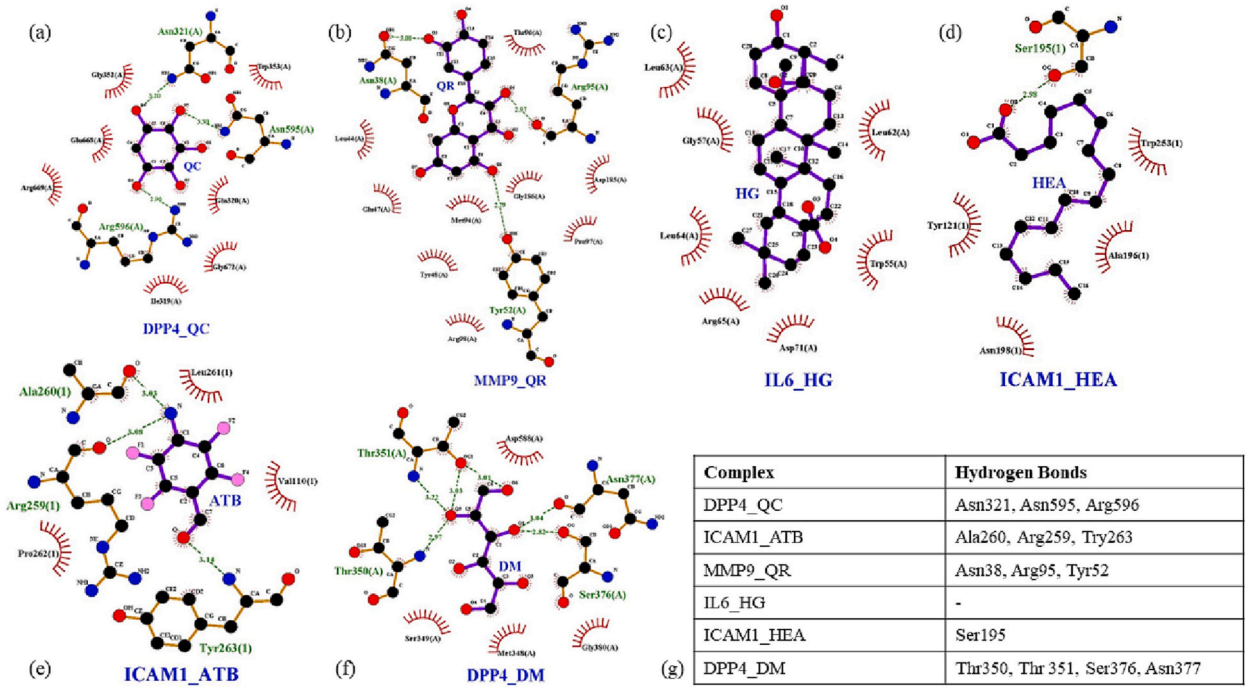
Common genes	Compounds
IL6	HG
MMP9	QR
ICAM1	HEA, ATB
DPP4	QC, DM

Table 4
Results of molecular docking using plant compounds against the COVID-19 responsible receptors. The binding energy were provided in kcal/mol.

	HG	QR	HEA	ATB	QC	DM
IL6	−6.6					
MMP9		−7.9				
ICAM1			−3.6	−4.9		
DPP4					−5.7	−4.8

target genes with other disease conditions such as hypertension, schizophrenia, and general immunodeficiency. Hence, targeting these genes can also help in reducing post-COVID-19-related side effects.

From the supplementary tables 2 and 3, it was clear that genes IL6, MMP9, ICAM1, and DPP4 were found to be common to both the phytocompound targeted receptors and COVID-19-associated signatures. So, these receptors were chosen for docking analysis to analyze the binding affinity between the targets and their respective phytocompounds [35]. Molecular docking studies were crucial in identifying the interactions of target compounds with their receptors at the atomic level. Docking analysis revealed that HEA, DM, and ATB have relatively low affinities (lesser than −5 kcal/mol) with their corresponding genes. QC interacts with DPP4 with the affinity of −5.7 kcal/mol. But, HG and QR showed higher binding strengths with IL6 and MMP9 respectively (−6.6 and -7.9 kcal/mol respectively). IL6 is known to play a key role in acute-phase response and hematopoiesis and has also been shown to be immunocompetent [36,37]. It is also a chief target in treating inflammatory diseases due to its pro- and anti-inflammatory properties [38,39]. IL6 is also found to participate in general immune processes like increased B-lymphocyte activity, ensuring optimal T-cell response, control over monocyte differentiation into macrophages and their phagocytosis, and prevention of viral-induced apoptosis in lung cells [40]. Similarly, MMP9 is also known to be involved in inflammatory immune processes and shows upregulation of tissue remodeling through the activation and recruitment of cytokines and chemokines [41,42]. Additionally, QR seems to bind with not only MMP9 but also with MMP3, which plays an important role in the inflammation process.



(g)

Complex	Hydrogen Bonds
DPP4_QC	Asn321, Asn595, Arg596
ICAM1_ATB	Ala260, Arg259, Try263
MMP9_QR	Asn38, Arg95, Tyr52
IL6_HG	-
ICAM1_HEA	Ser195
DPP4_DM	Thr350, Thr 351, Ser376, Asn377

Fig. 5. Visualization of receptor-compound interactions. (a-f) Two-dimensional interaction diagrams of receptors and compounds (self-labelled); (g) Table presenting the amino acid residues of receptors involving in hydrogen bond formation with the compounds.

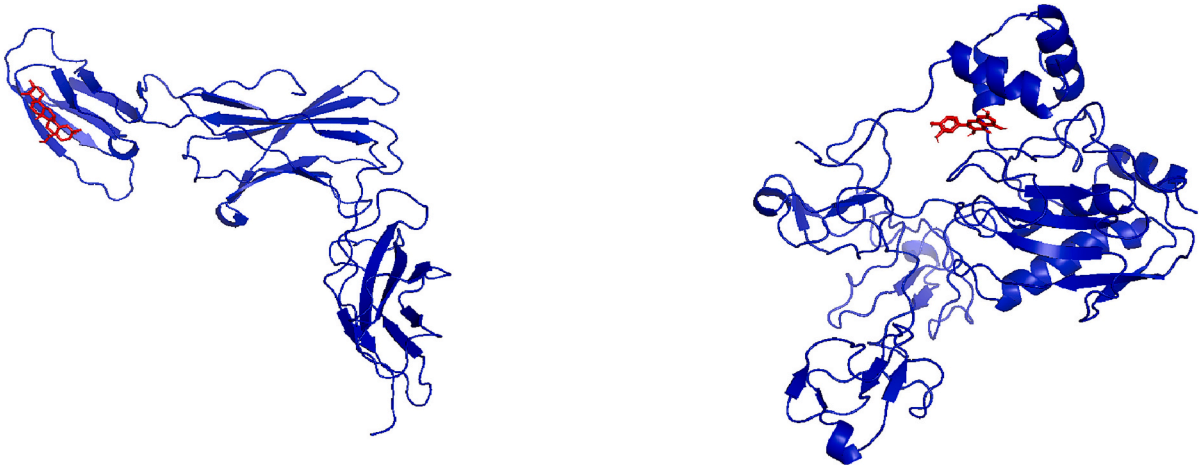


Fig. 6. Visualization of receptor and compound after molecular docking analysis. (a) IL6 and HG. (b) MMP9 and QR. Receptors were provided in blue color and compounds were provided in red.

These results indicate that *M. elengi* can be used as a significant candidate for synthesizing novel formulations to treat COVID-19.

This study integrates the concepts of cheminformatics and system pharmacology with conventional medicinal systems in order to identify novel therapeutic agents against COVID-19. The findings of this study can be regarded as an initial step for COVID-19 medication which ultimately requires clinical experimentations and validations.

5. Conclusion

In conclusion, this study provides compelling evidence for the potential use of compounds derived from the medicinal plant *M. elengi* as a novel therapeutic approach for treating COVID-19. Through in silico analysis, four targets of the 1431 receptors targeted by phytocompounds in *M. elengi* were identified as potential causes of COVID-19. Furthermore, among the 36 compounds from *M. elengi* evaluated, two compounds were found to have high efficacy for treating COVID-19. This study represents a novel and promising avenue for the discovery of new treatments for COVID-19, and serves as a valuable addition to the limited research on the pharmacological properties of *M. elengi*. However, it is important to note that in vitro and in vivo studies are needed to validate these findings and further explore the full potential of these compounds as a treatment for COVID-19. The results of this study also suggest that phytocompounds from *M. elengi* could be used in combination with other plant-based drugs, consistent with the principles of Ayurvedic medicine. Overall, this research opens up exciting new avenues for the treatment of COVID-19, and highlights the need for continued exploration of the pharmacological properties of *M. elengi*.

CRediT authorship contribution statement

Yuvaraj Dinakarkumar & Sai Ramesh: Conceptualization,

Methodology. Adarshan: Software and Original draft preparation, Naveen Kumar: Data curation, Writing. Thasleema Nasrin & Aarthi Shree: Initial Investigation. Muthusamy Karnan: Supervision. Hamad Lohedan & Jothi Ramalingam: Funding, Reviewing and Editing,

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: R. Jothi Ramalingam reports financial support was provided by Researchers Supporting Project.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijbiomac.2023.125553.

References

[1] W.J. Song, C.K.M. Hui, J.H. Hull, S.S. Birring, L. McGarvey, S.B. Mazzone, K. F. Chung, Confronting COVID-19-associated cough and the post-COVID syndrome: role of viral neurotropism, neuroinflammation, and neuroimmune responses, Lancet Respir. Med. 9 (5) (2021) 533–544, https://doi.org/10.1016/S2213-2600(21)00125-9.

[2] D.E. Freedberg, L. Chang, Gastrointestinal symptoms in COVID-19: the long and the short of it, Curr. Opin. Gastroenterol. 38 (6) (2022) 555–561, https://doi.org/10.1097/MOG.0000000000000876.

[3] M.R. Bianco, D.M. Modica, G.D. Drago, A. Azzolina, G. Mattina, M. De Natale, G. Rossi, M. Amata, G. Canzoneri, G. Manganaro, F. Di Gregorio, R. Russo, S. Pricoco, V. Saita, E. Allegra, Alteration of smell and taste in asymptomatic and symptomatic COVID-19 patients in Sicily, Italy, Ear Nose Throat J. 100 (2_suppl) (2021) 182S–185S, https://doi.org/10.1177/0145561320981447.

[4] Y. Zhou, J. Chi, W. Lv, Y. Wang, Obesity and diabetes as high-risk factors for severe coronavirus disease 2019 (Covid-19), Diabetes Metab. Res. Rev. 37 (2) (2021), e3377, https://doi.org/10.1002/dmrr.3377.

[5] N. Yazdanpanah, N. Rezaei, Autoimmune complications of COVID-19, J. Med. Virol. 94 (1) (2022) 54–62, https://doi.org/10.1002/jmv.27292.

[6] J.M. Leung, M. Niikura, C.W.T. Yang, D.D. Sin, COVID-19 and COPD, Eur. Respir. J. 56 (2) (2020) 2002108, https://doi.org/10.1183/13993003.02108-2020.

[7] R.B. Azevedo, B.G. Botelho, J.V.G. Hollanda, L.V.L. Ferreira, L.Z. Junqueira de Andrade, S.S.M.L. Oei, T.S. Mello, E.S. Muxfeldt, Covid-19 and the cardiovascular system: a comprehensive review, J. Hum. Hypertens. 35 (1) (2021) 4–11, https://doi.org/10.1038/s41371-020-0387-4.

[8] Q. Ye, B. Wang, J. Mao, Cytokine storm in COVID-19 and treatment, J. Inf. Secur. 80 (2020) 607–613.

[9] S. Montazersaheb, S.M. Hosseiniyan Khatibi, M.S. Hejazi, V. Tarhriz, A. Farjami, F. Ghasemian Sorbeni, R. Farahzadi, T. Ghasemnejad, COVID-19 infection: an overview on cytokine storm and related interventions, Virol. J. 19 (1) (2022) 92, https://doi.org/10.1186/s12985-022-01814-1.

[10] R. Sharma, A. Kabra, M.M. Rao, P.K. Prajapati, Herbal and holistic solutions for neurodegenerative and depressive disorders: leads from Ayurveda, Curr. Pharm. Des. 24 (22) (2018) 2597–2608, https://doi.org/10.2174/1381612824666180821165741.

[11] C. Veeresham, Natural products derived from plants as a source of drugs, J. Adv. Pharm. Technol. Res. 3 (4) (2012) 200–201, https://doi.org/10.4103/2231-4040.104709.

[12] C. Katiyar, A. Gupta, S. Kanjilal, S. Katiyar, Drug discovery from plant sources: an integrated approach, Ayu 33 (1) (2012) 10–19, https://doi.org/10.4103/0974-8520.100295.

[13] S. Adarshan, P. Muthuramalingam, R. Jeyasri, M.A. Lakshmi, R. Sathishkumar, S. K. Pandian, H. Shin, J.T. Chen, M. Ramesh, *Vitex negundo* L. derived specialized molecules unveil the multi-targeted therapeutic avenues against COPD: a systems pharmacology approach, Front. Biosci. 27 (3) (2022) 87, https://doi.org/10.31083/j.fbl2703087.

[14] I. Aanouz, A. Belhassan, K. El-Khatabi, T. Lakhlifi, M. El-Ldrissi, M. Bouachrine, Moroccan Medicinal plants as inhibitors against SARS-CoV-2 main protease: Computational investigations, J. Biomol. Struct. Dyn. 39 (8) (2021) 2971–2979, https://doi.org/10.1080/07391102.2020.1758790.

[15] Niranjan P. Sahu, Kazuo Koike, Zhonghua Jia, Tamotsu Nikaido, Novel triterpenoid saponins from Mimusopselengi, Tetrahedron 51 (48) (1995) 13435–13446, https://doi.org/10.1016/0040-4020(95)00879-D.

[16] Kar B, Kumar RBS, Karmakar I, Dolai N, Bala A, Mazumder UK, Haldar PK. Antioxidant and in vitro anti-inflammatory activities of Mimusopselengi leaves. Asian Pac. J. Trop. Biomed., (in press).

[17] J. Shaik, S.M. Khasim, P.B. Naidu, Protective activity of ethanolic leaf extract of Mimusopselengi Linn. on lipid peroxidation and antioxidant enzymes in experimental diabetic rats, Int. J. Adv. Pharm. Sci. 2 (2011) 264–269 (online).

[18] W. Mahavorasirikul, V. Viyanant, W. Chaijaroenkul, A. Itharat, K. Na-Bangchang, Cytotoxic activity of Thai medicinal plants against human cholangiocarcinoma, laryngeal and hepatocarcinoma cells in vitro, BMC Complement. Altern. Med. 10 (2010) 55.

[19] J, C.N., S, R. & S, H, *Mimusopselengi* Flower-Mediated Green Silver Nanoparticles Control *Staphylococcus aureus* and *Acinetobacter baumannii*. ApplBiochemBiotechnol 194, 2022, pp. 3066–3081, https://doi.org/10.1007/s12010-022-03882-z.

[20] A. Ghani, Medicinal Plants of Bangladesh, The Asiatic Society of Bangladesh, Dhaka, Bangladesh, 2003, p. 303.

[21] K.R. Kirtikar, B.D. Basu, Indian Medicinal Plants, 2nd ed., Lalit Mohan Basu, Allahabad, India, 1988, pp. 1494–1496.

[22] B. Kar, R.B. Kumar, A. Bala, N. Dolai, U.K. Mazumder, P.K. Haldar, Evaluation of antitumor activity of Mimusopselengi leaves on Ehrlich's ascites carcinoma-treated mice, J. Diet. Suppl. 9 (3) (2012) 166–177, https://doi.org/10.3109/19390211.2012.708714.

[23] A. Purnima, B.C. Koti, A.H. Thippeswamy, M.S. Jaji, A.H. Swamy, Y.V. Kurhe, A. J. Sadiq, Antiinflammatory, analgesic and antipyretic activities of Mimusopselengi Linn, Indian J. Pharm. Sci. 72 (4) (2010) 480–485, https://doi.org/10.4103/0250-474X.73908.

[24] Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, Amin N, Schwikowski B, Ideker T. Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res., 13(11), 2498–504.

[25] O. Trott, A.J. Olson, AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading, J. Comput. Chem. 31 (2) (2010) 455–461.

[26] A.M. Alsamman, H. Zayed, The transcriptomic profiling of SARS-CoV-2 compared to SARS, MERS, EBOV, and H1N1, PLoS One 15 (12) (2020), e0243270, https://doi.org/10.1371/journal.pone.0243270.

[27] B. Long, W.J. Brady, A. Koyfman, M. Gottlieb, Cardiovascular complications in COVID-19, Am. J. Emerg. Med. 38 (7) (2020) 1504–1507, https://doi.org/10.1016/j.ajem.2020.04.048.

[28] S. Villapol, Gastrointestinal symptoms associated with COVID-19: impact on the gut microbiome, Transl. Res. 226 (2020) 57–69, https://doi.org/10.1016/j.trsl.2020.08.004.

[29] S. Spudich, A. Nath, Nervous system consequences of COVID-19, Science 375 (6578) (2022) 267–269, https://doi.org/10.1126/science.abm2052.

[30] F. Salamanna, M. Maglio, M.P. Landini, M. Fini, Body localization of ACE-2: on the trail of the keyhole of SARS-CoV-2, Front. Med. 7 (2020), https://doi.org/10.3389/fmed.2020.594495.

[31] S. Kumar, G.J. Dobos, T. Rampp, The significance of ayurvedic medicinal plants, J. Evid.-Based Complement. Alternat. Med. 22 (3) (2017) 494–501, https://doi.org/10.1177/2156587216671392.

[32] J. Zhang, I.J. Onakpoya, P. Posadzki, M. Eddouks, The safety of herbal medicine: from prejudice to evidence, Evid. Based Complement. Alternat. Med. 2015 (2015), 316706, https://doi.org/10.1155/2015/316706.

[33] A. Aleem, A.B. Akbar Samad, A.K. Slenker, Emerging Variants of SARS-CoV-2 and Novel Therapeutics Against Coronavirus (COVID-19), StatPearls Publishing, In StatPearls, 2022.

[34] R. Jeyasri, P. Muthuramalingam, V. Suba, M. Ramesh, J.-T. Chen, *Bacopa monnieri* and their bioactive compounds inferred multi-target treatment strategy for neurological diseases: a cheminformatics and system pharmacology approach, Biomolecules 10 (4) (2020) 536, https://doi.org/10.3390/biom10040536.

[35] S. Adarshan, S. Akassh, K. Avinash, M. Bharathkumar, P. Muthuramalingam, H. Shin, V. Baskar, J.T. Chen, V. Bhuvaneshwari, M. Ramesh, Transcriptomics, cheminformatics, and systems pharmacology strategies unveil the potential bioactives to combat COVID-19, Molecules. 27 (18) (2022) 5955, https://doi.org/10.3390/molecules27185955.

[36] R.J. Simpson, A. Hammacher, D.K. Smith, J.M. Matthews, L.D. Ward, Interleukin-6: structure-function relationships, Protein Sci. 6 (5) (1997) 929–955, https://doi.org/10.1002/pro.5560060501.

[37] S. Rose-John, K. Winthrop, L. Calabrese, The role of IL-6 in host defence against infections: immunobiology and clinical implications, Nat. Rev. Rheumatol. 13 (7) (2017) 399–409, https://doi.org/10.1038/nrrheum.2017.83.

[38] S. Rose-John, K. Winthrop, L. Calabrese, The role of IL-6 in host defence against infections: immunobiology and clinical implications, Nat. Rev. Rheumatol. 13 (7) (2017) 399–409, https://doi.org/10.1038/nrrheum.2017.83.

[39] L. Velazquez-Salinas, A. Verdugo-Rodriguez, L.L. Rodriguez, M.V. Borca, The role of interleukin 6 during viral infections, Front. Microbiol. 10 (2019) 1057, https://doi.org/10.3389/fmicb.2019.01057.

[40] S.N. Lauder, E. Jones, K. Smart, A. Bloom, A.S. Williams, J.P. Hindley, B. Ondondo, P.R. Taylor, M. Clement, C. Fielding, A.J. Godkin, S.A. Jones, A.M. Gallimore, Interleukin-6 limits influenza-induced inflammation and protects against fatal lung

pathology, Eur. J. Immunol. 43 (10) (2013) 2613–2625, https://doi.org/10.1002/eji.201243018.
[41] M. Gelzo, S. Cacciapuoti, B. Pinchera, A. De Rosa, G. Cernera, F. Scialò, M. Comegna, M. Mormile, G. Fabbrocini, R. Parrella, G. Corso, I. Gentile, G. Castaldo, Matrix metalloproteinases (MMP) 3 and 9 as biomarkers of severity in COVID-19 patients, Sci. Rep. 12 (1) (2022) 1212, https://doi.org/10.1038/s41598-021-04677-8.
[42] A. Yabluchanskiy, Y. Ma, R.P. Iyer, M.E. Hall, M.L. Lindsey, Matrix metalloproteinase-9: many shades of function in cardiovascular disease, Physiology (Bethesda) 28 (6) (2013) 391–403, https://doi.org/10.1152/physiol.00029.2013.