ALAGAPPA UNIVERSITY

DEPARTMENT OF BIOINFORMATICS

(UGC-Innovative, DST- FIST, PURSE and DBT-BIC & NNP Sponsored)

DBT-Bioinformatics and Computational Biology Centre (BIC)

Project Title: Identification of Potent Drug for Life-Threatening Diseases

Sanctioned Amount: 183.8 Lakhs	**Duration:** 2022 to 2027
Project Co-ordinator and PI	**Co-PIs**
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Multi Drug-Resistant (MDR) pathogens are a global concern and threat to public health that cause serious nosocomial and health-care-associated infections. However, some MDR bacteria cause community-acquired infections directly associated with increased morbidity, mortality, health care cost, and antibiotic use. Community-associated (CA) MDR bacteria develop multi-drug resistance against the antibiotic, leading to the infection's dissemination. The nosocomial pathogens include *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter spp* are responsible for life-threatening infections worldwide and are collectively referred to as **"ESKAPE"** pathogens. With the advent of high-throughput techniques, rapid sequencing and generation of substantial bacterial whole genome sequence data storage were possible. Retrieving meaningful genomic information from the sequences is vital to understand the pathogenesis of the organism for better treatment. Genome annotation decodes the sequence's biological significance through detailed investigation and in-depth analysis.

Moreover, for the past years of research and trials, no vaccine is currently available for these diseases. Despite the years of research for viable medications, the intricacy of the disease has always remained the same. A validated drug target is necessary for the scientific community's to identify a potential drug molecule. Furthermore, the threat is amplified by diminished treatment efficacy due to developing resistant strains. The currently available drugs are only fully effective in some cases due to the administration of injectables, hospitalization, and the socioeconomic reality of patients. The current research focuses on cutaneous and visceral disease, and although existing medicines due to the long-term treatment courses, most are poorly tolerated or outright toxic leading to antimicrobial drug resistance. Therefore, it is necessary to identify potential drug targets and develop new drugs to combat nosocomial infections. Henceforth, we have processed computational studies to identify potent inhibitors for combating infectious and other life-threatening diseases in our current year.

a. NOSOCOMIAL INFECTION

Antibiotic resistance has become a global threat and has been a serious problem in recent years, necessitating the development of immediate therapeutics to combat drug resistance mechanisms. Extensive researches are still in progress to unveil the resistance mechanism conferred by drug targets in the bacterial species causing nosocomial infections. "**Nosocomial**" or "Healthcare-Associated Infections (HAI)" are widely used to refer to any class of disease affecting patients while undergoing medical care or even sometimes after treatment procedures. Gram-negative facultative anaerobe *Serratia marcescens* is a notorious pathogen belonging to the *Enterobacteriaceae* family. It is responsible for intravenous catheter-associated infections, urinary tract infections, blood-stream endocarditis, and septicemia in humans. Due to the presence of several virulence factors and misuse of antibiotics, the control and treatment of *S. marcescens* infections has become difficult. Exploring the binding of antibiotic streptomycin would provide more insights into understanding the process of resistance in detail, which will be more useful in designing inhibitor molecules. Our findings provide a basic understanding of the **Streptomycin adenylyltransferase (SMATase)** protein, and further biophysical analysis coupled with structural studies will provide more insights into how SMATase may help to overcome antibiotic resistance. The scientific results obtained from this study **(Prabhu.D, *et.al.* 2022)** could aid in the design of lead molecules that synergistically combat antibiotic resistance and *S. marcescens* infection when administered with appropriate antibiotics.

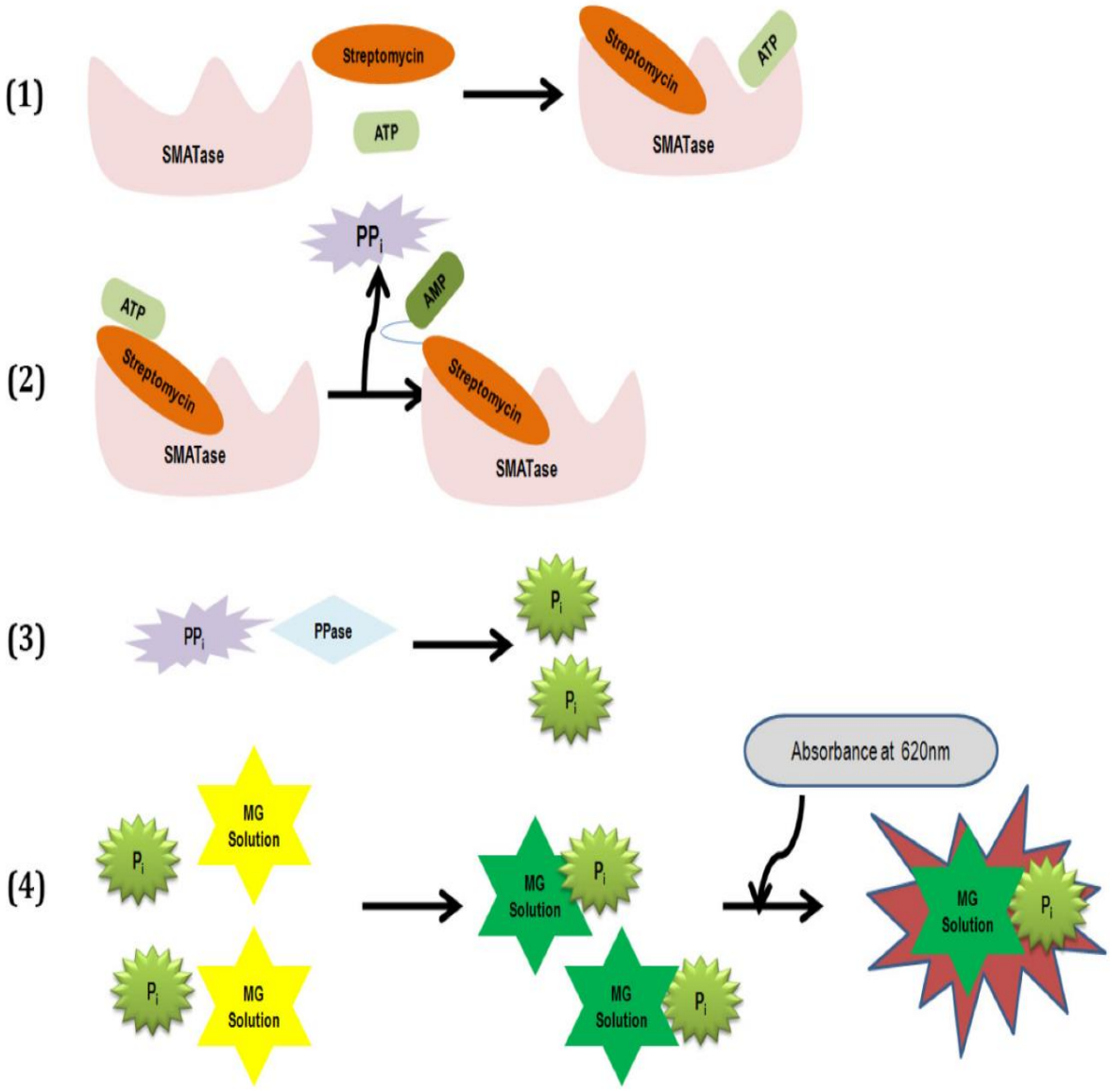


Figure 1: Schematic stepwise working principle of malachite green adenylation assay. Malachite green adenylation assay: detection of free phosphate liberated from the adenylation process is captured by malachite green solution at 620 nm.

b. COMPUTATIONAL INVESTIGATION ON COVID-19

The SARS-CoV-2 pandemic has significantly threatened human healthcare and the world economy. Furthermore, new variants of SARS-CoV-2 are being reported worldwide. More specifically, the variants reported in South Africa (501Y.V2) and the United Kingdom (B.1.1.7) were found to be more contagious than the wild type. There are also speculations that the variants might evade the host immune responses induced by currently available vaccines and develop resistance to drugs under consideration. The mutations in the RBD domain of spike protein in the new variants could modulate the protein-protein interaction with the hACE-2 receptor leading to increased virulence. Hence, our study, **(Murugan, N.A *et al*. 2022)**, unravelled the mechanism for the increased infection rate due to such mutations in these variants. We have also computationally studied the interaction of the spike protein in both wild-type and B.1.1.7 variant with hACE-2 receptor using combined molecular dynamics and binding free energy calculations using molecular mechanics-Generalized Born surface area (MM-GBSA) approach. Finally, we demonstrated that with state-of-the-art computational techniques, we could predict the more virulent nature of variants of SARS-CoV-2 and alert the world healthcare system.

In another study **(Murugan, N.A *et. al*. 2022),** a multi-level scoring approach was adopted to identify the multi-targeting potency of bioactive compounds in selected medicinal plants and compared its efficacy with two reference drugs, Nafamostat and Acalabrutinib which are under clinical trials to treat SARS-CoV-2. In particular, we employed molecular docking and implicit solvent free energy calculations and QM fragmentation approach for validating the potency of bioactive compounds from the selected medicinal plants against four different viral targets and one human receptor (Angiotensin-converting enzyme 2 -ACE-2), which facilitates the SARS-CoV-2 entry into the cell. The present study evidenced that Chebulagic acid, Geranine and Repandusinic acid act as multitargeting drug-cocktail by effectively inhibiting 3CLpro, PLpro and RdRp targets and weakening protein-protein interaction between spike protein and hACE-2. Moreover, Piperlonguminine and Piperine displayed significant inhibitory activity against human ACE-2 receptors. Therefore, the identified compounds can serve as potent multi-targeting phytomedicine for treating COVID-19.

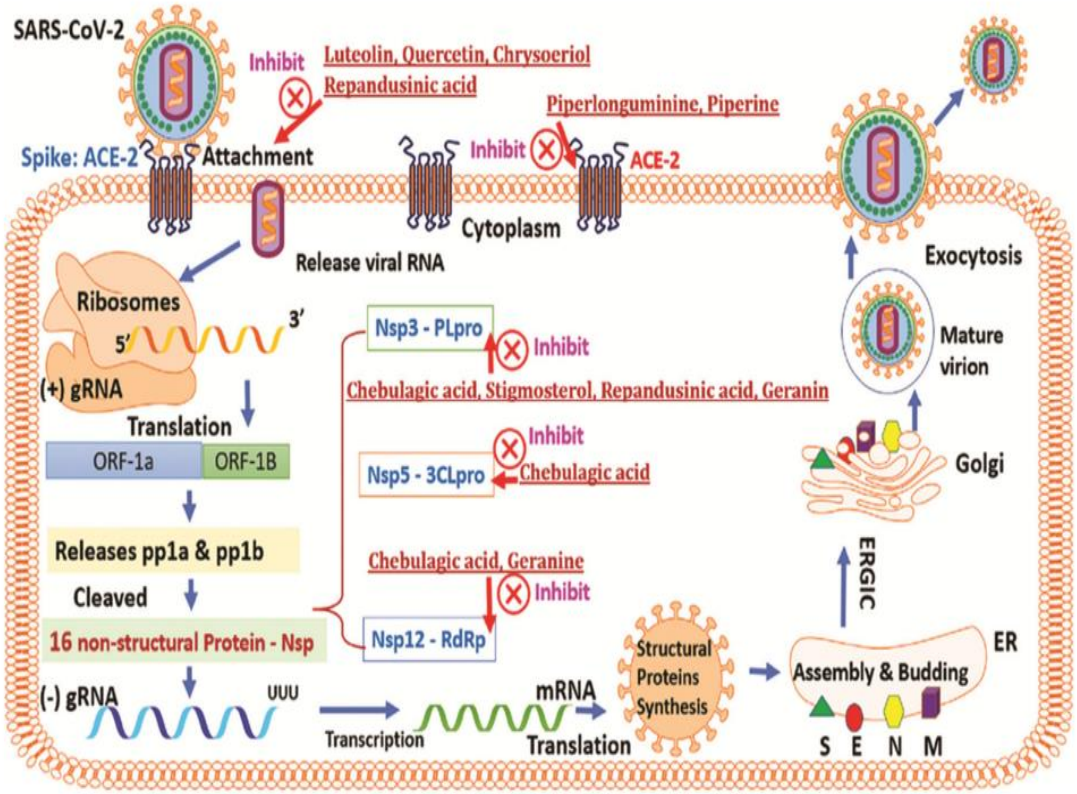


Figure 2: Mechanism of multi-targeting potential of selected phytochemicals

Several studies have focused only on hospitalized patients with 30 to 90 days after one cycle of illness, but post-acute sequelae of COVID-19 existing even after a year remain unclear. Moreover, long-term sequelae in outpatients have not been documented, and henceforth myriad clinical sequelae in long haulers continue to evolve. In our study **(Chitra, J, *et.al,* 2022),** we reported three cases representing a single family presenting several post-acute sequelae, one after the other, extending beyond one year of recovery. To our knowledge, such a case series has not been reported in earlier studies. Herein, we present the sequelae in various organs namely neuropsychiatric (tinnitus, anxiety, depression, insomnia, and posttraumatic stress disorder, cognitive decline), cardiovascular (tachycardia, bradycardia), gastrointestinal (appendicitis) and Dermatologic (erythematous rash and acne) besides ophthalmic manifestations (conjunctivitis and dry eyes) in Long-COVID-19 and recommend management strategies.

c. HIV

HIV-1 latency consists of viral DNA; integrated inside the host genome; it remains transcriptional silent. In this study **(Khan, M. A., & Singh, S.K, 2022)**, we have developed an atom-based 3 D-QSAR model by utilizing the 49 active compounds of the 5-substituted 2-acylaminothiazoles derivatives. These compounds are further randomly divided into training (37) and test (12) datasets, yielding statistically significant R^2 (0.90) and Q^2 (0.85) results, respectively. The internal and external validation of the model shows highly robust and reliable results. Next, the model was visualized to check the favourable and unfavourable groups in terms of hydrogen bond donor, electron-withdrawing and hydrophobic group on the most active compound 96 and least active compound 30. The investigated model reveals the structural insights required to obtain more leads that are potent.

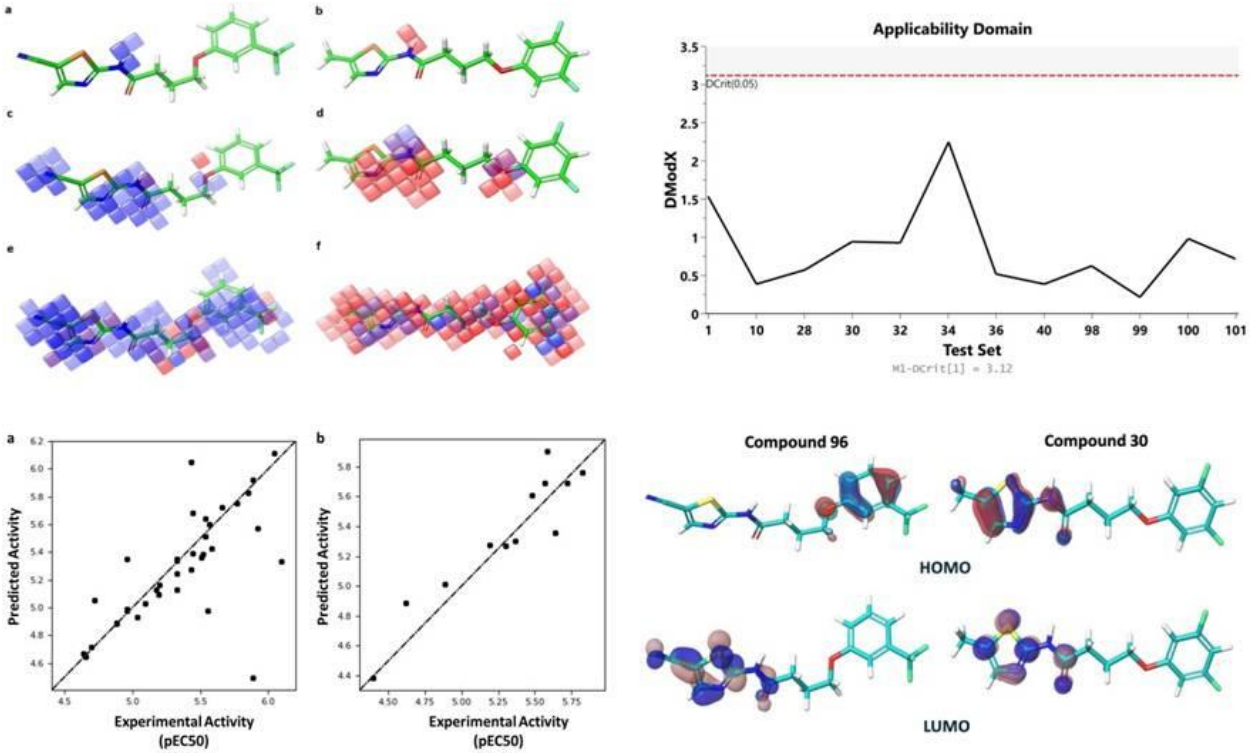


Figure 3: QSAR Model of experimentally studied compounds and their derivatives as HIV-1 latency-reversing agents

d. CANCER:

Cancer, the leading cause of death worldwide, accounts for 9.6 million deaths annually. Among the known drug targets, protein kinases predominates as therapeutic targets for treating cancer conditions. In the current therapeutic research, LIMK inhibitors are emerging as a potential therapeutic modality to treat cancer, exploiting the fact that LIMK aids in cell motility and is downstream of Rho kinase in cytoskeletal dynamics. In the current scenario, there is a paucity of effective LIMK inhibitors that are highly specific with minimal off-target effects. To date, the conformational transitions of LIMK2 from DFGinαCin (CIDI) (active) to DFGoutαCout (CODO) (inactive) states are yet to be probed and are essential for capturing the unique, druggable conformations. Therefore, this study **(Nagarajan.H, *et.al* 2022)** was intended to capture the diverse conformational states of LIMK2 for accelerating the rational identification of conformation-specific inhibitors through high-end structural bioinformatics protocols. Overall this study provides potential insights into the intermediate conformational druggable states of LIMK2 and the druggable conformations, especially the inactive states of LIMK2, as a specific therapeutic targeting mode. Thus, providing a widened avenue to ponder the allosteric sites or the isoform selectivity conformations for targeting LIMK2 in various disease conditions.

We also probed the efficacy of quercetin, a bioflavonoid, against various cancers. In the study **(Ramachandran, B. *et.al.* 2022)**, quercetin has been extracted from *Ocimum basilicum* and was used to evaluate its anticancer activity against human liver cancer cell lines (HepG2) by assessing cell viability (MTT) and variations in nuclear morphology (AO/EtBr dual staining) during apoptosis. The amount of quercetin extracted from O. basilicum leaves was found to be 0.82 mg with a retention time of 2.827 min. Quercetin showed dose dependent anticancer activity against HepG2 cells with IC50 value 50 μg/mL due to apoptosis that could have been mediated by Caspase-3 activity. Moreover, the study indicates the importance of water molecules in the catalytic site, which may suppress the growth of tumor cells which could assist in selecting potential leads for further analysis against liver cancer. Glioblastoma (GBM) is the most devastating and frequent type of primary brain tumor with high morbidity and mortality. GBM embodies a populace of cancer stem cells (GSCs) that is associated with tumor initiation, invasion, therapeutic

resistance, and post-treatment reoccurrence. However, understanding the potential mechanisms of stemness and their candidate biomarkers remains limited. Hence in this investigation **(Nayak, C, & Singh, S.K 2022)**, we aimed to illuminate potential candidate hub genes and key pathways associated with the pathogenesis of GSC in the development of GBM. Through integrated analysis and protein–protein interaction network analysis, five potential candidate hub genes (CTNNB1, ITGB1, TNC, EGFR, and SHOX2) were identified, which were positively correlated with the stemness of GBM and negatively correlated with the overall survival of patients. In our future perspective, we are aiming to design/discover/repurpose drug molecules targeting SHOX2 or TNC and characterize identified uncharacterized proteins to understand their role in gliomagenesis.

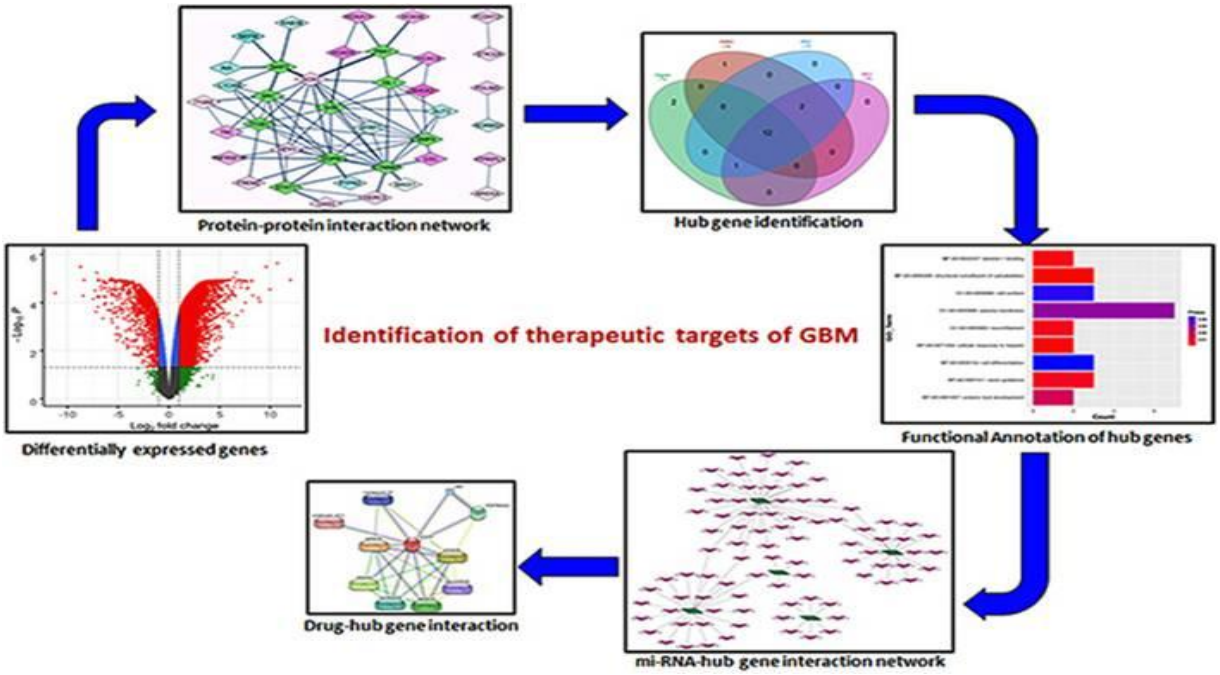


Figure 4: Protein-Protein interaction network, Venn diagram represents significant intersecting DEGs among four different sample analyzed.

e. DIABETES:

Diabetes mellitus (DM) is one of the significant health problems worldwide. WHO estimated that 439 million people may have DM by 2030. Several classes of drugs, such as sulfonylureas, meglitinides, thiazolidinediones etc., are available to manage this disease; however, there is no cure for this disease. Salt inducible kinase 2 (SIK2) is expressed several folds in adipose tissue than in normal tissues, and thus SIK2 is one of the attractive targets for DM treatment. Several analogues have been reported and experimentally proven against SIK for DM treatment. But, identifying potential SIK2 inhibitors with improved efficacy and good pharmacokinetic profiles will be helpful for the effective treatment of DM. The present study aims to identify selective SIK2 inhibitors with good pharmacokinetic profiles. Due to the unavailability of SIK2 structure, the modelled structure of SIK2 will be an important to understand the atomic level of SIK2 inhibitors in the binding site pocket. In this study **(Jayaprakash, P. *et.al,* 2022)**, different molecular modelling studies such as Homology Modelling, Molecular Docking, Pharmacophore-based virtual screening, MD simulations, Density Functional Theory calculations and WaterMap analysis were performed to identify potential SIK2 inhibitors. Five molecules from different databases, such as Binding_4067, TosLab_837067, NCI_349155, Lifechemicals_F2565-0113, and Enamine_7623111186 molecules were identified as possible SIK2 inhibitors.

f. PARKINSON'S DISEASE (PD)

Parkinson's disease (PD) is the second most common neurodegenerative disorder that affects dopaminergic neurons in the midbrain. A recent study suggests that Orphan Nuclear Receptor 1 (NURR1) impairment may contribute to PD pathogenesis. Our study **(John Marshal, J *et al.* 2023)** found three potent agonists for NURR1 protein based on structural and ligand-based screening methods. The pharmacophore is comprised of a hydrogen bond donor, a hydrophobic group, and two aromatic rings (DHRR). The Pharmacophore screening method screened 3142 compounds, of which 3 were screened using structure-based screening. An analysis of the molecules using Molecular Mechanics-Generalized Born

Surface Area (binding free energy) revealed a range of −46.77 to −59.06 Kcal/mol. After that, chemical reactivity was investigated by density functional theory, and molecular dynamics simulation was performed (protein-ligand stability). Based on the computational studies, Lifechemical_16901310, Maybridge_2815310, and NPACT_392450 are promising agonists with respect to NURR1. To confirm the potency of the identified compounds, further validation and experiments must be conducted.

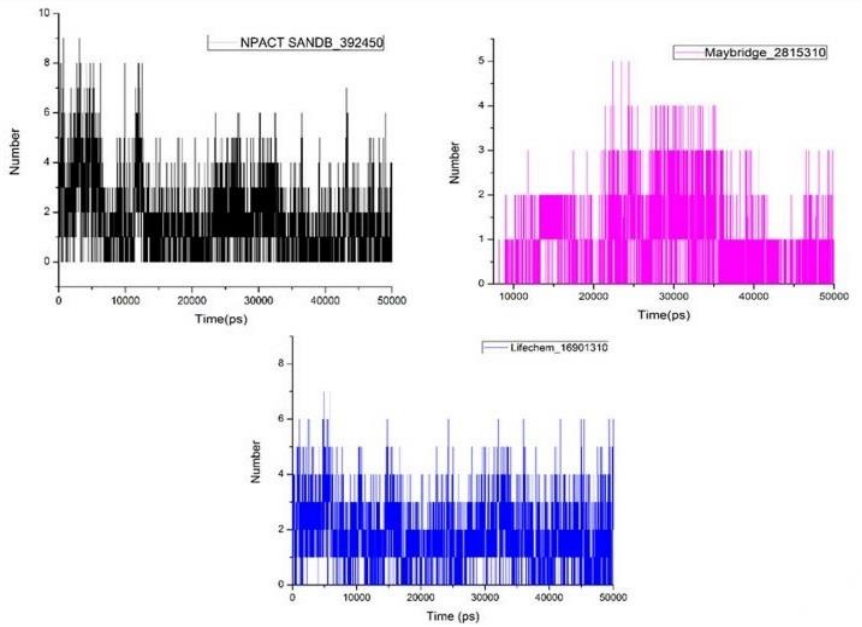


Figure 5: Total number of intermolecular interaction between n NURR1 protein and lead compounds.

g. TUBERCULOSIS (TB)

Tuberculosis (TB) is the most contagious illness in the world due to its emerging resistance to first-line anti-TB medications. According to the reports, the effectiveness of treating TB is severely impacted by drug resistance, notably resistance caused by mutations in the pncA gene-encoded pyrazinamidase (PZase) to the front-line drug pyrazinamide (PZA). In the present study (data to be published), we investigated the resistance mechanism caused by the mutations D12N, T47A and H137R to better

understand the structural and molecular events responsible for the resistance acquired by the pncA gene of *Mycobacterium tuberculosis* (MTB). The bioinformatics analysis predicted that all three mutations were deleterious and located near the active centre of the pncA, affecting its functional activity. Further, the simulation study results showed that mutations significantly reduced the structural stability and caused the rearrangement of FE^{2+} in the active centre of pncA. Moreover, essential dynamics analysis, including principal component analysis (PCA) and free energy landscape (FEL), concluded variations in the protein motion and decreased conformational space in the mutants. Also, the mutations potentially impacted the network topologies and altered the residual communications in the network. Furthermore, the MM-PBSA binding energy results confirmed that electrostatic interaction was the prime driving force for PZA binding, which further revealed a decrease in non-covalent interactions between pncA mutants and PZA drug was the primary cause of the drug resistance. This study provides a better understanding of the primary cause of the mechanism of PZA resistance and the structural dynamic behaviour of pncA mutants, thereby facilitating to design of new and potent chemical scaffolds to improve the efficacy of the available drugs against drug-resistant TB (DR-TB).

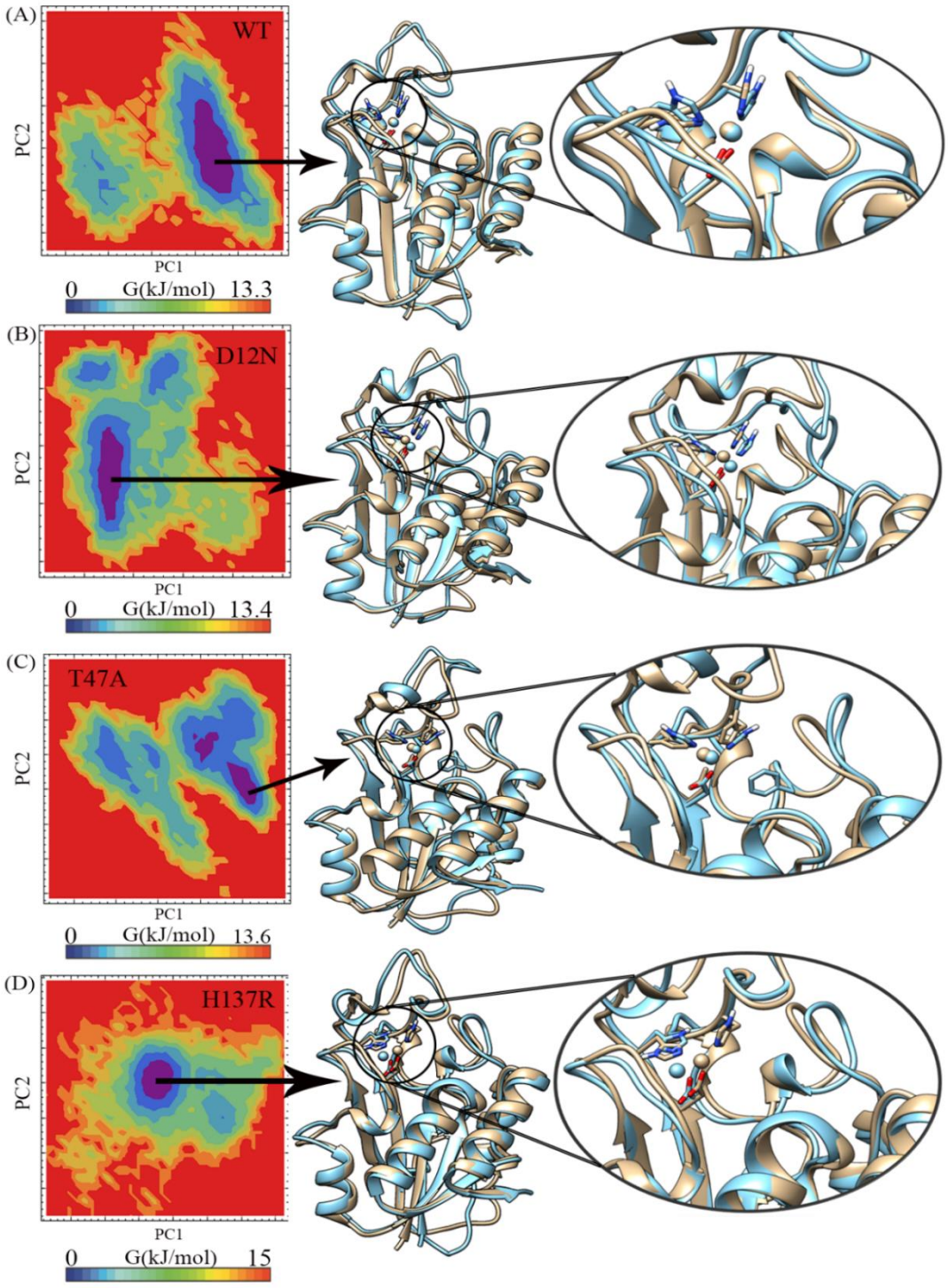


Figure 6: Principal Component-based Free Energy Landscape analysis (FEL) of WT and mutant pncA structures. The representative structure retrieved from the energy basin was superimposed with the initial structure. The rearrangement of FE^{2+} observed in the mutant structures.

h. FLAVIVIRUSES

Numerous pathogens affecting human is present in the flavivirus family namely west nile, dengue, yellow fever, and zika which involves in development of global burden and distressing the environment economically. Till date, no approved drugs are available for targeting these viruses. The recent outbreak of zika and dengue infections postured a solemn risk to worldwide public well-being. RNA-dependent RNA polymerase (RdRp) is the supreme adaptable enzymes of all the RNA viruses which is responsible for the replication and transcription of genome among the structural and nonstructural proteins of flaviviruses. It is understood that the RdRp of the flaviviruses are similar stating that the japanese encephalitis and west nile shares 70% identity with zika whereas the dengue serotype 2 and 3 shares the identity of 76% and 81%, respectively. In this study **(Aarthy M *et al*. 2022**), we investigated the binding site of four flaviviral RdRp and provided insights into various interaction of the molecules using the computational approach. Our study helps in recognizing the potent compounds that could inhibit the viral protein as a common inhibitor. Additionally, with the conformational stability analysis, we proposed the possible mechanism of inhibition of the identified common small molecule toward RdRp of flavivirus. Finally, this study could be an initiative for the identification of common inhibitors and can be explored further for understanding the mechanism of action through in vitro studies for the study on efficacy.

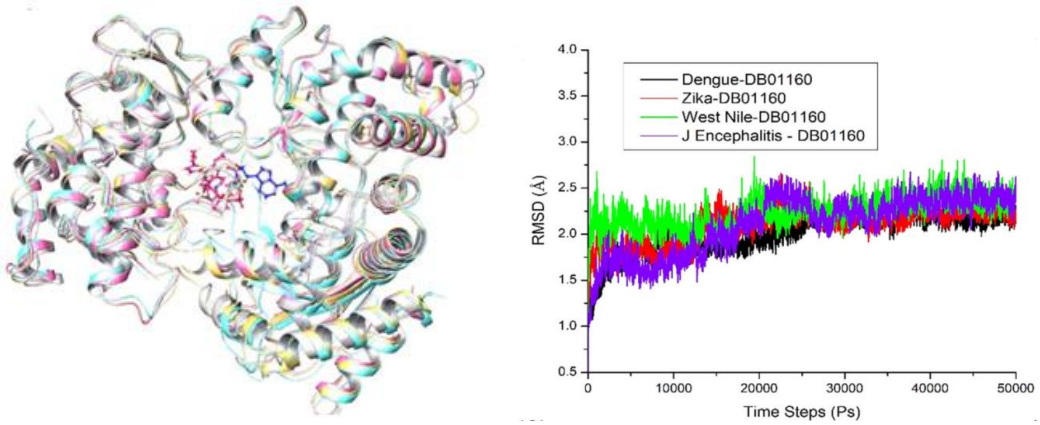


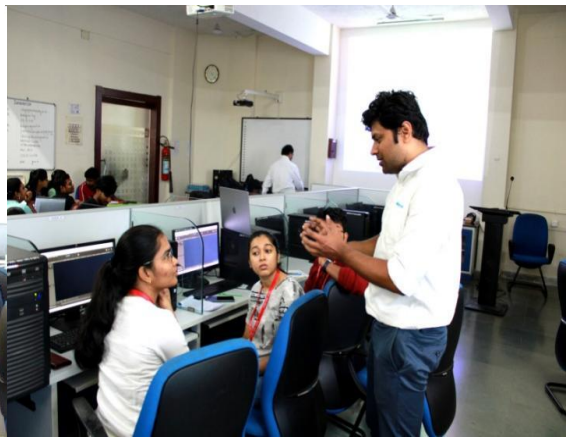
Figure 8. A) Ligand representation in the flavivirus stating the common active site
B) RMSD of the top four compounds in its bounded state with the four types of flavivirus

ICSBCADD-2022

Department of Bioinformatics organized five days International Conference cum Workshop on "***Recent Trends in Structural Bioinformatics and Computer Aided Drug Design***" ICSBCADD'2022 from 21st November to 25th November 2022. 38 distinguished scientists and eminent academicians from across India and countries like the USA, Singapore, Taiwan, and Japan participated. More than 200 participants from various countries across the world attained knowledge in Computational and Experimental Methodology regarding the problems in the healthcare sector which promotes a better understanding of biomolecular structure for the discovery of potent drugs against various diseases. It helped participants to develop technical proficiency in handling computational tools to respond to biological issues in the areas of Structural Biology, Structural Bioinformatics, Computer-Aided Drug Design, and Database development, Pharmacogenomics, Computational Genomics and Proteomics. It equipped the students and faculties to interact with renowned Scientists/ Experts in the above areas.

Each session focused on topics such as "Structural Biology in terms of advancements in synchrotron radiation and Cryo-EM with more emphasis on membrane proteins and the catalytic reactions of the enzymes". It was followed by a series of talks on "Bench to Bedside: On drug Discovery". In addition, the lectures were on topics such as "how bioinformatics transforms the patient care in terms of drug development and biomedical

applications" and "the significant involvement of Machine Learning and Artificial Intelligence in drug development process".

The hands-on training was given by the Schrodinger team to the participants in the areas of molecular modelling and drug discovery in our workshop. Schrodinger team explained the techniques to access the software step by step to develop novel medicines for critical public health needs. More than 200 participants and students acquired knowledge with hands-on work experience in drug discovery. This five-day-long interface has undoubtedly thrown up challenges, illuminating ideas, fresh insights and alternative ways of thinking about the competitive yet cooperative combat that the world of computational identification of compounds that have the potential of becoming better drugs than the existing ones is itself more fascinating.

DBT-BIC Infrastructure Facilities

High Performance Computing Facility (HPC)

Outcomes of the Project

Number of Publications (DBT-BIC Acknowledged) obtained till Feb 2024: 33

1. Jayaraman M, Gosu V, Kumar R**, Jeyaraman J**. Computational insights into potential marine natural products as selective inhibitors of Mycobacterium tuberculosis InhA: A structure-based virtual screening study. Comput Biol Chem. 2024 Feb;108:107991. doi: 10.1016/j.compbiolchem.2023.107991. **[I.F:3.1].**

2. Gupta, P., Panwar, U., & amp; **Singh, S. K**. "Novel scaffolds identification against Mpro of SARS-CoV-2 using shape based screening and molecular simulation methods". Chemical Physics Impact. 2024 Jan. S2667-0224(24)00040-9 Doi: https://doi.org/10.1016/j.chphi.2024.100496. **[I.F:2.2]**

3. Nathar S, Rajmichael R, Jeyaraj Pandian C, Nagarajan H, Mathimaran A, Kingsley JD, **Jeyaraman J.** Exploring Nocardia's ecological spectrum and novel therapeutic frontiers through whole-genome sequencing: unraveling drug resistance and virulence factors. Arch Microbiol. 2024 Jan 24;206(2):76. doi: 10.1007/s00203-023-03799-z. **[I.F:2.8]**

4. Sanjeevi M, Rajendran S, Ramachandran D, Rahul CN, **Jeyaraman J**, Kanagaraj S. A novel search engine for proteins involved in Notch crosstalk signaling pathways. J Biosci. 2024;49:8. **[I.F:2.9].**

5. Malaisamy Veerapandian, Nagarajan Hemavathy, Alagesan Karthika, Jayaraman Manikandan, Umashankar Vetrivel **& Jeyaraman Jeyakanthan** (2024) pH-Dependent conformational stability of SpeB from Thermus thermophilus HB8: insights from molecular dynamics simulation, Molecular Simulation, 2024 Jan, 50:3, 161-177, DOI: 10.1080/08927022.2023.2281987. **[I.F:2.1]**

6. Rangaswamy R, Hemavathy N, Subramaniyan S, Vetrivel U, **Jeyakanthan J**. Harnessing allosteric inhibition: prioritizing LIMK2 inhibitors for targeted cancer therapy through pharmacophore-based virtual screening and essential molecular dynamics. J Biomol Struct Dyn. 2023 Dec 8:1-18. doi: 10.1080/07391102.2023.2291171. **[I.F:4.4].**

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8. N.Aiswarya, C.N. Rahul, Gugan Kothandan, M.R.Prathapachandra Kurup, E. Manoj, P. Chandrasekaran, **Jeyakanthan Jeyaraman**, Kanagaraj Sekar, Crystal structure of 1-(E)-

[(5‑ bromo-2-hydroxybenzylidene amino) pyrrolidin-2-one]: Design, synthesis and computational evaluation of a novel racetam congener for epilepsy, Journal of Molecular Structure, Volume 1300, 2023 Nov, 137219, ISSN 0022-2860, https://doi.org/10.1016/j.molstruc.2023.137219. **[IF: 3.8]**

9. Sharma K, Panwar U, Madhavi M, Joshi I, Chopra I, Soni L, Khan A, Bhrdwaj A, Parihar AS, MohaVP, Prajapati L, Sharma R, Agrawal S, Hussain T, Nayarisseri A, **Singh SK**. Unveiling the ESR1 Conformational Stability and Screening Potent Inhibitors for Breast Cancer Treatment. Med Chem. 2023 Oct 27. doi: 10.2174/0115734064256978231024062937 **[I.F: 2.3]**

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13. Carlus, Fiona Hannah, L. Balasubramaniam Sujatha, Anbazhagan Ganesh Kumar, Lakshmanan Loganathan, **Karthikeyan Muthusamy**, and Silas Justin Carlus. "In silico prediction, molecular modeling, and dynamics studies on the targeted next-generation sequencing identified genes underlying congenital heart disease in Down syndrome patients". *Annals of Pediatric Cardiology* 16, 4, 2023 Aug, 266-275. DOI:10.4103/apc.apc_63_23 [**IF: 0.29**]

14. Karthika A, Hemavathy N, Amala M, Rajamanikandan S, Veerapandian M, Prabhu D, Vetrivel U, Jung Cheng C, JeyarajPandian C, **Jeyakanthan J**. Structural and functional characterization of 6-phosphogluconate dehydrogenase in Plasmodium falciparum (3D7) and identification of its potent inhibitors. J BiomolStructDyn. 2023 Aug 20:1-17. doi: 10.1080/07391102.2023.2248271. **[I.F: 4.4]**

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16. Khan MA, **Singh SK**. Atom-based 3D-QSAR and DFT analysis of 5-substituted 2-acylaminothiazole derivatives as HIV-1 latency-reversing agents. J Biomol Struct Dyn. 2023 Aug-Sep;41(14):6759-6774. doi: 10.1080/07391102.2022.2112078. **[I.F:4.4].**

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18. Loganathan L, Jeyakanthan J, Muthusamy K. HTNpedia: A Knowledge Base for Hypertension Research. Comb Chem High Throughput Screen. 2023 May 18. doi: 10.2174/1386207326666230518162439. **[IF: 1.8]**

19. Chitra Jeyaraj Pandian, N Arul Murugan, SM Rajendren & **Jeyakanthan Jeyaraman**. Computer-Aided vaccine design for selected positive-sense single stranded RNA viruses, 2023 Indian J. Biochem. & Biophy. 2023 April. Vol. 60, pp. 281-296. DOI: 10.56042/ijbb.v60i4.68236 **[I.F: 1.47]**

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Functional Characterization, Mechanism, and Mode of Action of Putative Streptomycin Adenylyltransferase from *Serratia marcescens*

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Abstract: Nosocomial infections are serious threats to the entire world in healthcare settings. The major causative agents of nosocomial infections are bacterial pathogens, among which *Enterobacteriaceae* family member *Serratia marcescens* plays a crucial role. It is a gram-negative opportunistic pathogen, predominantly affecting patients in intensive-care units. The presence of intrinsic genes in *S. marcescens* led to the development of resistance to antibiotics for survival. Complete scanning of the proteome, including hypothetical and partially annotated proteins, paves the way for a better understanding of potential drug targets. The targeted protein expressed in *E. coli* BL21 (DE3) pLysS cells has shown complete resistance to aminoglycoside antibiotic streptomycin (>256 MCG). The recombinant protein was purified using affinity and size-exclusion chromatography and characterized using SDS-PAGE, western blotting, and MALDI-TOF analysis. Free phosphate bound to malachite green was detected at 620 nm, evident of the conversion of adenosine triphosphate to adenosine monophosphate during the adenylation process. Similarly, in the chromatographic assay, adenylated streptomycin absorbed at 260 nm in AKTA (FPLC), confirming the enzyme-catalyzed adenylation of streptomycin. Further, the adenylated product of streptomycin was confirmed through HPLC and mass spectrometry analysis. In conclusion, our characterization studies identified the partially annotated hypothetical protein as streptomycin adenylyltransferase.

Keywords: functional annotation; antibiotic resistance; streptomycin adenylyltransferase; ANT

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1. Introduction

"Nosocomial" or "Healthcare-Associated Infections (HAI)" are widely used to refer to any class of disease affecting patients while undergoing medical care or even sometimes after treatment procedures. Prolonged stay in hospitals is found to be the root cause of HAI, and its risk factors range from simple to critical health infections, leading up to fatalities [1]. A recent study reported that these HAIs are rigorously intensifying in primary infections, even leading to deaths, with developing countries bearing 75% of the burden of infection-associated mortality, especially in neonates [2]. HAIs have become unavoidable complications in medical procedures due to (i) aging, (ii) prolonged stay of immune compromised patients in hospitals, (iii) rapid advancements in invasive devices-assisted diagnosis, and (iv) inappropriate usage of antimicrobial agents [3]. The causative agents of HAIs are microbes viz. bacteria, protozoa, fungi, viruses, and mycobacteria, but 90% of these infections are caused by bacteria [4]. *Staphylococcus aureus*, *Acinetobacter* spp., *Pseudomonas aeruginosa*, *Streptococcus* spp., and *Enterobacteriaceae* family members including *Klebsiella pneumoniae*, *Proteus mirabilis*, *Escherichia coli*, and *Serratia marcescens* are widely reported to be the bacterial species causing HAIs [1].

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Multi-level scoring approach to discover multi-targeting potency of medicinal plant phytochemicals against protein targets in SARS-CoV-2 and human ACE-2 receptor

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SARS-CoV-2 pandemic has become a major threat to human healthcare and world economy. Due to the rapid spreading and deadly nature of infection, we are in a situation to develop quick therapeutics to combat SARS-CoV-2. In this study, we have adopted a multi-level scoring approach to identify multi-targeting potency of bioactive compounds in selected medicinal plants and compared its efficacy with two reference drugs, Nafamostat and Acalabrutinib which are under clinical trials to treat SARS-CoV-2. In particular, we employ molecular docking and implicit solvent free energy calculations (as implemented in the Molecular Mechanics -Generalized Born Surface Area approach) and QM fragmentation approach for validating the potency of bioactive compounds from the selected medicinal plants against four different viral targets and one human receptor (Angiotensin-converting enzyme 2 -ACE-2) which facilitates the SARS-CoV-2 entry into the cell. The protein targets considered for the study are viral 3CL main protease (3CLpro), papain-like protease (PLpro), RNA dependent RNA polymerase (RdRp), and viral spike protein-human hACE-2 complex (Spike:hACE2) including human protein target (hACE-2). Herein, there liable multi-level scoring approach was used to validate the mechanism behind the multi-targeting potency of selected phytochemicals from medicinal plants. The present study evidenced that the phytochemicals Chebulagic acid, Stigmosterol, Repandusinic acid and Geranin exhibited efficient inhibitory activity against PLpro while Chebulagic acid was highly active against 3CLpro. Chebulagic acid and Geranin also showed excellent target specific activity against RdRp. Luteolin, Quercetin, Chrysoeriol and Repandusinic acid inhibited the interaction of viral spike protein with human ACE-2 receptor. Moreover, Piperlonguminine and Piperine displayed significant inhibitory activity against human ACE-2 receptor. Therefore, the identified compounds namely Chebulagic acid, Geranin and Repandusinic acid can serve as potent multi-targeting phytomedicine for treating COVID-19.

Keywords: 3CL Main protease, COVID-19, Molecular docking, Molecular mechanics-generalized born surface area approach, Papain-like protease, QM fragmentation scheme, RNA-directed RNA polymerase, SARS-CoV-2, Spike protein

Based on the pathophysiology of SARS-CoV-2, many existing antiviral drugs such as Ritonavir, Umifenovir, Favipiravir, Oseltamivir, Remdesivir *etc*. and other drugs including Tocilizumab, Azithromycin, Interferon β *etc*., are being tested in COVID-19 therapy[1]. Extensive researches are still in progress to discover effective therapeutics against SARS-CoV-2. Recently Ahmad *et al.* (2020)[2] have reported that the ATP binding site is located between palm and finger subdomains of RdRp and the inhibitors of RdRp of Hepatitis C virus can bind with this site. Considering the existing information about the plant mediated natural products as molecular frameworks for development of potent drugs, we believe that the medicinal plants as well as their secondary metabolites with anti-viral activity could shed light on the development and discovery of potent drugs or leads for COVID-19. Modern synthetic medicines emphasis only on killing the coronavirus but not on increasing the immunity of the host to recover and withstand severe infections[3]. However, phytochemicals in *Withania somnifera* and *Andrographis paniculata* showed both antiviral activity against chikungunya virus and immunomodulatory effects in human which can be used for all infected patients including immuno compromised individuals with minimum side effects. Medicinal plants are used for centuries in treatment of

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Unraveling the multi-targeted curative potential of bioactive molecules against cervical cancer through integrated omics and systems pharmacology approach

Murali Aarthy[1], Pandiyan Muthuramalingam[2], Manikandan Ramesh[2] & Sanjeev Kumar Singh[1✉]

Molecular level understanding on the role of viral infections causing cervical cancer is highly essential for therapeutic development. In these instances, systems pharmacology along with multi omics approach helps in unraveling the multi-targeted mechanisms of novel biologically active compounds to combat cervical cancer. The immuno-transcriptomic dataset of healthy and infected cervical cancer patients was retrieved from the array express. Further, the phytocompounds from medicinal plants were collected from the literature. Network Analyst 3.0 has been used to identify the immune genes around 384 which are differentially expressed and responsible for cervical cancer. Among the 87 compounds reported in plants for treating cervical cancer, only 79 compounds were targeting the identified immune genes of cervical cancer. The significant genes responsible for the domination in cervical cancer are identified in this study. The virogenomic signatures observed from cervical cancer caused by E7 oncoproteins serve as the potential therapeutic targets whereas, the identified compounds can act as anti-HPV drug deliveries. In future, the exploratory rationale of the acquired results will be useful in optimizing small molecules which can be a viable drug candidate.

In cancer biology, viruses possess a foremost role over the past two decades, and especially, the tumor viruses encompassing RNA and DNA with the fundamental contributions are highly responsible[1]. Numerous oncogenes carried by retroviruses that were derived from the cellular genes are involved in the signaling and control of cell growth. These oncogenes from the viral origin are requisite for the replication and cell transformation[2]. The organization of the genome in retroviruses differentiates the representations of the simple and complex viruses. Retroviruses which does not possess viral oncogenes like avian leukosis virus and mouse mammary tumor virus induce tumors in animals[2]. Further, the virus which is responsible for the development of malignancies with expanded latency in relation towards the environmental and host associated cooperating events exists. The oncogenicity of the virus and the mode of infection discriminate the nature from other carcinogenic agents. Better insights on the pathogenesis of viral infection and host responses are very important in understanding the cancers in detail. Oncogenic viruses belong to diverse families and employ varied mechanism for the development of cancer[3]. Martin and Gutkind states that the Hepatitis B virus (HBV), Human T-cell lymphotropic virus (HTLV), Epstein-Barr virus (EBV), Human papillomavirus (HPV), Hepatitis C virus (HCV), and Kaposi's associated sarcoma virus (KSHV) contributes towards 15% of the human cancer[4].

Italian physicist Ciuffo identified the etiology of warts in human around 1907 and identified the link with HPV in the 1970s. The infections caused by HPV in the cervix lead to cervical malignancy and other related warts. These viruses are non-enveloped double-stranded DNA viruses constituting triple segments namely the late, early and genomic regions[5]. The most common second malignant tumour that threatens the health of

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Atom-based 3D-QSAR and DFT analysis of 5-substituted 2-acylaminothiazole derivatives as HIV-1 latency-reversing agents

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ABSTRACT

HIV-1 latency consists of viral DNA; integrated inside the host genome; it remains transcriptional silent. Combined Antiretroviral Therapy (cART) and the host immune system fail to recognize the latency cells or reservoirs, representing a major barrier to eradicating the HIV-1 infection. The Shock and Kill emerged as a promising strategy to target these cells using Latency reversal agents (LRAs); partially succeeded in producing viral mRNA but failed to reduce the size of reservoirs. In this Context, 2-acylaminothiazole class derivatives appeared as promising HIV-1 latency-reversing agents. In this study, we have developed an atom-based 3 D-QSAR model by utilizing the 49 active compounds of the 5-substituted 2-acylaminothiazoles derivatives. These compounds are further randomly divided into training (37) and test (12) datasets, yielding statistically significant R^2 (0.90) and Q^2 (0.85) results, respectively. The internal and external validation of the model shows highly robust and reliable results. Next, the model was visualized to check the favourable and unfavourable groups in terms of hydrogen bond donor, electron-withdrawing and hydrophobic group on the most active compound 96 and least active compound 30. The investigated model reveals the structural insights required for obtaining more leads that are potent. Finally, DFT calculations on the most and least active compounds were performed to support the atom-based 3D-QSAR model. Overall, this study will aid in understanding the minimum structural requirement and functional group required for screening the novel potent leads as HIV-1 latency reversal agents.

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Introduction

The acquired immune deficiency syndrome (AIDS) is a major viral disease caused by the HIV-1 virus. According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), 37.7 million people are living with HIV worldwide and 36.3 million die because of HIV-1 infection (UNAIDS (Joint United Nations Programme on HIV/AIDS),), 2021). The combined antiretroviral therapy (cART) is available for HIV treatment, successfully targeted at the multiple stages of the HIV-1 life cycle and reduces the mortality rate and disease burden worldwide. However, cART failed in depleting the pool of latency-infected HIV reservoirs, once treatment interrupts by the individuals, the virus again re-emerge from the reservoirs causing infection, which represents a major barrier to eradicating the HIV-1 (Xing & Siliciano, 2013; Khan et al., 2020; Panwar et al., 2019; RV411 study group, 2018; Nayak et al., 2019; Deeks et al., 2015). The HIV-1 latent reservoirs established early, consist of integrated transcriptionally silent, replication-competent provirus in the long-lived resting memory $CD4^+$ T cells and other cell types (macrophages, monocytes, dendritic) (Wong et al., 2019; Chavez et al., 2015; Shan et al., 2017). The HIV-1 latency occurs due to a lack of viral transactivation of transcription (Tat) protein and seizure of crucial host transcription factors like Positive transcription elongation factor (P-TEFb), NF-κB, nuclear factor of activated T-cells (NFAT) and epigenetic silencing of the viral promoter, respectively, leads the cells in the quiescent stage (Margolis et al., 2016). The HIV-1 Tat is a small regulatory protein, consisting of 86–102 amino acids, a master regulator of the viral transcription. The expression of viral Tat protein is critical for activating the latent reservoirs (Mousseau & Valente, 2017). In the absence of Tat, viral transcription paused after forming a short transcript of approx. 60 nucleotides in length, transactivation responsive region (TAR) (Schulze-Gahmen & Hurley, 2018). When the Tat is produced, binds to the TAR at the 5'LTR promoter, and recruits the host positive transcription elongation factor b (P-TEFb), consisting of Cyc T1 and CDK9. Next, P-TEFb helps in the recruitment of super elongation complex (SEC) comprises ELL2, AF9 and AFF1/AFF4. P-TEFb phosphorylates the paused complex of the carboxy-terminal domain of RNA Pol II at Ser2, NELF-E subunit and the spt5 of DSIF. Thus, Tat released the paused promoter for productive transcription elongation leading to splicing and translation, producing the infective virions (Schulze-Gahmen et al., 2016; Egloff, 2021).

Recently, Shock and Kill strategy has emerged as a promising cure, which utilizes the latency reversal agents (LRAs) to

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Exploring the druggability of oxidized low-density lipoprotein (ox-LDL) receptor, LOX-1, a proatherogenic drug target involved in atherosclerosis

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ABSTRACT

Lectin-like oxidized low-density lipoprotein (ox-LDL) receptor 1 (LOX-1) is a vital scavenger receptor involved in ox-LDL binding, internalization, and subsequent proatherogenic signaling leading to cellular dysfunction and atherosclerotic plaque formation. Existing data suggest that modulation of ox-LDL – LOX-1 interaction can prevent or slow down atherosclerosis. Therefore, we utilized computational methods such as multi-solvent simulation and characterized two top-ranked druggable sites. Using systematic molecular docking followed by atomistic molecular dynamics simulation, we have identified and shortlisted small molecules from the NCI library that target two key binding sites. We demonstrate, using surface plasmon resonance (SPR), that four of the shortlisted molecules bind one-on-one to the purified C-terminal domain (CTLD) of LOX-1 receptor with high affinity (K_D), ranging from 4.9 nM to 20.1 μM. Further, we performed WaterMap analysis to understand the role of individual water molecules in small molecule binding and the LOX-1-ligand complex stability. Our data clearly show that LOX-1 is druggable with small molecules. Our study provides strategies to identify novel inhibitors to attenuate ox-LDL – LOX-1 interaction.

1. Introduction

Lectin-like oxidized low-density lipoprotein (ox-LDL) receptor-1 (LOX-1) [1] plays a critical role in the pathophysiology of atherosclerosis, mediating the uptake of ox-LDL in various cell types [2–5]. LOX-1 is overexpressed in the endothelial cells and macrophages of atherosclerotic lesions [6]. The expression of LOX-1 is auto-regulated in endothelial cells and dependent on ox-LDL concentration [7,8]. An increasing body of evidence shows that LOX-1 is a key molecular target in the development of atherosclerotic lesions. It mediates endothelial dysfunction [9,10], inflammation [11], expression of cell adhesion molecules [12], recruitment of activated monocytes/macrophages [13,14] and foam cell formation [15]. LOX-1 knockout mice data [3] clearly shows reduction in atherosclerotic plaque formation, suggesting that blocking the receptor mediated ox-LDL uptake may pave the way for developing novel anti-atherosclerotic therapeutics [16]. Currently, LOX-1 specific therapeutics are not available. Further, a thorough analysis of druggable sites on the LOX-1 receptor is lacking.

LOX-1 exists as a homodimer where two monomers are linked via an interchain disulfide bond between the Cys140 of the CTLD [17,18]. Two probable sites have been proposed to be involved in ox-LDL binding. First is the hydrophobic tunnel at the dimer interface,

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Article

Integrated Transcriptome Profiling Identifies Prognostic Hub Genes as Therapeutic Targets of Glioblastoma: Evidenced by Bioinformatics Analysis

Chirasmita Nayak and Sanjeev Kumar Singh*

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ABSTRACT: Glioblastoma (GBM) is the most devastating and frequent type of primary brain tumor with high morbidity and mortality. Despite the use of surgical resection followed by radio- and chemotherapy as standard therapy, the progression of GBM remains dismal with a median overall survival of <15 months. GBM embodies a populace of cancer stem cells (GSCs) that is associated with tumor initiation, invasion, therapeutic resistance, and post-treatment reoccurrence. However, understanding the potential mechanisms of stemness and their candidate biomarkers remains limited. Hence in this investigation, we aimed to illuminate potential candidate hub genes and key pathways associated with the pathogenesis of GSC in the development of GBM. The integrated analysis discovered differentially expressed genes (DEGs) between the brain cancer tissues (GBM and GSC) and normal brain tissues. Multiple approaches, including gene ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis, were employed to functionally annotate the DEGs and visualize them through the R program. The significant hub genes were identified through the protein−protein interaction network, Venn diagram analysis, and survival analysis. We observed that the upregulated DEGs were prominently involved in the ECM−receptor interaction pathway. The downregulated genes were mainly associated with the axon guidance pathway. Five significant hub genes (CTNNB1, ITGB1, TNC, EGFR, and SHOX2) were screened out through multiple analyses. GO and KEGG analyses of hub genes uncovered that these genes were primarily enriched in disease-associated pathways such as the inhibition of apoptosis and the DNA damage repair mechanism, activation of the cell cycle, EMT (epithelial−mesenchymal transition), hormone AR (androgen receptor), hormone ER (estrogen receptor), PI3K/AKT (phosphatidylinositol 3-kinase and AKT), RTK (receptor tyrosine kinase), and TSC/mTOR (tuberous sclerosis complex and mammalian target of rapamycin). Consequently, the epigenetic regulatory network disclosed that hub genes played a vital role in the progression of GBM. Finally, candidate drugs were predicted that can be used as possible drugs to treat GBM patients. Overall, our investigation offered five hub genes (CTNNB1, ITGB1, TNC, EGFR, and SHOX2) that could be used as precise diagnostic and prognostic candidate biomarkers of GBM and might be used as personalized therapeutic targets to obstruct gliomagenesis.

INTRODUCTION

Glioblastoma (GBM) is the most devastating and frequent type of primary brain tumor with high morbidity and mortality. Despite treatment regimens that include surgical resection with radiation and concomitant adjuvant chemotherapy, the median survival time for patients with GBM is 12−15 months, with survival rates of 25% and 10% after 2 and 5 years, respectively.[1−4] Accumulating evidence in recent years shows that GBM consists of the subpopulation of cells displaying various stem cell-like properties including long-term self-renewal with the capacity to generate phenotypically diverse hierarchical neoplastic progeny and stromal cells referred as glioma stem cells (GSCs).[5] GSCs also can recapitulate the essential phenotypes of the original tumor, such as tumor cell heterogeneity, invasiveness, and vascularity promoting resistance to chemotherapy and radiotherapy.[6,7] Thus, neoplastic cells displaying stem-like phenotypes are currently believed to be the main barriers for successful treatment of GBM that associated inexplicably in tumor growth and recurrence after therapy.[8−10]

The biggest challenge in glioma is to monitor the diagnosis and prognosis process. The typical way of disease monitoring in patients is radiographic utilizing computed tomography, magnetic resonance imaging, or positron emission tomography, which is entirely dependent on the experience of the

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Post-acute sequelae of SARS-CoV-2 Delta variant infection: A report of three cases in a single family

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Coronavirus disease 2019 (COVID-19) is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that has resulted in global pandemic and crisis in health care system. Several studies have focused only on hospitalized patients with 30 to 90 days after one cycle of illness but post-acute sequelae of COVID-19 existing even after a year remains unclear. Moreover, long-term sequelae in outpatients have not been documented and henceforth myriad clinical sequelae in long haulers continue to evolve. In this study, we report three cases represents a single family presenting several post-acute sequelae one after the other extending beyond one year of recovery. To our knowledge such a case series has not been reported in earlier studies. Herein, we present the sequelae in various organs namely neuropsychiatric (tinnitus, anxiety, depression, insomnia, and posttraumatic stress disorder, cognitive decline), cardiovascular (tachycardia, bradycardia), gastrointestinal (appendicitis) and Dermatologic (erythematous rash and acne) besides ophthalmic manifestations (*conjunctivitis and dry eyes)* in Long-COVID-19 and recommend management strategies.

Keywords: Antiviral Steroid therapy, Appendicitis, Case reports, COVID-19 survivors, Psychopathology, Tinnitus

SARS-CoV-2 has been spreading around the world since December, 2019 with high mortality rate or acute infection and World Health Organization (WHO) declared COVID-19 a pandemic. The delta (B.1.617.2) variant of SARS-CoV-2 was first identified India (Maharashtra) during late 2020 that outcompeted pre-existing lineages namely Kappa (B.1.617.1) and alpha (B.1.1.7)[1]. Experimental studies have reported six-fold and eight-fold less sensitive nature of B.1.617.2 to neutralizing antibodies of *convalescent serum* and vaccine-elicited antibodies, respectively, compared to wild-type Wuhan-1 SARS-CoV-2[2]. Moreover, B.1.617.2 showed lower neutralizing antibody titres in ChAdOx1 vaccines than BNT162b2 vaccines [3]. B.1.617.2 also had higher replication efficiency in airway epithelium or organoid with B.1.617.2 spike predominantly existing in cleaved state that further enhanced syncytium formation subsequently displaying lower sensitivity to neutralizing antibody[3]. The potential dominance of B.1.617.2 over other lineages could be due to increased spike mediated entry and high replication in B.1.617.2[3]. Also the mixed lineage circulation during Mid-2021 in India have reduced the efficacy of ChAdOx1 vaccine. This immune evasive B.1.617.2 caused tremendous burden to health care systems in India between April and June, 2021 with more than 200 million cases and high mortality rate. Though most of the patients recovered from acute infection of B.1.617.2, a subset of them sustain persistent symptoms that do not resolve even over a year. Post-acute sequelae of COVID-19 is diagnosed both in patients with severe and mild or asymptomatic infections[4]. Therefore, long-term follow-up investigations to evaluate the post-infectious sequelae in COVID-19 survivors are vital to enhance their diagnosis and survival. Earlier studies have reported that the COVID-19 patients discharged from hospital showed several health issues and persistent symptoms including impaired organ function, depression, detectable abnormalities in imaging techniques, anxiety and declined quality of life[5–8]. Most of the previous reports[5–8] have focused only on early follow-up (after 2-6 months of recovery)while later follow-up

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Molecular Diversity
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ORIGINAL ARTICLE

Designing of potent anti-diabetic molecules by targeting SIK2 using computational approaches

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Abstract

Diabetes mellitus (DM) is one of the major health problems worldwide. WHO have estimated that 439 million people may have DM by the year 2030. Several classes of drugs such as sulfonylureas, meglitinides, thiazolidinediones etc. are available to manage this disease, however, there is no cure for this disease. Salt inducible kinase 2 (SIK2) is expressed several folds in adipose tissue than in normal tissues and thus SIK2 is one of the attractive targets for DM treatment. SIK2 inhibition improves glucose homeostasis. Several analogues have been reported and experimentally proven against SIK for DM treatment. But, identifying potential SIK2 inhibitors with improved efficacy and good pharmacokinetic profiles will be helpful for the effective treatment of DM. The objective of the present study is to identify selective SIK2 inhibitors with good pharmacokinetic profiles. Due to the unavailability of SIK2 structure, the modeled structure of SIK2 will be an important to understand the atomic level of SIK2 inhibitors in the binding site pocket. In this study, different molecular modeling studies such as Homology Modeling, Molecular Docking, Pharmacophore-based virtual screening, MD simulations, Density Functional Theory calculations and WaterMap analysis were performed to identify potential SIK2 inhibitors. Five molecules from different databases such as Binding_4067, TosLab_837067, NCI_349155, Life chemicals_F2565-0113, Enamine_7623111186 molecules were identified as possible SIK2 inhibitors.

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Deciphering the conformational transitions of LIMK2 active and inactive states to ponder specific druggable states through microsecond scale molecular dynamics simulation

Hemavathy Nagarajan[1] · Ansar Samdani[2] · Vetrivel Umashankar[3] · Jeyaraman Jeyakanthan[1]

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Abstract

LIMK2 inhibitors are one of the potential therapeutic modalities for treating various diseases. In the current scenario, there is a paucity of effective LIMK inhibitors that are highly specific with minimal off-target effects. To date, the conformational transitions of LIMK2 from $DFG_{in}\alpha C_{in}$ (CIDI) (active) to $DFG_{out}\alpha C_{out}$ (CODO) (inactive) states are yet to be probed and are essential for capturing the unique, druggable conformations. Therefore, this study was intended to capture the diverse conformational states of LIMK2 for accelerating the rational identification of conformation specific inhibitors through high-end structural bioinformatics protocols. Hence, in this study, molecular modelling followed by an extensive microsecond timescale of molecular dynamics simulation was performed encompassing perturbation response scanning, metapath, and community analysis towards the conformational sampling of LIMK2. Overall this study precisely identifies the conformational ensemble of LIMK2 the intermediate inactive states namely, CIDO, CinterDinter, CIDinter, CinterDI, CinterDO, CODI, CODinter apart from CIDI and CODO. This also facilitated observing that β8 preceding XDFG, αC (F373, L374), and αD (L413) as the major effectors that may facilitate the regulation of varying conformational transitions among the states. Additionally, the conserved β sheets and the loops namely, C.l, b.l, and G/P.loop were observed to be involved in the metapath for allosteric communication among the intermediates with CIDI and CODO state. Moreover, only the CODO state was observed to have closed type A.l, while the CIDI and other intermediate states except for CIDO were observed to have open-DFG out type A.l, thereby enabling the binding of substrate. Apart from these, the druggable site analysis inferred that the CIDI and CODO states harbor prominent druggable sites spanning the conserved N-lobe, while the intermediates were observed to have unraveled allosteric druggable sites distal from the ATP binding site, majorly spanning the C-lobe of LIMK2. Thus, this study provides potential insights into the intermediate conformational druggable states of LIMK2 and also the druggable conformations, especially the inactive states of LIMK2, as a specific therapeutic targeting mode. Thus, providing a widened avenue to ponder the allosteric sites or the isoform selectivity conformations for targeting LIMK2 in various disease conditions.

Keywords LIMK2 · Microsecond · DFG · Activation loop · Active · Inactive · Molecular dynamics simulation

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Introduction

Protein kinases are one of the major crucial drug targets in humans that are highly dynamic in nature and could adopt varying conformational states to facilitate catalytic activity. It is of high importance to probe and understand the conformational states of protein kinases, as it defines the catalytic activity and protein–protein interactions. In addition, it also assists in determining kinase family-specific inhibitors with higher selectivity and the least off-target effects [1]. In general, protein kinases share a conserved kinase domain comprised of bilobal architecture containing 12 conserved

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ORIGINAL RESEARCH

Quercetin-induced apoptosis in HepG2 cells and identification of quercetin derivatives as potent inhibitors for Caspase-3 through computational methods

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Abstract

Quercetin is a bioflavonoid which possesses immune-enhancing activity, anti-inflammatory, antioxidant properties and considered effective against various cancers. In the present study, quercetin has been extracted from *Ocimum basilicum* and was used to evaluate its anticancer activity against human liver cancer cell lines (HepG2) by assessing cell viability (MTT) and variations in nuclear morphology (AO/EtBr dual staining) during apoptosis. Since Caspase-3 enables the activation of cascade which is responsible for apoptosis, their effects were also investigated using computational approaches like molecular docking, molecular dynamics, covalent docking, ADME prediction, DFT approaches, and pharmacophore modeling besides identifying the binding affinity, stability, drug likeliness properties of top-ranked compounds. Amount of quercetin extracted from *O. basilicum* leaves was found to be 0.82 mg with the retention time of 2.827 min. Quercetin showed dose-dependent anticancer activity against HepG2 cells with IC_{50} value 50 µg/mL due to apoptosis that could have been mediated by Caspase-3 activity. Computational analysis of quercetin inhibiting Caspase-3 showed better binding affinity of compounds ChEMBL_38464, ChEMBL_501025, and ChEMBL_525002 and no violations were observed in the Lipinski Rule of 5. The molecular dynamics simulation evidenced the presence of water molecule in the catalytic site stabilizes the complex. The DFT analysis also explored that the identified compounds have the least HOMO–LUMO gap. The identified compounds also exhibit the pharmacophoric features such as hydrogen bond acceptor, hydrogen bond donor, aromatic ring, and hydrophobic features. Moreover, the study indicates the importance of water molecule in the catalytic site which may suppress the growth of tumor cells which could assist in the selection of potential leads for further analysis against liver cancer.

Keywords Apoptosis · Caspase-3 · Quercetin · HepG2 cells · Molecular docking · Molecular dynamics · DFT analysis · Pharmacophore analysis · LigandScout

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Introduction

The uncontrolled growth and rapid dissemination of the abnormal or atypical cells are referred as cancer. According to WHO statistics, cancer is the leading cause for death globally. The comprehensive understanding of the molecular pathways will assist in investigating novel cancer chemotherapeutic targets which in turn would offer new opportunities for the discovery and development of new potential drugs [1, 2]. Liver cancer is leading among various cancers, which registers approximately 8,00,000 cases per year globally and turned out as the second leading cause of cancer-related deaths [3, 4]. The liver cancer frequently affects people suffering from liver diseases such as chronic hepatitis B and hepatitis C [5]. With the aid of recent developments, surgery,

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RESEARCH ARTICLE

Journal of Cellular Biochemistry WILEY

Mechanistic insights into the role of vitamin D and computational identification of potential lead compounds for Parkinson's disease

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Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disorder that affects dopaminergic neurons in the midbrain. A recent study suggests that Orphan Nuclear Receptor 1 (NURR1) impairment may contribute to PD pathogenesis. Our study found three potent agonists for NURR1 protein based on structural and ligand-based screening methods. The pharmacophore is comprised of a hydrogen bond donor, a hydrophobic group, and two aromatic rings (DHRR). The Pharmacophore screening method screened 3142 compounds, of which 3 were screened using structure-based screening. An analysis of the molecules using Molecular Mechanics-Generalized Born Surface Area (binding free energy) revealed a range of −46.77 to −59.06 Kcal/mol. After that, chemical reactivity was investigated by density functional theory, and molecular dynamics simulation was performed (protein-ligand stability). Based on the computational studies, Lifechemical_16901310, Maybridge_2815310, and NPACT_392450 are promising agonists with respect to NURR1. To confirm the potency of the identified compounds, further validation and experiments must be conducted.

KEYWORDS

binding free energy calculation, dopamine neurons, molecular dynamics, NURR1, Parkinson's disease, phamacophore generation

1 | INTRODUCTION

Parkinson's disease (PD) is generally a chronic disorder that affects the central nervous system of the brain resulting in aberrant motor function.[1] PD is caused by multifactorial complications including several genetic, dietary, and environmental factors that contribute to the predisposed expression of the mutations.[2] Clinically, it correlates with the pathological loss or loss of dopaminergic neurons in the midbrain's substantia nigra as well as the formation of neuronal Lewy Bodies.[3] Dopamine serves as a messenger between the nervous system and different brain cells by regulating the body's movement and regulation. Dopamine acts as a messenger between the nervous system and different parts of brain cells as a result of that which regulates the body's movement and regulation system.[4] PD affects 1% of the population; the prevalence rate increases with age. Over the age of >60 years, males are affected by PD approximately 50% more than women. Each year 60 000 Americans are diagnosed with this disease.[5] Vitamin D insufficiency has been linked to the development and etiology of PD.

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RESEARCH ARTICLE

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Drug repurposing toward the inhibition of RNA-dependent RNA polymerase of various *flaviviruses* through computational study

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Abstract

Numerous pathogens affecting human is present in the *flavivirus* family namely west nile, dengue, yellow fever, and zika which involves in development of global burden and distressing the environment economically. Till date, no approved drugs are available for targeting these viruses. The threat which urged the identification of small molecules for the inhibition of these viruses is the spreading of serious viral diseases. The recent outbreak of zika and dengue infections postured a solemn risk to worldwide public well-being. RNA-dependent RNA polymerase (RdRp) is the supreme adaptable enzymes of all the RNA viruses which is responsible for the replication and transcription of genome among the structural and nonstructural proteins of *flaviviruses*. It is understood that the RdRp of the *flaviviruses* are similar stating that the japanese encephalitis and west nile shares 70% identity with zika whereas the dengue serotype 2 and 3 shares the identity of 76% and 81%, respectively. In this study, we investigated the binding site of four flaviviral RdRp and provided insights into various interaction of the molecules using the computational approach. Our study helps in recognizing the potent compounds that could inhibit the viral protein as a common inhibitor. Additionally, with the conformational stability analysis, we proposed the possible mechanism of inhibition of the identified common small molecule toward RdRp of *flavivirus*. Finally, this study could be an initiative for the identification of common inhibitors and can be explored further for understanding the mechanism of action through in vitro studies for the study on efficacy.

KEYWORDS

Comparative studies, Molecular simulation, RdRp, Replication, Transcription

Murali Aarthy and Sushil Kumar provided equal contributions.

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Computational exploration of molecular flexibility and interaction of meropenem analogs with the active site of oxacillinase-23 in *Acinetobacter baumannii*

Balajee Ramachandran[1], Saravanan Muthupandian[2], Jeyakanthan Jeyaraman[1*†] and Bruno Silvester Lopes[3,4*†]

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Background: Carbapenem-resistant *Acinetobacter baumannii* is an opportunistic pathogen responsible for nosocomial infections and is one of the biggest global threats according to the World Health Organization (WHO), particularly causing substantial morbidity and mortality.

Objectives: This study aimed at using computational approaches to screen meropenem and its analogs against OXA-23-positive *Acinetobacter baumannii*, analyzing the correlations between kinetic and phenotypic characteristics.

Methods: A total of 5,450 compounds were screened using virtual screening workflow (HTVS, Glide-SP, and Glide-XP) to identify the best compounds based on their binding energy and interactions against OXA-23 and OXA-27 as they had phenotypic data available. Molecular dynamics simulation and density functional theory (DFT) studies were performed from the outcome of molecular docking analysis.

Results: During simulations, meropenem and its analogs exhibited high-level stable interactions with Ser79, Ser126, Thr217, Trp219, and Arg259 of OXA-23. Meropenem displayed a CovDock energy of about −3.5 and −1.9 kcal mol^{-1} against OXA-23 and OXA-27, respectively. Among the 5,450 compounds, Pubchem_10645796, Pubchem_25224737, and ChEMBL_14 recorded CovDock energy between −6.0 and −9.0 kcal mol^{-1}. Moreover, the infra-red (IR) spectrophotometric analysis revealed C=O and C-N atoms showing bands at 1,800 and 1,125 cm^{-1}, respectively. These observed data are in congruence with the experimental observations.

Conclusion: The identified compounds showed good agreement with the spectrophotometric analysis using DFT methods. In the earlier studies, meropenem's MIC value was 32 μg mL^{-1} in OXA-23-positive isolate A2265 compared to the MIC of 1 μg mL^{-1} in Δbla_{OXA-23} A2265. Comparing the CovDock energy and hydrogen-bonding interactions, the predicted results are in good agreement with the experimental data reported earlier. Our results highlight

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Combination of bendamustine-azacitidine against Syk target of breast cancer: an *in silico* study

Sankar Muthumanickam, Balajee Ramachandran, Pandi Boomi, Jeyaraman Jeyakanthan, Halliah Gurumallesh Prabu, Sonamuthu Jegatheswaran & Kumpati Premkumar

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Molecular Simulation

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Investigation of translation initiation factor through protein–protein interactions and molecular dynamics approaches

Prajisha Jayaprakash, Jayashree Biswal, Chitra Jeyaraj Pandian, Jemima Kingsley & Jeyaraman Jeyakanthan

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A Review

Computer-Aided vaccine design for selected positive-sense single stranded RNA viruses

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Spontaneous mutations and lack of replication fidelity in positive-sense single stranded RNA viruses (+ssRNA virus) result in emergence of genetic variants with diverse viral morphogenesis and surface proteins that affect its antigenicity. This high mutability in +ssRNA viruses has induced antiviral drug resistance and ability to overcome vaccines that subsequently resulted in rapid viral evolution and high mortality rate in human and livestock. Computer aided vaccine design and immunoinformatics play a crucial role in expediting the vaccine production protocols, antibody production and identifying suitable immunogenic regions or epitopes from the genome sequences of the pathogens. T cell and B cell epitopes can be identified in pathogens by immunoinformatics algorithms and methods that enhance the analysis of protective immunity, vaccine safety, immunity modelling and vaccine efficacy. This rapid and cost-effective computational vaccine design promotes development of potential vaccine that could induce immune response in host against rapidly mutating pathogens like +ssRNA viruses. Epitope-based vaccine is a striking concept that has been widely employed in recent years to construct vaccines targeting rapidly mutating +ssRNA viruses. Therefore, the present review provides an overview about the current progress and methodology in computer-aided vaccine design for the most notable +ssRNA viruses namely Hepatitis C virus, Dengue virus, Chikungunya virus and Coronaviruses. This review also highlights the applications of various immunoinformatics tools for vaccine design and for modelling immune response against +ssRNA viruses.

Keywords: Epitope prediction, Immunoinformatics, Hepatitis C virus, Dengue virus, Chikungunya virus, Coronaviruses

Introduction

Viruses are diverse and are classified into seven classes based on the genome replication and encapsidation. This includes i) single stranded (ss) DNA virus, ii) double stranded (ds) DNA virus, iii) mRNA sense ssRNA virus, iv) antisense ssRNA virus, v) antisense dsRNA virus, vi) reverse transcribing RNA virus and vii) reverse transcribing DNA virus[1]. Low replication fidelity due to lack of proof-reading mechanism by RNA dependent polymerases makes the RNA viruses to exhibit high mutation rate. This spontaneous mutation in the RNA viruses results in variety of mutants called 'quasispecies' that affects viral antigenicity by varying viral morphogenesis, altered surface glycoproteins, rapid viral evolution and antiviral resistance when compared to DNA viruses[2]. Another factor that influences the frequency of mutation in RNA viruses includes polarity of RNA namely positive-sense (5′ to 3′) ssRNA and negative- sense (3′ to 5′) ssRNA[3]. Positive-sense single stranded RNA (+ssRNA) viruses form one-third of known viral genera including various virulent pathogens that are also listed in potent bioterrorism agents. Positive strand RNA viruses use host machinery for its entry and replicate by modulating the host gene expression and also evades host innate immune system by co-opting the host factors[4]. +ssRNA adopts either of two strategies to evade host immune response namely covalent attachment of peptide and formation of 7-methulguanosine cap at the 5′ terminal of viral RNA. +ssRNA viral genome replication occurs in host cell cytoplasm tandemly along with nucleocapsid assembly which shows that there is a close association between species specific viral replication and nucleocapsid formation for genome packing. +ssRNA viral genome work as messenger RNA (mRNA) and act as template for viral replication by fostering interactions of host replication factors during various

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RESEARCH ARTICLE

HTNpedia: A Knowledge Base for Hypertension Research

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Abstract: ***Background***: Hypertension is notably a serious public health concern due to its high prevalence and strong association with cardiovascular disease and renal failure. It is reported to be the fourth leading disease that leads to death worldwide.

Objective: Currently, there is no active operational knowledge base or database for hypertension or cardiovascular illness.

Method: The primary data source was retrieved from the research outputs obtained from our laboratory team working on hypertension research. We have presented a preliminary dataset and external links to the public repository for detailed analysis to readers.

Result: As a result, HTNpedia was created to provide information regarding hypertension-related proteins and genes.

Conclusion: The complete webpage is accessible *via* www.mkarthikeyan.bioinfoau.org/HTNpedia.

Keywords: Hypertension, knowledge base, SNP, proteins, genes, drug molecules.

1. INTRODUCTION

It is widely known that the interaction between biological proteins is highly intricate. Furthermore, they are closely associated with biological, chemical and metabolic signalling pathway(s). Proteins are presumed to be the best molecular targets in drug discovery for many disorders. However, no definitive link between the proteins and the disease has been established [1, 2]. On the contrary, genomic data analysis revealed that proteins and genes are involved in a specific pathway. Alternative splicing and post-translational alterations contribute to this complexity [3, 4]. As a result, a comprehensive understanding of hypertension aetiology is expected to overcome barriers in hypertension management strategies [5].

A lot of evidence is available in public domains and open-source databases, which has a significant impact on the development of pathway-based drugs using *in silico* techniques. Evidence on signalling and metabolic pathway(s) provides a basic understanding of the role of cellular proteins in the development of hypertension, allowing for the identification of potential treatment targets [6]. In the event that the target protein does not respond to treatment, an alternate target from a disease-related biochemical pathway(s) may be used to address the issue [7]. The dispersed nature of information important to biochemical pathways and linked proteins in literature and online biological databases makes mining the necessary data extremely difficult [8, 9]. Even when a researcher obtains relevant data for a specific target protein from multiple sources, it is done separately, which takes time to establish a perfect link.

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2. MATERIALS AND METHODS

2.1. Data Acquisition

The hypertension related-data, including research articles and information related to genes, proteins, and drugs, *etc*., were manually collected from several resources available from primary databases, such as SwissProt [10], UniProtKB [11], and Ensembl genome browser [12]. For research articles, we used the Google Scholar search engine to find the most relevant articles matching our keywords. Further reviews and articles were filtered using a combination of keywords, including hypertension, RAAS pathway, protein, drug discovery, drug molecules, and anti-hypertensive treatment [13]. Finally, curated articles and information were obtained by excluding articles lacking relevant information and articles other than in the english language.

Open-source biological databases are critical for assisting life science researchers in gaining access to the most recent information derived from numerous distributed literature and databases in a concise and easily accessible manner. Changes in gene expression and its products (proteins) are universally acknowledged to cause dysfunction in biochemical pathways related to blood pressure regulation, drug metabolism, and homeostasis, among other factors, resulting in hypertension [14].

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Role of deleterious nsSNPs of klotho protein and their drug response: a computational mechanical insights

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Communicated by Ramaswamy H. Sarma

ABSTRACT

Worldwide, the burden of chronic kidney disease (CKD) has increased rapidly and is a lethal disease. The klotho protein plays a vital role in the regulatory mechanism in the progression of CKD. Particularly the decreased expression of klothoand its genetic variations might affect the potency of drugs. This study aims to identify a new drug molecule, which works equipotential in all types of klotholike wild and mutant variants. All non-synonymous SNPs were predicted by several SNP tools. Where, two missense variants were examined as vulnerable, significantly damaging, and also involved in the structural conformational changes of the protein. Based on structure-based screening, E-pharmacophore screening, binding mode analysis, binding free energy analysis, QM/MM, and molecular dynamics analysis a lead compound (Lifechemical_F2493-2038) was identified as an effective agonistic molecule hence the identified Lifechemical_F2493-2038 compound is well bound to the wild and mutant proteins which found to increase the expression of klotho.

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CKD; klotho; nsSNPs; virtual screening; QM/MM and molecular dynamics

Introduction

Chronic kidney disease (CKD) is a progressive non-communicable disease that irreversibly modifies the structure and function of the kidney during a period (Bikbov et al., 2020). The CKD prevalence has risen significantly in recent decades as a result of the world's aging population and the increasing frequency of hypertension, diabetes, and vitamin D deficiency, which are major risk factors for CKD (Buchanan et al., 2020). The gradual deterioration of the kidneys results in an increase in the number of systemic consequences, including osteoporosis, hyperphosphatemia, mineral-bone disorders, hypocalcemia, and cardiovascular diseases (Kooman et al., 2014). Over the last three decades, several studies on animals and humans have been carried out to discover risk factors and the pathophysiological process of CKD (Zou et al., 2018). The onset and progression of CKD are strongly related to a decrease in Klotho (KL) gene expression, which was originally classified as an anti-aging gene (Hu et al., 2011, 2013). The Klotho was first identified in 1997, it is mainly expressed in the kidneyand brain tissues (Kalaitzidis et al., 2016). The major function of Klotho enzymatic activity is to alter the transient receptor potential V5 on the renal tubules (Xu & Sun, 2015). Klotho'sglucuronidase-like activity regulates the sugar moieties, resulting in the long-term retention of kidney calcium transporters. The normal circulating level of klotho prevents calcinuriaby promoting calcium re-absorption (Nabeshima & Imura, 2008). Besides its suppression of Vitamin D metabolism through FGF-23, KL also has a calcium-retention effect in the kidneys that prevents vitamin D over-activation (Tsujikawa et al., 2003). Klotho has recently been found to affectthe sodium phosphate channel (NaPt2a), the primary transporter of phosphate in the kidney's proximal tubule as well as its involvement in calcium metabolism in the kidney (Hu et al., 2010). In CKD patients, the progression in the last stagedue tothe decreased expression of KL protein levels (Vervloet & Larsson, 2011). Clinical research in CKD patients has revealed that klotho levels in renal patients were lower than normal (519 ± 183 versus 845 ± 330 pg/mL, $p < .0001$), and that which could be significantly associated with serum calcium and inversely associated with FGF23, PTH and serum phosphate which could be a biomarker of CKD (Rotondi et al., 2015). The increased level of FGF23 leads to a low level of klotho expression. The VDR and CYP24A1 control the expression of klotho and vitamin D. The progressive decline of klotho leads to vitamin D deficiency which leads to the progression of CKD. Single-nucleotide polymorphisms (SNPs) are variations in the sequence of one base of DNA that is found in a substantial proportion of the population (Nelson et al., 2004). SNPs in the Klotho gene have significantly correlated with CKD, aging, Mineral bone disorder, and hypertension (Cambray et al., 2020; Kawano et al., 2002; Momeni-Moghaddam et al., 2019; Pereira et al., 2020). Single Nucleotide Polymorphisms (SNPs) change the structural stability and function of the protein, making it prone to pathogenicity and playing an important role in changing drug affinity and specificity to the protein target (Brown et al., 2017). However, new therapeutic molecules are needed to be addressed, to increase the expressions of KL protein.

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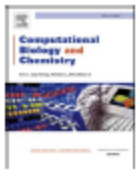

Multilayer precision-based screening of potential inhibitors targeting *Mycobacterium tuberculosis* acetate kinase using *in silico* approaches

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ABSTRACT

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (MTB), remains a major threat to global health, with the emergence of multi-drug and extensively drug-resistant strains posing a serious challenge. Thereby, understanding the molecular basis of MTB virulence and disease pathogenesis is critical for developing effective therapeutic strategies. Targeting proteins involved in central metabolism has been recognized as a promising therapeutic approach to combat MTB. In this regard, the enzyme AckA of the acetate metabolic pathway which produces acetate from acetyl phosphate, is an important drug target for various pathogenic organisms. Therefore, this study aimed to identify potential AckA inhibitors through *in silico* methods, including molecular modeling, molecular dynamics simulation (MDS), and high-throughput virtual screening (HTVS) followed by ADMETox, MMGBSA, Density Functional Theory (DFT) calculations. HTVS of one million compounds from the ZINC database against AckA resulted in the top five hits (ZINC82048449, ZINC1219737510, ZINC1771921358, ZINC119699567, and ZINC1427100376) with better binding affinity and optimal binding free energy. MDS studies on complexes revealed that key residues, Asn195, Asp266, Phe267, Gly314, and Asn318 played a significant role in stable interactions of the top-ranked compounds to AckA. These outcomes provide insights into the optimal binding of the leads to inhibit the acetate pathway and aid in the rational design of novel therapeutic agents. Thus, the identified leads may act as promising compounds for targeting AckA and may serve as a potential therapeutic modality for treating TB. Our findings offer valuable insights into the inhibition of the acetate pathway, while also serving as a blueprint for rational drug design. The identified leads hold promise as compelling compounds for targeting AckA, thereby offering a potential therapeutic avenue for tackling TB. Thus, our study uncovers a pathway toward promising TB therapeutics by elucidating AckA inhibitors. By leveraging *in silico* methodologies, potent compounds that hold the potential to thwart AckA's role in MTB's acetate pathway have been unveiled. This breakthrough fosters optimism in the quest for novel and effective TB treatments, addressing a global health challenge with renewed vigor.

1. Introduction

Tuberculosis (TB) is a contagious infection that usually infects the lungs, which is a leading cause of morbidity and mortality, with a death rate of 1.4 million per year, despite the use of various vaccines worldwide (Bouzeyen and Javid, 2022). It is caused by *Mycobacterium tuberculosis*, the bacterium which belongs to the family *Mycobacteriaceae*. It is estimated that half a million new multi-drug resistant TB cases have been reported in the past seven years. The spread of tuberculosis is exacerbated due to the development of drug resistance and enhanced susceptibility of HIV-infected individuals. Approximately 10% of tuberculosis-infected individuals develop illness, indicating that the innate immune system is affected in most cases (Burgos and Pym, 2002; Raj et al., 2017). *M. tuberculosis* is developing intrinsic resistance mechanisms to various antibiotics, leading to a decrease in the level of drugs for treatment. The most common *M. tuberculosis* strains such as H37Rv, Erdman, and CDC1551. Among these, H37Rv is a common laboratory strain and has retained its virulence, which was originally derived as a clinical isolate H37 from a patient (Firmani and Riley, 2002; Heinrichs et al., 2018). Current scientific investigations have resulted in,

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ORIGINAL ARTICLE

In silico prediction, molecular modeling, and dynamics studies on the targeted next-generation sequencing identified genes underlying congenital heart disease in Down syndrome patients

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ABSTRACT

Background : **Individuals with Down syndrome (DS) have a 40%–60% chance of being born with congenital heart disease (CHD). This indicates that CHD in individuals with DS is not solely caused by trisomy 21, and there may be other genetic factors contributing to the development of CHD in these children. A study has identified variants in the specific genes that contribute to the pathogenesis of CHD in children with DS, isolated DS, and the CHD group. Computational studies on these identified variants, which, together with trisomy 21, determine the risk for CHD in DS cases, were limited. Here, we aimed to identify the impact of the identified variants that contribute to the pathogenesis of CHD in children with DS through in silico prediction, molecular modeling, and dynamics studies.**

Methodology and Results : **The target single-nucleotide polymorphisms included in the study were examined for pathogenicity, residue conservation, and protein structural changes. The structural predictions were done using I-TASSER, Robetta, SWISS-MODEL, and Phyre2 tools. Further, the predicted models were validated through the PROCHECK server and molecular dynamics simulation using GROMACS software. The conservation analysis conducted on the identified variant highlights its significance in relation to the genetic disorders. Furthermore, a dynamics simulation study revealed the impact of the variant on protein structural stability (≤3 Å), providing valuable insights into its pathogenicity. We have also observed that the structure of the centrosomal protein of 290 kDa gene is relatively unstable, which may be attributed to its exclusive inclusion of helices within its secondary structural components.**

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Article

Impact of Surface Charge-Tailored Gold Nanorods for Selective Targeting of Mitochondria in Breast Cancer Cells Using Photodynamic Therapy

Nadar Manimaran Vinita, Umapathy Devan, Sabapathi Durgadevi, Selvaraj Anitha, Muthusamy Govarthanan, Arockiam Antony Joseph Velanganni, Jeyaraman Jeyakanthan, Pitchan Arul Prakash, Mohamed Sultan Mohamed Jaabir, and Ponnuchamy Kumar*

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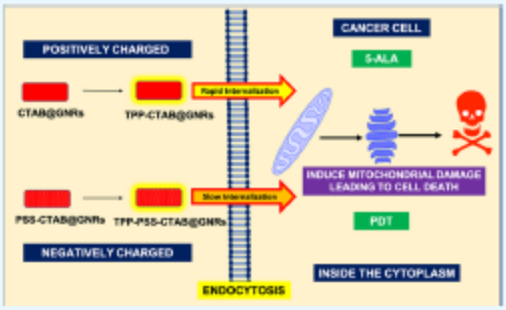
ABSTRACT: Herein, the impact of surface charge tailored of gold nanorods (GNRs) on breast cancer cells (MCF-7 and MDA-MB-231) upon conjugation with triphenylphosphonium (TPP) for improved photodynamic therapy (PDT) targeting mitochondria was studied. The salient features of the study are as follows: (i) positive (CTAB@GNRs) and negative (PSS-CTAB@GNRs) surface-charged gold nanorods were developed and characterized; (ii) the mitochondrial targeting efficiency of gold nanorods was improved by conjugating TPP molecules; (iii) the conjugated nanoprobes (TPP-CTAB@GNRs and TPP-PSS-CTAB@GNRs) were evaluated for PDT in the presence of photosensitizer (PS), 5-aminolevulinic acid (5-ALA) in breast cancer cells; (iv) both nanoprobes (TPP-CTAB@GNRs and TPP-PSS-CTAB@GNRs) induce apoptosis, damage DNA, generate reactive oxygen species, and decrease mitochondrial membrane potential upon 5-ALA-based PDT; and (v) 5-ALA-PDT of two nanoprobes (TPP-CTAB@GNRs and TPP-PSS-CTAB@GNRs) impact cell signaling (PI3K/AKT) pathway by upregulating proapoptotic genes and proteins. Based on the results, we confirm that the positively charged (rapid) nanoprobes are more advantageous than their negatively (slow) charged nanoprobes. However, depending on the kind and degree of cancer, both nanoprobes can serve as efficient agents for delivering anticancer therapy.



1. INTRODUCTION

On a nanoscale, gold is a versatile metal well studied for its tunable optical properties with various applications ranging from catalysis,[1] biology,[2] nonlinear optics,[3] electronics,[4] and unimaginable domains in the technology field and medicine.[5] Over the past decades, remarkable progress has been accomplished by using gold nanoparticles (GNPs).[6,7]

For example, gold nanoparticles as small molecules and drug conjugates enhance targeting with adequate release kinetics.[8−11] Moreover, the mounting evidence of nanoparticle size and surface charge determines their innate behavior in a biological system and intracellular fate.[12−15] For instance, the ability of hybrid gold nanoparticles with modified shapes to deliver doxorubicin is remarkable.[16−18] In this aspect, elongated (nanorods) and spiky (nanoprisms) gold nanoparticles are mostly appropriate for biomedical applications.[19−22]

In this journey, gold nanorods (GNRs) exert localized surface plasmon resonance (LSPR) with two absorption bands.[23,24] The most convenient method is the use of hexadecyltrimethylammonium bromide (CTAB) as a template for the growth of GNRs. Being a toxic agent, CTAB can be modified with derivatives or macromolecules that can be taken for improved biomedical applications.[25,26] Leonov et al. achieved biocompatible GNRs by detoxification with polystyrene, an anionic polyelectrolyte, for long-term stability in physiological conditions.[27]

Mirza and Shamshad fabricated doxorubicin-functionalized PSS-coated GNRs to resist CTAB.[28] In addition, Du et al. reported the highly efficient poly(ethylene glycol)-capped GNRs for photothermal ablation (PTA) of hepatocellular carcinoma.[29] Also, a plethora of reports is available on the surface modification of GNRs for improved drug delivery applications.[30−32]

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Differential gene expression analysis combined with molecular dynamics simulation study to elucidate the novel potential biomarker involved in pulmonary TB

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ABSTRACT

Tuberculosis (TB) is a lethal multisystem disease that attacks the lungs' first line of defense. A substantial threat to public health and a primary cause of death is pulmonary TB. This study aimed to identify and investigate the probable differentially expressed genes (DEGs) primarily involved in Pulmonary TB. Accordingly, three independent gene expression data sets, numbered GSE139825, GSE139871, and GSE54992, were utilized for this purpose. The identified DEGs were used for bioinformatics-based analysis, including physical gene interaction, Gene Ontology (GO), network analysis and pathway studies using the Kyoto Encyclopedia of Genes and Genomes pathway (KEGG). The computational analysis predicted that TNFAIP6 is the significant DEG in the gene expression profiling of TB datasets. According to gene ontology analysis, TNFAIP6 is also essential in injury and inflammation. Further, TNFA1P6 is strongly linked to arsenic poisoning, evident from the results of NetworkAnalyst, a comprehensive and interactive platform for gene expression profiling *via* network visual analytics. As a result, the TNFAIP6 gene was ultimately chosen as a candidate DEG and subsequently employed for *in silico* structural characterization studies. The tertiary structure of TNFAIP6 was modelled using the ROBETTA server, followed by validation with SAVES and ProSA webserver. Additionally, structural dynamic studies, including molecular dynamics simulation (MDS) and essential dynamics analysis, including principal component (PC) based free energy landscape (FEL) analysis, was used for checking the stability of TNFAIP6 models. The dynamics result established the structural rigidity of modelled TNFAIP6 through RMSD, RMSF and RoG results. The FEL analysis revealed the restricted conformational flexibility of TNFAIP6 by displaying a single minimum energy basin in the contour plot. The comprehensive computational analysis established that TNFAIP6 could serve as a viable biomarker to assess the severity of pulmonary TB.

1. Introduction

Tuberculosis (TB) is a highly lethal disease caused by the bacterium *Mycobacterium tuberculosis* (MTB) and has become a public health threat by impacting 10.6 million individuals globally in 2021 [1]. Pulmonary TB affects people of all ages and from all nations. Further, MTB strains such as drug-resistant TB (DR-TB), multidrug-resistant TB (MDR TB), extensively drug-resistant TB (XDR TB), and now totally drug-resistant-TB (TDR-TB) continue to be lethal and increase the morbidity rate in developing nations including India accounting for over 38% of all TB deaths worldwide recorded in a 2021 survey [2,3].

MTB secretes a small amount of DNA into macrophages, which is detected by the cytosol DNA sensor molecule c-GAS (Cyclic GMP-AMP (cGAMP) synthase) and causes the release of the type-I interferon (IFN) molecule. IFNs act as an antiviral mediator, but in bacteria, it acts

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Theoretical investigation on known renin inhibitors and generation of ligand-based pharmacophore models for hypertension treatment

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ABSTRACT

The renin enzyme is considered a promising target for hypertension and renal diseases. Over the last three decades, several experimental and theoretical studies have been engaged in the discovery of potent renin inhibitors. The identified inhibitors that undergo clinical trials are still failing to meet the criteria of potency and safety. To date, there is no specific FDA-approved drug for renin inhibition. Our theoretical opinion describes that the most potent compounds identified in experimental studies but lacking safety and overdose issues could be solved by finding similar molecules that are stable, very active, and have no side effects, which will kick start the drug discovery process. Here, we utilized the most potent direct renin inhibitors reported earlier, followed further by our theoretical study reported in 2019. Ligand-based virtual screening, density functional theory, and dynamic simulation studies were employed to explore the identified compounds and co-crystallized molecule in the protein structure. From the diverse databases, we have identified several identical molecules based on their structural features, such as functional groups like hydrophobic (H), aromatic rings (R), hydrogen bond acceptor (A), and donor (D). The HHHPR five-point pharmacophore feature was identified as a template pharmacophore to search the potential compounds from the Enamine and LifeChemical databases and have a good fitness score with known renin inhibitors. Furthermore, theoretical validation was done through several studies that confirmed the activity of the identified molecules. Overall, we propose that these compounds might break the failure in adverse events and improve the potency of hypertension treatment.

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KEYWORDS
Hypertension; ligand-based drug design; renin; molecular dynamics; pharmacophore; direct renin inhibitors

Introduction

Globally, cardiovascular disease has the highest mortality rate of any other cause in humans. The WHO has reported 1.28 billion adults in the range of 30–79 years of age have reported with hypertension in 2021 ('Hypertension Guidelines: 2021 USPSTF Recommendation, 2018 ESC/ESH, 2017 ACC/AHA, and the 2014 JNC8 guideline | Hypertension | JAMA Network,' n.d.). The percentage of adults with controlled hypertension is estimated to have only 21% (i.e. ~1 in 5 adults) (WHO, 2018). Hypertension is a multifactorial cardiovascular disease and it is a significant risk factor for renal damage, kidney disease, stroke, heart failure, and heart attack. In similar cases, hypertension has highly influenced the development of diabetes mellitus and chronic kidney disease. It has been found predominantly and has a higher risk among individuals with secondary complications. It leads to end-stage organ damage of vital organs, even death if left untreated (Blacher et al., 2016; Fang et al., 2018). The current treatment strategies include more than one class of drugs for known and novel targets that involve maintaining blood pressure. For chronic treatment of hypertension, Renin Angiotensin Aldosterone System (RAAS) pathway is considered the most significant pathway that involves not only hypertension but also other cardiovascular regulatory elements. RAAS, a multi-complex enzyme system, acts as a cornerstone for up-and-down regulation pressure and electro-fluid balance by controlling sodium and water homeostasis in the kidney (Engeli et al., 2000). Renin is the key first-line rate-limiting step of RAAS, produced and released into the bloodstream by juxtaglomerular cells of the kidneys (Kurtz et al., 1998; Weir, 2007). Renin synthesis is mediated by stimulants such as arterial BP, Na + balance, sympathetic nerves and prostaglandins activity (Weir, 2007). The aspartyl protease renin catalyzes the conversion of angiotensinogen to Ang I which is then converted to Ang II by ACE. Ang II exerts it effects by binding to AT1R and AT2R. AT1R promotes vasoconstriction and aldosterone synthesis thus increasing BP, whereas AT2R promotes vasodilation and release of nitric oxide (Paulis et al., 2015).

In RAAS pathway, renin is an attractive target as well as the primary option to control the blood pressure regulation (Scurrah et al., 2017). Hitherto, among RAAS inhibitors, direct renin inhibitors have not yet been found to be more potent and need a detailed review of their pharmacological action and structural property modification.

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RESEARCH ARTICLE

Unveiling the ESR1 Conformational Stability and Screening Potent Inhibitors for Breast Cancer Treatment

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Abstract: ***Background***: The current study recognizes the significance of estrogen receptor alpha (ERα) as a member of the nuclear receptor protein family, which holds a central role in the pathophysiology of breast cancer. ERα serves as a valuable prognostic marker, with its established relevance in predicting disease outcomes and treatment responses.

Methods: In this study, computational methods are utilized to search for suitable drug-like compounds that demonstrate analogous ligand binding kinetics to ERα.

Results: Docking-based simulation screened out the top 5 compounds - ZINC13377936, NCI35753, ZINC35465238, ZINC14726791, and NCI663569 against the targeted protein. Further, their dynamics studies reveal that the compounds ZINC13377936 and NCI35753 exhibit the highest binding stability and affinity.

Conclusion: Anticipating the competitive inhibition of ERα protein expression in breast cancer, we envision that both ZINC13377936 and NCI35753 compounds hold substantial promise as potential therapeutic agents. These candidates warrant thorough consideration for rigorous *In vitro* and *In vivo* evaluations within the context of clinical trials. The findings from this current investigation carry significant implications for the advancement of future diagnostic and therapeutic approaches for breast cancer.

Keywords: Cancer, ESR1, Erα, virtual screening, docking based simulation, binding affinity, R programming.

1. INTRODUCTION

Breast Cancer, a heterogeneous disease at the molecular level, is the most well-known reason for women's mortality around the world. Numerous studies revealed that epigenetic alterations play a prominent role as an early and common mediator for multiple events causing cancer [1]. The significance of DNA methylation, an epigenetic change, in determining the carcinogenic potential, rate of progression, andoverall prognosis of numerous human malignancies has been highlighted by recent studies. Prominently, the turn of events and spread of breast cancer is firmly associated with the enrichment of DNA methylation seen at promoter regions of important tumor suppressor genes, like p16, ESR1, GSTP1, and PITX [2, 3].

The nuclear receptor protein family that controls and regulates most estrogen-responsive genes (ERG) includes estrogen receptor-a (ESR1). The onset of breast cancer is linked to any anomaly in its expression pattern. A poor prognosis is caused by the methylation of the ESR1 promoter in this specific malignancy [4]. According to a study by Andrew *et al*, differential DNA hypermethylation primarily affects estrogen-responsive enhancers rather than promoter

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Crystal structure of 1-(*E*)- [(5-bromo-2-hydroxybenzylidene amino) pyrrolidin-2-one]: Design, synthesis and computational evaluation of a novel racetam congener for epilepsy

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ABSTRACT

The present investigation illustrates the conceptualization, synthesis, crystallographic analysis, and computational assessment of a new racetam derivative with a pyrrolidone ring as the pharmacophore. The compound demonstrates drug-like characteristics similar to LEV, an approved anti-epileptic drug, indicating its potential for developing novel epilepsy drugs. Molecular docking and molecular dynamic simulations were used to evaluate the binding affinity between the compound and SV2A, a protein-ligand complex. The protein-ligand complex attained structural equilibrium in the final 50 nanoseconds of the 200 nanosecond molecular dynamics simulation. The analysis reveals that regions with higher flexibility are primarily located in the extramembrane regions of the protein. Intermolecular contact analysis reveals hydrogen bonding and hydrophobic interactions as the primary types of interactions. The Molecular Mechanics Poisson-Boltzmann Surface Area (MMPBSA) calculation highlights the energetic aspects of ligand binding and the participation of important residues in the binding pocket. Unique interactions like those involving bifurcated hydrogen bonding, and novel pi-anion interaction makes the study significant. Quantum chemical calculations for the compound (LIG) done using DFT corroborates the protein-ligand interactions on the basis of Molecular Electrostatic Potential (MEP) maps. The study establishes the structure-activity relationship (SAR) of the newly developed pyrrolidone-based compound, identifying it as a promising lead molecule for epilepsy treatment.

1. Introduction

Epilepsy is a prevalent and incapacitating chronic neurological condition with an annual incidence rate of 67.8 per 100,000 individuals [1]. Despite the effectiveness of currently available Anti-Epileptic Drugs (AEDs) in managing seizures, approximately one-third of individuals with epilepsy globally do not achieve full seizure control [2]. Over twenty anticonvulsant drugs have been identified for clinical use, each exhibiting diverse mechanisms of action [3]. These drugs, while managing seizures, often fall short in addressing associated conditions, urging the search for new anticonvulsants [2,4]. Therefore, it is becoming increasingly imperative to explore novel compounds with anticonvulsant properties for the management of epilepsy.

Racetams represent a category of AEDs that exhibit a shared chemical structure consisting of a pyrrolidone nucleus and are distinguished by their enhanced tolerability with reduced incidence of adverse neurotoxic effects [5]. Research conducted on the mechanism of their action reveals diverse pharmacological effects. Pyrrolidones have been the focus of scientific investigation and have garnered significant attention in the pharmaceutical field for over three decades. Piracetam, a pharmacological compound classified as a nootropic agent, represents the pioneering pyrrolidone derivative that was introduced into clinical application during the 1970s. Since then, approximately 1600 pyrrolidones have been synthesized, with over 300 of them undergoing preclinical studies [6,7]. Among these, a dozen compounds, including levetiracetam and piracetam, have been granted licenses for advanced

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Computational approach on *Moringa oleifera* as an inhibitor against SARS-CoV-2 structural proteins

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The lethal pandemic has been brought on by the emergence of the SARS-CoV-2. The moringa leaves have a rich nutritional value in the host immunity and act as an immune booster against SARS-CoV-2. Tea was formulated from the moringa leaves, and dried at ambient temperature for serving health benefits. The results provide evidence that the application of heat on moringa leaves improves the flavor and quality of tea without degrading the nature of phenolic and flavonoid compounds present in moringa leaves. The molecular docking result among the screened compounds from moringa leaves has a good docking score varying from -10.657 to -13.735 kcal/mol for the Main protein, while Spike glycoprotein has a docking score ranging from -8.559 to -10.522 kcal/mol and Membrane protein docking score from -7.208 to -10.411 kcal/mol. The atomic configuration and electron profile of the docked complex were subjected to the DFT calculations. The molecular dynamics simulation study shows that the selected compounds have maintained stable conformation in the simulation period and interact with the target. Thus, we conclude that *Moringa oleifera* leaves compounds to support the antagonist activity against SARS-CoV-2's structural proteins and the leaf-based product could be a good immune booster for SARS-CoV-2 infection.

Keywords: Coronavirus, Immune booster, Molecular docking, Moringa Tea, Phytochemicals

Moringa oleifera Lam. a miracle tree is cultivated in subtropical and tropical regions, potential for its nutritional and medicinal properties. The bark, leaves, seeds and roots of moringa are rich in minerals, carbohydrate, protein, fats, fiber, and also contain significant amounts of iron, calcium, vitamins such as A, B and C, hence all the part of the plant is used for food, medication and industrial purposes[1,2]. The moringa leaves also attributes with several Phytochemicals such as carotenoids, flavonoids, saponins, steroids, tannins, terpenoids, alkaloids, anthocyanin, anthraquinone, cardiac glycosides etc., which are potent to possess antioxidants, antimicrobial, antifungal, antiviral activity antihypertensive, antitumor, anticancer, antihyperlipidemic, antipyretic, and anti-inflammatory properties[3,4]. The nutrients and phytochemicals present in the leaves play an important role in activating enzymes and hormones that enhance the growth, function, and maintenance of life process in both human and animals[1,5].

The moringa leaves act as a valuable food for the malnutrition children, pregnant and lactating women. The leaves are generally consumed in the form of vegetable curry, soup or seasoning by both rural and urban population, due to the health awareness about moringa, alongside value added products (noodles, bread, Chutney, biscuits, cakes and porridge)[6-9]. The leaves can be consumed as fresh or after boiling or it can be dried and used in the form of powder for culinary purpose[10]. Due to the presence of phenol and flavonoids in the leaves, the research is focused on development of moringa leaves extract as beverage like tea or soup. The Phytochemicals in tea act as free radical scavenger and induce the human immunity that manages the blood pressure, glucose level and serve as an energy booster[11]. Hence, tea was formulated as a value-added product of moringa leaves, which can be prepared and consumed by people of all economic classes, particularly those in rural areas of India. This tea will energize their life better with the locally available moringa leaves. The

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Harnessing allosteric inhibition: prioritizing LIMK2 inhibitors for targeted cancer therapy through pharmacophore-based virtual screening and essential molecular dynamics

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ABSTRACT

The therapeutic potential of small molecule kinase inhibitors in cancer treatment is well recognized. However, achieving selectivity remains a formidable challenge, primarily due to the structural similarity of ATP binding pockets among kinases. Allosteric inhibition, which involves targeting binding pockets beyond the ATP-binding site, provides a promising alternative to overcome this challenge. In this study, a meticulous approach was implemented to prioritize type 3 inhibitors for LIMK2, employing a range of techniques including Molecular Dynamics (MD) simulations, e-pharmacophore-guided High Throughput Virtual Screening (HTVS), MM/GBSA and ADMETox analyses, Density Functional Theory (DFT) calculations, and MM/PBSA investigations. The e-pharmacophore model identifies a hypothesis featuring five essential pharmacophoric elements (RRRAH). Through virtual screening of the ZINC compound database, we identified only five compounds that align with all four pharmacophoric features: ZINC1044382792, ZINC1433610865, ZINC1044109145, ZINC952869440, and ZINC490621334. These compounds not only exhibit higher binding affinity but also demonstrate favorable ADME/Tox profiles. Molecular dynamics simulations underscore the stability of hydrogen bond interactions with critical cryptic LIMK2 pocket residues, Asp469 and Arg474, only for two compounds: ZINC143361086 and ZINC1044382792. These compounds also exhibit superior occupancy interactions, as indicated by HOMO-LUMO analysis. Additionally, binding free energy calculations highlight the significant affinities of these two compounds when complexed with LIMK2: −83.491 ± 1.230 kJ/mol and −90.122 ± 1.248 kJ/mol for ZINC1044382792 and ZINC1433610862, respectively. Hence, this comprehensive investigation identifies ZINC1433610862 and ZINC1044382792 as prospective hits, representing promising leads for targeting LIMK2 in cancer therapeutics.

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LIMK2; Type 3 inhibitor; pharmacophore screening; molecular dynamics simulation

Introduction

LIM kinases (LIMKs) are the essential regulators for the cell cytoskeleton, which plays a major role in the development of various neurological disorders and also in the progression and spread of cancer. There are two homologs in the family of LIMK, including LIMK1 and LIMK2. Both are distinguishable in terms of expression profile, function, and intracellular localization. The core substrate of the LIMK is cofilin, which is a member of a family of actin-depolymerizing factor (ADF) proteins. The regulation of the actin cytoskeleton is carried out by LIM-kinases, which achieves this by phosphorylating cofilin at Ser3, as well as the substrates for Cdc42/Rac-PAK (Morales-Quinones et al., 2020; Sumi et al., 1999). This phosphorylation hinders the activity of cofilin, resulting in reduced depolymerization of actin filaments and thereby stabilizing it. LIM-kinase plays a role in a signal transduction pathway that facilitates the transmission of environmental signals *via* small GTPases of the Rho family through a protein kinase cascade (Maekawa et al., 1999). This pathway plays a crucial role in governing actin cytoskeleton responses, including cell movement, establishing the intracellular cytoplasmic organization, cell polarity, and various other functions that are vital for maintaining cellular homeostasis and ensuring survival. The regulation of cell progression can be influenced by the translocation of LIMKs into the nucleus. LIMKs possess a distinct feature, making them promising candidates for therapeutic targeting in tumors that lack merlin, like NF2.

The LIM kinases are involved in various cellular functions and also over-expressed in various types of cancers, however, the mechanism remains unclear. Recent studies have discovered that LIMK modulates the activity of the development of cancer, including cell proliferation, survival, and viability. The LIM domains exhibit auto-inhibition of the kinase domain of the proteins, which become activated *via* phosphorylation. Although LIMK1 is linked to the spread of cancer, LIMK2 activation facilitates advancement through the cell cycle. LIM

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pH-Dependent conformational stability of SpeB from *Thermus thermophilus* HB8: insights from molecular dynamics simulation

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ABSTRACT

N(1)-aminopropyl agmatine ureohydrolase (SpeB) is considered an essential enzyme for the growth and survival of thermophiles, it is involved in the biosynthesis of polyamines. The present study investigates the conformational stability and flexibility of *Thermus thermophilus* HB8 SpeB and its interactions with substrate, N1-aminopropyl agmatine at different physiological conditions to probe the optimal conditions that provide insights on biotechnological applications. As the 3D structure of SpeB is yet to be crystallized, it was modelled and validated using structural bioinformatics methods. To understand the conformational dynamics and also to assess the impact of pH and temperature variables on the tertiary structure of SpeB , atomistic molecular dynamics simulation (MDS) was employed. The MD investigation revealed that 300 K is not optimal for SpeB (*apo* form) at both acidic pH 4.5, and alkaline pH 8.5, since it exhibited decreased stability and compactness with higher residual flexibility. Further, the stable and strong binding of N1-aminopropyl agmatine with SpeB was observed at following conditions, neutral pH 7 at 353.15 K and alkaline pH 11 at 300 K. Thus, this *in silico* study provides significant insights into the structural investigations on SpeB along with optimal pH as well as temperature for its ideal enzymatic function.

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KEYWORDS
SpeB; *Thermus thermophilus*; thermostability; molecular dynamics simulation; molecular docking

Highlights

- Structural and dynamic characteristics of *T. thermophilus* SpeB have been explored in detail
- Comparative Molecular dynamics simulations were performed to evaluate the effects of both pH and temperature on the structural stability of SpeB
- SpeB showed pH and temperature-dependent conformational changes that potentially affect substrate binding
- Structural stability of *apo* form of SpeB is not optimal at high temperature (363.15 K) in both acidic (pH 5.5) and neutral pH
- Stable and strong binding affinity of substrate molecule was observed in a neutral pH 7 at 353 K and alkaline pH 11 at 300K

1. Introduction

Polyamines are polycationic compounds that are most abundant in all organisms and are essential for numerous biological functions, including transcription, RNA modification, protein synthesis, and modulation of enzyme activities [1]. Moreover, polyamines are critical for both cell differentiation and proliferation . The roles of polyamines can be divided into two categories; (1) to maintain cell viability [2] and (2) to stimulate cell growth [3]. In cells and tissues, common polyamines such as putrescine, spermidine, and spermine are found in relatively high concentrations [4]. The polyamine content of cells is elaborately regulated by biosynthesis, degradation, uptake, and excretion [5,6].

A variety of unusual polyamines, including those that are extraordinarily long and branching [7], are produced by the extreme thermophile *Thermus thermophilus*, and its whole genome sequences of the strains HB8 and HB27 are currently available [8]. These unusual long and branched polyamines protect and stabilise nucleic acids (both single and double-stranded) [9,10] and activate cell-free polypeptide synthesis at high temperatures [11,12]. In the typical biosynthetic pathway of polyamines, the enzyme ornithine decarboxylase can produce the putrescine directly from ornithine. An additional or alternative pathway is also present in plants and most bacteria to produce putrescine from arginine [13–15]. The enzyme arginine decarboxylase converts arginine to agmatine, which is further converted to putrescine either immediately by agmatine ureohydrolase or sequentially by agmatine deiminase and N-carbamoyl putrescine amidohydrolase. The enzymes spermidine synthase (SPDS) and spermine synthase (SPMS) convert putrescine and spermidine into spermidine and spermine, respectively, by adding an aminopropyl group from decarboxylated S-adenosylmethionine (dcSAM) [16]. The research conducted by Ohnuma *et al.*, [17] hypothesised that

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A novel search engine for proteins involved in Notch crosstalk signaling pathways

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To regulate biological activity in humans, the Notch signaling pathway (NSP) plays an essential role in a wide array of cellular development and differentiation process. In recent years, many studies have reported that aberrant activation of Notch is associated with the tumor process; but no appropriate database exists to fill this significant gap. To address this, we created a pioneering database NCSp, which is open access and comprises intercommunicating pathways and related protein mutations. This allows scientists to understand better the cause of single amino acid mutations in proteins. Therefore, NCSp provides information on the predicted functional effect of human protein mutations, which aids in understanding the importance of mutations linked to the Notch crosstalk signaling pathways in cancerous and non-cancerous systems. This database might be helpful for therapeutic mutation analysis, molecular biology, and structural biology researchers. The NCSp database can be accessed through *https://bioserver3.physics.iisc.ac.in/cgi-bin/ncspd/*.

Keywords. Cancer; crosstalk pathway; database; mutations effect; Notch signalling; pathways; proteins

Abbreviations: AKT1, RAC-alpha serine/threonine-protein kinase; AMPK, adenosine monophosphate-activated protein kinase; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; ErbB-2, epidermal growth factor receptor-2; GLI2, GLI-Kruppel family member GLI2; Hh, hedgehog; IKK, IkappaB kinase; JAK-STAT, janus kinases - signal transducer and activator of transcription proteins; KEGG, Kyoto Encyclopedia of Genes and Genomes; KRAS, GTPase KRas; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NCSp, Notch crosstalk signaling pathway; NF-κB, nuclear transcriptional factor kappa B; NFAT, nuclear factors of activated T-cells; NICD, Notch intracellular domain; NSP, Notch signaling pathway; PI3K, phosphatidylinositol-3-kinase; P53, phosphoprotein 53; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor-alpha; TCR, T cell receptor; VEGF, vascular endothelial growth factor.

1. Introduction

The Notch signaling pathway is evolutionarily conserved in eukaryotic organisms and plays a significant role in cell differentiation, survival, and proliferation (Brzozowa-Zasada *et al.* 2016). In mammals, there are four types of Notch receptors (Notch 1–4) and five significant ligands that include delta-like ligands (DLL 1, 3, and 4) and jagged (JAG 1 and 2). These ligands can be classified further into several derivatives based on their domain composition. Moreover, all the receptors and ligands are large single-pass type 1 transmembrane proteins with extracellular domains that consist of multiple epidermal growth factors (EGF)-like repeats (Li *et al.* 2017). The Notch signaling system is crucial in the development of invertebrates and

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ORIGINAL PAPER

Exploring *Nocardia's* ecological spectrum and novel therapeutic frontiers through whole-genome sequencing: unraveling drug resistance and virulence factors

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Abstract

Nocardia farcinica is the leading pathogen responsible for nocardiosis, a life-threatening infection primarily affecting immunocompromised patients. In this study, the genomic sequence of a clinically isolated *N. farcinica* sample was sequenced. Subsequently, the assembled genome was annotated to identify antimicrobial resistance and virulence genes, as well as plasmid and prophages. The analysis of the entire genome size was 6,021,225 bp, with a GC content of 70.78% and consists of 103 contigs and N50 values of 292,531 bp. The genome analysis revealed the presence of several antimicrobial resistance genes, including RbpA, mtrA, FAR-1, blaFAR-1, blaFAR-1_1, and rox. In addition, virulence genes such as relA, icl, and mbtH were also detected. The present study signifies that *N. farcinica* genome is pivotal for the understanding of antimicrobial resistance and virulence genes is crucial for comprehending resistance mechanism, and developing effective strategies to combat bacterial infections effectively, especially adhesins and toxins. This study aids in identifying crucial drug targets for combating multidrug-resistant *N. farcinica* in the future.

Keywords *Nocardia farcinica* · DNA sequencing · Antimicrobial resistance gene · Drug resistance and virulence gene

Introduction

Antibiotic resistance is a global healthcare concern, and *Nocardia farcinica* poses a significant threat due to its inherent resistance to multiple antibiotics. The genus of *Nocardia* belongs to the actinomycetes, a group of aerobic bacilli that are found commonly in soil and water (Mehta and Shamoo 2020; Conville et al. 2017). Although, there are more than 80 species in *Nocardia*, approximately 54 species notably *N. nova* complex, *N. abscessus* complex, *N. transvalensis* complex, *N. farcinica*, *N. asteroides* type VI (*N. cyriacigeorgica*), *N. brevicatena*/*N. paucivorans* complex, and *N. brasiliensis* are pathogenic to humans (Duggal and Chugh 2020). In *Nocardia*, the pathogenesis mechanism is not completely understood (Ji et al. 2020). *Nocardia* species are regarded in the aerobic actinomycete group and virulence in *Nocardia* has been ascribed to its ability to survive and grow in various human cells and evade the immune response by producing antioxidant enzymes (catalase/superoxide dismutase (SOD)), inhibiting formation phagolysosome complex, reducing levels of phosphomonoesterases II in tissue macrophages, secreting toxins and hemolysin (in few cases) (Mehta and Shamoo 2020; Conville et al. 2017). Since the disease is difficult to diagnose and can be left untreated, it can spread to other organs of the body, including the spine and brain (Kövér et al. 2023). Nocardiosis of the brain or spinal cord leads to mortality for more than 85% of them (https://www.cdc.gov/nocardiosis/infection/index.html). Nocardiosis infections can spread through injuries to the subcutaneous tissue. It may result in closely related cellulitis, pyoderma, abscess formation, and *Staphylococcal* or *Streptococcal* infections. However, disseminating the

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Novel scaffolds identification against Mpro of SARS-CoV-2 using shape based screening and molecular simulation methods

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Computational insights into potential marine natural products as selective inhibitors of *Mycobacterium tuberculosis* InhA: A structure-based virtual screening study

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ABSTRACT

Several factors are associated with the emergence of drug resistance mechanisms, such as impermeable cell walls, gene mutations, and drug efflux systems. Consequently, bacteria acquire resistance, leading to a decrease in drug efficacy. A new and innovative strategy is required to combat drug resistance in tuberculosis (TB) effectively. Therefore, targeting the mycolic acid biosynthesis pathway, which is involved in synthesising mycolic acids (MAs), essential structural components responsible for mycobacterial pathogenicity, has garnered interest in TB research and the concept of drug resistance. In this context, InhA, which plays a crucial role in the fatty acid synthase-II (FAS-II) system of the MA biosynthetic pathway, was selected as a druggable target for screening investigation. To identify potential lead molecules against InhA, diverse marine natural products (MNPs) were collected from the comprehensive marine natural products database (CMNPD). Virtual screening studies aided in selecting potential lead molecules that best fit within the substrate-binding pocket (SBP) of InhA, forming crucial hydrogen bond interaction with the catalytic residue Tyr158. Three MNPs, CMNPD30814, CMNPD1702, and CMNPD27355, were chosen as prospective alternative molecules due to their favorable pharmacokinetic properties and lack of toxicity according to ProTox-II predictions. Additionally, improved reactivity of the MNPs was observed in the results of density functional theory (DFT) studies. Furthermore, comparative molecular dynamics simulation (MDS), principal component (PC)-based free energy landscape (FEL) analysis, and molecular mechanics Poisson-Boltzmann surface area (MM-PBSA) were employed to show enhanced structural stability, increased H-bond potential, and high binding affinity toward the target InhA. Moreover, the hot spot residues that contributed to the high binding energy profile and anchored the stability of the complexes were revealed with their individual interaction energy. The computational insights from this study provide potential avenues to combat TB through the multifaceted mode of action of these marine lead molecules, which can be further explored in future experimental investigations.

1. Introduction

Over the past few decades, tuberculosis (TB) has evolved into one of the deadliest infections worldwide, following the resurgence of the human immunodeficiency virus/AIDS, in comparison to other fatal diseases (Baker et al., 2022). As a result, it requires special attention for

Abbreviation: DSSP, Dictionary of Secondary Structure of Proteins; FEL, Free Energy Landscape; HOMO, Highest Occupied Molecular Orbital; HTVS, High-Throughput Virtual Screening; LUMO, Lowest Unoccupied Molecular Orbital; MDS, Molecular Dynamics Simulation; MMGBSA, Molecular Mechanics with Generalised Born and Surface Area Solvation; MMPBSA, Molecular Mechanics Poisson-Boltzmann Surface Area; MNP, Marine Natural Product; MTB, Mycobacterium tuberculosis; PCA, Principal Component Analysis; PDB, Protein Data Bank; RMSD, Root Mean Square Deviation; RMSF, Root Mean Square Fluctuation; RoG, Radius of Gyration; SBP, Substrate Binding Pocket; TB, Tuberculosis; TIP3P, Transferable intermolecular potential with 3 points; WHO, World health organization.

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