International Research Journal of Multidisciplinary Scope (IRJMS), 2024; 5(1): 631-639

Original Article | ISSN (O): 2582-631X DOI: 10.47857/irjms.2024.v05i01.0300

Transcriptomic Insight and Structural Integration: Repositioning FDA-Approved Methotrexate Derivative for Precision Therapy in Lung Cancer through Drug-Drug Similarity Analysis and Cavity-Guided Blind Docking

Harshal Tare[1]*, Vaishali Vaidya[2], Swati Fulmali[2], Sayali Jadhao[2], Mayuri Wankhade[2], Manish Bhise[2]

[1]Sharadchandra Pawar College of Pharmacy, Otur, Affiliated to Savitribai Phule Pune University, Pune, Maharashtra, India. [2]SGSPS Institute of Pharmacy, Akola, Affiliated to Sant Gadge Baba Amravati University, Amravati, Maharashtra, India. *Corresponding Author's Email: harshaltare51@gmail.com

Abstract

In the pursuit of advancing precision therapy for lung cancer, this study explores the repositioning potential of a FDA-approved methotrexate derivative, with a specific focus on its interaction with the Dihydrofolate Reductase (DHFR) enzyme. Leveraging transcriptomic insights and structural integration, our research employs a multifaceted approach, encompassing drug-drug similarity analysis and cavity-guided blind docking. The investigation commences with the identification of transcriptomic profiles closely resembling established lung cancer therapeutics, revealing a subset of compounds, including the methotrexate derivative, exhibiting high similarity. Subsequent to the structural refinement of the DHFR enzyme through meticulous preprocessing, our study unveils alterations that enhance the accuracy of the protein model, establishing a reliable foundation for further analyses. The application of cavity detection techniques on DHFR exposes potential binding sites crucial for enzyme activity. Employing blind docking strategies, we elucidate the interaction patterns and binding affinities of the methotrexate derivative within these identified cavities. The results highlight the potential of the studied compound, shedding light on its role as a promising candidate for precision therapy in lung cancer through targeted modulation of the DHFR enzyme. This integrative approach, combining transcriptomic insights and structural analyses, contributes valuable knowledge to the repositioning of FDA-approved methotrexate derivatives for enhanced therapeutic efficacy in lung cancer treatment.

Keywords: Lung cancer, methotrexate, Transcriptomic similarity, Repurposing and docking.

Introduction

Lung cancer remains a formidable global health challenge, necessitating innovative approaches to drug discovery and development (1, 2). Amidst the array of existing pharmaceuticals, the repositioning of FDA-approved drugs presents a compelling strategy, leveraging established safety profiles and known pharmacological properties (3, 4). This study delves into the potential repositioning of a derivative of FDA-approved methotrexate, a drug with a well-documented history in various therapeutic contexts. Focusing on precision therapy for lung cancer, our research integrates advanced computational techniques, specifically transcriptomic similarity analysis and cavity-guided blind docking, to unravel novel avenues for therapeutic intervention (5, 6).

The dysregulation of molecular pathways is a hallmark of cancer, and this study centers around the identification and optimization of a methotrexate derivative targeting lung cancer (7). By employing transcriptomic similarity analysis, we aim to unveil compounds whose gene expression profiles closely mirror established lung cancer therapeutics, providing a foundation for subsequent investigations (8, 9). A pivotal aspect of our approach involves the structural integration of

(Received 25th November 2023; Accepted 13th January 2024; Published 30th January 2024)

these compounds with the target biomolecule, guided by the Dihydrofolate Reductase (DHFR) enzyme (10). The intricate dance between transcriptomics and structural analyses aims to identify compounds with the potential for precision therapy in lung cancer, grounded in their ability to modulate critical pathways (11, 12).

The study progresses with the refinement of the DHFR enzyme's crystallographic structure, ensuring a reliable foundation for subsequent virtual screening endeavors. Structure-based cavity detection techniques reveal potential binding sites on the DHFR enzyme, setting the stage for blind docking studies. Methotrexate derivatives are getting a makeover for lung cancer! Tweaking their structure lets them hit specific lung cancer weaknesses, bypass resistance, and even team up with other therapies. This targeted approach, backed by early data and exciting theories, could unlock personalized lung cancer solutions, offering hope for patients who need it most. Through the integration of these diverse computational methodologies, we seek to characterize the interaction patterns and binding affinities of the methotrexate derivative and other selected compounds within these cavities, ultimately aiming to repurpose this FDA-approved drug for enhanced precision therapy in lung cancer (13).

Lung cancer research is blazing trails in three exciting areas: repurposing old drugs for new battles, decoding gene whispers with RNA analysis, and unlocking protein secrets with 3D blueprints. These innovations, woven together, promise a brighter future for lung cancer patients, with personalized and powerful therapies targeting the disease's unique complexities (14, 15).

This research endeavors to contribute to the evolving landscape of lung cancer treatment by providing a rational and computational framework for the repositioning of FDA-approved methotrexate derivatives (16, 17). Repurposing methotrexate derivatives in cancer research holds promise due to their existing safety profile, proven anti-cancer activity, and flexibility for improved potency, targeting, and resistance-busting. They might even team up with other therapies for a stronger punch, all while potentially being faster and economical to develop (18, 19). The insights derived herein are anticipated to guide subsequent experimental validations, offering a promising pathway towards the development of innovative and effective strategies for precision therapy in lung cancer (20, 21).

Methods

Transcriptomic analysis for drug-drug similarity

Large-scale transcriptomic datasets were employed to assess the similarity between FDA-approved methotrexate derivative and established lung cancer therapeutics. The analysis focused on identifying common gene expression patterns, providing insights into potential shared mechanisms of action (22). Transcriptome analysis plays a pivotal role in the methodological framework. It involves the study of gene expression patterns in response to drug treatments. The transcriptomic similarity analysis presented in the study focuses on identifying drugs with profiles closely resembling known breast cancer therapeutics, with a specific emphasis on lung cancer using the A549 cell line (23). The transcriptomic data provides a molecular signature that aids in the identification of potential candidates for drug repurposing based on their similarity to established cancer therapeutics (24). The study utilizes transcriptome insights to potentially identify lung cancer biomarkers or pathways. By analyzing gene expression patterns in response to drug treatments, the study aims to identify drugs with transcriptomic profiles closely resembling known breast cancer therapeutics (25). The genes affected by these drugs may be associated with specific pathways or biomarkers relevant to lung cancer. This approach allows for the identification of potential therapeutic candidates that not only exhibit transcriptomic similarity but also potentially target pathways implicated in lung cancer progression (26).

The Clue Connectivity Map Touchstone tool (https://clue.io/touchstone) was utilized for Drug-Drug Transcriptomic Similarity Analysis. The tool accessed the extensive Touchstone dataset, containing expression profiles of various perturbagens, including FDA-approved drugs. The connectivity mapping analysis compared the input

gene expression signature with the dataset, with prioritization given to compounds exhibiting high transcriptomic similarity. Subsequent exploration of connections between identified drugs and the input query informed hypotheses on shared molecular pathways and therapeutic targets, laying the groundwork for further investigation (27, 28).

The drug-drug similarity analysis is another key aspect of the methodological approach. This involves comparing the molecular profiles of drugs to identify similarities in their mechanisms of action. In this study, the similarity analysis is likely based on various molecular features, such as chemical structure, pharmacological properties, or known target proteins. The selection of drugs for comparison is crucial, and in this case, the study compares the methotrexate derivative to a range of medications (29, 30).

Structural integration and blind docking

The crystallographic structure of the target biomolecule, Dihydrofolate Reductase (DHFR) enzyme, was refined using the PDB-REDO server, ensuring accuracy for subsequent analyses. Cavity detection techniques were employed to unveil potential binding sites on the DHFR enzyme (31, 32). Molecular docking simulations were conducted using the AutoDock tool from the cb-dock server to assess the binding affinity and interaction patterns of the FDA-approved methotrexate derivative and other selected compounds (33, 34). The Dihydrofolate Reductase enzyme (PDB ID: 1DDR) served as the docking target (Figure 1). Virtual screening results were meticulously analyzed based on docking scores, ranking compounds according to predicted binding affinities. Compounds demonstrating high binding affinity, favorable interaction patterns, and structural compatibility with the DHFR enzyme were identified as potential lead compounds for precision therapy in lung cancer (35).

The study employs cavity-guided blind docking as a crucial methodological approach. This involves the identification and characterization of potential binding sites (cavities) on the target protein, in this case, the DHFR enzyme. The cavities detected through structure-based cavity detection provide essential information on the spatial arrangement and volume of potential interaction sites. Subsequently, blind docking simulations are performed to predict the binding affinity and interaction modes of drugs within these cavities, allowing for the identification of potential candidates for drug repurposing (36, 37).

This integrated methodological approach combines transcriptomic insights with structural analyses, aiming to provide a comprehensive understanding of the repositioning potential of the FDA-approved methotrexate derivative for precision therapy in lung cancer (38).

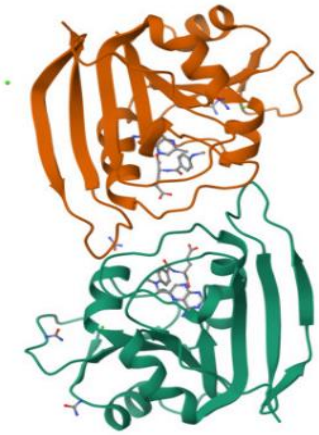

Figure 1: Crystal structure of Dihydrofolate Reductase

Results

Transcriptomic similarity

Identification of methotrexate -based drugs with transcriptomic profiles closely resembling known breast cancer therapeutics (Table 1).

The Table 1 lists the top 11 drugs for potential repurposing in lung cancer based on transcriptomic similarity using the A549 cell line. Among these, Pefloxacin stands out, showing a high score of 99.7, and subsequent molecular docking reveals its favorable interaction within Cavity 2 of Chain A and Chain B. The residues involved in the interaction include ILE14, GLY15, MET16, GLU17, ASN18, ALA19, MET20, TRP22, LEU28, HIS45, THR46, SER49, ILE94, GLY95, GLY96, GLY97, TYR100, and THR123 in Chain A, and ASN23 and ALA145 in Chain B. This suggests a potential binding affinity of Pefloxacin to these specific amino acid residues in the target proteins. While this docking information is promising, further experimental validation is

essential to confirm the drug's efficacy and safety in the context of lung cancer.

Molecular docking: protein pre-preparation using PDB REDO

Significant structural changes were observed in the DHFR enzyme shown in Table 2 following the preprocessing and refinement performed by the PDB-REDO server. The data from the table indicates that the PDB-REDO refinement process has generally improved the crystallographic metrics and model quality scores compared to the original values. The refinement resulted in a lower R-factor and R-free, suggesting a better fit of the model to the experimental data. Additionally, improvements are observed in bond length and bond angle RMS Z-scores, indicating enhanced geometric accuracy. Model quality scores, such as Ramachandran plot normality and rotamer normality, show slight increases but remain within acceptable ranges. Notably, the PDB-REDO process significantly improved coarse packing and fine packing scores, reflecting better overall packing quality. The reduction in bump severity also suggests improved stereochemistry.

Table 1: List of top 10 drugs that can be repurposed for lung cancer based on transcriptomic similarity using A549 cell line (Hypotriploid alveolar basal epithelial cells)

Rank	Score	ID	Name	Description
1	100	BRD-K59456551	Methotrexate	Dihydrofolate reductase inhibitor
2	99.83	BRD-K47780086	Penciclovir	DNA directed DNA polymerase inhibitor
3	99.7	BRD-K55034111	Pefloxacin	Bacterial DNA gyrase inhibitor
4	99.58	BRD-K66896231	Brd-k66896231	Acetylcholinesterase inhibitor
5	99.19	BRD-K06467078	Corynanthine	Adrenergic receptor antagonist
6	99.17	BRD-K50214219	Cs-1657	PARP inhibitor
7	98.87	BRD-A88774919	Doxycycline	Bacterial 30S ribosomal subunit inhibitor
8	98.86	BRD-A50311610	Meclozine	CAR agonist
9	98.79	BRD-K70358946	Aripiprazole	Serotonin receptor agonist
10	98.69	BRD-A34751532	Homosalate	HSP inducer
11	98.63	BRD-K40919711	Bapta-am	Potassium channel blocker

Table 2: Results of Crystallographic structure of the Dihydrofolate Reductase after PDB-REDO refinement

Validation Metric	Original	PDB-REDO
Crystallographic Refinement		
R	0.1820	0.1659
R-free	0.2129	0.2557
Bond Length RMS Z-score	0.611	0.603
Bond Angle RMS Z-score	0.869	0.908
Model Quality		
Ramachandran Plot Normality	5	14
Rotamer Normality	13	16
Coarse Packing	78	91
Fine Packing	5	13
Bump Severity	22	17
Hydrogen Bond Satisfaction	16	25

However, there is a slight decrease in hydrogen bond satisfaction, indicating a potential area for further refinement. Overall, the PDB-REDO refinement has positively impacted the structural quality, enhancing both accuracy and packing quality.

Results of structure-based cavity detection

Five cavities were detected in the protein structure of aromatase all are illustrated in Figure 2 and Table 3.

Results of AutoDockVina-based molecular docking

The AutoDockVina-based molecular docking results reveal the binding affinities of various drugs with their respective targets (Table 4). Methotrexate, a dihydrofolatereductase inhibitor, demonstrates the highest docking score of -7.3, suggesting a strong interaction with its target. Pefloxacin, a bacterial DNA gyrase inhibitor, also exhibits a notable score of -8.1, indicating favorable binding (Figure 3). These results align with its high transcriptomic similarity score for potential repurposing in lung cancer. Additionally, drugs like Doxycycline, Aripiprazole, and Homosalate show positive scores, suggesting potential interactions with their respective targets. However, it's crucial to interpret these scores cautiously, as they represent predicted binding affinities and further experimental validation is necessary to confirm these interactions and assess the drugs' efficacy in the context of lung cancer treatment. Overall, the docking results provide valuable insights into potential drug-target interactions, guiding future experimental studies for drug repurposing in lung cancer therapy.

Table 3: List of cavities detected in structure of DHFR enzyme

Pocket ID	Cavity volume (Å3)	Center (x, y, z)	Cavity size (x, y, z)
C1	2071	25, 68, 49	22, 17, 26
C2	704	14, 55, 23	15, 17, 23
C3	414	21, 63, 28	9, 14, 12
C4	144	14, 49, 32	8, 7, 9
C5	122	12, 82, 51	8, 7, 7

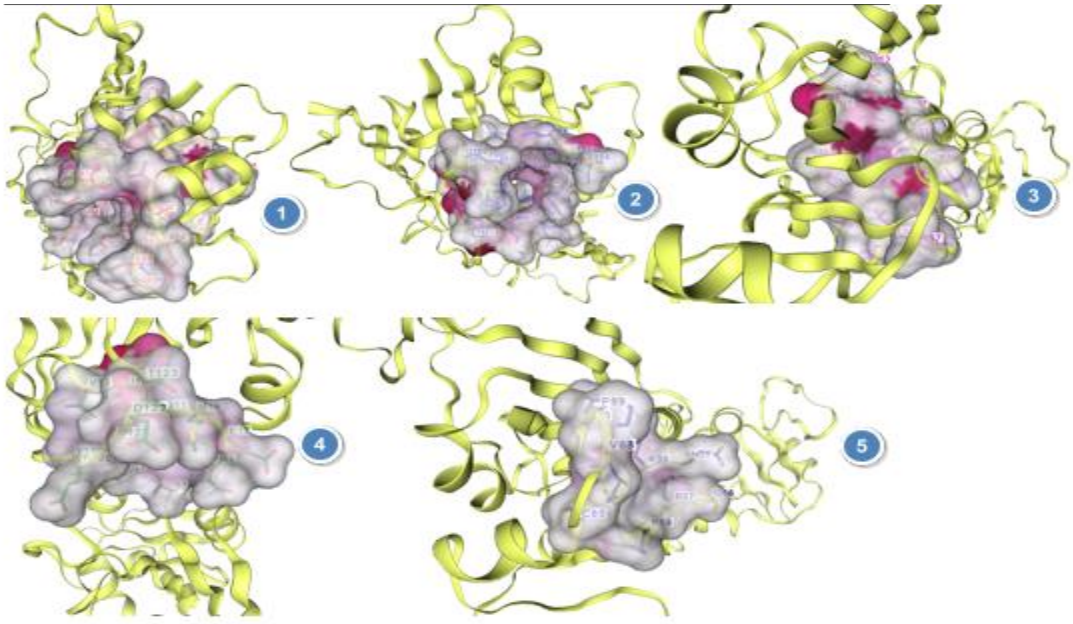

Figure 2: Cavities detected in DHFR Enzyme by structure-based cavity detection

Table 4 : Results of AutoDockVina-based molecular docking

Sr. No.	Score	Name	Description
1	-7.3	Methotrexate	Dihydrofolate reductase inhibitor
2	-6.6	Penciclovir	DNA directed DNA polymerase inhibitor
3	-8.1	Pefloxacin	Bacterial DNA gyrase inhibitor
4	-5.5	Brd-k66896231	Acetylcholinesterase inhibitor
5	-6.2	Corynanthine	Adrenergic receptor antagonist
6	-6.4	Cs-1657	PARP inhibitor
7	7.1	Doxycycline	Bacterial 30S ribosomal subunit inhibitor
8	4.8	Meclozine	CAR agonist
9	7.5	Aripiprazole	Serotonin receptor agonist
10	7.1	Homosalate	HSP inducer
11	6.0	Bapta-am	Potassium channel blocker

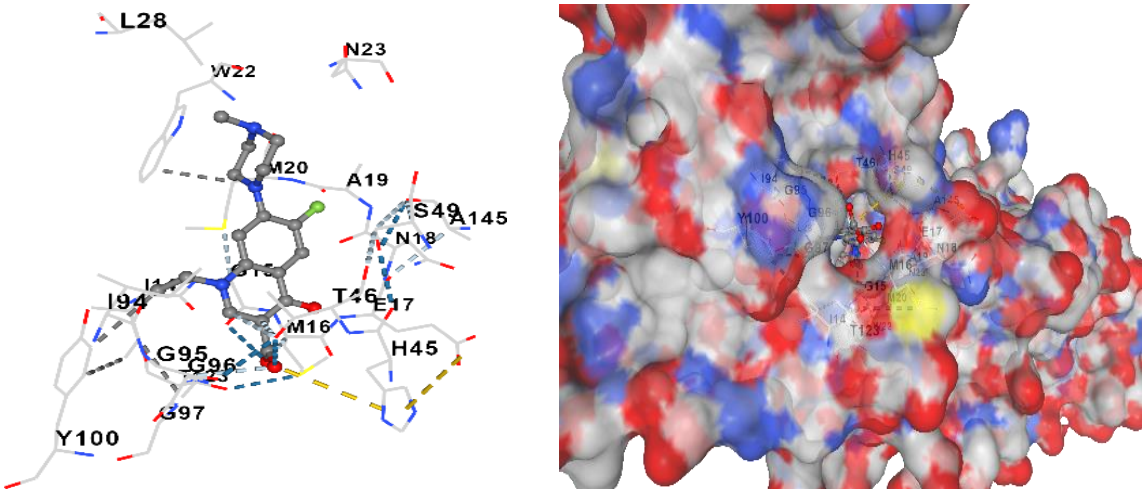

Figure 3: Interaction between Pefloxacin and DHFR enzyme in structure-based Blind Docking

Discussion

The presented study explores the potential repurposing of drugs for lung cancer treatment through a comprehensive analysis encompassing transcriptomic similarity, molecular docking, and structural refinement of the target enzyme, dihydrofolate reductase (DHFR) (39, 40). The results are organized into three main sections: transcriptomic similarity, structural refinement using PDB-REDO, and AutoDockVina-based molecular docking (41, 42).

The study begins by identifying drugs with transcriptomic profiles closely resembling known breast cancer therapeutics, with a focus on lung cancer using the A549 cell line (43). Pefloxacin stands out as a promising candidate, exhibiting a high score of 99.7 in transcriptomic similarity. Subsequent molecular docking reveals specific amino acid residues in the DHFR enzyme that may interact favorably with Pefloxacin (44). While these findings provide a valuable starting point for drug repurposing, the authors rightly emphasize the necessity for further experimental validation to confirm efficacy and safety in the context of lung cancer (45).

The structural refinement of the DHFR enzyme using the PDB-REDO server is detailed in Table 2. The results show improvements in various crystallographic metrics and model quality scores, indicating enhanced geometric accuracy and overall packing quality (46). The reduction in bump severity and improvements in coarse and fine packing scores suggest better stereochemistry. The slight decrease in hydrogen bond satisfaction

suggests an area for further refinement. Overall, the PDB-REDO process positively impacts the structural quality, enhancing accuracy and packing quality (47).

Cavities detected in the DHFR enzyme are presented in Table 3, indicating their volume, center coordinates, and size. This information is crucial for understanding the structural characteristics of the enzyme and provides insights into potential binding sites for drug molecules (48).

The AutoDockVina-based molecular docking results (Table 4) reveal the binding affinities of various drugs with their respective targets, including DHFR. Methotrexate, a known DHFR inhibitor, demonstrates the highest docking score, consistent with its role as a therapeutic agent. Pefloxacin, identified earlier for its high transcriptomic similarity, also exhibits a notable score, aligning with its potential for repurposing in lung cancer. The docking results provide valuable insights into potential drug-target interactions, guiding future experimental studies (49).

This multifaceted approach integrates transcriptomic analysis, structural refinement, and molecular docking to identify potential candidates for drug repurposing in lung cancer treatment. The combination of in silico methods provides a comprehensive understanding of the potential interactions between drugs and their target proteins (50). However, the authors emphasize the importance of experimental validation to confirm these interactions and assess the drugs' efficacy in a clinical context. The findings presented here contribute to the growing field of drug repurposing and pave the way for further research in lung cancer therapeutics.

Conclusion

In this comprehensive research, a multi-faceted approach was employed to identify and repurpose potential drugs for lung cancer treatment. Transcriptomic similarity analysis using the A549 cell line highlighted Pefloxacin as a standout candidate with a high score, corroborated by AutoDockVina-based molecular docking results, indicating a strong interaction with the Dihydrofolate Reductase (DHFR) enzyme. The structural refinement through PDB-REDO further improved the crystallographic metrics of DHFR, enhancing accuracy and packing quality. Structure-based cavity detection revealed multiple binding pockets in the enzyme, supporting the identification of potential drug binding sites. The research underscores the promise of Pefloxacin, along with other drugs like Methotrexate, in targeting lung cancer through distinct mechanisms. However, the findings necessitate cautious interpretation, emphasizing the need for rigorous experimental validation to confirm drug efficacy and safety in the context of lung cancer. This integrative approach, combining transcriptomic analysis, structural refinement, cavity detection, and molecular docking, provides a robust foundation for further investigations into drug repurposing for lung cancer therapy.

Abbreviations

FDA; Food and Drugs Administration,
DHFR: Dihydrofolate Reductase

Acknowledgement

The Authors are thankful to anonymous reviewers of the journal.

Author contributions

HT, MB – Writing, VV, SF – Revisions, SJ, MW – Proofreading.

Conflict of interest

Nil

Ethics approval

Not Applicable

Funding

Self funded

References

1. Deo SV, Sharma J, Kumar S. GLOBOCAN 2020 report on global cancer burden: challenges and opportunities for surgical oncologists. Annals of surgical oncology. 2022 Oct;29(11):6497-500.
2. Afzaal H, Altaf R, Ilyas U, Zaman SU, Abbas Hamdani SD, Khan S, Zafar H, Babar MM, Duan Y. Virtual screening and drug repositioning of FDA-approved drugs from the ZINC database to identify the potential hTERT inhibitors. Frontiers in Pharmacology. 2022 Nov 18;13:4816.

3. Qayed WS, Ferreira RS, Silva JR. In silico study towards repositioning of FDA-approved drug candidates for anticoronaviral therapy: Molecular docking, molecular dynamics and binding free energy calculations. Molecules. 2022 Sep 14;27(18):5988.
4. Bradley RK, Anczuków O. RNA splicing dysregulation and the hallmarks of cancer. Nature Reviews Cancer. 2023 Mar;23(3):135-55.
5. Wińska P, Sobiepanek A, Pawlak K, Staniszewska M, Cieśla J. Phosphorylation of Thymidylate Synthase and Dihydrofolate Reductase in Cancer Cells and the Effect of CK2α Silencing. International Journal of Molecular Sciences. 2023 Feb 3;24(3):3023.
6. Pereira T, Abbasi M, Oliveira RI, Guedes RA, Salvador JA, Arrais JP. Deep generative model for therapeutic targets using transcriptomic disease-associated data—USP7 case study. Briefings in Bioinformatics. 2022 Jul 18;23(4):bbac270.
7. Allahgholi M, Rahmani H, Javdani D, Sadeghi-Adl Z, Bender A, Módos D, Weiss G. DDREL: From drug-drug relationships to drug repurposing. Intelligent Data Analysis. 2022 Jan 1;26(1):221-37.
8. 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.
9. Liu Y, Grimm M, Dai WT, Hou MC, Xiao ZX, Cao Y. CB-Dock: A web server for cavity detection-guided protein–ligand blind docking. Acta Pharmacologica Sinica. 2020 Jan;41(1):138-44.
10. Nemade M, Patil K, Bedse A, Chandra P, Ranjan R, Tare H, Bhise M. Phenol Glucosides as Potential Inhibitors of SGLT1 for Enhanced Diabetes Mellitus Treatment in Patients with Declining Renal Function. International Journal of Drug Delivery Technology. 2023;13(3):948-954.
11. Nemade M, Patil K, Bedse A, Chandra P, Ranjan R, Tare H, Patil S. Computational Exploration of Anti-Alzheimer Potential of Flavonoids against Inducible Nitric Oxide Synthetase: An In-silico Molecular Docking and ADMET Analysis Approach. International Journal of Drug Delivery Technology. 2023;13(3):899-903.
12. 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.
13. Patil K, Nemade M, Bedse A, Chandra P, Ranjan R, Tare H, Patil S. In-silico Exploration for Novel CDK8 Inhibitors: A Virtual Study by Pharmacophore Screening. International Journal of Drug Delivery Technology. 2023;13(3):904-907.
14. Teli MK, GK R. Computational repositioning and experimental validation of approved drugs for HIF-prolyl hydroxylase inhibition. Journal of chemical information and modeling. 2013 Jul 22;53(7):1818-24.
15. Inyang KE, Folger JK, Laumet G. Can FDA-approved immunomodulatory drugs be repurposed/repositioned to alleviate chronic pain?. Journal of Neuroimmune Pharmacology. 2021 Sep;16(3):531-47.
16. Kong R, Wong ST. Repositioning of Drug–New Indications for Marketed Drugs. Drug Selectivity: An Evolving Concept in Medicinal Chemistry. 2017 Nov 21:55-78.
17. Baek MC, Jung B, Kang H, Lee HS, Bae JS. Novel insight into drug repositioning: Methylthiouracil as a case in point. Pharmacological Research. 2015 Sep 1;99:185-93.
18. Raynal NJ, Da Costa EM, Lee JT, Gharibyan V, Ahmed S, Zhang H, Sato T, Malouf GG, Issa JP. Repositioning FDA-approved drugs in combination with epigenetic drugs to reprogram colon cancer epigenome. Molecular cancer therapeutics. 2017 Feb 1;16(2):397-407.
19. Adasme MF, Bolz SN, Adelmann L, Salentin S, Haupt VJ, Moreno-Rodríguez A, Nogueda-Torres B, Castillo-Campos V, Yepez-Mulia L, De Fuentes-Vicente JA, Rivera G. Repositioned drugs for chagas disease unveiled via structure-based drug repositioning. International Journal of Molecular Sciences. 2020 Nov 20;21(22):8809.
20. Lo YC, Senese S, France B, Gholkar AA, Damoiseaux R, Torres JZ. Computational cell cycle profiling of cancer cells for prioritizing FDA-approved drugs with repurposing potential. Scientific reports. 2017 Sep 12;7(1):11261.
21. Bhattarai D, Singh S, Jang Y, Hyeon Han S, Lee K, Choi Y. An insight into drug repositioning for the development of novel anti-cancer drugs. Current topics in medicinal chemistry. 2016 Aug 1;16(19):2156-68.
22. Ugurel OM, Mutlu O, Sariyer E, Kocer S, Ugurel E, Inci TG, Ata O, Turgut-Balik D. Evaluation of the potency of FDA-approved drugs on wild type and mutant SARS-CoV-2 helicase (Nsp13). International Journal of Biological Macromolecules. 2020 Nov 15;163:1687-96.
23. Vilar S, Harpaz R, Uriarte E, Santana L, Rabadan R, Friedman C. Drug—drug interaction through molecular structure similarity analysis. Journal of the American Medical Informatics Association. 2012 Nov 1;19(6):1066-74.
24. Huang L, Luo H, Li S, Wu FX, Wang J. Drug–drug similarity measure and its applications. Briefings in Bioinformatics. 2021 Jul;22(4):bbaa265.
25. Ferdousi R, Safdari R, Omidi Y. Computational prediction of drug-drug interactions based on drugs functional similarities. Journal of biomedical informatics. 2017 Jun 1;70:54-64.
26. Vilar S, Uriarte E, Santana L, Lorberbaum T, Hripcsak G, Friedman C, Tatonetti NP. Similarity-based modeling in large-scale prediction of drug-drug interactions. Nature protocols. 2014 Sep;9(9):2147-63.
27. Rohani N, Eslahchi C. Drug-drug interaction predicting by neural network using integrated similarity. Scientific reports. 2019 Sep 20;9(1):13645.

28. Brown AS, Patel CJ. MeSHDD: literature-based drug-drug similarity for drug repositioning. Journal of the American Medical Informatics Association. 2017 May 1;24(3):614-8.
29. Udrescu L, Bogdan P, Chiș A, Sîrbu IO, Topîrceanu A, Văruț RM, Udrescu M. Uncovering new drug properties in target-based drug–drug similarity networks. Pharmaceutics. 2020 Sep 16;12(9):879.
30. Yan C, Duan G, Zhang Y, Wu FX, Pan Y, Wang J. IDNDDI: An integrated drug similarity network method for predicting drug-drug interactions. InBioinformatics Research and Applications: 15th International Symposium, ISBRA 2019, Barcelona, Spain, June 3–6, 2019, Proceedings 15 2019 (pp. 89-99). Springer International Publishing.
31. Shtar G, Solomon A, Mazuz E, Rokach L, Shapira B. A simplified similarity-based approach for drug-drug interaction prediction. Plos one. 2023 Nov 9;18(11):e0293629.
32. Zeng X, Jia Z, He Z, Chen W, Lu X, Duan H, Li H. Measure clinical drug–drug similarity using electronic medical records. International journal of medical informatics. 2019 Apr 1;124:97-103.
33. Shtar G, Rokach L, Shapira B. Detecting drug-drug interactions using artificial neural networks and classic graph similarity measures. PloS one. 2019 Aug 1;14(8):e0219796.
34. Sridhar D, Fakhraei S, Getoor L. A probabilistic approach for collective similarity-based drug–drug interaction prediction. Bioinformatics. 2016 Oct 15;32(20):3175-82.
35. Vilar S, Hripcsak G. The role of drug profiles as similarity metrics: applications to repurposing, adverse effects detection and drug–drug interactions. Briefings in Bioinformatics. 2017 Jul 1;18(4):670-81.
36. Ibrahim H, El Kerdawy AM, Abdo A, Eldin AS. Similarity-based machine learning framework for predicting safety signals of adverse drug–drug interactions. Informatics in Medicine Unlocked. 2021 Jan 1;26:100699.
37. Jofily P, Pascutti PG, Torres PH. Improving blind docking in DOCK6 through an automated preliminary fragment probing strategy. Molecules. 2021 Feb 25;26(5):1224.
38. Azmi MB, Khan F, Asif U, Khurshid B, Wadood A, Qureshi SA, Ahmed SD, Mudassir HA, Sheikh SI, Feroz N. In Silico Characterization of Withania coagulans Bioactive Compounds as Potential Inhibitors of Hydroxymethylglutaryl (HMG-CoA) Reductase of Mus musculus. ACS omega. 2023 Jan 30;8(5):5057-71.
39. Azmi MB, Khan W, Azim MK, Nisar MI, Jehan F. Identification of potential therapeutic intervening targets by in-silico analysis of nsSNPs in preterm birth-related genes. Plos one. 2023 Mar 7;18(3):e0280305.
40. 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.
41. Liang F, Shi Y, Cao W, Shi J. The inhibition mechanisms of pancreatic lipase by apigenin and its anti-obesity mechanisms revealed by using network pharmacology. Food Bioscience. 2022 Feb 1;45:101515.
42. Edet UO, Mbim EN, Ezeani E, Henshaw OU, Ibor OR, Bassey IU, Asanga EE, Antai EE, Nwaokorie FO, Edet BO, Bebia GP. Antimicrobial analysis of honey against Staphylococcus aureus isolates from wound, ADMET properties of its bioactive compounds and in-silico evaluation against dihydropteroate synthase. BMC complementary medicine and therapies. 2023 Dec;23(1):1-6.
43. Patel RD, Kumar SP, Patel CN, Shankar SS, Pandya HA, Solanki HA. Parallel screening of drug-like natural compounds using Caco-2 cell permeability QSAR model with applicability domain, lipophilic ligand efficiency index and shape property: A case study of HIV-1 reverse transcriptase inhibitors. Journal of Molecular Structure. 2017 Oct 15;1146:80-95.
44. Goh NY, Razif MF, Yap YH, Ng CL, Fung SY. In silico analysis and characterization of medicinal mushroom cystathionine beta-synthase as an angiotensin converting enzyme (ACE) inhibitory protein. Computational biology and chemistry. 2022 Feb 1;96:107620.
45. Mir MA, Altuhami SA, Mondal S, Bashir N, Dera AA, Alfhili MA. Antibacterial and Antibiofilm Activities of β-Lapachone by Modulating the Catalase Enzyme. Antibiotics. 2023 Mar 14;12(3):576.
46. Hetényi C, van der Spoel D. Blind docking of drug-sized compounds to proteins with up to a thousand residues. FEBS letters. 2006 Feb 20;580(5):1447-50.
47. Davis IW, Raha K, Head MS, Baker D. Blind docking of pharmaceutically relevant compounds using RosettaLigand. Protein science. 2009 Sep;18(9):1998-2002.
48. Liu Y, Yang X, Gan J, Chen S, Xiao ZX, Cao Y. CB-Dock2: Improved protein–ligand blind docking by integrating cavity detection, docking and homologous template fitting. Nucleic acids research. 2022 Jul 5;50(W1):W159-64.
49. Grosdidier A, Zoete V, Michielin O. Blind docking of 260 protein–ligand complexes with EADock 2.0. Journal of computational chemistry. 2009 Oct;30(13):2021-30.
50. Hetényi C, Spoel DV. Toward prediction of functional protein pockets using blind docking and pocket search algorithms. Protein Science. 2011 May;20(5):880-93.