Contents lists available at Curevita Journals

CUREVITA INNOVATION OF BIODATA INTELLIGENCE

Journal homepage: www.curevitajournals.com

In Silico Design and Molecular Docking of Esp C-terminal Domain Inhibitors in *Enterococcus faecalis*

Aastha Shrivastava[1], Usha Chouhan[2], Deedhiti Mistry[3] and Sonu Kurmi[4]

Article info

Article history: Received 2nd Sept 2025, Revised 18 Nov 2025, Accepted 4th Dec 2025, Published Dec 2025

Keywords: Computer-Aided Drug Design, *Enterococcus Faecalis,* Enterococcal Surface Protein, Molecular Docking, Biofilm Inhibition.

Authors: Dr Usha Chouhan, Prof., Department of Bioinformatics, Maulana Azad National Institute of Technology, Bhopal, Madhya Pradesh, India. **Email ID:** chouhanu@manit.ac.in

[1]Student, Amity Institute of Biotechnology, Amity University Chhattisgarh, Raipur, India.
[3]Research Scholar, Department of Mathematics, Bioinformatics and Computer Applications, MANIT Bhopal, Madhya Pradesh, India.
[4]Research Scholar, Department of Mathematics, Bioinformatics and Computer Applications, MANIT Bhopal, Madhya Pradesh, India.

Citation: Shrivastava Aastha, Chouhan Usha, Mistry Deedhiti.2025.In Silico Design and Molecular Docking of Esp C-terminal Domain Inhibitors in *Enterococcus faecalis.*Curevita Innovation of BioData Intelligence. 2,1,1-22.

Publisher: Curevita Research Pvt Ltd

Enterococcus faecalis, a gram-positive bacterium linked to hospital-acquired infections, exhibits strong biofilm formation mediated by the Enterococcus Surface Protein (Esp), contributing to its persistence and antibiotic resistance. This study computationally evaluated small-molecule inhibitors targeting the Esp C-terminal adhesion domain. The Esp structure was prepared using AutoDock Tools, and ligands were optimized via Open Babel and docked with AutoDock 4.2. Top hits were filtered with AutoDock Vina, and binding interactions were visualized using MGLTools. SwissADME analysis assessed physicochemical and pharmacokinetic profiles. Baicalein, curcumin, and pyridazinone displayed high binding affinity (up to −9.63 kcal/mol), with baicalein analogues achieving −10.1 kcal/mol. The lead compound demonstrated drug-like properties, indicating strong potential as a therapeutic candidate.

Abstract

Article Highlight:

What is already known:

- *Enterococcus Faecalis* is the major cause of hospital-acquired infection and is highly resistant to multiple antibiotics.
- Enterococcus Surface Protein (Esp) is a critical virulence factor that promotes adhesion and biofilm formation.
- In silico drug discovery method, which includes molecular docking and ADMET analysis, which are widely used to identify novel anti-virulence agents.

What this paper adds:

- Identification of potential small-molecule inhibitors of the C-terminal adhesion domain of Esp protein in *Enterococcus Faecalis*.
- It demonstrates that compounds like baicalein and zinc compound (ZINC21992165) derivatives exhibit strong binding affinities(up to -10.1 kcal/mol).
- ADMET and physicochemical profiles of lead candidates to confirm the favorable drug-like properties and high gastrointestinal absorption.

Introduction

Enterococci are a genus of gram-positive bacteria that are commensal organisms of the human gut but have emerged as a leading cause of hospital-acquired infections(HAIs) across the world, posing a significant public health threat (Schlech, 2019). They have a remarkable ability to develop resistance to multiple antibiotics and form robust biofilm, which makes treating enterococcal infection challenging (Koopmans et al., 2023). The intrinsic and acquired resistance mechanisms in enterococcus species, such as high-level resistance to vancomycin, have made them particularly difficult to manage(de Noordhout et al., 2014; Sabet et al., 2005). According to a systematic review and meta-analysis, the global burden of antimicrobial resistance in clinical *Enterococcus faecalis* is rapidly increasing, highlighting the

urgent need for new therapeutic strategies (Brogi, 2019)

The persistence and pathogenesis of enterococcal infections can form biofilm, which is are complex community of microorganisms encased in self-produced extracellular polymeric substances (EPS) matrix (Rogalla & Bomar, 2023; (Osek et al., 2022). Biofilm formation provides a protective barrier against the host immune response and antibiotics, which makes enterococcal infection difficult to eradicate (Personnic et al., 2010). Enterococcus surface protein(Esp) is a cell wall-anchored protein that has been identified as a crucial virulence factor that significantly enhances biofilm formation in both *Enterococcus faecalis* and *Enterococcus faecium (*Ortega et al., 2017). The Studies have shown that the presence of the esp gene correlates with increased biofilm production and the ability to cause disease.

The growing issue of antimicrobial resistance and the crucial role of biofilm in enterococcal pathogenesis has an urgent need to develop novel anti-virulence strategies that can disrupt these protective bacterial communities (Schlech, 2019) . Rather than focusing on the bacteriostatic and protective agents, which play a significant role in resistance development, an anti-virulence approach targets specific factors that contribute to a pathogen's ability to cause diseases, such as biofilm production. The Esp protein presents an ideal target to such an approach due to its central role in biofilm formation and its stability (Personnic et al., 2010). The protein has been shown to strengthen enterococcal biofilm, which makes them resilient to external stressors.

Molecular docking is a powerful tool in screening and identification of potential drug candidates that bind to the specific site of the target protein (Gedde et al., 2000). This method stimulates the interaction between small molecules and proteins, predicting their binding affinity and also their orientation (Lee et al., 2022, Gedde et al., 2000; Lee et al., 2022).

Various studies have investigated the anti-biofilm properties of compounds such as curcumin, caffeic acid phenyl ester (CAPE) against various bacteria, including *Enterococcus faecalis* (Kulkarni et al., 2025; Trott & Olson, 2010). Curcumin, a compound from turmeric, has shown antibacterial and anti-biofilm properties, while berberine, an alkaloid found in various plants, has been studied for its effect on metabolic diseases and its antimicrobial potential (Kulkarni et al., 2025). These natural compounds offer a promising starting point for identifying new anti-virulence agents.

In this *in silico* study, we aim to identify potential inhibitors of the Enterococcal surface protein (Esp) using molecular docking (Kumar Suryawanshi et al., 2022). Here, the utilisation of a combination of publicly available databases and bioinformatics tools is used to perform the virtual screening (Wong et al., 2022). This approach would allow us to identify and characterise novel small-molecule compound inhibitors of Esp, providing a new direction for combating the increasing threat of drug-resistant enterococcal infection.

Methodology

Protein and Ligand Structure from the Database

The 3D conformation of the C-terminal adhesion domain PDB ID: 6ORI, as mentioned in Figure 1, was downloaded from the Protein Data Bank in PDB format. The part of Esp was selected for its critical role in anchoring the protein to the bacterial surface, and in turn enables colonization and persistence.

A database of small-molecule ligands possessing antimicrobial or antibiofilm activity was gathered from both PubChem and Zinc databases as shown in Figure 2. The included compounds were curcumin, baicalein, luteolin, resveratrol, and berberine, synthetic drug-like molecules such as Fosfomycin and divinyl sulfone.

The ligand from the ZINC database was further added to boost the chemical diversity represented. First, all the ligands were downloaded in SDF file format and further converted into PDB file format using Open Babel. This process was done in order to allow compatibility within the process of docking process.

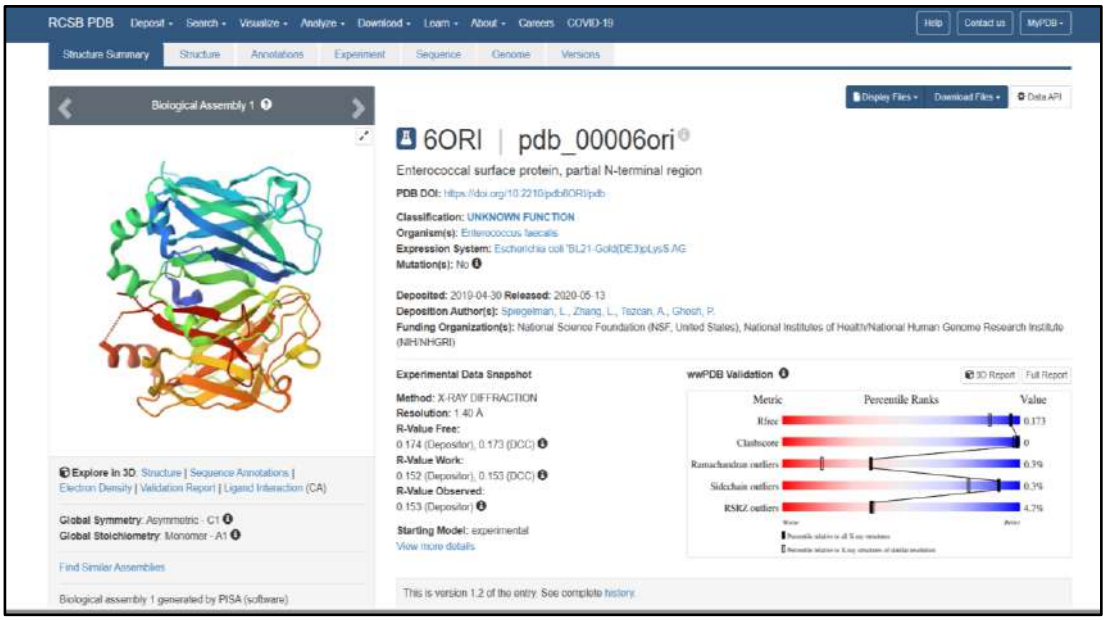

Figure 1 Structure retrieval of target protein using Protein Database (PDB)

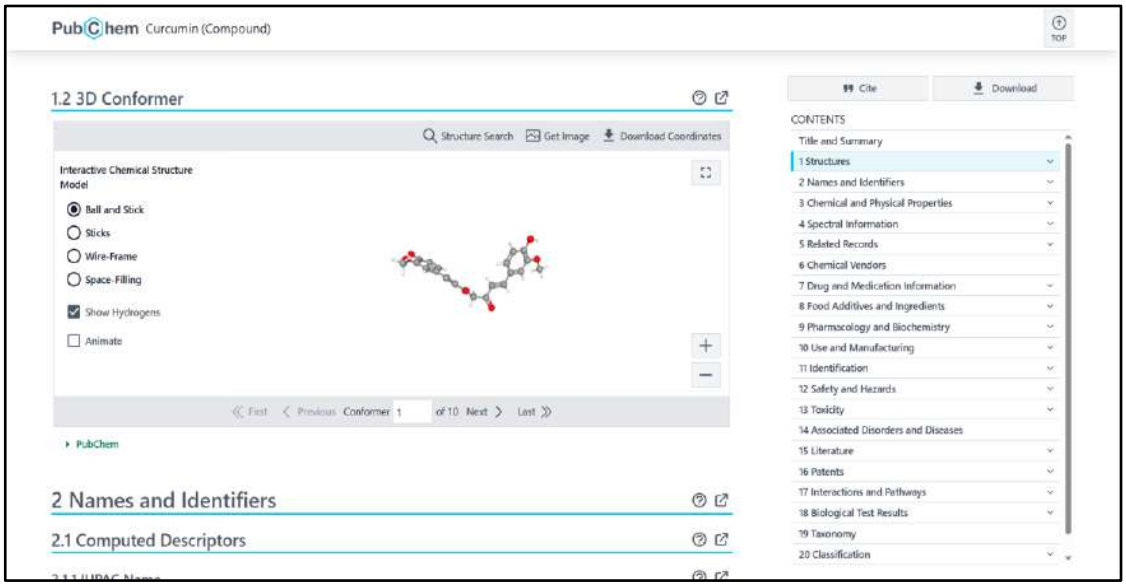

Figure 2 Curcumin Structure retrieval from PubChem

Preparation of Protein and Ligand for Docking

The proper preparation of ligand and macromolecule is crucial to achieve consistent, prominent results in docking(Verma & Chouhan, 2018a). The preprocessing of protein was done using AutoDock Tools in Mgl Tools software, and this process involves the removal of crystallographic water, which can potentially interfere with docking simulation, the Addition of small polar hydrogen atoms to improve consideration of actual protonation states, and the Assignment of Kollman charges to the protein to produce an accurate electrostatic representation

The ligand preparation process involves assigning torsional flexibility to rotatable bonds, geometrical optimization of these ligands, and inclusion of hydrogen atoms. Energy minimization was carried out to produce low-energy structures, further converting each ligand to PDBQT format required during docking. The above process is designed to accurately account for the conformational flexibility of a small molecule upon binding target protein.

Molecular Docking

Docking was performed to identify and refine binding sites, which particularly include two methods which were blind docking was performed using AutoDock 4.2; here, the grid box dimension was set sufficiently large x,y,z, coordinates of 126 Å to cover the whole protein surface. This step was performed on possible binding sites throughout the Esp structure. Fixed Docking was subsequently used for optimizing ligand binding structures. Here, the grid box size was particularly set to x,y,z coordinates with 80 Å to cover the potential area of the targeted Ligand and Target Protein. Analysis of docking results was done to predict the binding energy

(kcal/mol), number of conformations, and clustering statistics. Lower binding energy values indicate an increasing binding affinity. Additionally, Root Mean Square Deviation (RMSD) was calculated to check the binding mode stability.

Visualization of Molecule Interaction Analysis

Visualization after docking was carried out using AutoDock Tools to inspect the protein–ligand complexes. Special efforts were made to identify hydrogen bonds, hydrophobic interactions, and π–π stacking between residues in the Esp adhesion domain. Visual clustering of the binding conformations served to identify the most stable and abundant binding poses, thus increasing assurance in the interactions proposed.

Performing Virtual Screening

In efforts to enlarge the chemical space, structurally related analogs of high binding affinity ligands were retrieved from PubChem via similarity searches. Compounds were screened using AutoDock Vina, a software that offers a nuanced scoring function and higher convergence speed. It was analyzed how the docking scores across the analogs could reveal structural changes that enhanced binding affinity. Interestingly, Lipinski's Rule of Five was employed to pre-select compounds based on molecular weight, hydrogen bond acceptors and donors, and lipophilicity to ensure that selected molecules exhibited favorable drug-like properties (Bandyopadhyay et al., 2016).

ADMET Profiling of Ligand

Pharmacological relevance was evaluated in recognized ligands using SwissADME, a web-based bioinformatics drug-likeness

evaluation software package (Pandey et al., 2017, Verma & Chouhan, 2018b). We analysed the parameters, including physicochemical properties-molecular weight, clogP, hydrogen donors and acceptors, topological polar surface area (TPSA), and rotatable bonds—and pharmacokinetics, such as gastrointestinal absorption (GI), blood–brain barrier penetration (BBB), cytochrome P450 interactions, and skin permeability. Compounds exhibiting significant binding affinity during docking screening, good ADME properties, and compliance with drug-likeness criteria were identified as lead scaffolds.

Results and Discussion

This Research study involves the in-silico technique, which integrates molecular docking, virtual screening, and visualization to identify the potential inhibitor for the Enterococcal Surface Protein of *Enterococcus faecalis.* It enables prioritization of compounds with strong binding affinities and favorable pharmacological properties.

This methodology addresses the urgent requirement for innovative pharmaceuticals that focus on bacterial pathogens instead of inhibiting growth. A variety of effective Esp inhibitors exhibiting strong binding affinities to Esp have been researched. Notable compounds identified include: Curcumin, Resveratrol, Luteolin, Berberine, 1,8-Naphthyridine, Ajoene, Baicalein, Caffeic Acid, Fosfomycin, and Divinyl Sulfone.

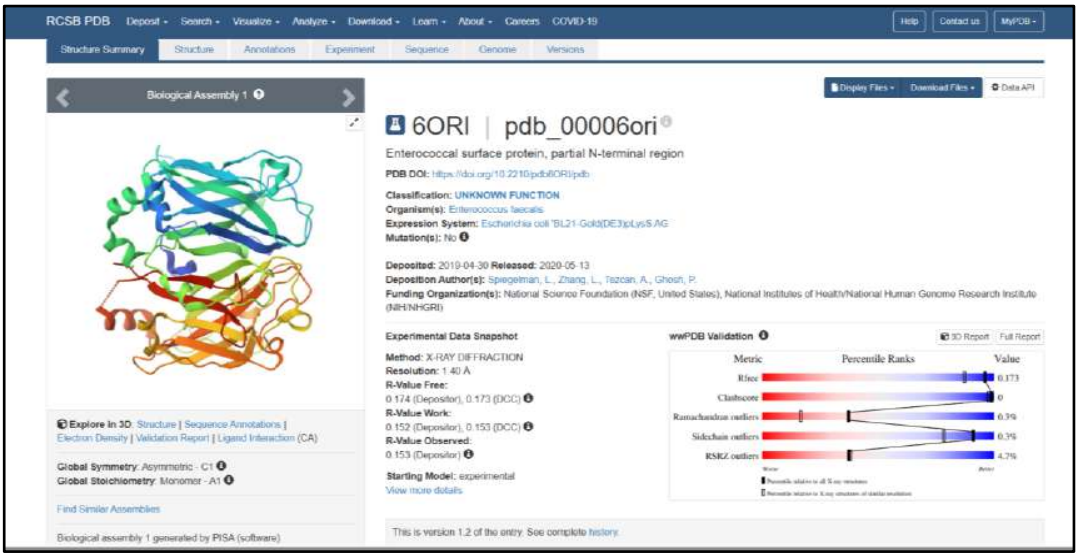

Figure 1 Structure retrieval of target protein using Protein Database (PDB)

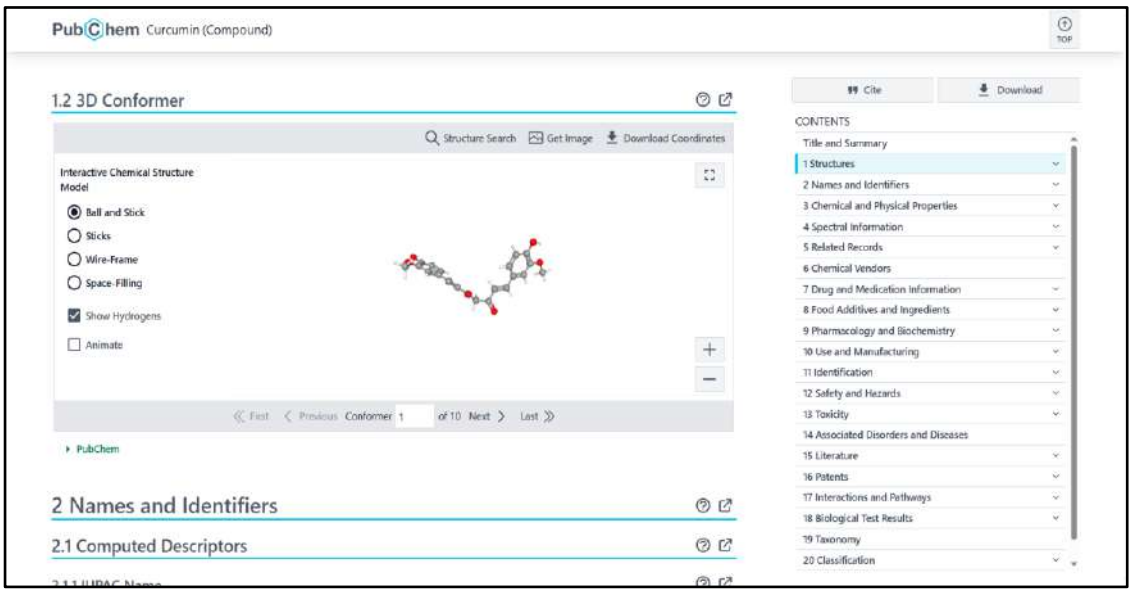

Figure 2 Curcumin Structure retrieval from PubChem

Molecular Docking and Binding Affinity Analysis

Molecular docking analysis, as shown in Table 1, has revealed several small molecules with strong inhibitory potential against the C-terminal adhesion domain of the Enterococcal Surface Protein (Esp) in *Enterococcus faecalis.* Among the analysed ligands, the pyridazinone consistently exhibited the most favourable binding affinity with a binding energy with a docking score of -9.58 kcal/mol in blind docking and -9.63 kcal/mol in fixed docking. Other compounds such as berberine and baicalein also demonstrated promising interaction, while curcumin, luteolin, and resveratrol displayed moderate affinity where whereas ajoene and divinyl sulfonate were among the weaker, narrower range, indicating limited inhibitory potential. RSMD clustering value validates binding conformation reliability, and clustering analysis points to the binding points in the lead ligands. The alignment between the blind and fixed docking results suggests that the Esp adhesion domain has a conformationally rigid and energetically favorable binding site available for small-molecule inhibitors.

Table 1: RSMD value Analysis of different compounds.

Sr No.	Source	Compound ID	Compound Name	Blind Dock (kcal/mol)	Fixed Dock (kcal/mol)
1.	**Zinc database**	**ZINC21992165**	**Pyridazinone**	**-9.58**	**-9.63**
2.	PubChem	2353	berberine	-8.23	-7.33
3.	PubChem	689043	Caeffic Acid	-7.80	-7.60
4.	PubChem	5281605	Baicalein	-7.65	-7.83
5.	PubChem	5280445	Luteolin	-7.62	-6.46
6.	PubChem	969519	Curcumin	-6.76	-7.21
7.	PubChem	136069	1,8-naphthyridine	-5.51	-5.60
8.	PubChem	5386591	Ajoene	-5.52	-4.95
9.	PubChem	445154	Resvetrol	-5.13	-5.48
10.	PubChem	6496	Divinyl Sulfone	-4.72	-4.73

Visualization of the Binding Interaction of Target-ligand

The docked compound visualization showed molecular information regarding the binding determinants. On the visualization of the molecule, Pyridazinone forms connections through the formation of hydrogen bonds and hydrophilic interactions with residues in the Esp adhesion pocket, including LysB6, AlaB4, and LeuC5B.

In contrast to curcumin and resveratrol showed fewer permanent contacts and therefore lower binding affinities, baicalein established a mix of hydrogen and π–π stacking interactions consistent with the flavonoid scaffold. This study highlights the efficiency and structural significance of baicalein, such as aromatic ring and polar substitute for stabilizing Esp-ligand interaction.

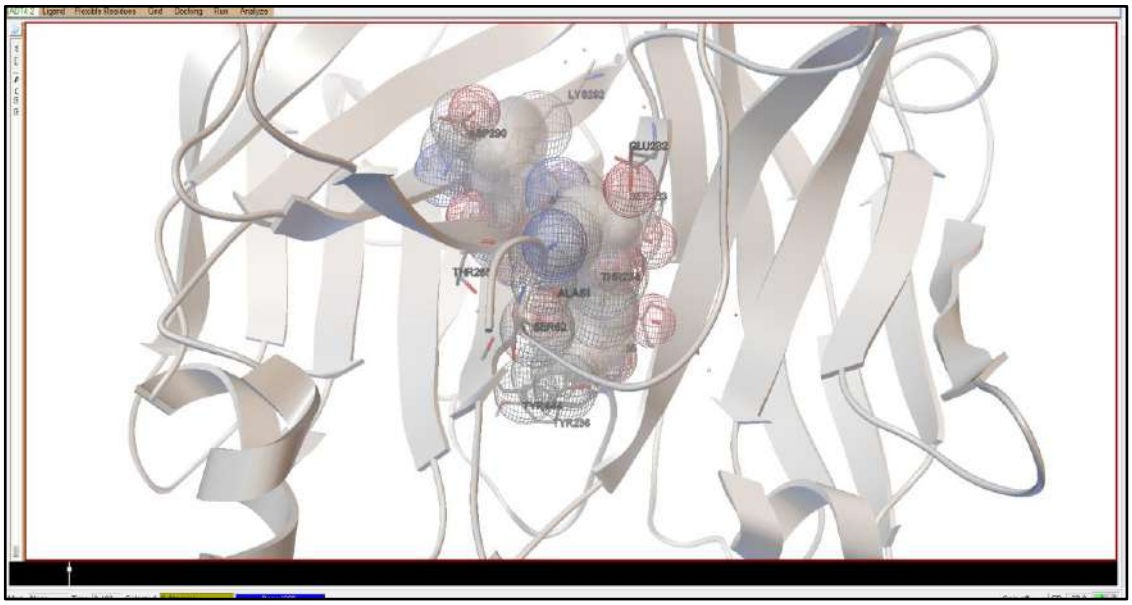

Figure 3: Visualization Result of pyridazinone and Target Ligand interaction

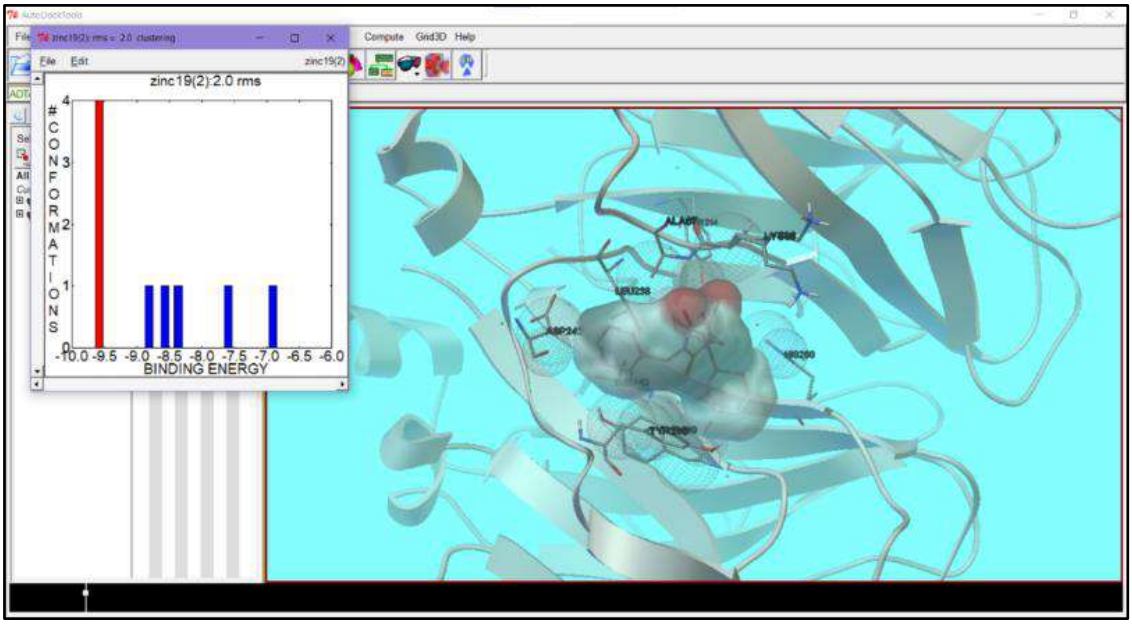

Figure 4 Visualization Result of pyridazinone compound at -9.5 kcal/mol binding energy

Virtual Screening

The similar structure compounds of high Binding affinity compounds are further taken and filtered based on Lipinski's rule, as shown in Table 2, and evaluated using AutoDock Vina as shown in Table 3. Here, the similar structure compound of Baicalein showed the highest binding affinity, surpassing the main compound, Resveratrol, and curcumin derivatives also demonstrated the improved interaction and increased binding energy. In contrast, Naphthyridine and Divinyl sulfone derivatives remained on the weaker binder list. This result suggests that scaffold modification may enhance Esp inhibition and should be further studied and explored through structural activity relationship studies.

Table 2 Lipinski-Based filter of Selected Compound

Compound Name	Compound Id	Before
Curcumin	969516	
Baicalein	969516	
Divinyl Sulfone	6496	
1,8-Naphthyridine	136069	

Table 3: Virtual screening Result using AutoDock Vina

Compound Name	Blind Dock Vina	Fixed Dock Vina
Baicalein	**-10.1**	**-10.1**
Resvetrol	-8.8	-8.7
Curcumin	-8.6	-8.4
1,8-Naphthyridine	-6.7	-6.8
Divinyl Sulfone	-4.3	-4.6

ADMET Profiling of Screened Compounds

As stated in Tables 4 and 5, SwissADME pharmacokinetic and physicochemical analyses validated the potential therapeutic use of these substances. With molecular weights ranging from 230 to 350 g/mol, cLogP values within the ideal range, and appropriate hydrogen bond donor/acceptor numbers, the majority of lead candidates met Lipinski's Rule of Five. High gastrointestinal absorption and the capacity to pass through the blood–brain barrier were predicted by SwissADME. Solubility forecasts stayed within acceptable ranges, while synthetic accessibility scores (1.8–3.2) indicated that these compounds could be produced without significant difficulties. All of these results point to the derivatives of baicalein as promising lead candidates with advantageous pharmacological and binding characteristics.

The Esp inhibition is an anti-virulence technique that aims to disrupt adhesion and biofilm formation, hence minimizing the chance of resistance development, in contrast to conventional antibiotics that target bacterial viability. The consistent

performance of some compounds, such as zinc ligands and baicalein derivatives, across the docking and pharmacokinetics analysis has provided a potential scaffold for further optimization and future studies.

Among these screened molecules, the Pyridazinone was identified to be the most promising candidate, possessing high binding affinity in the docking process. In parallel, baicalein analogs and baicalein demonstrated reliable efficacy, supporting our postulation that natural product-derived flavonoid scaffolds are amenable to further optimization. These results are in line with earlier findings demonstrating baicalein and curcumin analogs to be excellent inhibitors of biofilm-linked protein activity in other pathogenic organisms.

The computational results are promising but cannot fully account for the protein flexibility, solvent dynamics, and metabolic processes, so experimental validation is therefore required. These experimental studies may include biofilm inhibition assays, protein-ligand interaction studies and *in vivo* evaluation and pharmacokinetics, and toxicity. Further refinement of this compound could lead to the development of novel anti-virulence agents, either as standalone therapies or in combination with existing antibiotics against resistant *Enterococcus faecalis* strains.

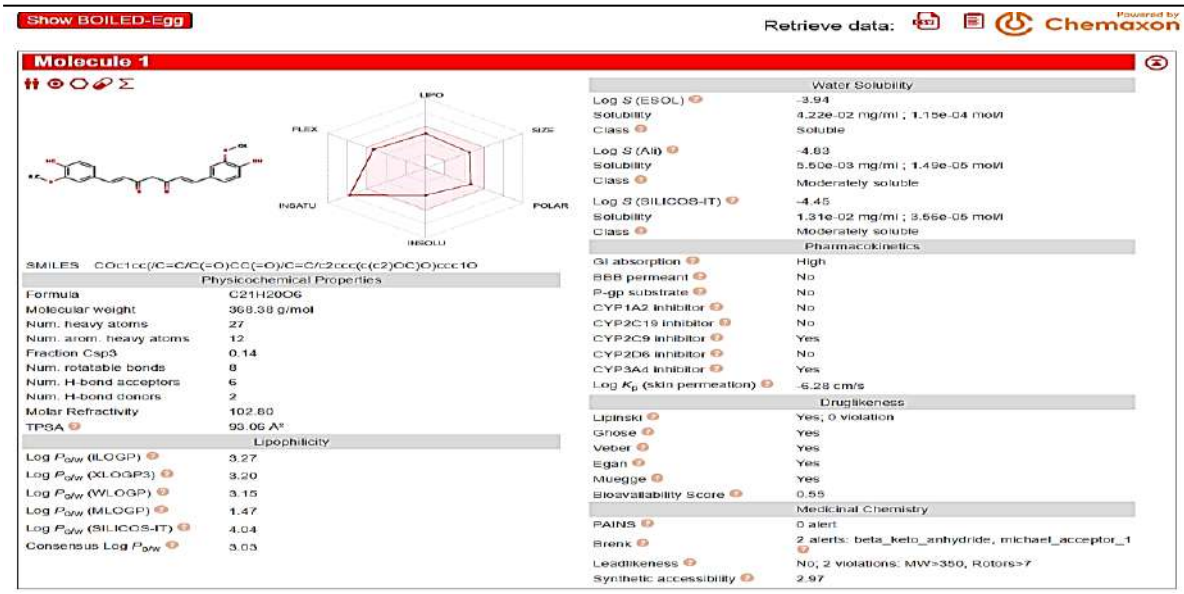

Figure 5: SwissADME Result of the listed Compound

Table 4: Swiss ADME Physicochemical Parameter Result

ID	Formula	GI Absorption	BBB Permeation	Skin Permeation	Bioavailability	Synthetic Accessibility
20842398	C21H20O5	High	Yes	-5.79	0.55	3.01
172021767	C19H18O5	High	Yes	-5.67	0.56	2.92
56838478	C18H16O4	High	Yes	-5.65	0.55	2.61
637455	C20H22O4	High	Yes	-5.61	0.55	2.59
129716876	C14H14O3	High	Yes	-5.52	0.55	1.84
58711180	C14H12O3	High	Yes	-5.47	0.55	2.2
129716876	C14H14O3	High	Yes	-5.52	0.55	1.84
12261165	C17H14O5	High	Yes	-5.59	0.55	3.12
14372618	C17H14O5	High	Yes	-6.15	0.55	3.24
129670	C17H14O4	High	Yes	-5.46	0.55	3.14
163569289	C10H11N3	High	Yes	-6.17	0.55	1.61
131994129	C9H9N3	High	Yes	-6.25	0.55	1.77
166834668	C10H11N3	High	Yes	-6.14	0.55	1.63
123639410	C10H11N3	High	Yes	-6.15	0.55	1.67

Table 5 Swiss ADME Pharmacokinetics Parameter Result

ID	Formula	GI Absorption	BBB Permeation	Skin Permeation	Bioavailability	Synthetic Accessibility
20842398	C21H20O5	High	Yes	-5.79	0.55	3.01
172021767	C19H18O5	High	Yes	-5.67	0.56	2.92
56838478	C18H16O4	High	Yes	-5.65	0.55	2.61
637455	C20H22O4	High	Yes	-5.61	0.55	2.59
129716876	C14H14O3	High	Yes	-5.52	0.55	1.84
58711180	C14H12O3	High	Yes	-5.47	0.55	2.2
129716876	C14H14O3	High	Yes	-5.52	0.55	1.84
12261165	C17H14O5	High	Yes	-5.59	0.55	3.12
14372618	C17H14O5	High	Yes	-6.15	0.55	3.24
129670	C17H14O4	High	Yes	-5.46	0.55	3.14
163569289	C10H11N3	High	Yes	-6.17	0.55	1.61
131994129	C9H9N3	High	Yes	-6.25	0.55	1.77
166834668	C10H11N3	High	Yes	-6.14	0.55	1.63
123639410	C10H11N3	High	Yes	-6.15	0.55	1.67

Conclusion

The study highlights the *in-silico* approach in identifying novel therapeutic candidates against the pathogen *Enterococcus faecalis,* known for its biofilm-associated infections and multidrug resistance. Integration of molecular docking, visualization, virtual screening, and ADME analysis, which evaluate a diverse set of natural and synthetic compounds targeting the Esp C-terminal adhesion domain, which plays a critical role in adhesion and biofilm formation. The greatest binding affinities were consistently shown by derivatives of baicalein among the investigated ligands..

This research provides information about the effective early-stage drug development process. Targeting Esp is an antivirulence tactic intended to disarm pathogenic pathways without directly putting microbial life under selective pressure, in contrast to conventional antibiotics that have bactericidal or bacteriostatic effects.

Future research must thus concentrate on experimental validation using in vivo testing of pharmacological profiles, protein–ligand interaction investigations, and *in vitro* biofilm inhibition experiments. All things considered, this study develops a computational approach that not only finds putative Esp inhibitors but also reaffirms how bioinformatics may speed up the development of novel antivirulence treatments to fight drug-resistant *Enterococcus faecalis*.

References

Kumar Suryawanshi, S., Chouhan, U., & Kant Choudhari, J. (2022). Insilico Anticancer Peptide Prediction from Curcuma longa. *Molecular & Cellular Biomechanics*, *19*(4), 191–208. https://doi.org/10.32604/mcb.2022.023911

Heikens, E., Bonten, M.J.M. & Willems, R.J.L., 2007. Enterococcal surface protein Esp is important for

biofilm formation of *Enterococcus faecium* E1162. *Journal of Bacteriology*, 189(21), pp.7797–7805. doi:10.1128/jb.01205-07.

Verma, N., & Chouhan, U. (2018a). In-silico analysis of phenyl propanoic acid derivatives to design potent peroxisome proliferator-activated receptor (PPAR) dual agonists for type 2 diabetes mellitus therapy. *Oriental Journal of Chemistry*, *34*(3), 1400. DOI:10.13005/ojc/340329

Verma, N., & Chouhan, U. (2018b). ADMET Prediction of Dual PPARα/γ Agonists for Identification of Potential Anti-diabetic Agents. In *Machine Intelligence and Signal Analysis* (pp. 355-362). Singapore: Springer Singapore.

Pandey, D., Chouhan, U., & Verma, N. (2017). Identification and analysis of lead compounds against HIV-1 integrase enzyme using ADMET prediction and docking analysis. *International Journal of Pharmaceutical Sciences and Research*, *8*(10), 4129-4137.

Tendolkar, P.M., Baghdayan, A.S., Gilmore, M.S. & Shankar, N., 2004. Enterococcal surface protein, Esp, enhances biofilm formation by *Enterococcus faecalis*. *Infection and Immunity*, 72(10), pp.6032–6039. doi:10.1128/IAI.72.10.6032-6039.2004.

Hollenbeck, B.L. & Rice, L.B., 2012. Intrinsic and acquired resistance mechanisms in *Enterococcus*. *Virulence*, 3(5), pp.421–433. doi:10.4161/viru.21282

Toledo-Arana, A. et al., 2001. The enterococcal surface protein, Esp, is involved in *Enterococcus faecalis* biofilm formation. *Applied and Environmental Microbiology*, 67(10), pp.4538–4545. doi:10.1128/AEM.67.10.4538-4545.2001.

Hota, S., Patil, S.R. & Mane, P.M., 2025. Enterococcus: Understanding their resistance mechanisms, therapeutic challenges, and emerging threats. *Cureus*, 17(2), p.e79628. doi:10.7759/cureus.79628.

Spiegelman, L. et al., 2022. Strengthening of enterococcal biofilms by Esp. *PLoS Pathogens*, 18(9), p.e1010829. doi:10.1371/journal.ppat.1010829

Windaryanti, D. et al., 2022. The potential of 24-Propylcholestrol as antibacterial oral bacteria of *Enterococcus faecalis* ATCC 29212 and inhibitor biofilms formation: in vitro and in silico study. *Advances in Applied Bioinformatics & Chemistry*, 15, pp.99–111. doi:10.2147/AABC.S372337.

Guan, L. et al., 2024. Global status of antimicrobial resistance in clinical *Enterococcus faecalis* isolates: systematic review and meta-analysis. *Annals of Clinical Microbiology and Antimicrobials*, 23(1), p.80. doi:10.1186/s12941-024-00728-w.

Brinkwirth, S., Ayobami, O., Eckmanns, T. & Markwart, R., 2021. Hospital-acquired infections caused by enterococci: a systematic review and meta-analysis, WHO European Region, 2010–2020. *Euro Surveillance*, 26(45), p.2001628. doi:10.2807/1560-7917.ES.2021.26.45.2001628.

Alsedfy, M.Y. et al., 2024. Investigating the binding affinity, molecular dynamics, and ADMET

properties of curcumin-IONPs as a mucoadhesive bioavailable oral treatment for iron deficiency anemia. *Scientific Reports*, 14(1), p.22027. doi:10.1038/s41598-024-72577-8.

Kim, S. et al., 2019. PubChem 2019 update: improved access to chemical data. *Nucleic Acids Research*, 47(D1), pp.D1102–D1109. doi:10.1093/nar/gky1033.

Shankar, N., Baghdayan, A.S. & Gilmore, M.S., 2002. Modulation of virulence within a pathogenicity island in vancomycin-resistant *Enterococcus faecalis*. *Nature*, 417(6890), pp.746–750. doi:10.1038/417746a.

Eberhardt, J., Santos-Martins, D., Tillack, A.F. & Forli, S., 2021. AutoDock Vina 1.2.0: New docking methods, expanded force field, and Python bindings. *Journal of Chemical Information and Modeling*, 61(8), pp.3891–3898. doi:10.1021/acs.jcim.1c00203.

Trott, O. & Olson, A.J., 2010. AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *Journal of Computational Chemistry*, 31(2), pp.455–461. doi:10.1002/jcc.21334.

Daina, A., Michielin, O. & Zoete, V., 2017. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific Reports*, 7, p.42717. doi:10.1038/srep42717.

Belwal, T. et al., 2020. Phytopharmacology and clinical updates of *Berberis* species against diabetes and other metabolic diseases. *Frontiers in Pharmacology*, 11, p.41. doi:10.3389/fphar.2020.00041.

Zhao, T. et al., 2019. *Scutellaria baicalensis* Georgi. (Lamiaceae): a review of its traditional uses, botany, phytochemistry, pharmacology and toxicology. *Journal of Pharmacy and Pharmacology*, 71(9), pp.1353–1369. doi:10.1111/jphp.13129.

Pourhajibagher, M., Javanmard, Z. & Bahador, A., 2024. Molecular docking and antimicrobial activities of photoexcited inhibitors in antimicrobial photodynamic therapy against *Enterococcus faecalis* biofilms in endodontic infections. *AMB Express*, 14, p.94. doi:10.1186/s13568-024-01751-y.

Agrawal, D.K. & Mishra, P.K., 2010. Curcumin and its analogues: potential anticancer agents. *Medicinal Research Reviews*, 30(5), pp.818–860. doi:10.1002/med.20188.

Falagas, M.E., Vouloumanou, E.K., Samonis, G. & Vardakas, K.Z., 2016. Fosfomycin. *Clinical Microbiology Reviews*, 29(2), pp.321–347. doi:10.1128/CMR.00068-15.

Dehbanipour, R. & Ghalavand, Z., 2022. Anti-virulence therapeutic strategies against bacterial infections: recent advances. *Germs*, 12(2), pp.262–275. doi:10.18683/germs.2022.1328.

Taysi, S. et al., 2023. Caffeic acid phenethyl ester: A review on its pharmacological importance, and its association with free radicals, COVID-19, and radiotherapy. *Phytotherapy Research*, 37(3), pp.1115–1135. doi:10.1002/ptr.7707.

Bandyopadhyay, B., Verma, N., & Chouhan, U. (2016). In Sillico analysis of newly identified potential drug lead compound against VP40 for the treatment of ebola virus infection. *International Journal of Advanced Biotechnology and Research*, *7*(4), 1357-1365.

Morris, G.M. et al., 2009. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. *Journal of Computational Chemistry*, 30(16), pp.2785–2791. doi:10.1002/jcc.21256