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Research Article

A new investigation into the molecular mechanism of cholecalciferol towards reducing cytokines storm.

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ABSTRACT

Cytokine storm, also referred to as cytokine release syndrome (CRS), is a condition characterized by an excessive production of inflammatory signals by the immune system, potentially leading to organ failure and death. This phenomenon has garnered significant attention due to its association with the COVID-19 pandemic, wherein it appears to contribute to severe symptoms in certain individuals infected with the SARS-CoV-2 virus. In efforts to combat cytokine storm, researchers have explored natural substances as potential therapeutics. In this study, we investigated the efficacy of cholecalciferol in targeting key cytokines involved in cytokine storm. Through molecular docking analyses, molecular dynamics simulations, and assessment of pharmacokinetic properties, we evaluated the stability and potential of cholecalciferol in mitigating cytokine storm. Our findings indicate that cholecalciferol exhibits strong binding affinity with several cytokines, with binding energies exceeding −6.5 kcal/mol. Furthermore, post-molecular dynamics analysis revealed remarkable stability of cholecalciferol with these cytokines. Pharmacokinetic measurements further supported its potential as a therapeutic agent, demonstrating favorable characteristics in terms of absorption, distribution, metabolism, and excretion. This research suggests that cholecalciferol may hold promise in reducing cytokine storm and alleviating severe symptoms associated with conditions such as COVID-19.

1. Introduction

Cytokines, small proteins secreted by cells, play a crucial role in cell communication and interactions (1). They encompass various types such as lymphokine cytokines, produced by lymphocytes, monokines primarily by monocytes and macrophages, and chemokines guiding leukocyte movement (2). Interleukin cytokines, produced by one leukocyte acting on others, also fall into this category. Cytokines are further classified based on their functions, such as T-helper-1 cytokines like IL-2, IL-12, TNF-a, and IFN-γ, T-helper-2 cytokines including IL-3, IL-4, IL-5, and IL-13, and T-helper-3 cytokines like IL-10 and TGF-β (2). Chemokines like CCL2 and CXCL10, termed signaling proteins, induce directed chemotaxis in nearby cells and are secreted as part of the inflammatory response (3). Understanding cytokine storm is crucial, especially in diseases like COVID-19 caused by SARS-CoV-2, where the immune system's role is paramount

(4). Immunopathogenesis, an uncontrolled immune response to a disease, can lead to severe inflammation and fatalities (5). While most SARS-CoV-2-infected individuals experience a controlled immune response clearing the virus from the lungs, some exhibit dysregulated responses leading to a cytokine storm, causing extensive lung inflammation. Vitamin D3, also known as cholecalciferol, is a fat-soluble vitamin that helps the body absorb calcium and phosphorus (6). It's important for bone and muscle strength, and immune function. When human body is exposed to sunlight, UV-B photons penetrate the epidermis, leading to the photolysis of 7-dehydrocholesterol, a component of the plasma membrane of keratinocytes, into previtamin D3 (6). This previtamin D3 is transiently formed and promptly undergoes thermodynamically unstable isomerization to vitamin D3. Under physiological conditions at 37 °C, approximately 80% of previtamin D3 is converted to vitamin D3 within 8 hours (7). Subsequently, the generated vitamin D3 is released from the plasma membrane into the extracellular space, from where it enters the capillary bed and binds to plasma proteins. It's worth noting that under optimal circumstances, skin synthesis accounts for 80–90% of the body's vitamin D pool (6). Multiple studies have provided evidence for the role of cholecalciferol in modulating the immune system (8,9). Cholecalciferol has the capability to inhibit cytokine production while simultaneously bolstering the innate immune system, thereby reducing viral load, and mitigating the excessive activation of the adaptive immune system in response to viral load (10,11). Some researchers have proposed the potential of cholecalciferol in dampening cytokine storm during the 1918–1919 viral influenza pandemic. Additionally, cholecalciferol's involvement in enhancing immune response to influenza and previous coronaviruses has been suggested. It has also been demonstrated that cholecalciferol plays a crucial role in protecting against various infections, including those affecting the respiratory tract (12,13). This protective effect is mediated through the regulation of the immune system via cholecalciferol receptors, which in turn leads to a reduction in the production of pro-inflammatory cytokines. Research also suggests a correlation between cytokine storm severity and disease progression in SARS-CoV-2 infection (14). Patients with COVID-19 show elevated plasma levels of various cytokines and chemokines compared to healthy individuals, with more severe cases exhibiting higher levels of certain pro-inflammatory cytokines and chemokines compared to milder cases (14). Advancements in powerful cheminformatics and various in silico tools have driven drug design and discovery, marking the emergence of the 'bioinformatics era'. The in-silico approach integrates concepts from computer algorithms and statistical methods with advancements in high-performance computation within biological science (15). As a result, bioinformatics and computational biology have become pivotal in accelerating the process and reducing the cost of identifying new potential candidates for targeted diseases. Despite their limitations, two major approaches, namely structure- and ligand-based virtual screening, have been extensively employed in discovering lead compounds. Integrating these in silico techniques appears to be a reliable strategy for identifying potential candidates for improved therapeutic applications. Utilizing these techniques, we chose cholecalciferol to assess its potential efficacy against seventeen cytokines in this study.

Materials and methods

Preparation of Compound and proteins

For this study, seventeen cytokines were chosen, namely IL-2, IL-3, IL-4, IL-5, IL-6, IL-13, IFN-γ, IL-8, IL-12, IL-17, G-GSF, GM-CSF, IP10, M-CSF, MiP1α, MiP1β, and TNF-α. The crystal structures of these cytokines were obtained from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB). Subsequently, all ligand molecules, heteroatoms, and water molecules were removed from the cytokine structures using the Discovery Studio 4.0 client. Additionally, the 3D structure of cholecalciferol (depicted in Figure 01) was retrieved from the PubChem database and prepared for molecular docking analysis (16).

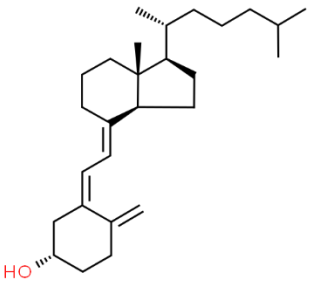

Figure 1: Structure of cholecalciferol.

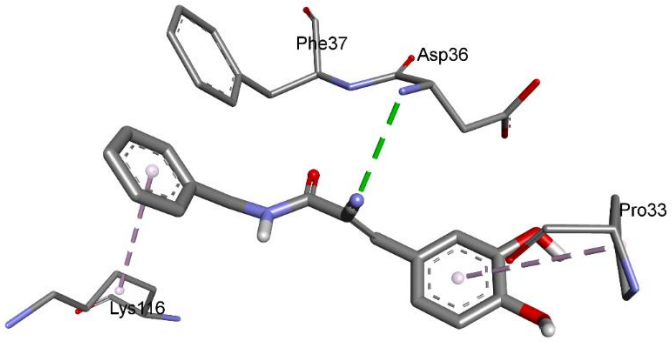

Figure 2: Interactions of IL-3 with AG-490 as control.

Table 1: List of the cytokines selected for this study and their classification and roles.

Cytokine	PDB Code	Category	Source	Receptor	Target Cell	Function
G-CSF	3UEZ	Pro-inflammatory	Fibroblasts, Endothelial cells	CD114	Stem cells in Bone Marrow	Stimulates granulocyte production
GM-CSF	2GMF	Adaptive immunity	T cells, Macrophages, Fibroblasts	CD116, CDw131	Stem cells	Promotes growth and differentiation of monocytes and eosinophils
M-CSF	1HMC	Adaptive immunity	Fibroblasts, Endothelial cells	CD115	Stem cells	Induces monocyte production and activation
IL-2	4NEJ	Adaptive immunity	Th1 cells	CD25	Activated T and B cells, NK cells	Stimulates proliferation of B cells and activated T cells; enhances NK cell function
IL-3	5UWC	Adaptive immunity	T cells	CD123, CDw131	Stem cells	Promotes proliferation and differentiation of hematopoietic precursors
IL-4	2B8U	Adaptive immunity	Th cells	CD124	B cells, T cells, Macrophages	Stimulates proliferation of B and cytotoxic T cells; enhances MHC class II expression; stimulates IgG and IgE production
IL-5	3QT2	Adaptive immunity	Th2 cells, Mast cells	CDw125, CDw131	Eosinophils, B-cells	Stimulates B-cell proliferation and maturation; promotes IgA and IgM production
IL-6	1ALU	Pro-inflammatory	Th cells, Macrophages, Fibroblasts	CD126, CD130	B-cells, Plasma cells	Promotes B-cell differentiation
IL-8	1IL8	Pro-inflammatory	Macrophages	IL-8R	Neutrophils	Attracts neutrophils and T cells
IL-10	1ILK	Anti-inflammatory	T cells, B cells, Macrophages	CDw210	B cells, Macrophages	Inhibits cytokine production and mononuclear cell function
IL-12	1F45	Anti-inflammatory	T cells, Macrophages, Monocytes	CD212	NK cells, Macrophages, Tumor cells	Activates NK cells; promotes phagocyte activity; induces tumor cytotoxicity
IL-13	3BPO	Anti-inflammatory	Th2 cells, Mast cells, Eosinophils	IL13Rα1	Monocytes, Fibroblasts, B cells	Regulates eosinophilic inflammation and mucosal secretion

IL-17	6HGO	Pro-inflammatory	Th17 cells	IL-17R	Monocytes, Neutrophils	Attracts monocytes and neutrophils to infection sites; activates other cytokines and chemokines
IFN-γ	6E3L	Pro-inflammatory	T cells, NK cells	CDw119 (IFNGR1)	Various	Anti-viral; activates macrophages; increases neutrophil and monocyte function; enhances MHC I and II expression
TNF-α	2AZ5	Pro-inflammatory	Macrophages	CD120a, CD120b	Macrophages	Activates phagocyte cells; induces endotoxic shock
MIP-1α	2X6G	Pro-inflammatory	Macrophages, Monocytes	-	Hematopoietic cells	Promotes immune responses towards infection and inflammation
MIP-1β	4RAL	Pro-inflammatory	Macrophages, Monocytes	-	Hematopoietic cells	Promotes immune responses towards infection and inflammation
IP-10	1O7Y	Pro-inflammatory	Monocytes, Endothelial cells	-	-	Exhibits antitumor activity and inhibits bone marrow colony formation and angiogenesis

Table 2: Cholecalciferol's ADME properties:

Parameters	Results
Num. H-bond acceptors	1
Num. H-bond donors	1
Molecular weight (g/mol)	384.64 g/mol
Lipinski violation	1 violation
GI absorption	low
BBB permeant	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_P (skin permeation) (cm/s)	−3.00 cm/s
PAINS	0 alert
Brenk	0 alert
Synthetic accessibility	6.02

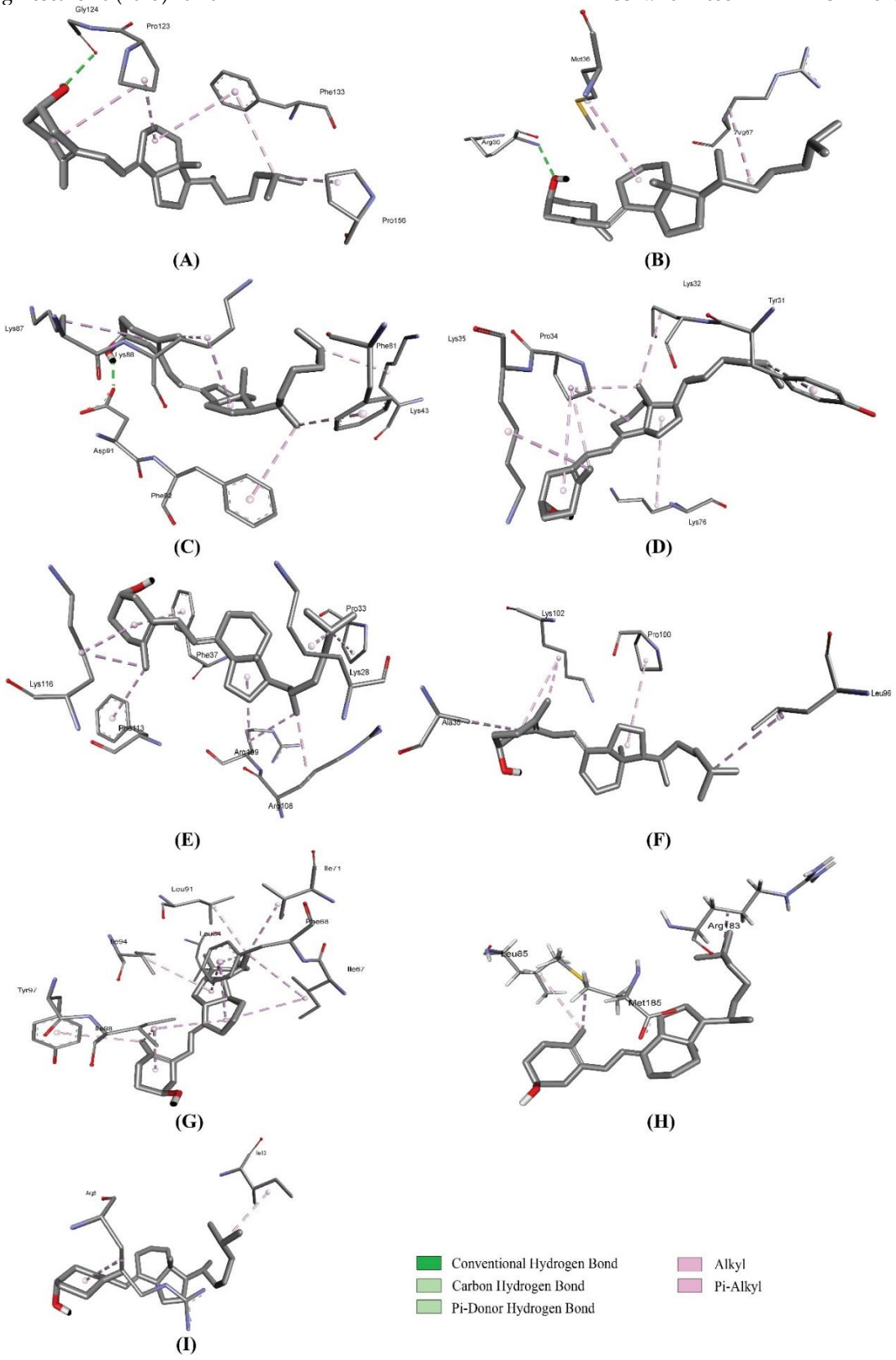

Figure 3: Interactions of GCSF (A), GMCSF (B), IFN-γ (C), IL2 (D), IL3 (E), IL4 (F), IL5 (G), IL6 (H) and IL8 (I) with cholecalciferol.

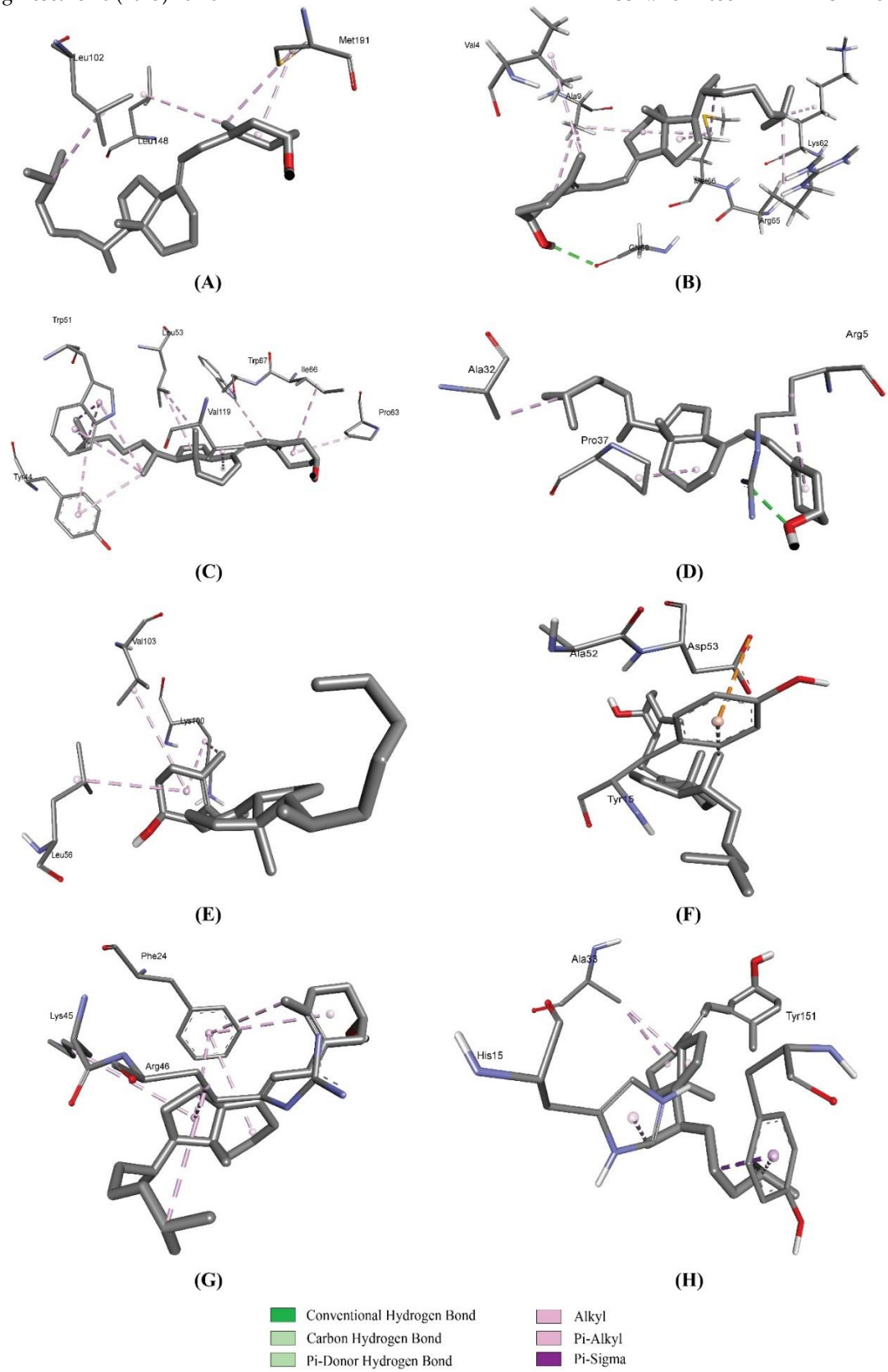

Figure 4: Interactions of IL12 (A), IL13 (B), IL17 (C), IP10 (D), MCSF (E), MiP1A (F), MiP1B (G), TNFα (H) with cholecalciferol.

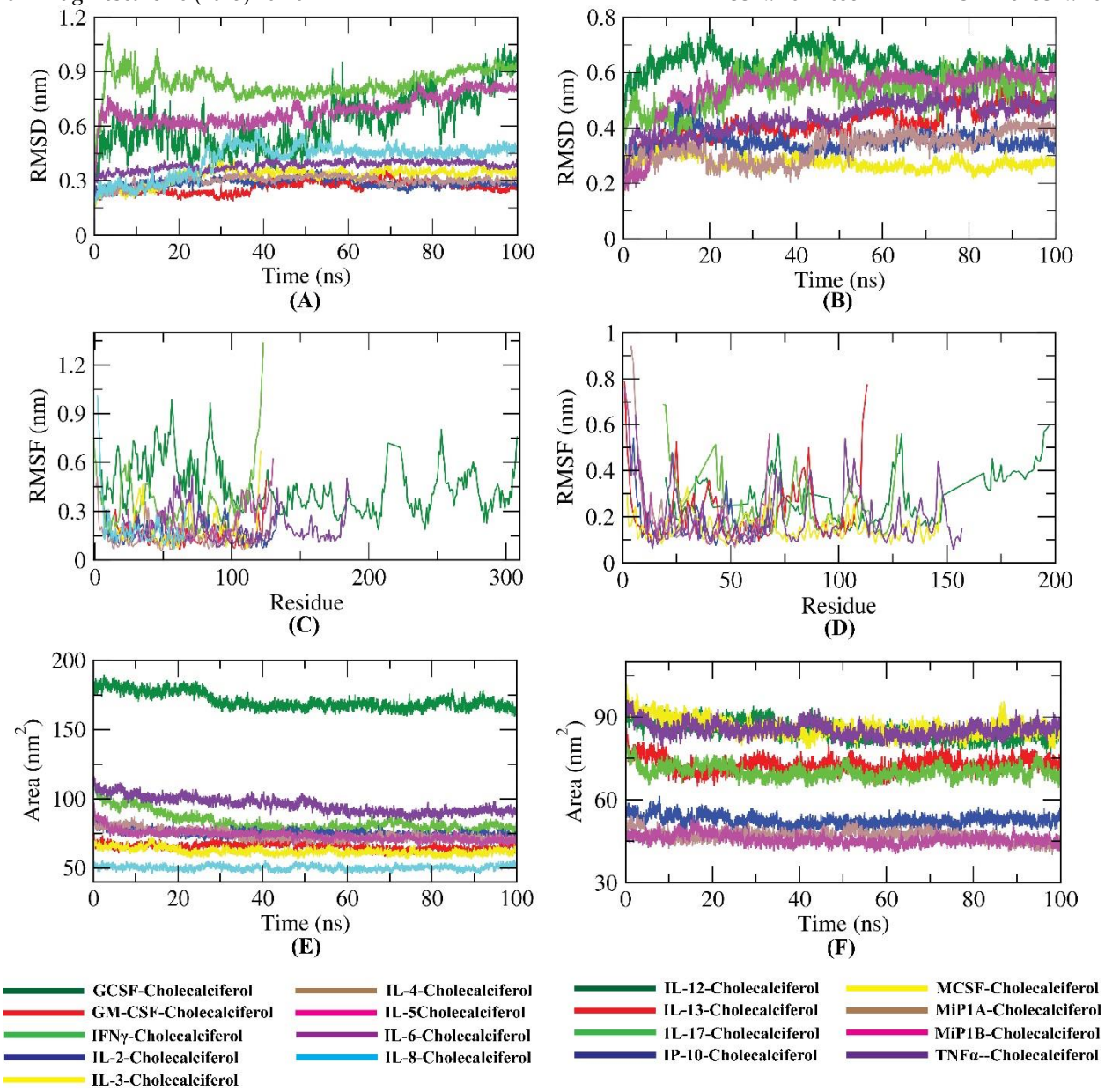

Figure 5: RMSD (A-B), RMSF (C-D) and SASA (E-F) results of the cytokine-cholecalciferol complexes.

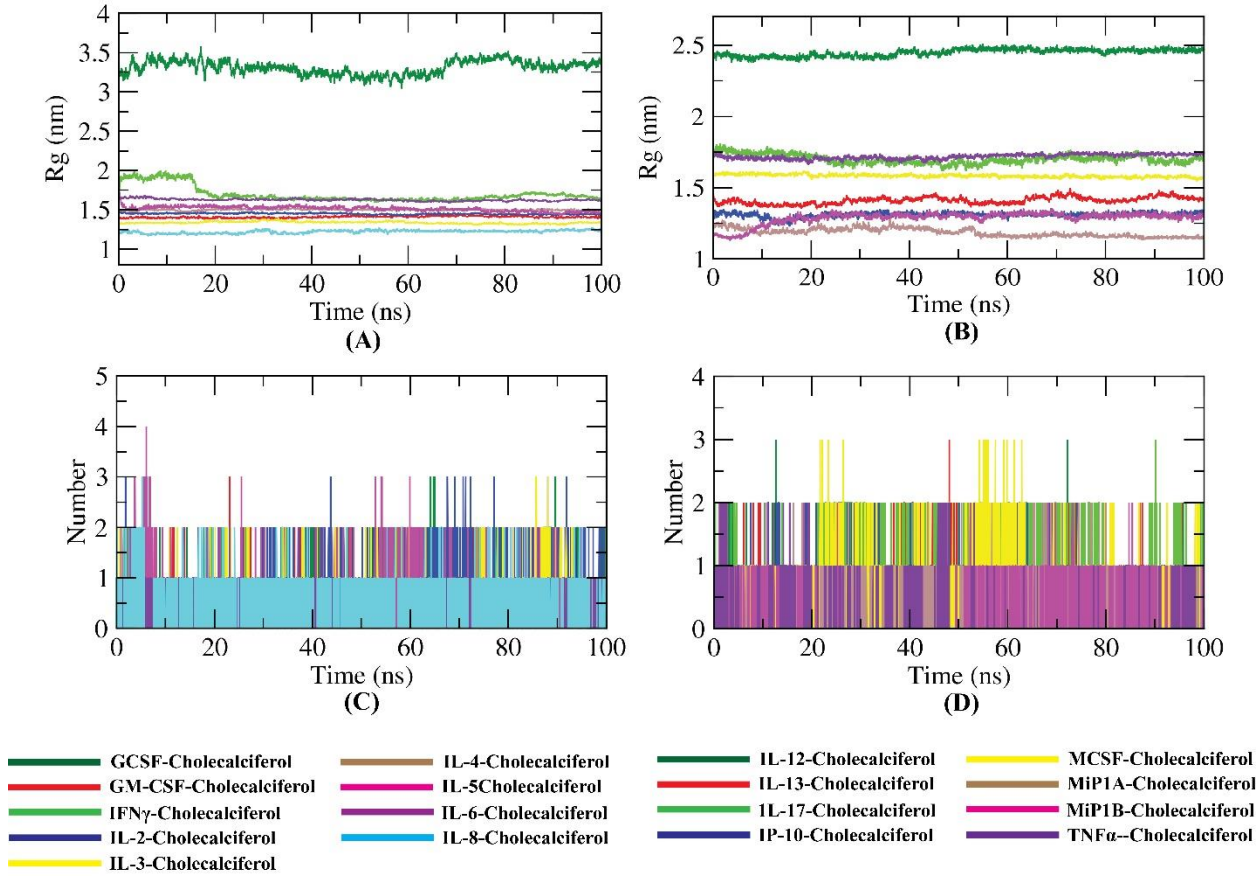

Figure 6: Rg (A-B) and hydrogen bond (C-D) analysis results of the cytokine-cholecalciferol complexes.

Molecular docking of cholecalciferol with the cytokines

Molecular docking was conducted using PyRX, an open-source virtual screening software, to assess receptor-ligand interactions (17). The key ligand binding site residues were identified using the CASTp server and were enclosed within suitable parameters of grid box dimensions. AutoDock Vina (ADV) within PyRX facilitated all docking simulations within the specified parameters (18). Subsequently, protein-ligand interactions were visualized using Discovery Studio 4.0 client and Pymol 1.1 (19).

Molecular dynamics simulation of protein-ligand complexes

For Molecular Dynamics (MD) Simulation Analysis, GROMACS 2021.1 software was utilized (20). The GROMOS96 54a7 force field was employed for the cytokines, and ligand topologies were generated using the PRODRG server. The protein-ligand complexes were solvated in a rectangular box using simple point charge (SPC) water molecules (21). Neutralization of the simulation system was achieved by adding Na+ and Cl- ions to achieve a 0.15 mol/L salt concentration. Energy minimization of solvated systems was performed using the steepest descent method for 5000 steps. Subsequently, NVT and NPT series were carried out at 300 K temperature and 1 atm pressure for 300 ps each. The V-rescale thermostat and Parrinello–Rahman barostat were selected for simulation (22). Finally, a production run was conducted at 300 K for 100 ns. Stability analysis was performed by measuring root-mean-square deviation (RMSD), root-mean-square fluctuation (RMSF), radius of gyration (Rg), solvent-accessible surface area (SASA), and hydrogen bonds. Analysis results were represented using the Xmgrace program.

ADME Analysis

The SwissADME online tool was employed to assess the pharmacokinetic properties of cholecalciferol (23).

Results

Molecular Docking Analysis of cholecalciferol with the Cytokines

AutoDock Vina generated nine potential binding positions for each compound as output. The optimal position for each compound was determined based on the lowest docking energy. The docking energy scores of all cytokines with Cholecalciferol ranged from -4.2 to -8.9 kcal/mol. To validate

the docking, we docked the compound AG-490 against IL-3 as control and found the docking score as -8.7 kcal/mol (24). The 3D interaction of this binding is shown in Figure 2. Amino acid interactions of Cholecalciferol with the cytokines were also identified. IL-3, IL-5, and G-GSF exhibited higher docking energies exceeding 7.0 kcal/mol with Cholecalciferol. The IL-5-Cholecalciferol complex displayed the highest number of interactions (8), while a hydrogen bond was found to be formed between G-CSF, GM-CSF, IFN-γ, IL-13 and IP-10 complexes. Detailed docking results and interactions with Cholecalciferol are presented in Table 2 and Figures 3 and 4.

Molecular Dynamics (MD) Simulation Results

The study utilized RMSD calculations to view the stability of protein-ligand complexes from the atomic movements and conformational changes of Cα atoms. Results revealed that, except for IL5, all complexes demonstrated stable behavior with RMSD values below 1.0 nm, indicating minimal fluctuations (Figure 5A-5B). Furthermore, the flexibility of cytokine residues was assessed through RMSF analysis, highlighting slight flexibility induced by compound binding in specific regions (Figure 5C-5D). Except the GCSF complex, all the complexes exhibited lower fluctuations as evident from the RMSF results. The interaction between protein-ligand complexes and solvents was examined through solvent-accessible surface area (SASA) calculations. Interestingly, all cytokines exhibited a minor reduction in surface area over the simulation period, indicating a relatively lower SASA value compared to the initial state (Figure 5E-5F). The compactness of the complexes was evaluated using the radius of gyration (Rg), with consistent Rg values observed across most complexes, except for the GCSF and IL-12 complexes, which displayed slightly larger Rg values (Figure 6A-6B). Hydrogen bonding, crucial for structural stabilization, was investigated, revealing that all the cytokines formed at least two hydrogen bonds on average with cholecalciferol (Figure 6C-6D).

ADME Assessment

Cholecalciferol's ADME properties were assessed using the SwissADME server (Table 2). The compound exhibited noteworthy values in several aspects. Notably, it adhered to Lipinski's rule of five. Moreover, it showed only 1 inhibition of cytochrome P450 enzyme isoform among many. Its skin permeation coefficient (log kp) fell within a favorable range, indicating potential efficacy in crossing the blood-brain barrier. No PAINS and brenk alert confirmed the absence of catechol moieties in the compound, and its synthetic accessibility values were also notably low.

Discussion

In contemporary drug discovery and development, computer-assisted drug design (CADD) techniques have emerged as efficient tools, complementing traditional methodologies. Among these, molecular docking and molecular dynamics simulations are widely employed for virtual screening of compounds, elucidating the mechanisms through which ligands interact with targets and ensuring their stability towards specific proteins. The ongoing advancement of robust computational techniques enables comprehensive assessment of the pharmacological properties of drugs prior to embarking on experimental trials. Thus, in this study, we rigorously applied CADD methodologies to assess the drug potential of cholecalciferol against a spectrum of cytokines. Recognizing the crucial role of cytokines and chemokines in mediating immune responses, particularly in maintaining anti-viral immunity, we evaluated the efficacy of cholecalciferol against various cytokines by examining both its binding affinity and conformational stability. For this purpose, cholecalciferol was screened against seventeen cytokines. We conducted molecular docking analysis to determine cholecalciferol's binding affinities towards diverse cytokines. The results revealed favorable binding energies for most cytokines, ranging between −4.2 and −8.9 kcal/mol, surpassing the minimum binding energies observed for MiP1α, IP10, IL-8, and IL-2. Importantly, stable interactions with active site residues were observed across nearly all cytokines, facilitated by hydrogen bonding interactions, as well as other interactions such as carbon-hydrogen bonding and Pi-Alkyl interactions. The stability of cholecalciferol’s interactions with the respective cytokines was subsequently confirmed through MD simulation analyses of the protein-ligand complexes. Notably, the RMSD (root-mean-square deviation) plot demonstrated the stability of all complexes, with minimal fluctuations in RMSD values over time. Additionally, the complexes exhibited negligible variability within an acceptable range, as indicated by RMSF (root-mean-square fluctuation) analysis. The radius of gyration (Rg) data further corroborated the comparable compactness characteristics of each complex, while the solvent-accessible surface area (SASA) data indicated a slight reduction in volume. Moreover, a substantial number of hydrogen bonds were identified throughout the simulation, underscoring the conformational stability of cholecalciferol-bound cytokine complexes. Consequently, cholecalciferol demonstrates the potential to interfere with cytokine actions, thereby modulating critical immune functions such as granulocyte and monocyte production, as well as B and T cell proliferation, ultimately mitigating cytokine storm. In terms

of ADMET characteristics, cholecalciferol exhibits low gastrointestinal absorption potency and complies with Lipinski's rule of five, suggesting its potential mimicry by other natural cytokine ligands. Additionally, its inability to penetrate the blood-brain barrier and absence of catechol groups, as per the Pan-assay interference chemicals (PAINS) filter, further enhance its suitability for experimental use. Despite the promising results in silico findings, it is essential to acknowledge the study's limitations, primarily its reliance on computational analyses. Experimental validation in animal models is imperative to ascertain the therapeutic efficacy of cholecalciferol. Thus, further experimental investigations are warranted to corroborate these findings and ensure translational success.

Conclusion

Our research evaluated cholecalciferol, against several critical cytokines implicated in cytokine storms. The binding of this compound to the target cytokines could potentially disrupt their actions and reduce their production. We observed favorable outcomes in terms of both binding to the proteins, efficient oral bioavailability, and reduced toxicity. Through an analysis encompassing binding affinities, protein interactions, and ADME (absorption, distribution, metabolism, and excretion) profile, we investigated and confirmed the stability of protein-ligand complexes using MD simulations, yielding intriguing findings for all complexes tested. The outcomes of our study serve as valuable insights for future experimental endeavors in designing potent cytokine regulators. Therefore, pending further in vitro and in vivo investigations, cholecalciferol holds promise as a therapeutic agent against cytokine storms.

Ethical consideration: All the participants in this study gave their informed permission.

Conflicts of Interest

No conflicts of interest are disclosed.

References

[1] Zhang JM, An J. Cytokines, Inflammation and Pain. Int Anesthesiol Clin [Internet]. 2007 Mar [cited 2022 May 4];45(2):27. Available from: /pmc/articles/PMC2785020/

[2] Morán GAG, Parra-Medina R, Cardona AG, Quintero-Ronderos P, Rodríguez ÉG. Cytokines, chemokines and growth factors. 2013 Jul 18 [cited 2024 Apr 20]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK459450/

[3] Hughes CE, Nibbs RJB. A guide to chemokines and their receptors. Febs J [Internet]. 2018 Aug 1 [cited 2024 Apr 20];285(16):2944. Available from: /pmc/articles/PMC6120486/

[4] Jarczak D, Nierhaus A. Cytokine Storm—Definition, Causes, and Implications. Int J Mol Sci [Internet]. 2022 Oct 1 [cited 2024 Apr 20];23(19). Available from: /pmc/articles/PMC9570384/

[5] Mohamed Khosroshahi L, Rokni M, Mokhtari T, Noorbakhsh F. Immunology, immunopathogenesis and immunotherapeutics of COVID-19; an overview. Int Immunopharmacol [Internet]. 2021 Apr 1 [cited 2024 Apr 20];93:107364. Available from: /pmc/articles/PMC7784533/

[6] Janoušek J, Pilařová V, Macáková K, Nomura A, Veiga-Matos J, Silva DD da, et al. Vitamin D: sources, physiological role, biokinetics, deficiency, therapeutic use, toxicity, and overview of analytical methods for detection of vitamin D and its metabolites. Crit Rev Clin Lab Sci [Internet]. 2022 [cited 2024 Apr 20];59(8):517–54. Available from: https://pubmed.ncbi.nlm.nih.gov/35575431/

[7] Borel P, Caillaud D, Cano NJ. Vitamin D bioavailability: state of the art. Crit Rev Food Sci Nutr [Internet]. 2015 Jul 29 [cited 2024 Apr 20];55(9):1193–205. Available from: https://pubmed.ncbi.nlm.nih.gov/24915331/

[8] Daneshkhah A, Agrawal V, Eshein A, Subramanian H, Roy HK, Backman V. Evidence for possible association of vitamin D status with cytokine storm and unregulated inflammation in COVID-19 patients. Aging Clin Exp Res [Internet]. 2020 Oct 1 [cited 2024 Apr 20];32(10):2141–58. Available from: https://link.springer.com/article/10.1007/s40520-020-01677-y

[9] Aranow C. Vitamin D and the immune system. J Investig Med [Internet]. 2011 Aug 1 [cited 2024 Apr 20];59(6):881–6. Available from: https://journals.sagepub.com/doi/full/10.2310/JIM.0b013e31821b8755?casa_token=4uAPj6fIyF8AAAAA%3AQWroCn0FJmqtX_5Hk24bhkxRQlh9-SC2exZaaE0RoTf7N-V0Jf4z5J0Z3MdolxJNVphvrNkYEGC-

[10] Grant WB, Giovannucci E. The possible roles of solar ultraviolet-B radiation and vitamin D in reducing case-fatality rates from the 1918-1919 influenza pandemic in the United States. Dermatoendocrinol [Internet]. 2009 Jul [cited 2024 Apr 20];1(4):215–9. Available from: https://pubmed.ncbi.nlm.nih.gov/20592793/

[11] Goncalves-Mendes N, Talvas J, Dualé C, Guttmann A, Corbin V, Marceau G, et al. Impact of Vitamin D Supplementation on Influenza Vaccine Response and Immune Functions in Deficient Elderly Persons: A Randomized Placebo-Controlled Trial. Front Immunol [Internet]. 2019 [cited 2024 Apr 20];10(FEB). Available from: https://pubmed.ncbi.nlm.nih.gov/30800121/

[12] Nnoaham KE, Clarke A. Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis. Int J Epidemiol [Internet]. 2008 [cited 2024 Apr 20];37(1):113–9. Available from: https://pubmed.ncbi.nlm.nih.gov/18245055/

[13] Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ [Internet]. 2017 [cited 2024 Apr 20];356. Available from: https://pubmed.ncbi.nlm.nih.gov/28202713/

[14] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England) [Internet]. 2020 Feb 15 [cited 2024 Apr 20];395(10223):497–506. Available from:

https://pubmed.ncbi.nlm.nih.gov/31986264/
[15] Yu W, Mackerell AD. Computer-Aided Drug Design Methods. Methods Mol Biol [Internet]. 2017 [cited 2023 Aug 28];1520:85–106. Available from: https://pubmed.ncbi.nlm.nih.gov/27873247/
[16] Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, et al. PubChem in 2021: new data content and improved web interfaces. Nucleic Acids Res [Internet]. 2021 Jan 8 [cited 2024 Apr 20];49(D1):D1388–95. Available from: https://dx.doi.org/10.1093/nar/gkaa971
[17] Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx. Methods Mol Biol [Internet]. 2015 [cited 2022 Feb 28];1263:243–50. Available from: https://pubmed.ncbi.nlm.nih.gov/25618350/
[18] Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading. J Comput Chem [Internet]. 2010 [cited 2021 Oct 9];31(2):455. Available from: /pmc/articles/PMC3041641/
[19] Rigsby RE, Parker AB. Using the PyMOL application to reinforce visual understanding of protein structure. Biochem Mol Biol Educ [Internet]. 2016 Sep 10 [cited 2022 Feb 28];44(5):433–7. Available from: https://pubmed.ncbi.nlm.nih.gov/27241834/
[20] GROMACS - A PARALLEL COMPUTER FOR MOLECULAR-DYNAMICS SIMULATIONS — the University of Groningen research portal [Internet]. [cited 2021 Sep 30]. Available from: https://research.rug.nl/en/publications/gromacs-a-parallel-computer-for-molecular-dynamics-simulations
[21] Mark P, Nilsson L. Structure and Dynamics of the TIP3P, SPC, and SPC/E Water Models at 298 K. J Phys Chem A [Internet]. 2001 Nov 1 [cited 2024 Apr 20];105(43):9954–60. Available from: https://pubs.acs.org/doi/abs/10.1021/jp003020w
[22] Saito H, Nagao H, Nishikawa K, Kinugawa K. Molecular collective dynamics in solid para-hydrogen and ortho-deuterium: The Parrinello–Rahman-type path integral centroid molecular dynamics approach. J Chem Phys [Internet]. 2003 Jul 8 [cited 2024 Apr 20];119(2):953–63. Available from: /aip/jcp/article/119/2/953/534940/Molecular-collective-dynamics-in-solid-para
[23] Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Reports 2017 71 [Internet]. 2017 Mar 3 [cited 2024 Apr 20];7(1):1–13. Available from: https://www.nature.com/articles/srep42717
[24] Zambrano A, Otth C, Mujica L, Concha II, Maccioni RB. Interleukin-3 prevents neuronal death induced by amyloid peptide. BMC Neurosci [Internet]. 2007 Oct 3 [cited 2024 Jun 13];8:82. Available from: /pmc/articles/PMC2089076/