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Computational modeling and virtual screening of natural compounds against the *GlmU* Protein of *Corynebacterium pseudotuberculosis*

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Abstract

A Gram-positive bacterium, Corynebacterium pseudotuberculosis, is responsible for severe infections in livestock and leads to significant economic losses in the agricultural sector of agriculture. Antibiotic resistance is growing day by day, and there is an urgent need for alternative therapeutic agents as natural compounds. In the current study, a bifunctional enzyme, GlmU, was selected that is involved in bacterial cell wall formation and peptidoglycan biosynthesis. GlmU was investigated as a potential drug target. Experimental techniques did not resolve the 3D structure of GlmU. 3D structure was predicted by using homology modeling, threading, and ab initio approaches, along with their validation through various web-based structure assessment tools. According to ERRAT, verify 3D, and Ramachandran plot values, the Robetta model 3 was selected for further experimentation. Molecular docking studies were applied to virtually screen the natural compounds to inhibit GlmU. It was observed that rutin showed the highest binding affinity with a binding energy of -9.3 kcal/mol, followed by ginkgetin and crocin with energies of -8.4 kcal/mol and -8.2 kcal/mol, respectively. It was observed that the screened compounds bound at the active site of GlmU, suggesting their potential to inhibit its enzymatic activity. Overall, this study highlights that the reported natural compounds have the potential for the development of novel anti-C. pseudotuberculosis therapies by targeting GlmU.

How to Cite

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Introduction

Corynebacterium pseudotuberculosis is a Grampositive, facultative intracellular bacterium that serves as the primary causative agent of caseous lymphadenitis in sheep and goats, ulcerative lymphangitis in horses, and pyogranulomatous infections in cattle [1]. This pathogen causes significant economic losses in the livestock industries due to reduced meat, wool, and milk production, as well as carcass condemnation [2]. Transmission primarily occurs through direct contact with infected animals, contaminated fomites, or breaches in the skin and mucous membranes [3]. Once inside the host, C. pseudotuberculosis can survive and replicate within macrophages, leading to persistent infections that are difficult to eradicate. Infected animals often become asymptomatic carriers, further complicating control [4].

Treatment of *C. pseudotuberculosis* infections typically relies on antibiotics; however, the emergence of antimicrobial resistance has become a major challenge [5]. Resistance to commonly used drugs restricts treatment options and underscores the urgent need to identify novel therapeutic targets and alternative strategies that circumvent traditional resistance mechanisms [6].

One promising drug target is the bifunctional enzyme GlmU (N-acetylglucosamine-1-phosphate uridyltransferase/glucosamine-1-phosphate

acetyltransferase) [7]. It plays a vital role in bacterial cell wall biosynthesis by catalyzing the final steps in the formation of UDP-N-acetylglucosamine (UDP-GlcNAc). an essential key precursor peptidoglycan and lipopolysaccharide synthesis [8]. Inhibition of it disrupts cell wall integrity, increases susceptibility to osmotic stress, and ultimately leads to bacterial lysis. Hence, GlmU represents an attractive therapeutic target for the development of new antimicrobials [9]. Natural compounds that inhibit GlmU offer a promising alternative to synthetic antibiotics, particularly against -resistant strains of C. pseudotuberculosis [10]. Since this protein is essential for bacterial viability, its inhibition could reduce the likelihood of resistance development [11].

In recent years, *in silico* molecular docking has emerged as a powerful and cost-effective approach in early-stage drug discovery [12-14]. Through advanced computational algorithms, docking techniques enable researchers to predict the binding interactions between potential drug candidates and target proteins at the molecular level [15]. The

strategy accelerates the identification of promising compounds, minimizes the need for extensive wet-lab experiments, and significantly reduces research costs and time [16-18]. Consequently, *in silico* docking provides a rational and efficient pathway for screening large chemical libraries and prioritizing compounds with the greatest potential for subsequent biological validation.[13, 19]

Materials and Methods

The amino acid sequence of the glmU-encoded bifunctional enzyme (487 amino acids) from Corynebacterium pseudotuberculosis was retrieved from UniProt Knowledgebase (UniProt ID A0AAU8Q5V8) in FASTA format [20]. To identify a suitable template for structural modeling, the retrieved sequence was subjected to a BLASTp search against the Protein Data Bank (PDB) [21]. The BLASTp analysis identified three significant homologous templates based on sequence similarity, query coverage, and E-value [22]. The suitably aligned templates were selected for homology modeling and included GlmU structures from Mycobacterium tuberculosis (PDB ID: 3FOQ), Streptococcus pneumoniae (PDB ID: 4AAW), and Staphylococcus aureus (PDB ID: 9DQF).

Comparative modeling of the *C. pseudotuberculosis* GlmU protein was performed using three independent modeling approaches: **MODELLER** 9v15, AlphaFold, and Robetta servers. **MODELLER** employs spatial restraints derived from the alignment between the target and template sequences, while AlphaFold and Robetta use advanced deep learning and fragment-based prediction strategies to enhance model accuracy [23, 24]. The combination of these approaches ensured a robust prediction of the protein's conformation and allowed cross-validation of structural consistency.

Model quality assessment is an essential step in computational structure prediction to ensure structural reliability and correctness. The predicted models were evaluated using several structure validation tools. The ERRAT server was employed to analyze non-bonded atomic interactions and generate an overall quality factor for each model. VERIFY 3D was used to assess the compatibility of the 3D model with its amino acid sequence by evaluating environmental profiles. Additionally, PROCHECK was used to generate Ramachandran plots for the analysis of dihedral angles, providing information on residues located in favored, allowed, and outlier regions. Models with the highest percentage of residues in favored regions and

the highest overall quality factor were considered reliable for downstream analysis.

Molecular docking was performed using the AutoDock Vina tool integrated within PyRx 0.8 to identify potential natural inhibitors of GlmU. A natural compound library from MedChem Express, having 6015 compounds, was utilized for virtual screening. Ligand structures were prepared and energy-minimized before docking, and the GlmU protein model was prepared by removing water molecules, adding polar hydrogens, and assigning Gasteiger charges. The grid box parameters center (X: 22.1302, Y: -38657, Z: -37.1094) and dimensions (X: 62.6983, Y: 93.2638, Z: 108.0057) were defined to cover the predicted active site of the enzyme comprehensively. Binding affinities (kcal/mol) were used to rank the compounds, and the top hits were selected for detailed interaction analysis.

The docking results were analyzed and visualized using UCSF Chimera 1.8. The protein-ligand complexes were examined to identify hydrogen bonds, hydrophobic contacts, and other key noncovalent interactions. The visual representations highlighted binding conformations within the active pocket, illustrating the orientation of ligands and the involvement of specific amino acid residues in binding. Binding energies, interacting residues, and bond types were summarized to provide a comprehensive ligand-protein overview of interactions. The ADMET analysis of screened compounds was performed with the help of the admetSAR server. The utilized methodology has been reported extensively for the identification of novel compounds [25-30].

Results

The present study aimed to identify a natural compound capable of inhibiting the activity of the GlmU protein in *C. pseudotuberclosis*. The 3D structure of GlmU from this organism has not yet been experimentally determined; homology modeling was employed to predict its structure using suitable crystal templates. The modeled structure demonstrated high accuracy, particularly within the active site region of the protein. Comparative modeling and molecular

docking were performed using the AutoDock tool integrated within PyRx. The amino acid sequence of GlmU (487 residues) was retrieved from the UniProt database (accession number A0AAU8Q5V8). Template identification through BLASTp revealed three homologous template structures having PDB IDs 3FOO, 4AAW, and 9DOF, which were selected based on optimal alignment, query coverage, similarity, and E-values (Table 1). The 3D models of GlmU were generated using MODELLER 9v15 and validated through online web servers. Model validation was carried out using ERRAT, Verify 3D, and PROCHECK tools. The predicted models were compared based on Ramachandran plot, ERRAT overall quality factors, and VERIFY 3D score. Among the 36 models generated, the suitable models were selected based on validation scores (Fig. 1) and further visualized using UCSF Chimera 1.8 (Fig. 2). The selected GlmU model achieved an overall quality factor of 94.89% and a z-score of 82.75%, confirming its reliability for the subsequent docking studies.

The molecular docking was performed against the selected natural compound library, having 6015 compounds. It was observed that rutin showed the highest binding affinity and lowest binding energy of -9.3 kcal/mol (Fig. 3) against GlmU. The residues Gly-20, Gly-18, Ala-17, Gln-89, Gln-86, Gly-91, Glu-209, Tyr-211, Thr-92, Asp-116, Asn-114, Asn-183, Gly-185, Ser-184, Val-240, Asn-241, Lys-29, Arg-22, and Gly-151 were observed as the key interacting residues. The lowest binding energy suggested a stable interaction between rutin and GlmU. Interestingly, it was observed that other natural compounds showed significant binding affinities (Table 2), highlighting their potential against GlmU. These compounds interact with key amino acid residues against the GlmU active site, which may interfere with its enzymatic function. ADMET properties of the screened compounds showed significant results (Table 3).

GlmU plays a crucial role in bacterial cell wall biosynthesis by catalyzing the formation of UDP-N-acetylglucosamine. The inhibition of GlmU activity by the screened top-ranked natural compounds in this study could disrupt the bacterial cell wall formation, and this disruption may act as an antimicrobial agent.

Table 1: Suitable templates for GlmU sorted by their overall query coverage and identity

Template	Query coverage	Percentage Identity	PDB ID
Bifunctional protein GlmU (Mycobacterium tuberculosis)	98%	58.91%	3FOQ
Bifunctional protein GlmU (Staphylococcus aureus)	92%	42.67%	9DQF
Bifunctional protein GlmU (Streptococcus pneumoniae)	94%	40.09%	4AAW

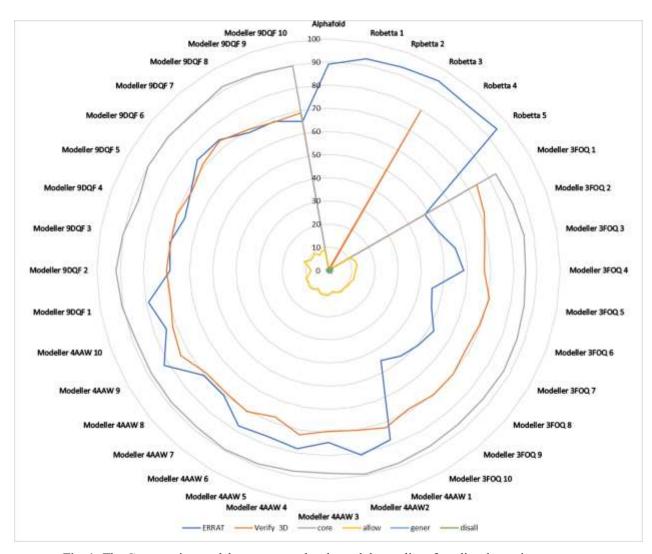


Fig. 1: The Comparative model assessment plot showed the quality of predicted protein structures.

Table 2: Top-ranked screened compounds against GlmU.

Compound	Catalogue Number	Binding Energy (kcal/mol)
Rutin	HY-N0148	-9.3
Ginkgetin	HY-N0889	-8.4
Crocin	HY-N0697	-8.2
Fiestin	HY-N0182	-8.1
Quercetin	HY-18085	-8.1
β-Carotene	HY-N0411	-8.0
Panaxadiol	HY-N0596	-7.9
Catechin	HY-N0898	-7.7
Withaferin A	HY-N2065	-7.7

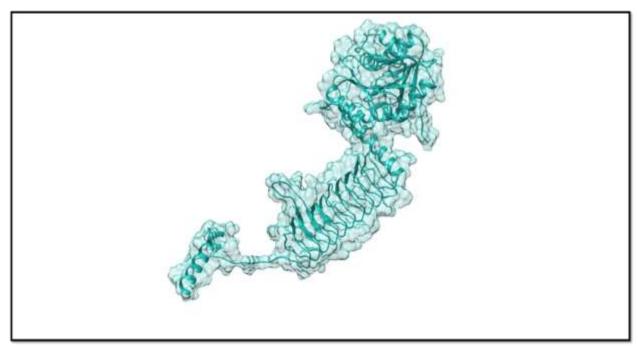


Fig. 2: 3D Structure of GlmU.

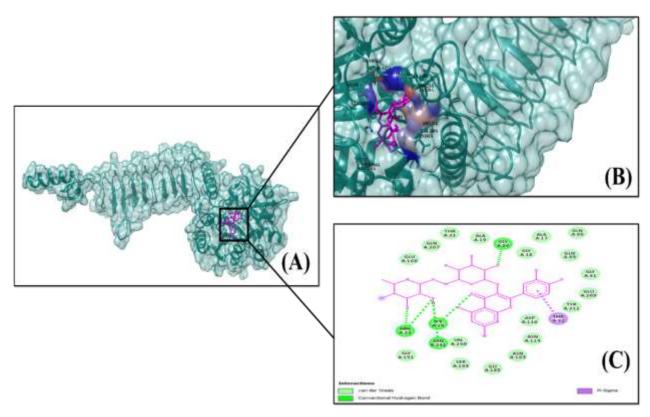


Fig. 3: The binding interactional analysis of rutin and GlmU. A) docked complex of rutin and GlmU. B) the interactional site of GlmU. C) the interacting region of the active site residues of GlmU.

Table 3. ADMET ana	lysis of screened	l compounds against	GlmU protein.

ADMET Properties	Rutin	Ginkgetin	Crocin	Fiestin	Quercetin	B-Carotene	Panaxadiol	Catechin	Wit-A
Blood-Brain Barrier	0.8542	0.6718	0.8314	0.5116	0.5711	0.9647	0.8730	0.5331	0.8697
Human Intestinal	0.8041	0.9502	0.8126	0.9833	0.9650	0.9963	1.0000	0.9654	0.8086
Absorption									
AMES Toxicity	0.5118	0.9311	0.9132	0.5905	0.7220	0.6543	0.7725	0.7658	0.9192
Carcinogens	0.9608	0.9248	0.9406	0.9309	0.9450	0.6907	0.9148	0.9539	0.9549
Fish Toxicity(mg/l)	0.9182	0.8939	0.5314	0.9766	0.9564	0.9855	0.9301	0.8659	0.9426
Honey Bee Toxicity	0.6326	0.6752	0.7595	0.6228	0.6330	0.8116	0.7367	0.6416	0.7981
Acute Oral Toxicity	0.5971	0.6505	0.5725	0.7187	0.7348	0.8007	0.5097	0.6433	0.5780
Carcinogenicity	0.6741	0.6328	0.6766	0.5926	0.6750	0.4813	0.6574	0.5825	0.5377

Discussion

Corynebacterium pseudotuberculosis is a pathogenic bacterium that causes caseous lymphadenitis, which affects livestock. This bacterium damages the economy and also veterinary health [31]. Antibiotic resistance is increasing globally among various bacterial pathogens, including *C. pseudotuberculosis*. Thus, there is an urgent need for alternative therapeutic strategies [32]. The targeted inhibition of essential bacterial enzymes involved in cell wall biosynthesis is another promising approach to inhibit by using bioactive compounds derived from various natural sources [33]. Bioinformatics is an interdisciplinary domain that helps researchers solve biological problems by applying computational power [34].

GlmU is a bifunctional enzyme involved in the synthesis of UDP-N-acetylglucosamine. It plays a key role in the formation of the bacterial cell wall [7]. GlmU is responsible for two essential reactions, such as the acetylation of glucosamine-1-phosphate and uridylation. Both reactions are necessary for the production of precursors for peptidoglycan synthesis [35]. GlmU has a strategic drug target for the development of new antimicrobial agents [11]. It has a vital role in cell wall integrity and bacterial survival. In the present study, 3D structure prediction of GlmU was carried out by applying homology modeling, threading, and ab initio approaches. The predicted structures were further evaluated by using various validation tools, and the most suitable structure was selected for further analyses. The validated models were subsequently used for molecular docking studies to screen potential inhibitors from a natural compound library.

Rutin showed the highest binding affinity and lowest binding energy of –9.3 kcal/mol against GlmU. It was observed that rutin interacted with the active site residues. This interaction may induce conformational changes that disrupt the catalytic activity. This

inhibition could prevent the formation of UDP-Nacetylglucosamine, thereby halting peptidoglycan biosynthesis and compromising bacterial cell wall integrity. It was reported that terric acid was also used to inhibit the activity of GlmU in Klebsiella pneumoniae [36] . Methyl 2-amino-2-deoxyl-α-dglucopyranoside 6-phosphate, methyl 2-amino-2deoxyl-β-d-glucopyranoside 6-phosphate, and 2azido-2-deoxy-α-d-glucopyranosyl phosphate were designed as GlmU inhibitors to suppress the growth of Mycobacterium tuberculosis [9]. The use of natural compounds as inhibitors offers several advantages over traditional antibiotics, including lower toxicity, structural diversity, and reduced risk of resistance development. Rutin presents a novel class of antimicrobial candidates that may overcome the limitations ofconventional antibiotics. antimicrobial effect of rutin and quercetin against methicillin-resistant Staphylococcus aureus was also reported [37]. Rutin also inhibited the growth of E.coli [38]. The identification of such compounds is particularly significant in the face of rising multidrug resistance, which threatens the effectiveness of existing treatment.

Conclusion

3D structure of GlmU was predicted, and a natural compound library was screened against the selected target. It was observed that rutin showed the lowest binding energy. The current findings are based on computational predictions; they provide a valuable starting point for further experimental validation. Future work should involve *in vitro* enzymatic assays, bacterial growth inhibition studies, and structure-activity relationship (SAR) analyses to confirm the inhibitory potential of rutin and related compounds against GlmU.

Conflict of interest

The authors declare no conflict of interest.

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