VIRTUAL SCREENING AND MOLECULAR DYNAMICS SIMULATION OF PHYTOCHEMICALS AS POTENTIAL INHIBITORS OF EXTENDED-SPECTRUM BETA-LACTAMASES

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The Relevance and Aim of the Study

The global spread of extended-spectrum β-lactamases (ESBLs) Klebsiella pneumoniae, particularly the SHV-1 and SHV-2 variants, represents a critical challenge in the management of hospital-acquired infections [1]. Point mutations in ESBL enzymes expand the active site, thereby conferring resistance to third-generation cephalosporins and reducing the efficacy of classical β-lactamase inhibitors.

The purpose of the study is to investigate the potential of phytochemical core structures as alternative non-β-lactam inhibitors to counteract these resistance mechanisms. Some of them may have good potential for inhibiting β-lactamases and could be used in combination with antibiotics to treat bacterial infections (particularly those caused by bacteria that have developed resistance to cephalosporins).

Materials and methods of the virtual screening

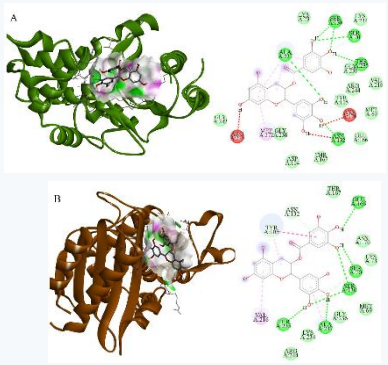

Fig. 1 3D and 2D representations of molecular interactions of EGCG with 1SHV (A) and 1N9B (B)

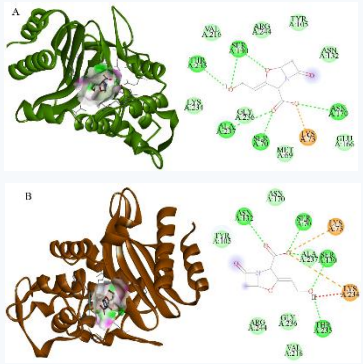

Fig. 2 3D and 2D representations of molecular interactions of Clavulanic acid with 1SHV (A) and 1N9B (B).

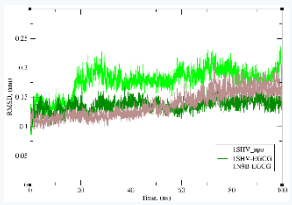

Fig. 3 GROMACS analysis of backbone RMSD As a function of time for β-lactamases: apo form (light green), wild-type β-lactamase–EGCG complex (dark green), and point-mutant β-lactamase–EGCG complex (brown) over 100 ns simulation

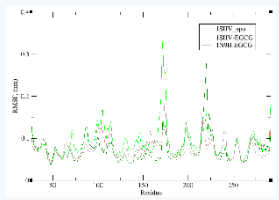

Fig. 4 GROMACS analysis of backbone RMSF of amino acid residues in β-lactamases: apo form (light green), wild -type β-lactamase–EGCG complex (dark green), and point-mutant β-lactamase–EGCG complex (brown) over 100 ns simulation

Research findings

Among the compounds investigated, Epigallocatechin gallate (EGCG) demonstrated the strongest binding affinities toward both protein variants across both docking platforms. EGCG exhibited binding energies of -8.0 kcal/mol for the wild-type enzyme (1SHV) and -10.0 kcal/mol for the mutant (1N9B). CB-Dock2 produced comparable results of -7.7 kcal/mol (1SHV) and -8.8 kcal/mol (1N9B). Both docking methods consistently showed stronger binding to the Gly238Ser mutant compared to the wild-type structure.

Clavulanic acid was selected as a reference inhibitor of class A β-lactamases. The in-silico docking study demonstrated that clavulanic acid exhibited weaker predicted binding affinities in both docking approaches with binding energies of -6.1 kcal/mol for 1SHV and -7.2 kcal/mol for 1N9B, while CB-Dock2 yielded -6.6 kcal/mol and -6.3 kcal/mol, respectively. These less negative docking scores indicate lower predicted non-covalent affinity compared to the investigated flavonoids.

Conclusion

Pubchem CID	Name	MW, g/mol	LogP	HbD	HbA	Topological Polar Surface Area, Å^2	ΔG (AutoDock vina) (1SHV)	ΔG (AutoDock vina) (1N9B)
65064	EGCG (Epigallocatechin Gallate)	458.4	1.2	8	11	197	(-8.0)	(-10.0)
5280980	Clavulanic acid	199.16	-1.2	2	5	87.1	(-6.1)	(-7.2)

Molecular dynamics simulations revealed that EGCG exhibits stable binding and structural stability in complexes with both SHV-1 and SHV-2 β-lactamases. Our findings emphasize that integrating computational binding affinity data with dynamic stability analysis and structural insights is essential for predicting effective inhibitors of sulfhydryl variable β-lactamases that contribute to antibiotic resistance.

Bibliography

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[2] O. Trott, and A. J. Olson, Journal of computation chemistry. 31, 2 (2010). http://doi.org/10.1002/jcc.21334