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2-(3,4-Dihydroxyphenyl)-5,7-Dihydroxy-4H-Chromen-4-One Flavones Based Virtual Screening for Potential JAK Inhibitors in Inflammatory Disorders

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Abstract

This computational work uses ligand-based virtual screening and molecular docking simulations to uncover and characterize anti-inflammatory flavones. Flavones with experimental validation and anti-inflammatory activities were chosen for the investigation. The three-dimensional structure of Janus kinase (JAK) from Protein Data Bank (PDB) was extensively processed to ensure its quality and reliability. R and R-free values, bond angle, and length RMS Z-score were assessed before and after crystallographic refinement using PDB-REDO. Multiple methods confirmed the protein model's quality and dependability. SwissSimilarity, a web tool for ligand-based virtual screening, revealed 400 possible interactions, 10 of which were from virtual compound libraries. CB-Dock molecular docking simulations with detailed interaction visualization demonstrated strong binding affinities between particular flavones and JAK. ADMETTox confirmed the flavones' safety and drug-likeness. One interesting candidate was CHEMBL1779470, which had great water solubility, moderate lipophilicity, and good physicochemical qualities. The drug had minimal GI absorption, was not a P-gp substrate or BBB permeant, and did not inhibit the primary cytochrome P450 enzymes. Toxicity models show that CHEMBL1779470 is not organ-damaging, carcinogenic, immunological, mutagenic, or cytotoxic. However, it affected nuclear receptor signalling pathways, suggesting impacts on AhR and ER. The computational results show that CHEMBL1779470 is a flavone with high JAK binding, drug-like properties, and expected safety. This supports experimental verification and research of CHEMBL1779470 as an inflammatory disease therapy.

Keywords: Flavones, Janus kinase inhibitors, Computational exploration, Ligand-based virtual screening, Molecular docking and inflammatory disorders.

Introduction

Inflammatory disorders pose significant health challenges, necessitating the exploration of innovative therapeutic strategies to address their complex etiology (1). The Janus Kinase (JAK) signaling pathway has emerged as a crucial target in the modulation of inflammatory responses, making it a focal point for therapeutic intervention (2). Computational biology, with its advanced methodologies, provides a promising avenue to explore the potential of bioactive compounds as JAK inhibitors (3).

Flavones, a subgroup of flavonoids known for their diverse biological activities, are the subject of this computational investigation aimed at assessing their potential as JAK inhibitors (4). Leveraging Ligand-Based Virtual Screening, Molecular Docking, and ADMET Analysis, this study seeks to comprehensively examine the interaction between flavones and JAK, offering insights into their therapeutic applications in inflammatory disorders (5).

As chronic inflammation underlies various

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diseases, including autoimmune conditions, the need for targeted therapies is paramount. This paper aims to contribute to the ongoing efforts in this field by providing a detailed exploration of flavones as potential JAK inhibitors. Through computational insights, we aim to shed light on the molecular interactions between flavones and JAK, offering a foundation for further experimental validation and the development of novel therapeutic strategies for inflammatory disorders (6-16).

Methods

Selection of flavones

For this study, identifying possible flavones required a thorough review of the literature and methodical database searches. Priority was given to compounds with proven anti-inflammatory properties and those that could be verified in experiments. To guarantee a thorough assessment, the structural diversity of flavones was also taken into account during the selection process (17).

JAK protein structure pre- processing preparation and quality assessment

The Janus Kinase (JAK) protein's three-dimensional structure (PBD ID: 7ree) was got from a dependable database, like the Protein Data Bank (PDB). Using PDB REDO server, strict preparation methods were used, which included energy minimization, hydrogen atom addition, and water molecule removal. Using the SAVES and ProSAweb servers, the prepared protein structure's quality was evaluated (18-28).

Ligand-based virtual screening

Virtual screening of ligands was performed using the SwissSimilarity website (http://www.swisssimilarity.ch). Query was a particular flavone molecule in SMILES format (Figure 1). A wide range of compounds, including licenced medications, bioactive materials, and an extra 200 million virtual compounds, were included in the screening database. For the screening procedure, the ChEMBL database (version 29) with Bioactive and Extended connectivity circular fingerprint was used. Databases: ChEMBL database (version 29) with Bioactive and Extended connectivity circular fingerprint, Swiss Similarity web tool. Parameters: Ligand-based virtual screening using circular fingerprints (29, 30).

Molecular docking

Using molecular docking simulations, the relationship between flavones and JAK was investigated. For this, cavity-detection guided Blind Docking tool, CB-Dock, was utilised. Cavity detection, docking centre and box size determination, molecular docking simulations, and the assessment of binding positions based on docking scores to determine maximum dynamically favourable binding conformations were all included in the workflow. Parameters: CB-Dock for molecular docking simulations. Computational Tools used: CB-Dock and PDB-REDO server (31-40).

ADMETox filtering

Using in-silico tools like SwissADME and Pro-ToX-II, ADMET properties of chosen flavone were evaluated. This investigation shed light on the chosen compounds' safety profiles, bioavailability, and drug-likeness (41-50).

C1=CC(=C(C=C1C2=CC(=O) C3=C(C=C(C=C3O2)O)O)O)O

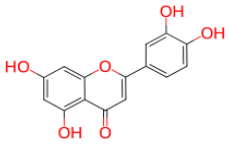


Figure 1: Structure and SMILES of 2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4H-chromen-4-one flavones

Results

Selection of flavones

Thorough reviews of the literature and database searches were done to find possible flavones for the investigation. Priority was given to compounds with proven anti-inflammatory qualities and viability for experimental validation. The selection was made with the intention of providing a wide variety of flavones for a thorough analysis.

Preprocessing and assessment of protein structure quality

Protein Data Bank (PDB), a dependable database, provided the 3-dimensional structure of Janus Kinase (JAK). PDB REDO prepared the structure with extreme care, adding hydrogen atoms, removing water molecules, and minimising energy. The JAK structure's remarkable quality and dependability were validated by quality assessment instruments such as the Ramachandran plot (92.07%), verify3d Score (89.42%), ProSAweb Z-Score (-6.74), and ERRAT score (100%).

In assessment of crystallographic refinement, notable differences exist between the original and PDB-REDO datasets, as evidenced by distinct values in various validation metrics. The refinement indicators, R and R-free, exhibit marginal improvements in the PDB-REDO iteration. Notably, there is a noticeable reduction in the Bond length RMS Z-score, reflecting enhanced precision in the PDB-REDO refinement.

Examining the Model Quality metrics, deviations are observed in parameters such as Ramachandran Plot Normality, Rotamer Normality, Coarse Packing, Fine Packing, Bump Severity, and Hydrogen Bond Satisfaction. Of particular interest is the substantial improvement in Bump Severity in the PDB-REDO dataset, indicating a more refined and optimized model with significantly fewer clashes.

The assessment of Significant Structural Changes highlights alterations in Rotamers, Side Chains, Waters, and Peptides. Notably, the PDB-REDO iteration showcases a considerable reduction in Bump Severity, reflecting enhanced structural integrity and a meticulous treatment of clashes. Additionally, improvements are noted in Rotamer Normality, Coarse Packing, and Fine Packing, suggesting a refined and well-packed structure in the PDB-REDO dataset. It's evident that the PDB-REDO refinement process has led to improvements in various facets of the structural model, showcasing a meticulous treatment of clashes, enhanced packing quality, and improved adherence to stereochemical norms.

PDB-REDO optimization improved the crystallographic refinement of a protein structure, resulting in a marginal decrease in R and R-free values, enhanced precision with reduced bond length and angle RMS Z-scores, and improved model quality metrics. Despite structural changes, hydrogen bond satisfaction and residues fitting density remained unaffected, affirming PDB-REDO's success in fine-tuning the protein's accuracy and quality.

The Kleywegt-like plot for the Human HER2 kinase domain crystal structure (PDB ID: 7ree) displays a well-defined backbone and precise side-chain modeling with minimal deviations in phi and psi angles. Bond lengths and angles fall within standard ranges, indicating robust geometry (Figure 2).

A low RMSD value and Real-Space R value demonstrate a commendable fit with experimental data, while balanced B-factors suggest appropriate structural flexibility. These collectively affirm a well-refined and reliable macromolecular structure, comparable to high-quality reference structures.

The Ramachandran plot analysis of studied structure reveals exceptional outcomes (Figure 3), with 89.5% of remains in most ideal regions and 10.5% in permitted regions. Importantly, no residues fall into generously allowed or disallowed regions, highlighting the model's accuracy. These findings, consistent with criteria from a dataset of 118 structures, affirm the structural integrity and reliability of the studied molecular conformation.

The ERRAT analysis of the JAK crystal structure (PDB ID: 7ree) demonstrates a high overall model quality, with a substantial proportion of error values falling below the 95% rejection limit. This aligns with the standards for good high-resolution structures, indicating structural precision. Even at lower resolutions, the observed overall quality factor of around 91% supports the robustness of the structural representation, instilling confidence in its reliability for subsequent structural and functional investigations (Figure 4).

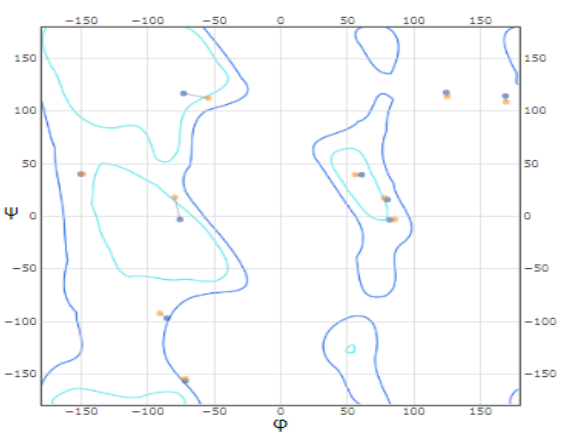


Figure 2: Kleywegt-like plot

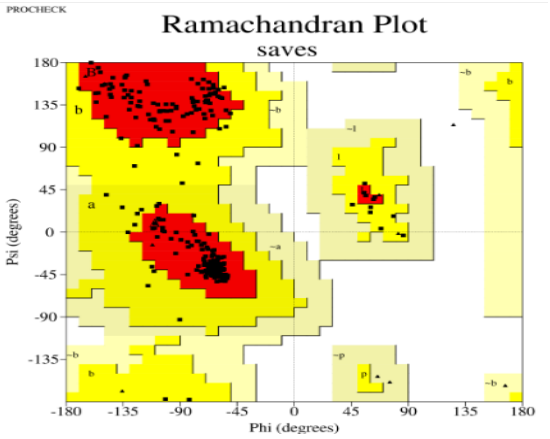


Figure 3: Ramachandran plot

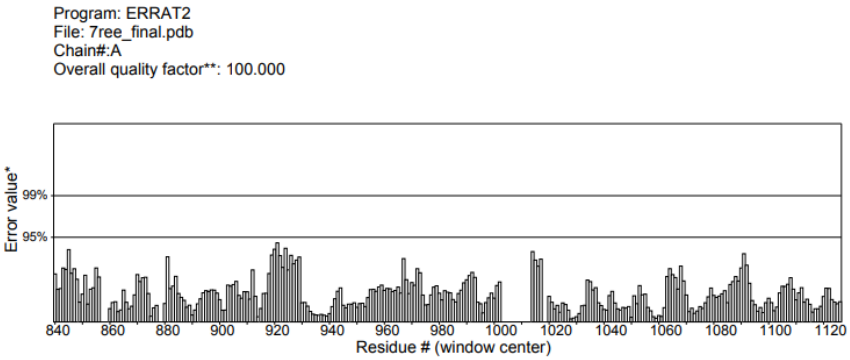


Figure 4: ERRAT chart

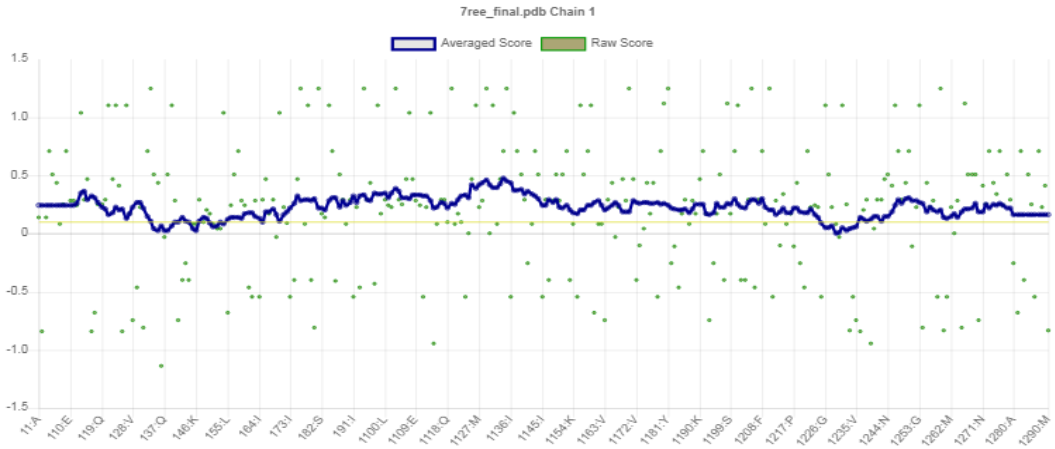
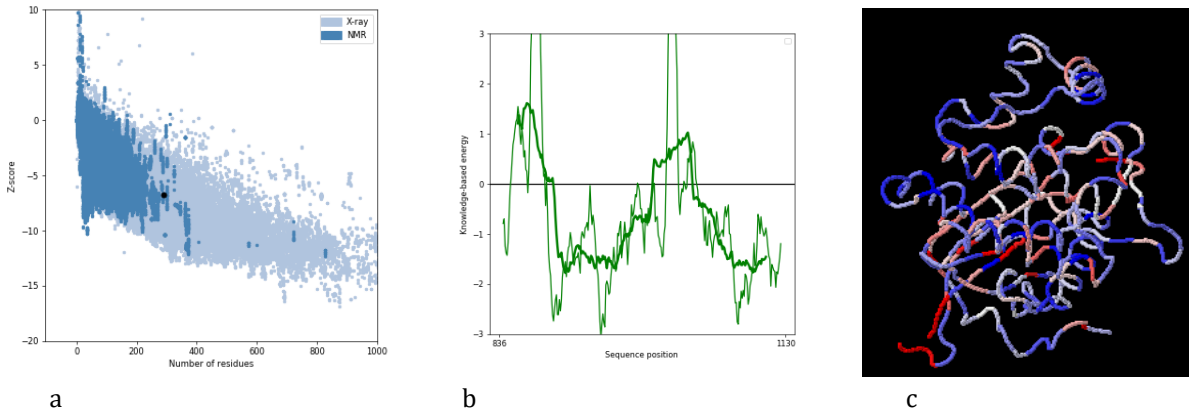


Figure 5: VERIFY3D chart

The VERIFY3D analysis affirms the high-quality three-dimensional (3D) structural integrity of the studied molecular structure, with 92.07% of residues exceeding the critical 3D-1D score threshold. Meeting the criterion of at least 80% of amino acids scoring 0.1 or higher in 3D/1D profile further strengthens overall validation. These results support the robustness and reliability of the molecular structure, validating its suitability for subsequent analyses and functional investigations (Figure 5).



a b c

Figure 6: ProSA Chart: a: Overall model quality : Z-Score: -6.74 b: Local model quality c: Jmol Ca Trace

The ProSA-web analysis contrasts the z-scores of X-ray crystallography (light blue) with nuclear magnetic resonance (dark blue) protein chains in the PDB. Chains with <1000 residues and z-scores >10 are plotted, with 7ree-A highlighted. The Energy plot of 7ree-A displays residue energies, and the Jmol Ca trace color-codes residues based on increasing energy from blue to red (Figure 6).

Table 1: Result of ligand-based virtual screening

Compound	Score	Structure
CHEMBL151	1.000	OC1=CC(O)=C2C(=O)C=C(OC2=C1)C1=CC(O)=C(O)C=C1
CHEMBL1779470	0.825	OC1=CC(O)=C2C(=O)C=C(OC2=C1)C1=CC(=C(O)C=C1)C1=C(O)C=CC(=C1) C1=CC(=O)C2=C(O)C=C(O)C=C2O1
CHEMBL28	0.795	OC1=CC=C(C=C1)C1=CC(=O)C2=C(O)C=C(O)C=C2O1
CHEMBL471181	0.738	OC1=CC(O)=C2C(=O)C=C(OC2=C1)C1=CC=C(Br)C=C1
CHEMBL457821	0.738	OC1=CC(=CC=C1)C1=CC(=O)C2=C(O)C=C(O)C=C2O1
CHEMBL4087126	0.738	OC1=CC(O)=C2C(=O)C=C(OC2=C1)C1=CC=C(C=C1)C1=CC=CC=C1
CHEMBL1990497	0.735	OC1=CC(O)=C2C(=O)C=C(OC2=C1)C1=CC(=C(O)C(O)=C1)C1=C(O)C=C2OC(=CC(=O)C2=C1O)C1=CC(O)=C(O)C=C1
CHEMBL247484	0.732	OC1=CC(O)=C2C(=O)C=C(OC2=C1)C1=CC(O)=C(O)C(O)=C1
CHEMBL117	0.732	OC1=CC(O)=C2C(=O)C=C(OC2=C1)C1=CC=CC=C1
CHEMBL1821732	0.727	OC1=CC(O)=C2C(=O)C=C(OC2=C1)C1=CC=C(F)C(F)=C1
CHEMBL264037	0.721	OC1=CC(O)=C2C(=O)C=C(OC2=C1)C1=CC=C(Cl)C=C1

Ligand-based virtual screening

Ligand-Induced the SwissSimilarity web tool was used for virtual screening, with a focus on a large database containing bioactive substances, approved medications, and a multitude of virtual compounds. In the current study, a circular fingerprint with extended connectivity and bioactivity was used. A total of 400 hits from the screening process were found to have promising interactions based on the extended connectivity circular fingerprint. Notably, the virtual compounds library accounted for ten of these hits, indicating new directions for synthesis and additional experimental validation (Table 1).

Molecular docking

Molecular docking simulations were run using CB-Dock, a Cavity-detection guided Blind Docking program. Robust binding affinities between JAK

andchosen flavones were demonstrated by the simulations. The highest binding affinity was shown by, with binding energies ranging from -8.1 to -8.5. Figure 7 shows structure of most active compound and Figure 8 shows how compound interact with the protein. CHEMBL1779470 compound having highest score -11.1 binds in Pocket C1 in Chain A having hydrogen bond donor, acceptor, hydrophobic and aromatic pi bond interactions with amino acids namely LYS354 GLU357 ASN358 TYR361 ASN421 VAL422 PRO423 TYR424 PHE427 GLN428 PHE430 MET444.

ADMETox analysis

The safety profiles and drug-likeness of the chosen flavones were evaluated by the ADMET analysis. With its good water solubility, moderate lipophilicity, and favorable physicochemical characteristics, the compound CHEMBL1779470 is a good contender for additional drug development (Table 2).

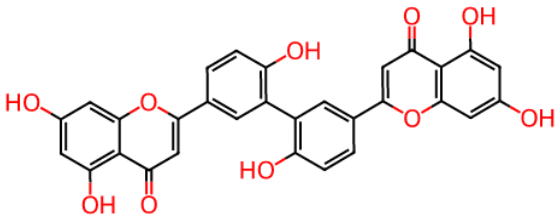


Figure 7: Most active compound with -11.1 Auto dock vina score

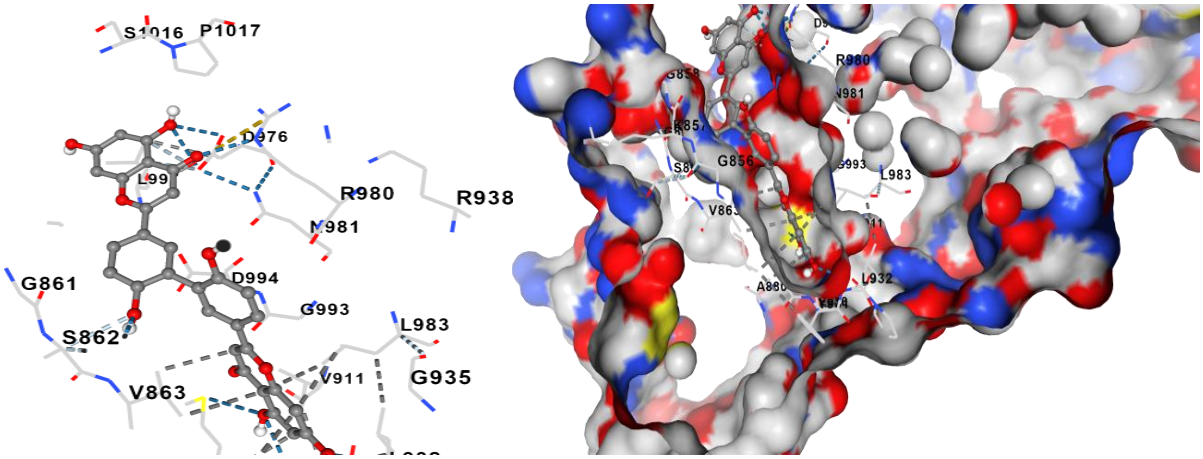


Figure 8: Interactions of CHEMBL1779470 compound with JAK

Table 2: Results of ADME Analysis using SwissADME online tool

Property	Value
Consensus Log Po/w	3.65
Water Solubility	
Solubility	1.07e-06 mg/ml; 1.98e-09 mol/l
Log S (SILICOS-IT)	-8.70
Class	Poorly soluble
Pharmacokinetics	
P-gp substrate	No
BBB permeant	No

GI absorption	Low
CYP2C19 inhibitor	No
CYP1A2 inhibitor	No
CYP2D6 inhibitor	No
CYP2C9 inhibitor	No
CYP3A4 inhibitor	No
Log Kp (skin permeation)	-6.01 cm/s
Druglikeness	
Ghose	No; 2 violations: MW>480, MR>130
Lipinski	No; 2 violations: MW>500, NHorOH>5
Egan	No; 1 violation: TPSA>131.6
Veber	No; 1 violation: TPSA>140
Bioavailability Score	0.17
Muegge	No; 3 violations: XLOGP3>5, TPSA>150, H-don>5
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	4.17

The results of the computational investigation indicate that CHEMBL1779470, among the selected flavones, exhibits robust binding affinity to JAK and possesses favorable drug-like properties. This lays the groundwork for further experimental validation and exploration of CHEMBL1779470 as a potential therapeutic agent for inflammatory disorders.

The toxicity model report for CHEMBL1779470 suggests that the compound is generally inactive for organ toxicity, mutagenicity, immunotoxicity, carcinogenicity, and cytotoxicity. However, it exhibits activity in specific pathways, including AhR, ER, ER-LBD, MMP, Tumor Suppressor p53, and ATPase family ATAD5. Interactions involving nuclear receptor signaling and stress response pathways have been predicted based on these models. It is important to interpret these results cautiously, considering the probabilities associated with each prediction, and experimental validation is recommended to confirm the predictions and assess the compound's safety profile comprehensively. Discovered JAK Inhibitor shows promising characteristics including Good water solubility, moderate lipophilicity, Favorable physicochemical properties, Not a P-gp substrate or BBB permeant and No inhibitory effects on major cytochrome P450 enzymes (Table 3).

Conclusion

In this research paper, a meticulous computational exploration of flavones as potential Janus Kinase (JAK) inhibitors for inflammatory disorders was conducted. The study employed a systematic approach, encompassing the selection of flavones,

Table 3: Toxicity model report of CHEMBL1779470

Classification	Target	Prediction	Probability
Organ toxicity	Hepatotoxicity	Inactive	0.76
Toxicity end points	Immunotoxicity	Inactive	0.82
Toxicity end points	Carcinogenicity	Inactive	0.69
Toxicity end points	Cytotoxicity	Inactive	0.98
Toxicity end points	Mutagenicity	Inactive	0.71
Tox21-Nuclear receptor signaling pathways	Androgen Receptor (AR)	Active	0.98
Tox21-Nuclear receptor signaling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	Inactive	0.99

Tox21-Nuclear receptor signaling pathways	Aromatase	Inactive	0.54
Tox21-Nuclear receptor signaling pathways	Aryl hydrocarbon Receptor (AhR)	Inactive	0.83
Tox21-Nuclear receptor signaling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	Active	0.83
Tox21-Nuclear receptor signaling pathways	Estrogen Receptor Ligand Binding Domain (ER-LBD)	Active	0.51
Tox21-Nuclear receptor signaling pathways	Estrogen Receptor Alpha (ER)	Inactive	0.67
Tox21-Stress response pathways	ATPase family AAA domain-containing protein 5 (ATAD5)	Inactive	0.77
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	Inactive	0.78
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	Active	0.69
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	Active	0.95
Tox21-Stress response pathways	Heat shock factor response element (HSE)	Active	0.95

assessment of protein structure quality, molecular docking simulations, ligand-based virtual screening, and inclusive ADMETTox analysis. The crystallographic refinement of the JAK structure using PDB-REDO demonstrated improvements in various validation metrics, reaffirming the exceptional quality and reliability of the protein model. Ligand-based virtual screening, leveraging the SwissSimilarity web tool, identified 400 hits with promising interactions, including novel compounds from virtual libraries. Molecular docking simulations using CB-Dock revealed strong binding affinities between selected flavones and JAK, with detailed interactions elucidated.

The ADMETTox study that zeroed in on CHEMBL1779470 praised the compound's moderate lipophilicity and excellent water solubility, among other desirable qualities. Compound exhibited low gastrointestinal absorption, was not a BBB permeant or P-glycoprotein substrate, and showed no inhibitory effects on major cytochrome P450 enzymes. As far as organ toxicity, cancer risk, immunotoxicity, mutagenicity, and cytotoxicity go, CHEMBL1779470 was projected to be inactive by toxicity models. However, it was anticipated to be active in certain nuclear receptor signaling pathways. CHEMBL1779470: Robust binding affinity, favorable drug-like properties, and predicted safety profiles as compared to proven 2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4H-chromen-4-one flavones

The findings collectively designate CHEMBL1779470 as a promising candidate for further experimental validation and potential therapeutic development for inflammatory disorders. The robust binding affinity to JAK, coupled with favorable drug-like properties and predicted safety profiles, positions CHEMBL1779470 as a valuable lead compound in the pursuit of effective anti-inflammatory agents. Still this research virtual screening results needs experimental validation, computational predictions may not always reflect real-world outcomes, biological systems are intricate and virtual screening may oversimplify interactions and unpredicted side effects or interactions may occur *in vivo*.

This research provides a foundation for future experimental studies to validate the in silico findings and advance the development of novel therapeutics for inflammatory conditions.

Abbreviations

JAK: Janus Kinase, PDB: Protein data bank, BBB: Blood Brain Barrier

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Author Contributions

HT, SD – Writing, PT, UT, AB – Revisions, VW, VW – Proofreading.

Conflict of interest

Nil

Ethics approval

Not applicable

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References

1. Roberti A, Chaffey LE, Greaves DR. NF-κB signaling and inflammation—Drug repurposing to treat inflammatory disorders?. Biology. 2022 Feb 26;11(3):372.
2. Tanaka Y, Luo Y, O'Shea JJ, Nakayamada S. Janus kinase-targeting therapies in rheumatology: a mechanisms-based approach. Nature Reviews Rheumatology. 2022 Mar;18(3):133-45.
3. Chagas MD, Behrens MD, Moragas-Tellis CJ, Penedo GX, Silva AR, Gonçalves-de-Albuquerque CF. Flavonols and flavones as potential anti-inflammatory, antioxidant, and antibacterial compounds. Oxidative Medicine and Cellular Longevity. 2022 Sep 6;2022.
4. Agnihotry S, Pathak RK, Singh DB, Tiwari A, Hussain I. Protein structure prediction. InBioinformatics 2022 Jan 1 (pp. 177-188). Academic Press.
5. Wiederstein C, Sippl MJ. ProSA-web: interactive web service for the recognition of errors in three-dimensional structures of proteins. Nucleic Acids Research. 2007;35:W407-W410.
6. Sippl MJ. Recognition of Errors in Three-Dimensional Structures of Proteins. Proteins. 1993;17:355-362.
7. Joosten RP, Long F, Murshudov GN, Perrakis A. The PDB_REDO server for macromolecular structure model optimization. IUCrJ. 2014 Jul 1;1(4):213-20.
8. Bragina ME, Daina A, Perez MAS, Michielin O, & Zoete V. SwissSimilarity 2021 Web Tool: Novel Chemical Libraries and Additional Methods for an Enhanced Ligand-Based Virtual Screening Experience. Int J Mol Sci. 2022; 23(2): 811.
9. Zoete V, Daina A, Bovigny C, & Michielin O. SwissSimilarity: A Web Tool for Low to Ultra High Throughput Ligand-Based Virtual Screening. J Chem Inf Model. 2016; 56(8*):* 1399.
10. Yang Liu, Maximilian Grimm, et al . CB-Dock: a web server for cavity detection-guided protein–ligand blind docking. Acta PharmacologicaSinica, 2019.
11. Tiwari S, Nagarajan K, Gupta A. SwissADME: An in-silico ADME examination tool. InEmerging Trends in IoT and Computing Technologies 2022 Oct 30 (pp. 219-225). Routledge.
12. Banerjee P, Eckert AO, Schrey AK, Preissner R. ProTox-II: a webserver for the prediction of toxicity of chemicals. Nucleic acids research. 2018 Jul 2;46(W1):W257-63.
13. Patil K, Nemade M, Bedse A, Chandra P, Ranjan R, Tare H, Bhise M. Virtual Screening, Molecular Docking, and ADMET Analysis of Flavonoids as a Potential Pi3k Inhibitor for Cancer Treatment. International Journal of Drug Delivery Technology. 2023;13(3):966-970.
14. Kumar RM, Kumar H, Bhatt T, Jain R, Panchal K, Chaurasiya A, Jain V. Fisetin in cancer: attributes, developmental aspects, and nanotherapeutics. Pharmaceuticals. 2023 Jan 28;16(2):196.
15. Awasthi M, Singh S, Pandey VP, Dwivedi UN. Molecular docking and 3D-QSAR-based virtual screening of flavonoids as potential aromatase inhibitors against estrogen-dependent breast cancer. Journal of Biomolecular Structure and Dynamics. 2015 Apr 3;33(4):804-19.
16. Wang X, Yang Z, Su F, Li J, Boadi EO, Chang YX, Wang H. Study on structure activity relationship of natural flavonoids against thrombin by molecular docking virtual screening combined with activity evaluation in vitro. Molecules. 2020 Jan 20;25(2):422.
17. Bhattacharya A, Guha PS, Chowdhury N, Bagchi A, Guha D. Virtual screening and molecular docking of flavone derivatives as a potential anticancer drug in the presence of dexamethasone. Biointerface Res. Appl. Chem. 2023;13(3):19.
18. Yadav A, Kumar R, Sunkaria A, Singhal N, Kumar M, Sandhir R. Evaluation of potential flavonoid inhibitors of glyoxalase-I based on virtual screening and in vitro studies. Journal of Biomolecular Structure and Dynamics. 2016 May 3;34(5):993-1007.
19. Mohd Amin SN, Md Idris MH, Selvaraj M, Mohd Amin SN, Jamari H, Kek TL, Salleh MZ. Virtual screening, ADME study, and molecular dynamic simulation of chalcone and flavone derivatives as 5-Lipoxygenase (5-LO) inhibitor. Molecular Simulation. 2020 Apr 12;46(6):487-96.
20. Dong X, Zhou X, Jing H, Chen J, Liu T, Yang B, He Q, Hu Y. Pharmacophore identification, virtual screening and biological evaluation of prenylated flavonoids derivatives as PKB/Akt1 inhibitors. European journal of medicinal chemistry. 2011 Dec 1;46(12):5949-58.
21. Oliveira AP, Lima DR, Bezerra LL, Monteiro NK, Loiola OD, Silva MG. Virtual screening of flavonoids from Chamaecrista genus: ADME and pharmacokinetic properties, interactions of flavonoid–DNA complex by molecular docking and molecular dynamics. Journal of Biomolecular Structure and Dynamics. 2023 Nov 2;41(16):7677-85.
22. Umar AB, Uzairu A, Shallangwa GA, Uba S. Docking-based strategy to design novel flavone-based arylamides as potent V600E-BRAF inhibitors with prediction of their drug-likeness and ADMET properties. Bulletin of the National Research Centre. 2020 Dec;44:1-1.

23. Nishinarizki V, Hardianto A, Gaffar S, Muchtaridi M, Herlina T. Virtual screening campaigns and ADMET evaluation to unlock the potency of flavonoids from Erythrina as 3CLpro SARS-COV-2 inhibitors. Journal of Applied Pharmaceutical Science. 2023 Feb 5;13(2):078-88.
24. Zhou P, Zhao XN, Ma YY, Tang TJ, Wang SS, Wang L, Huang JL. Virtual screening analysis of natural flavonoids as trimethylamine (TMA)-lyase inhibitors for coronary heart disease. Journal of Food Biochemistry. 2022 Dec;46(12):e14376.
25. James JP, Fabin AM, Sasidharan P, Kumar P. Virtual Screening, Molecular Docking and Pharmacophore Modeling of Phytoconstituents of Flavones as Aldose Reductase Inhibitors. Journal of Pharmaceutical Research International. 2021 Aug 21;33(41B):94-107.
26. Mai TT, Phan MH, Thai TT, Lam TP, Lai NV, Nguyen TT, Nguyen TV, Vo CV, Thai KM, Tran TD. Discovery of novel flavonoid derivatives as potential dual inhibitors against α-glucosidase and α-amylase: virtual screening, synthesis, and biological evaluation. Molecular Diversity. 2023 Jun 27:1-22.
27. Masumi M, Noormohammadi F, Kianisaba F, Nouri F, Taheri M, Taherkhani A. Methicillin-resistant Staphylococcus aureus: docking-based virtual screening and molecular dynamics simulations to identify potential penicillin-binding protein 2a inhibitors from natural flavonoids. International journal of microbiology. 2022 May 4;2022.
28. Goyal M, Grover S, Dhanjal JK, Goyal S, Tyagi C, Grover A. Molecular modelling studies on flavonoid derivatives as dual site inhibitors of human acetyl cholinesterase using 3D-QSAR, pharmacophore and high throughput screening approaches. Medicinal Chemistry Research. 2014 Apr;23:2122-32.
29. Umamaheswari M, Madeswaran A, Asokkumar K. Virtual screening analysis and in-vitro xanthine oxidase inhibitory activity of some commercially available flavonoids. Iranian journal of pharmaceutical research: IJPR. 2013;12(3):317.
30. Abelyan N, Grabski H, Tiratsuyan S. In silico screening of flavones and its derivatives as potential inhibitors of quorum-sensing regulator LasR of Pseudomonas aeruginosa. Molecular Biology. 2020 Jan;54:134-43.
31. Abelyan N, Grabski H, Tiratsuyan S. Identification of flavone and its derivatives as potential inhibitors of transcriptional regulator LasR of Pseudomonas aeruginosa using virtual screening. BioRxiv. 2019 Jan 18:523381.
32. Majumder A, Mondal SK, Mukhoty S, Bag S, Mondal A, Begum Y, Sharma K, Banik A. Virtual screening and docking analysis of novel ligands for selective enhancement of tea (Camellia sinensis) flavonoids. Food chemistry: X. 2022 Mar 30;13:100212.
33. Laskar MA, Choudhury MD, Chetia PA. In silico screening of cardioprotective activity of some flavonols. International Journal of Pharmacy and Pharmaceutical Sciences. 2014;6(2):528-31.
34. Batool F, Mughal EU, Zia K, Sadiq A, Naeem N, Javid A, Ul-Haq Z, Saeed M. Synthetic flavonoids as potential antiviral agents against SARS-CoV-2 main protease. Journal of Biomolecular Structure and Dynamics. 2022 May 24;40(8):3777-88.
35. Narwal M, Haikarainen T, Fallarero A, Vuorela PM, Lehtiö L. Screening and structural analysis of flavones inhibiting tankyrases. Journal of medicinal chemistry. 2013 May 9;56(9):3507-17.
36. Kumar KA, Jagannath P, Saleshier MF. Discovery of novel flavonoid analogues as angiotensin converting enzyme inhibitors based on pharmacophore modelling and virtual screening techniques. Research Journal of Pharmacy and Technology. 2018;11(10):4370-8.
37. Lu G, Pan F, Li X, Zhu Z, Zhao L, Wu Y, Tian W, Peng W, Liu J. Virtual screening strategy for anti-DPP-IV natural flavonoid derivatives based on machine learning. Journal of Biomolecular Structure and Dynamics. 2023 Jul 18:1-5.
38. Hengphasatporn K, Garon A, Wolschann P, Langer T, Yasuteru S, Huynh TN, Chavasiri W, Saelee T, Boonyasuppayakorn S, Rungrotmongkol T. Multiple virtual screening strategies for the discovery of novel compounds active against dengue virus: A hit identification study. Scientia pharmaceutica. 2020;88(1):2.
39. Majumder R, Mandal M. Screening of plant-based natural compounds as a potential COVID-19 main protease inhibitor: an in silico docking and molecular dynamics simulation approach. Journal of Biomolecular Structure and Dynamics. 2022 Jan 26;40(2):696-711.
40. Ibrahim MA, Mohamed EA, Abdelrahman AH, Allemailem KS, Moustafa MF, Shawky AM, Mahzari A, Hakami AR, Abdeljawaad KA, Atia MA. Rutin and flavone analogs as prospective SARS-CoV-2 main protease inhibitors: In silico drug discovery study. Journal of Molecular Graphics and Modelling. 2021 Jun 1;105:107904.
41. Cui X, Teng Y, Hu Y, Li Q, Pei H, Yang Z. Therapeutic potential of a synthetic dual JAK1/TYK2 inhibitor in inflammatory bowel disease. International Immunopharmacology. 2024 Jan 5;126:111238.
42. Heidari A, Ghane Y, Heidari N, Sadeghi S, Goodarzi A. A systematic review of Janus kinase inhibitors and spleen tyrosine kinase inhibitors for Hidradenitis suppurativa treatment. International Immunopharmacology. 2024 Jan 25;127:111435.
43. Benucci M, Bernardini P, Coccia C, Levani J, Economou A, Damiani A, Russo E, Amedei A, Guiducci S, Bartoloni E, Manfredi M. JAK inhibitors and autoimmune rheumatic diseases. Autoimmunity Reviews. 2023 Jan 14:103276.
44. Caiazzo G, Caiazzo A, Napolitano M, Megna M, Potestio L, Fornaro L, Parisi M, Luciano MA, Ruggiero A, Testa A, Castiglione F. The Use of JAK/STAT Inhibitors in Chronic Inflammatory Disorders. Journal of Clinical Medicine. 2023 Apr 14;12(8):2865.
45. Maccora I, Land P, Miraldi Utz V, Angeles-Han ST. Therapeutic potential of JAK inhibitors in juvenile idiopathic arthritis-associated uveitis. Expert Review of Clinical Immunology. 2023 May 12:1-4.
46. Huang D, Zhang Y, Kong L, Lu J, Shi Y. Janus kinase inhibitors in autoimmune bullous diseases. Frontiers in Immunology. 2023;14.

47. Huo R, Huang X, Yang Y, Lin J. Potential Use of Janus Kinase Inhibitors in the Treatment of Systemic Lupus Erythematosus. Journal of Inflammation Research. 2023 Dec 31:1471-8.
48. Paik JJ, Lubin G, Gromatzky A, Mudd Jr PN, Ponda MP, Christopher-Stine L. Use of JAK Inhibitors in Dermatomyositis: A Systematic Literature Review. Clinical and experimental rheumatology. 2023 Mar;41(2):348.
49. Radu AF, Bungau SG, Negru AP, Uivaraseanu B, Bogdan MA. Novel Potential Janus Kinase Inhibitors with Therapeutic Prospects in Rheumatoid Arthritis Addressed by In Silico Studies. Molecules. 2023 Jun 12;28(12):4699.
50. Deore S, Kachave R, Gholap P, Mahajan K, Tare H. Computational Identification of Methionyl-tRNA-Synthetase Inhibitors for Brucella melitensis: A Hybrid of Ligand-based Classic 3-Point Pharmacophore Screening and Structure Cavity Guided Blind Docking Approach. International Journal of Pharmaceutical Quality Assurance. 2023;14(4):1151-1157.