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Molecular Docking Insights into Cannabidiol's Antimicrobial Potential Against Resistant Bacteria

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Abstract:
Background*: The global rise in antimicrobial resistance (AMR) has made traditional antibiotics increasingly ineffective. Cannabidiol (CBD), a compound from Cannabis sativa, has gained attention for its antimicrobial potential, particularly due to its unique mechanisms and effectiveness against resistant bacteria.*
Materials and Methods*: Researchers used molecular docking to study CBD's interaction with bacterial proteins from both Gram-positive and Gram-negative species. Proteins were selected from the Protein Data Bank, prepared using PyMOL, and docked with CBD using the DockThor server. Interactions were analyzed via PoseView to identify binding affinities and key amino acid contacts.*
Results*: CBD showed strong binding affinity with several bacterial proteins, notably with Salmonella enterica (7CBG), which demonstrated the highest affinity. Binding energy, van der Waals, and electrostatic interactions were evaluated. Structural analysis revealed specific hydrogen bonds and hydrophobic interactions contributing to CBD's antimicrobial effect.*
Conclusion: *CBD demonstrates promising interaction with bacterial proteins linked to resistance, suggesting it may serve as an effective therapeutic agent against multidrug-resistant bacteria. Its unique binding patterns and energetic stability support further research and development.*
Key Word*: Cannabidiol, Docking, Resistance, Proteins.*

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I. Introduction

Antimicrobial resistance (AMR) is one of the most pressing challenges facing global public health today[1,2]. As bacteria and other pathogens become increasingly resistant to conventional treatments, many commonly used antibiotics are losing their effectiveness. This growing crisis is largely driven by the overuse and misuse of antibiotics, which accelerates the emergence and spread of resistant strains[3]. In light of this, there is an urgent need to explore alternative therapeutic strategies beyond traditional antimicrobial drugs[4].

One promising avenue is the use of cannabidiol (CBD), a non-psychoactive compound derived from *Cannabis sativa*, which has recently attracted scientific interest for its potential antimicrobial properties[5]. Alongside CBD, various natural products - including herbal extracts, phytotherapeutics, and essential oils - are gaining renewed attention. These substances have a long history in traditional medicine and are increasingly being validated by modern scientific research[6,7].

Many plant-derived compounds exhibit broad-spectrum antimicrobial activity and tend to cause fewer side effects than synthetic drugs. Moreover, they often act through mechanisms to which pathogens have not yet developed resistance, making them valuable candidates for novel treatments[8,9]. Their chemical diversity - including phenolics, terpenes, and alkaloids - enables them to disrupt microbial membranes, inhibit key enzymes, or interfere with metabolic pathways[10,11].

In this context, computational tools such as molecular docking offer a powerful approach for predicting how natural compounds interact with specific bacterial targets. These simulations can help identify the most promising candidates before laboratory testing, saving both time and resources[12,13]. This study aims to investigate the antibacterial potential of CBD using molecular docking techniques, with the goal of assessing its viability as an alternative therapeutic agent in the fight against AMR.

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II. Material And Methods

Acquisition of Bacterial Proteins

Target proteins were retrieved from the RCSB Protein Data Bank (RCSB PDB). Five co-crystallized protein structures, each bound to their respective inhibitors and available in PDB format, were selected for this study. These proteins represent the following bacterial species: 1BLH from *Staphylococcus aureus* (Gram-positive cocci), 3KR6 from *Escherichia coli* (Gram-negative bacillus), 7CBG from *Salmonella enterica* (Gram-negative bacillus), 9FZE from *Pseudomonas aeruginosa* (Gram-negative bacillus), and 5FQB from *Bacillus cereus* (Gram-positive bacillus).

Preparation of Proteins as a Receptor

The 3D structure of cannabidiol (PubChem ID: 644019) was obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The compound was searched using its name or PubChem identifier. The 3D ligand structure were downloaded in SDF format to preserve spatial configuration and then converted to MOL2 format for docking preparation.

Molecular Docking

Docking simulations were performed using the DockThor server (https://dockthor.lncc.br/), which supports flexible protein-ligand interaction modeling. Proteins devoid of water molecules and co-crystallized ligands were uploaded, followed by the prepared ligands. The docking grid was defined based on the previously identified binding site coordinates, ensuring the active region of the protein was targeted. Docking runs were executed, and resulting protein-ligand complexes were evaluated based on binding energy and molecular interactions. The most stable complexes were selected for further structural and biochemical analysis.

Ligand Interactions with Amino Acid Residues

Molecular interactions between the ligands and target proteins were analyzed using the PoseView server (https://poseview.zbh.uni-hamburg.de/), which generates 2D interaction diagrams. Protein structures were saved in PDB format, ensuring only the polypeptide chains were included. Ligands, positioned according to their docked coordinates, were also converted to PDB format. Both files were uploaded to the server, which automatically generated interaction maps. These 2D diagrams highlighted key molecular interactions, such as hydrogen bonds, hydrophobic contacts, and ionic interactions, facilitating the interpretation of binding behavior. The results were reviewed to identify critical amino acid residues involved in ligand binding, providing insights into the affinity and stability of the studied complexes.

III. Result

Visualization of Protein Three-Dimensional Structures

The three-dimensional structures of the proteins analyzed in this study are illustrated in detail in Figures 1A, 1B, 1C, 1D, and 1E, corresponding respectively to the structural models from entries 1BLH, 3KR6, 7CBG, 9FZE, and 5FQB.

Figure no 1A. 3D structure of 1BLH

Figure no 1B. 3D structure of 3KR6

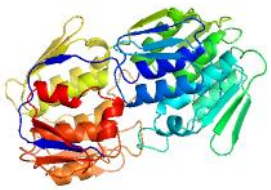


Figure no 1C. 3D structure of 7CBG

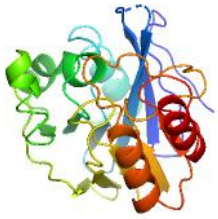


Figure no 1D3. D structure of 9FZE

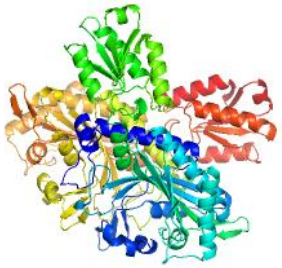


Figure no 1E. 3D structure of 5FQB

Binding Sites Identified for Docking Simulations

The definition of the grid box for molecular docking simulations was based on the previously identified binding sites for each protein. To ensure accurate exploration of the active regions by the docking algorithm, the positions of the co-crystallized ligands within the three-dimensional structures were used as references. Detailed coordinate data used for setting up the docking boxes are presented in Table no 1.

Table no 1: Information on Bacterial Proteins and Definition of Molecular Docking.

PBD ID	Bacteria	Protein	X	Y	Z	Inhibitor	Reference
1BLH	*S. aureus*	β-lactamase	3.77	-9.31	-9.74	FOS	Chen et al.,[14]
3KR6	*E. coli*	MurA	53.73	49.96	154.19	FFQ	Han et al.,[15]
7CBG	*S. enterica*	ThrRS	-0.73	9.22	36.11	FQL	Guo et al.,[16]
9FZE	*P. aeruginosa*	PBP3	11.91	23.41	1.42	MER	Smith et al.,[17]
5FQB	*B. cereus*	MBL	62.06	-0.04	18.49	OK3	Brem et al.,[18]

Docking Results Using the DockThor Server

Table 2 presents the interaction data between the ligands and the target proteins, including Affinity, Total Energy, Van der Waals (vdW) Energy, and Electrostatic Energy parameters. Affinity scores ranged from -6.444 to -8.508, with the 7CBG protein showing the highest affinity (-8.508) and 5FQB the lowest (-6.444). Total energy values ranged from 52.308 to 428.517, with 1BLH showing the lowest (52.308) and 5FQB the highest (428.517). vdW energy values ranged from -25.366 to 332.386, with the lowest observed for 3KR6 (-25.366) and the highest again for 5FQB (332.386). Electrostatic energy values ranged from -4.016 to 3.064, with the most negative value recorded for 3KR6 (-2.960) and the most positive for 9FZE (3.064).

Table no 2: Molecular Docking Results Using DockThor Server.

PBD ID	Affinity	Total Energy	vdW Energy	Elec. Energy
1BLH	-7.954	52.308	-20.419	-5.445
3KR6	-7.492	57.677	-25.366	-2.960
7CBG	-8.508	64.740	-15.451	-4.458
9FZE	-7.212	241.044	129.253	3.064
5FQB	-6.444	428.517	332.386	-4.016

Ligand Interactions with Amino Acid Residues

In protein 1BLH, hydrogen bonding was observed with residue Ser97A, along with a hydrophobic interaction with Ile206A (Figure 2A). For protein 3KR6, the ligand formed hydrophobic interactions with Val162A and Phe327A, a π–π stacking interaction with Phe327A, and a hydrogen bond with Arg119A (Figure 2B). In 5FQB, multiple hydrophobic interactions were identified with residues Trp149A, Val45A, Ile75A, Phe127A, Val199A, Leu16A, Ile155A, Val20A, Leu150A, Val157A, Val148A, and Leu35A (Figure 2C). Protein 7CBG showed hydrogen bonds with Trp31B, Glu38A, and two bonds with Lys54B, in addition to a

hydrophobic interaction with Lys54B (Figure 2D). Lastly, in 9FZE, hydrophobic interaction was noted with His114A, while hydrogen bonds were formed with Asn234A (two interactions) and Glu127A (Figure 2E).

Figure no 2A

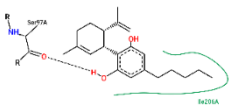


Figure no 2B

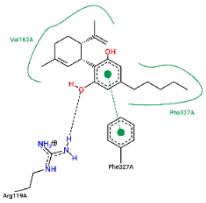


Figure no 2C

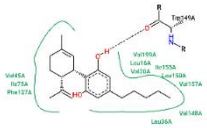
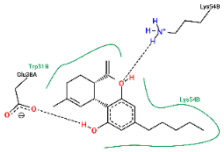


Figure no 2D



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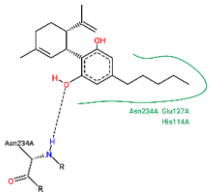

IV. Discussion

Affinity, reflecting the strength of the interaction between a protein and its ligand, was highest for PDB entry 7CBG, suggesting a stronger and potentially more effective binding interaction. In contrast, 5FQB exhibited the lowest affinity, indicating a weaker binding capability. Analysis of the total energy, which is associated with the stability of the protein-ligand complex, revealed that PDB 1BLH had the lowest value, indicating a more stable structural configuration. Conversely, 5FQB showed the highest total energy, pointing to reduced complex stability. Regarding van der Waals energy, PDB 3KR6 had the most negative value, indicative of more favorable molecular interactions between the protein and ligand. On the other hand, 5FQB displayed the most positive vdW energy, suggesting less favorable interactions. As for electrostatic energy, 3KR6 again stood out with the most negative value, reflecting more stable and favorable electrostatic interactions. In contrast, 9FZE showed the most positive electrostatic energy, potentially indicating less favorable electrostatic contributions. Overall, the data suggest that 7CBG is the most promising in terms of binding affinity, while 1BLH demonstrates the greatest energetic stability. Conversely, 5FQB presented unfavorable values across all metrics, making it a less suitable candidate for ligand interaction.

The results further highlight that ligands engage in distinct interaction patterns with their target proteins, which can directly influence their binding affinity and selectivity. In 1BLH, the presence of a hydrogen bond with Ser97A and a hydrophobic interaction with Ile206A suggests that the ligand is well-positioned in the active site, combining stability with specificity. Protein 3KR6 exhibited a more diverse interaction profile, including a notable π–π interaction with Phe327A, which may enhance binding through aromatic stacking, in addition to a hydrogen bond with Arg119A that likely anchors the compound. For 5FQB, multiple hydrophobic contacts were observed, potentially indicative of deep ligand insertion into a nonpolar cavity. While such

interactions can support stable binding, they may lack specificity. In 7CBG, the significant number of hydrogen bonds, particularly involving Lys54B, suggests a more stable and specific interaction, further reinforced by hydrophobic contacts. In the case of 9FZE, two hydrogen bonds with Asn234A, one with Glu127A, and a hydrophobic interaction with His114A suggest that the ligand establishes multiple connections, indicating good complementarity with the active site. These molecular interactions provide valuable insights into ligand-binding potential and support future structural optimizations aimed at enhancing efficacy and selectivity against the target proteins.

Over the past decade, scientific interest has grown in investigating cannabidiol (CBD) as an antimicrobial agent, particularly against multidrug-resistant (MDR) bacteria. Studies have shown that CBD exhibits potent antibacterial activity against various Gram-positive strains, including methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterococcus faecalis*, *Clostridioides difficile*, and multidrug-resistant *Streptococcus pneumoniae*. In these cases, minimal inhibitory concentrations (MICs) ranging from 1 to 2 μg/mL and comparable minimum bactericidal concentrations (MBCs) were reported, suggesting strong bactericidal activity. Time-kill assays further demonstrated rapid MRSA eradication within two hours of exposure[19].

CBD has also demonstrated efficacy against pathogens involved in periodontal disease. Studies report activity against *Fusobacterium nucleatum* and *Actinomyces naeslundii*, with MICs between 0.39 and 3.12 μg/mL and significant inhibition of biofilm formation ($MICB_{50}$ ranging from 0.39 to 1.56 μg/mL). Notably, in vivo experiments using zebrafish models showed no significant toxicity, supporting the potential for safe topical applications[20]. Similarly, researchers have found that CBD inhibits both growth and biofilm formation by *Streptococcus mutans*, with MIC and MBIC values around 5 μg/mL, making it a promising candidate for managing cariogenic pathogens[21].

On the other hand, CBD displays limited activity against Gram-negative bacteria when used alone. However, synergistic effects have been reported when combined with polymyxin B, effectively targeting MDR strains such as colistin-resistant *Klebsiella pneumoniae* and *Acinetobacter baumannii*. Evidence suggests that CBD acts by disrupting the bacterial cell membrane, leading to lysis, as demonstrated through permeability assays and electron microscopy[22]. Additionally, studies indicate that CBD inhibits the release of outer membrane vesicles in Gram-negative bacteria, potentially impairing their virulence and resistance mechanisms[23].

Despite these promising findings, a notable gap remains in the scientific literature regarding the in silico analysis of CBD's antimicrobial mechanisms. Few studies have explored molecular docking with specific bacterial targets, ligand-receptor interaction predictions, or structural modeling to elucidate the effects of CBD on essential cell wall or membrane components. Expanding these computational approaches could not only deepen our understanding of CBD's mode of action but also support the rational design of novel formulations or CBD-derived compounds with enhanced efficacy and target specificity.

V. Conclusion

The molecular docking analysis conducted in this study reveals that cannabidiol (CBD) exhibits significant binding affinity to key bacterial proteins associated with antimicrobial resistance. The results indicate that CBD interacts favorably with various Gram-positive and Gram-negative bacterial targets, demonstrating distinct interaction patterns that enhance its potential as an effective antimicrobial agent. Notably, the highest affinity was observed with the 7CBG protein, suggesting a strong and specific binding capability, while the stability of the complexes was highlighted by the favorable total energy values for several proteins. These findings provide a compelling foundation for further exploration of CBD as a novel therapeutic option in the fight against multidrug-resistant infections.

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