RESEARCH ARTICLE

In-silico Discovery of Potential *Mycobacterium tuberculosis* Cell Division Protein FtsZ Inhibitors: A Natural Ligand Piperine-Derived 3-Point Pharmacophore Screening and Structure-Guided Blind Docking Study

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ABSTRACT

This research employs a computational strategy to identify potential inhibitors against *Mycobacterium tuberculosis* FtsZ, a crucial cell division protein. The crystal structure of FtsZ was meticulously validated, serving as the foundation for pharmacophore-based virtual screening and subsequent molecular docking simulations. Piperine, a natural ligand derived from black pepper, guided the development of a 3-point pharmacophore model, which successfully screened a diverse chemical database. Ten top-ranking compounds emerged with promising pharmacophore scores, demonstrating potential interactions with the FtsZ binding site. Molecular docking simulations revealed specific compounds, including ZINC000012440615 and ZINC000014658239, displaying consistent preferences for pocket C5 and C1, respectively. The structural analysis of FtsZ unveiled a diverse set of pockets (C1–C5) with varying volumes and sizes, emphasizing the complexity of the protein's architecture. These findings provide crucial insights into potential inhibitors for further experimental validation and drug development against *M. tuberculosis*.

Keywords:*Mycobacterium tuberculosis*, FtsZ protein, Molecular docking, Pharmacophore screening, Computational drug discovery, Piperine, Crystal structure validation, Virtual screening, Lead compounds, Pocket analysis.

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INTRODUCTION

The causative agent of tuberculosis (TB), *Mycobacterium tuberculosis*, continues to pose a serious threat to world health due to the rise of drug-resistant strains and the ongoing burden of new infections.[1-6] In *M. tuberculosis*, cell division is an essential process that is controlled by proteins like Filamenting temperature-sensitive mutant Z (FtsZ), an essential part of the divisome machinery. Potential treatment approaches to fight this infectious disease include the creation of novel anti-tubercular medicines by inhibition of FtsZ activity.[7]

This work starts an *in-silico* investigation of possible inhibitors that target the *Mycobacterium* TB cell division protein FtsZ. We use a dual strategy, combining structure-guided blind docking with natural ligand-inspired pharmacophore screening, to fully utilize the potential of computational approaches. This study's natural ligand of interest is piperine, a bioactive substance with well-established pharmacological characteristics.[8–11]

Piperine, derived from black pepper (*Piper nigrum*), has exhibited diverse biological activities, including anti-inflammatory and antimicrobial effects. By harnessing the inherent structural features of piperine, we construct a 3-point pharmacophore model, exploring the key elements crucial for effective binding to the FtsZ active site. This pharmacophore

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model serves as a powerful screening tool against a chemical database, facilitating the identification of potential lead compounds with the ability to disrupt FtsZ function.[12-17]

We use structure-guided blind docking in conjunction with pharmacophore screening to decipher the dynamic interactions between the chosen ligands and the FtsZ protein. Through our computational investigation, we want to find drugs with strong interactions, advantageous binding modes, and promising inhibitory potential against *M. tuberculosis* FtsZ.[18–20]

The combination of blind docking and pharmacophore-based screening offers a thorough approach to the *in-silico* identification of FtsZ inhibitors. The computational endeavor yielded valuable insights that could facilitate additional experimental validation and lead to the development of novel anti-tubercular medicines with lower resistance profiles and increased efficacy. New methods, like the one shown, help in the continued attempts to combat this ongoing public health problem as the global battle against tuberculosis continues.[21–23]

MATERIALS AND METHODS

Protein Selection and Preparation

A reliable protein structure database provided the crystal structure of *M. tuberculosis* Cell Division Protein FtsZ (PDB ID: 2Q1Y), guaranteeing accuracy and study-relevantness. Water molecules and other heteroatoms were eliminated to prepare the protein structure for further simulations, missing hydrogen atoms were added, and the proper charges were assigned.[24]

Ligand Selection and Preparation

Piperine, a natural ligand with known pharmacological properties and derived from black pepper, was chosen as the reference molecule for pharmacophore screening. The three-dimensional structure of piperine was retrieved from PubChem, and optimization and energy minimization were performed using molecular modeling software.[25]

Pharmacophore-Based Virtual Screening

A 3-point pharmacophore model was constructed based on the essential molecular features required for effective binding to the FtsZ active site. The pharmacophore model incorporated critical elements such as hydrogen bond donors, hydrogen bond acceptors, and hydrophobic regions. This model, inspired by the structural features of piperine, served as a filter for screening potential lead compounds.

The generated pharmacophore model was employed to screen a zinc drug diverse chemical database for compounds exhibiting a high degree of complementarity to the FtsZ binding site. A thorough virtual screening was performed, and the top-ranking compounds were selected for further analysis based on their pharmacophore scores.[26]

Molecular Docking Simulations and Selection of Top Candidates

The 3D structure of FtsZ was prepared for molecular docking simulations by addressing any missing atoms or residues. Blind docking simulations were conducted using CB Dock server based on auto dock vina advanced docking software, allowing ligands to explore potential binding sites within the entire FtsZ structure. The results were analyzed to identify ligand binding modes, interactions, and binding energies.

Ligand binding poses were scored based on binding energy calculations obtained from the docking simulations. The top-ranking compounds were selected as potential inhibitors against *M. tuberculosis* FtsZ. Further analysis of these hits' binding interactions and structural features was performed to prioritize the most promising candidates for experimental validation.[27]

RESULTS

Crystal Structure Validation

The RCSB Protein Data Bank provided the crystal structure of the cell division protein FtsZ from *Mycobacterium* TB in association with GTP-gamma-S (PDB ID: 2Q1Y), which is displayed in Figure 1. The structure's dependability and applicability were guaranteed for ensuing computational trials. Our computational screening and docking studies were conducted with the molecular target being the three-dimensional structure of FtsZ.[28]

Pharmacophore-Based Virtual Screening and Identification of Potential Lead Compounds

Piperine was used as a reference molecule to successfully build the 3-point pharmacophore model seen in Figure 2, which was developed based on the critical properties for binding to the FtsZ active site. In order to select possible lead compounds, this model included essential components such as hydrophobic areas, hydrogen bond acceptors, and donors. The zinc drug

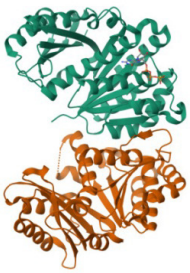


Figure 1: The crystal structure of the *Mycobacterium* TB cell division protein FtsZ in combination with GTP-gamma-S (PDB ID: 2Q1Y)

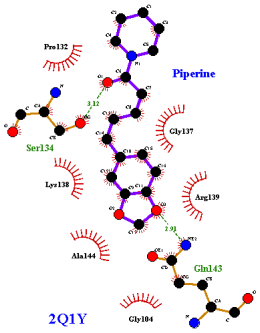
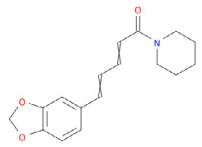
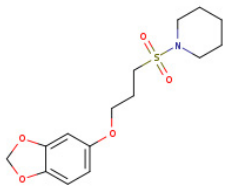
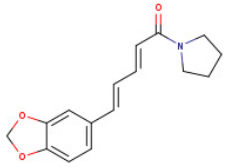
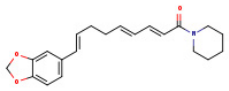
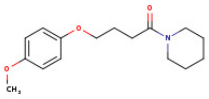
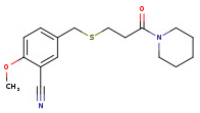
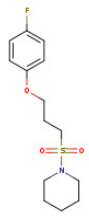
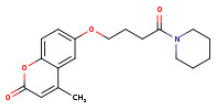
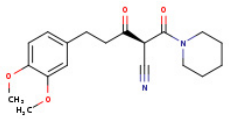
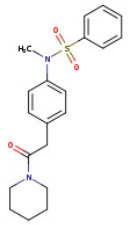
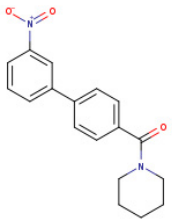


Figure 2: Piperine-derived pharmacophore model

Table 1: List of compounds screened by piperine-derived pharmacophore model

Compound ID	*Similarity score*	*2D Structure*
ZINC 000019892375	1.000	
ZINC 000012440615	0.675	
ZINC 000001531693	0.662	
ZINC 000014658239	0.635	
ZINC 000050078406	0.592	
ZINC 000096005552	0.583	
ZINC 000012440744	0.569	
ZINC 000005678824	0.554	
ZINC 000103502519	0.548	
ZINC 000225981532	0.537	
ZINC 000085210077	0.523	

database, a broad chemical library, was then searched using the pharmacophore model to find compounds that showed a high level of complementarity with the FtsZ binding site.[29,30] Table 1 lists the compounds that were screened using the Piperine-derived pharmacophore model.

The virtual screening process resulted in the identification of 10 top-ranking compounds from the zinc drug database based on their pharmacophore scores.[31,32] These compounds exhibited favorable interactions with the FtsZ active site, suggesting their potential as inhibitors of *M. tuberculosis* FtsZ.

Molecular Docking Simulations

Molecular docking simulations were performed to further assess the binding affinities and interactions of the selected compounds with the 3D structure of FtsZ. Blind docking simulations using the CB Dock server and AutoDock Vina advanced docking software allowed the ligands to explore potential binding sites within the entire FtsZ structure. The results provided insights into ligand binding modes, key interactions, and binding energies.[33]

Ligand binding poses were scored based on the binding energy calculations obtained from the docking simulations. The top-ranking compounds exhibiting the most favorable

Table 2: Pockets cavity volume, center and cavity size found in FtsZ

CurPocket ID	*Cavity volume (Å3)*	*Center (x, y, z)*	*Cavity size (x, y, z)*
C1	5396	-12, 62, 13	30, 30, 17
C2	2347	-7, 62, -4	30, 20, 27
C3	616	-1, 81, -10	11, 13, 12
C4	601	1, 34, -11	12, 19, 10
C5	515	9, 39, 9	11, 14, 17

binding affinities and interactions with FtsZ, were selected as potential inhibitors against *M. tuberculosis* FtsZ. These lead compounds ' structural features and binding interactions were further analyzed to prioritize the most promising candidates for experimental validation.[34]

The analysis of the provided data on pockets in FtsZ reveals a diverse landscape of structural features. These pockets, labeled C1 to C5, exhibit significant variation in cavity volume, with C1 possessing the largest volume at 5396 Å³, and C5 having the smallest at 515 Å³. The center coordinates of these pockets, representing their central points in three-dimensional space, provide insight into their spatial distribution. For instance, C1 is located at (-12, 62, 13), while C5 is positioned at (9, 39, 9). Additionally, the cavity sizes, denoted by dimensions in the x, y, and z directions, further differentiate these pockets (Figure 3). Notably, C1 stands out for its large volume and substantial size in all three dimensions (30, 30, 17 Å). Conversely, C2, while having a relatively large volume, exhibits a distinctive elongation in the z-direction (30, 20, 27 Å). The smaller volumes of C3, C4, and C5 and their varied sizes suggest structural diversity within the FtsZ protein. This information is crucial for understanding the potential functional implications of these pockets in biological processes, contributing to a comprehensive view of the protein's architecture (Tables 2 and 3).[35]

The molecular docking results obtained from the CB Dock Server provide insights into the interactions between various compounds and specific pockets in the FtsZ protein (Figures 4-6). Notably, compounds ZINC000012440615, ZINC000001531693, ZINC000050078406, and others exhibit

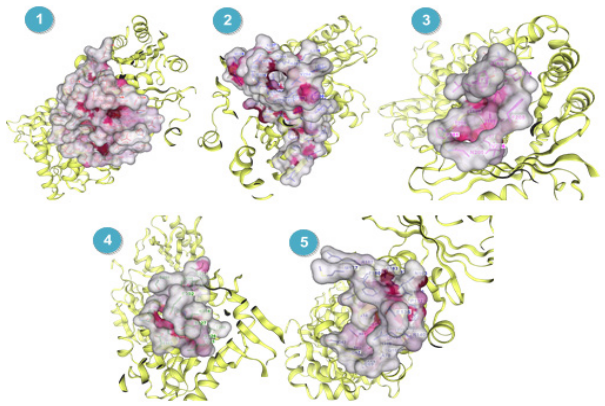


Figure 3: Cavities found in FtsZ

Table 3: Results of molecular docking studies by CB dock server

S. No.	*Compound ID*	*Auto dock vina score*
STD	ZINC000019892375 Piperine	-7.5
1	ZINC000012440615	-7.7
2	ZINC000001531693	-7.2
3	ZINC000014658239	-7.9
4	ZINC000050078406	-6.9
5	ZINC000096005552	-7.1
6	ZINC000012440744	-7.1
7	ZINC000005678824[4-Methyl-6-(4-oxo-4-(1-piperidinyl)butoxy)-2h-chromen-2-one]	-8.5
8	ZINC000103502519	-7.7
9	ZINC000225981532	-7.6
10	ZINC000085210077[3-Nitro-4'-(piperidinocarbonyl)biphenyl]	-8.5

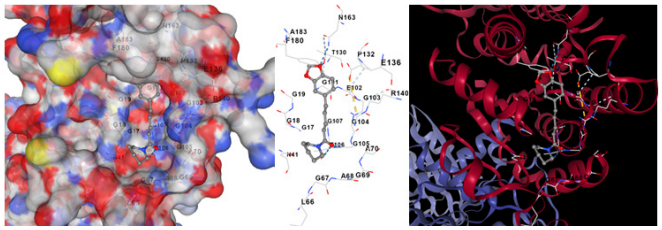


Figure 4: Interactions of FtsZand piperine (Auto dock Vina Score -7.5)

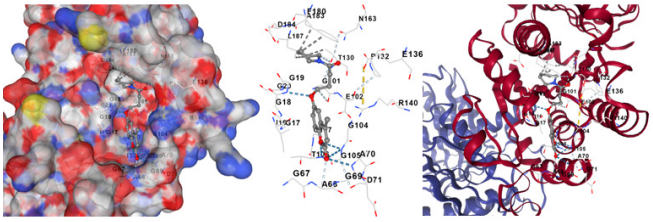


Figure 5: Interactions of FtsZ and 4-Methyl-6-(4-oxo-4-(1-piperidinyl) butoxy)-2h-chromen-2-one (Auto dock Vina Score -8.5 Vs -7.5 of Piperine)

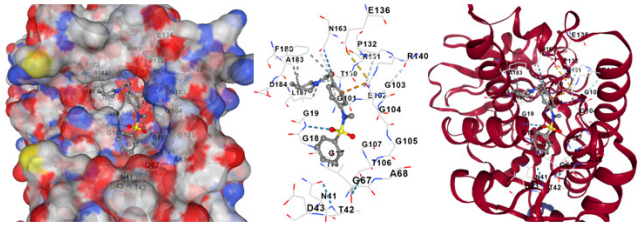


Figure 6: Interactions of FtsZ and 3-Nitro-4'-(piperidinocarbonyl) biphenyl (Auto dock Vina Score -8.5 Vs -7.5 of Piperine)

a consistent preference for interacting with pocket C5, as indicated by their docking scores ranging from -6.9 to -7.7. The amino acid residues involved in these interactions include GLY17, GLY18, GLY19, ASN41, THR42, LEU66, GLY67, ALA68, GLY69, ALA70, GLY101, GLU102, GLY103, GLY104,

GLY105, THR106, GLY107, THR130, PRO132, GLU136, ARG140, ASN163, PHE180, and ALA183. The conserved nature of these interacting residues suggests a potential binding site with functional significance. Additionally, the compound ZINC000014658239 exhibits interactions with pocket C1, involving amino acid residues from chains A and B, such as ASP84, GLU87, GLU88, ARG91, GLY103, GLY104, ARG131, PRO132, PHE133, SER134, GLU136, GLY137, LYS138, ARG139, ALA144, and ASP164. These findings provide valuable information for understanding the binding preferences and potential functional implications of these compounds in relation to the FtsZ protein.[36]

The docking studies highlight specific compounds with a strong affinity for pocket C5, indicating a potential binding site with a conserved set of amino acid residues. The diversity in compound structures, as exemplified by ZINC000005678824 and ZINC000085210077, suggests a range of chemical features that contribute to their interactions with the FtsZ protein. Further experimental validation and detailed structural analyses are warranted to confirm and explore the functional implications of these interactions, contributing to the development of potential therapeutic interventions targeting the FtsZ protein.

CONCLUSION

In conclusion, this research aimed to identify potential inhibitors against *M. tuberculosis* FtsZ through a comprehensive computational approach. The crystal structure of FtsZ was validated and utilized as the molecular target for pharmacophore-based virtual screening and molecular docking simulations. Piperine, a natural ligand derived from black pepper, served as the reference molecule for pharmacophore screening. The generated 3-point pharmacophore model successfully filtered a diverse chemical database, identifying 10 top-ranking compounds with promising pharmacophore scores. The subsequent molecular docking simulations provided crucial insights into the binding affinities and interactions of the selected compounds with the FtsZ protein. Compounds such as ZINC000012440615, ZINC000001531693, and ZINC000050078406 exhibited a consistent preference for interacting with pocket C5, implicating a potential binding site with a conserved set of amino acid residues. Additionally, ZINC000014658239 showed interactions with pocket C1, further expanding the potential repertoire of binding sites on FtsZ. The structural analysis of the FtsZ protein revealed a diverse landscape of pockets with varying volumes, center coordinates, and sizes (C1 to C5). Notably, Pocket C1 exhibited the largest volume and substantial dimensions, suggesting its significance in the protein's structure and function. The combination of pharmacophore-based virtual screening and molecular docking simulations identified lead compounds with potential inhibitory activity against *M. tuberculosis* FtsZ. Overall, the findings of this study contribute valuable insights into the molecular interactions between potential inhibitors and FtsZ, providing a foundation for experimental validation and further optimization of these compounds for targeted drug development. The structural diversity observed in the FtsZ pockets highlights the complexity of the protein's architecture and emphasizes the need for a multifaceted approach in drug discovery efforts. The identified lead compounds present promising candidates for future experimental studies, bringing us one step closer to developing novel therapeutics against *M. tuberculosis*.

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