ECB 2025 Conference

The 3rd International Electronic Conference on Biomedicines

12-15 May 2025 | online

Bioinformatics Institute — BII

Tarbiat Modares University

MDPI

Unveiling Natural Inhibitors For ABCC1 (MRP1) Membrane Transporter Through Molecular Docking And Molecular Dynamics Simulations

•Roya Rahimivaghar [a,c], Seyed Shahriar Arab [a], Justin Tze-Yang Ng [c], Yaw Sing Tan [c]

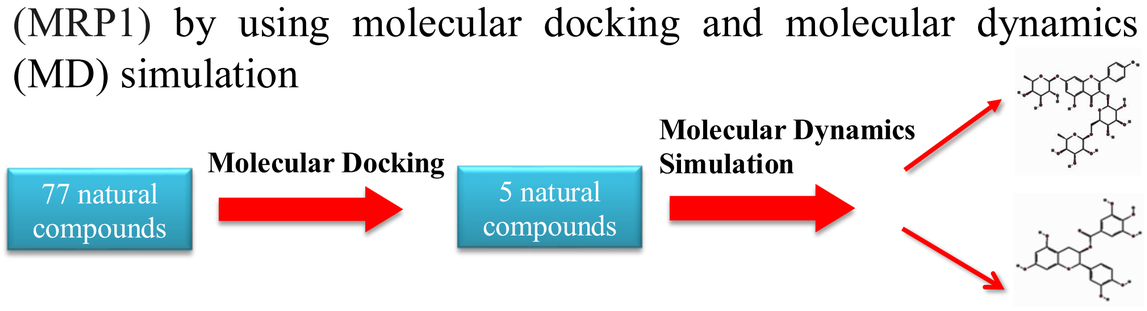
[a] Department of Biophysics, Faculty of Biological Sciences, Tarbiat Modares University, Tehran, Iran

•[c] Bioinformatics Institute, Agency for Science, Technology and Research (A*STAR), 30 Biopolis Street, #07-01 Matrix, Singapore 138671, Singapore

INTRODUCTION & AIM

ABC transporters are fascinating proteins responsible for transporting a variety of substrates by hydrolysis of ATP. Some ABC transporters are multidrug-resistant (MDR), commonly associated with human cancers and pathogenic microbes. Their ability to transport toxic substances and drugs across membranes, even against the concentration gradient, leads to a reduced concentration of drugs inside cells, which diminishes the drug's effectiveness. Natural compounds, such as polyphenols and flavonoids, have anticancer properties. By inhibiting ATP hydrolysis, they can potentially inhibit MDRs in cancer cells, reduce the activity of these proteins, and enhance the therapeutic effects of anticancer drugs.

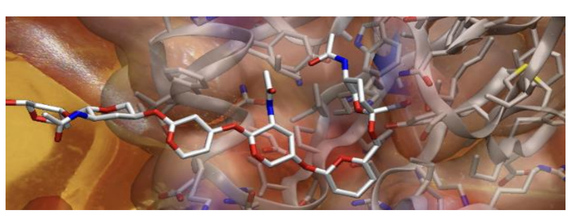
In this study, we investigate the inhibitory effects of 77 of these compounds on the nucleotide-binding domains (NBD) of ABCC1 (MRP1) by using molecular docking and molecular dynamics (MD) simulation

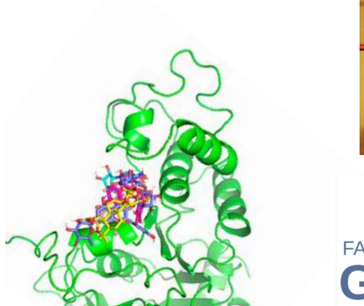


METHODS

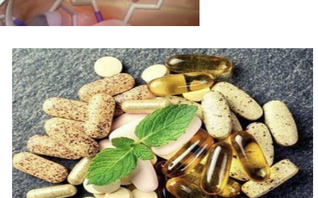
Molecular interactions between 4C3Z, 8F4B, and 77 experimentally validated natural compounds were evaluated utilizing the molecular docking applied to dock the ligands to the putative binding site of natural compounds (at NBDs of ABC transporters mediated MDR). We used the AutoDock Vina 4.2 algorithm to find the feasible protein-ligand interaction among 77 selected natural compounds from the literature with anti-cancer properties.

Simulations were performed using the GROMACS 2020-2 package . The AMBER-99SB force field was applied to conduct MD simulations of all complexes. Topology parameters of all compounds were generated using the cgenff server. Minimization energy was performed with the steepest descent for 0.01 ns; minimization was stopped when energy reached 10 kJ/mol. NVT and NPT ensembles were performed respectively to equilibrate the system for 1 ns each with dt 0.002 fs at 310 K and 1 atm using Verlet cut-off. Berendsen was used as a pressure coupling at the NPT ensemble. System conditions were regulated as isotropic, PME (Particle Mesh Ewald) was used for long-range electrostatic and v-rescale of modified Berensen thermostat were performed for temperature coupling MD production was performed for 300 ns under the same conditions. MD trajectory analysis is a comparison analysis to compare the stability and strength of protein-ligand complexes for proteins based on some topological parameters root-mean-square deviation (RMSD), and hydrogen bond (HB) formation.



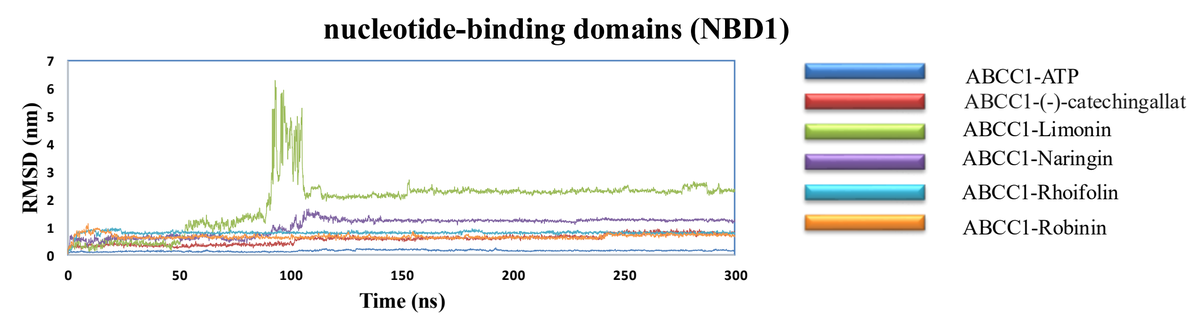


FAST. FLEXIBLE. FREE. GROMACS



RESULTS & DISCUSSION

The results indicate that five compounds, (-)-catechingallat, limonin, naringin, rhoifolin, and robinin with -7.8,-8.5, -8.3, -8.3 and -8.5 of binding affinity in NBD1 and -7.1, -7.9, -8.2, -7.9 and -7.7 in NBD2 respectively in comparison with ATP with -6.8 and -7.1 in NBD1 and NBD 2 respectively of binding affinity, had high binding affinities and occupied the same binding site, Asp793 and Tyr831 in NBD1 and Arg1445 in NBD2, with ATP. Molecular dynamics trajectory analysis of the NBDs and ligands revealed these domains were stable throughout 300ns MD simulations. The MD simulations confirm the stability of the complex formed by the interaction of two ligands, (-)-catechingallat and robinin, with both NBD, characterized by structural compactness and minimal to no fluctuations.



CONCLUSION

RMSD values remained stable for all interactions of NBDs except with limonin. However, interactions of (-)-catechingallat and robinin demonstrate greater stability compared to the protein-ATP interaction. H-bond analysis reveals that (-)-catechingallat and robinin forms more favorable electrostatic interactions than limonin, naringin, rhoifolin, with NBDs, evidenced by higher H-bond intensity. The binding pocket for flavonoids was studied, revealing that these natural products compete with ATP for the binding site within the NBD.

FUTURE WORK / REFERENCES

This in silico study offers key information for developing potential ATP inhibitors that NBDs could be the suitable binding site for the flavonoid family. The discovery of novel MDR-inhibiting compounds has the potential to make cancer treatment more effective for all types of cancers, making it a comprehensive solution to drug resistance.

1. Xiao, H., et al., *Clinically-relevant ABC transporter for anti-cancer drug resistance.* Frontiers in pharmacology, 2021. **12**: p. 648407.
2. Dehghani-Ghahnaviyeh, S., K. Kapoor, and E. Tajkhorshid, *Conformational changes in the nucleotide-binding domains of P-glycoprotein induced by ATP hydrolysis.* FEBS letters, 2021. **595**(6): p. 735-749.
3. Tinoush, B., I. Shirdel, and M. Wink, *Phytochemicals: potential lead molecules for MDR reversal.* Frontiers in pharmacology, 2020. **11**: p. 832.