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Computational Drug Design and Docking Studies for The Identification of Treatments for Leprosy

Shravani Vanarase[1]
[1]Dr. Babasaheb Ambedkar Technological University

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Abstract: By mimicking the interactions between ligands and protein targets, molecular docking is a widely used computational technique that yields both quantitative and qualitative data on binding affinity. It is a key component of Computer-Aided Drug Design (CADD), which is a major component of modern drug development. Subcategories of CADD include Ligand Based Drug Design (LBDD), which makes use of information from known active compounds, and Structure-Based Drug Design (SBDD), where docking is a crucial method. Molecular docking makes it easier to identify and optimize medicinal medications logically because it accurately mimics ligand-protein interactions. Leprosy, often known as Hansen's disease, is a chronic infectious disease caused by Mycobacterium leprae. Despite the availability of efficient multi-drug therapy (MDT), the emergence of resistant strains has made it necessary to investigate new and more potent drug combinations. This article focuses on computational drug design and molecular docking studies to identify a feasible therapy for leprosy. Rifampicin and Clofazimine, two crucial components of MDT, are compared with Dapsone, the main focus drug. To identify its possible mode of action, dapsone's binding interactions with a typical Mycobacterium leprae protein were investigated using computer aided drug design (CADD) and molecular docking approaches. The three-dimensional molecular structures of clofazimine, dapsone, and rifampicin were displayed

Keywords: Clofazimine, Dapsone, Rifampicin, Mycobacterium leprae, Drug Design, Molecular Docking, Leprosy

I. INTRODUCTION

Leprosy, also known as Hansen's disease, is a chronic infectious disease caused by *Mycobacterium leprae*, an acid-fast bacillus discovered by Norwegian physician Gerhard Armauer Hansen in 1873. The disease primarily affects the skin, peripheral nerves, upper respiratory tract, and eyes. *M. leprae* is characterized by its slow growth rate and unique affinity for Schwann cells of peripheral nerves, leading to nerve damage and sensory loss. If left untreated, leprosy can result in severe deformities, disability, and social stigma. Although the global prevalence of leprosy has significantly decreased due to multidrug therapy (MDT), the disease continues to remain a major public health concern in several developing countries, particularly India, Brazil, and Indonesia. According to the World Health Organization, India contributes a significant proportion of newly reported leprosy cases worldwide, emphasizing the continued need for effective diagnosis, treatment, and drug development strategies [1].

Multidrug therapy recommended by the World Health Organization includes the combined administration of Rifampicin, Dapsone, and Clofazimine. Among these, Clofazimine plays a crucial role due to its potent antimycobacterial and anti-inflammatory properties. Clofazimine is a riminophenazine dye that exhibits bactericidal activity against *M. leprae* by interfering with bacterial DNA replication and generating reactive oxygen species within microbial cells. Rifampicin acts by inhibiting bacterial RNA synthesis through interaction with DNA-dependent RNA polymerase, whereas Dapsone inhibits folic acid synthesis in bacterial cells. The combination of these drugs has substantially reduced relapse rates and drug resistance. However, prolonged therapy duration and adverse effects associated with anti-leprosy medications have encouraged researchers to explore novel therapeutic approaches using computational and molecular modeling techniques [2].

Computational drug design and molecular docking have emerged as powerful in-silico methods in modern pharmaceutical research. Molecular docking is a computer-aided technique used to predict the interaction between a ligand (drug molecule) and a target protein or receptor. This method helps in understanding the binding affinity, molecular interactions, and stability of drug-receptor complexes. In recent years, molecular docking studies have become increasingly important in antimicrobial drug discovery because they reduce

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experimental costs and save research time. The present project focuses on the molecular docking analysis of major anti-leprosy drugs, particularly Clofazimine, and compares its interaction profile with other commonly used drugs such as Rifampicin and Dapsone against a representative *Mycobacterium leprae* receptor. Visualization of three-dimensional molecular structures and binding Interactions provides valuable insight into the mechanism of action of these therapeutic agents [3].

The study utilizes student-friendly computational software and publicly available molecular databases to demonstrate the basic principles of structure-based drug design. Three-dimensional structures of anti-leprosy drugs are obtained from chemical databases, while receptor structures are retrieved from protein data repositories. Docking simulations are performed to evaluate parameters such as binding energy, hydrogen bonding, hydrophobic interactions, and ligand orientation within the receptor binding site.

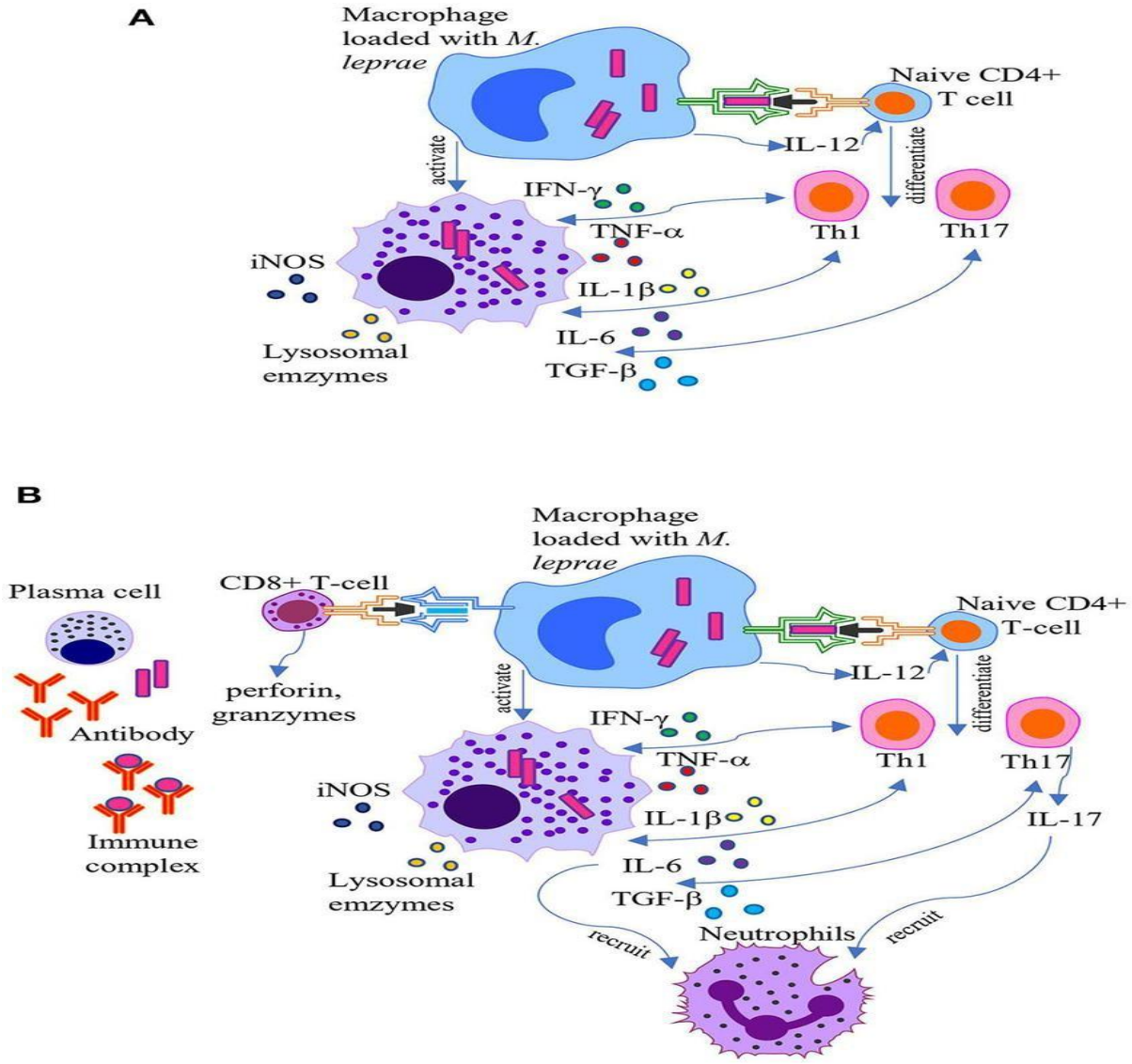

Figure 1: Leprosy pathogenesis and currently available treatments for leprosy.

Such computational approaches allow pharmacy students and researchers to better understand the relationship between molecular structure and biological activity. Furthermore, in-silico studies provide a preliminary platform for screening potential drug candidates before

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conducting extensive laboratory experiments [4].is the term for this kind of docking. In recent years, docking has also been carried out between two macromolecules, such as protein-protein docking. [4]

II. DRUG DISCOVERY & DEVELOPMENT

In order to guarantee the quality and safety of newly developed therapeutic entities that are released onto the market, drug discovery is a very costly and time-consuming procedure. For a single novel tiny molecule, the numerous phases from target assessment to regulatory approval can take up to 14 years and cost more than $1 billion, according to reports. It is also commonly known that one of the greatest failure rates is seen in the pharmaceutical industry. Actually, only one or two compounds out of every 10,000 that are analyzed are believed to have the potential to be used as drugs.

Another major barrier in the medical field is the enormously increased chemical space that makes up the "drug-like" environment. Calculations indicate that such a concept would contain roughly 1060 little molecules, which is more than the number of seconds of existence in the entire universe. Studying such a vast chemical field is even more challenging from an experimental perspective. Even if the most sophisticated high-throughput screening (HTS) methods could evaluate the on-target activity of hundreds of thousands of compounds every week, their capacity would never be able to match the order of magnitude of the potential candidates for that biological entity. This limitation can be overcome by medicinal chemists by shifting the candidate selection process from a laboratory setting to a "virtual environment." One of the first ideas that surfaced was the use of computers to do molecular "virtual" screenings before the experimental ones. Previously referred to as "high-throughput virtual screening" (HTVS), this approach remains one of the main applications of computational methods in drug discovery.[5]

➢ *The Application of Computational Methods in Drug Discovery*

According to the United States Food and Drug Administration (US FDA), the drug discovery process consists of five main steps. The initial phase, referred known as "finding and development," includes hit-to-lead (H2L), hit identification, and lead optimization. In the first of these, a few molecular candidates with a promising activity profile against the chosen target are identified, and pharmacokinetic (PK) or pharmacodynamic (PD) restrictions are discussed. The hit compounds usually have a micromolar (μM) range of action and are not very selective in terms of on-target efficacy. Despite all of these pharmacological problems, the hit compounds are essential for giving the drug design teams some direction and are great starting points for further modifications. The second section discusses the hit-to-lead optimization step. This stage involves altering the hit compounds using a variety of approaches while closely monitoring their PK/PD profile in order to improve their on-target activity and selectivity.

The refined molecular candidates that result from this process are known as "lead" compounds, and they are frequently very selective and active (potency-wise, in the nanomolar range). These drugs then go to the second significant stage, known as the preclinical experimental phase, where animal and organoid models are used to assess their efficacy and safety. The third and longest phase consists of human clinical studies.

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➢ *CADD*

Computer-aided drug design encompasses all computer-assisted techniques for identifying, designing, and refining biologically active compounds that may be used as pharmaceuticals. The three pre-clinical phases of the drug development process that come before clinical trials are target selection, lead identification, and clinical candidate selection. Rapid advances in computer technology and structural biology have made structure-based computer-aided drug design (CADD), which employs target/structure focusing combinatorial chemistry, virtual screening, library design, and docking techniques, a powerful tool in the multi-step drug development phase.

To turn physiologically active molecules into suitable medications by improving their physicochemical, pharmaceutical, and ADMET/PK properties, CADD is used to identify active drug

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candidates, select leads, and optimize leads. In pharmaceutical research, the term "biological target" is often used to refer to the native protein in the body whose activity is altered by a medication, producing a desired therapeutic effect.

➢ ***Capabilities of CADD Include:***

Virtual screening of datasets with over 6 million different chemicals employing high-throughput docking, 2D similarity searches, and 3D pharmacophore searches Targetfocused compound library design; lead optimization using structure- or ligand-based design; chemical library profiling and filtering for molecules with desired drug-like and DMPK properties; quantitative structure activity relationships (QSARs) establishment; computer modeling of DMPK properties, including CYP inhibition and metabolism

➢ *The Following are the Two Primary Techniques to Drug Design Using CADD:*

- Direct approach/ Structure-based medication design
- Indirect approach/ Ligand-based drug design [6]

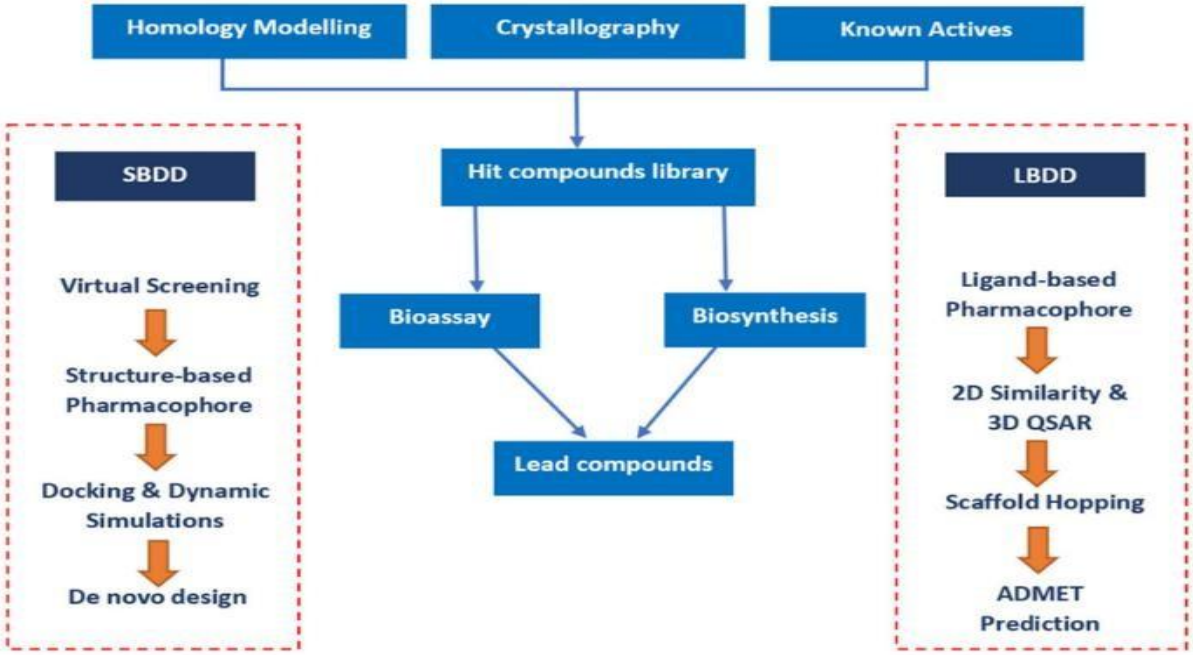

Figure 2 : Traditional approaches in ligand-based drug design (LBDD) and structure-based drug design (SBDD) use different techniques. Whereas LBDD depends on known ligand properties, SBDD concentrates on target biomolecule structures. [1]

➢ ***Structure-Based Drug Design (SBDD)***

The trend in computational drug design methodologies shifted toward alternative approaches that could also consider the three-dimensional interactive features of the molecules with respect to the target due to the exponential growth in the availability of three-dimensional structures of proteins and nucleic acids, which began about in the 2000s. In fact, the scientists were greatly aided by their prior understanding of the biological entity of interest, which allowed them to create new chemical species based on the properties of its binding site. The family of "structure-based drug design" (SBDD), which is by far the most popular method in computational drug discovery, includes all techniques based on this type of data.

SBDD is lock-and-key binding, in which a drug molecule attaches itself to a particular location on the target protein in a manner like how a key fits into a lock. Depending on the type of interaction, the drug molecule binding to the target protein may either promote or inhibit the protein function. Finding the target protein's three-dimensional structure is the initial stage in SBDD. Techniques like cryoelectron microscopy, NMR spectroscopy, and X-ray crystallography can be used to do this. Finding tiny compounds that can attach to the target protein and

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alter its activity comes next once the target protein structure has been determined.

A computational method for predicting how tiny compounds will connect to the target protein is called "molecular docking." Molecular docking involves screening a library of small molecules for their capacity to attach to the binding site of the target protein. For additional testing, the compounds that exhibit the best fit are chosen. [7]

➢ ***Ligand-Based Drug Design (LBDD)***

Ligand-based drug design (LBDD), another name for indirect drug design, helps find new small compounds that bind to protein targets. To predict putative active sites, generate similar structures, perform molecular docking with active ligands, catalyze binding interactions, and optimize the lead ones to improve their binding properties, efficacy, and safety, the drug molecules supported by bioinformatics tools are identified by the silico procedures used here. These molecules are then further investigated on various platforms.

Substances can now be identified as targets very systematically using specific, state-of-the-art computational techniques because there is no reliable 3D macromolecular structure. The potency of a lead compound as well as its absorption, distribution, metabolism, excretion, and toxicity (ADMET) characteristics are predicted using matched molecular pair (MMP) analysis, Free-Wilson models, and quantitative structure-activity relationship (QSAR) models based on experimental data sets.

Conformational analysis plays a major role in determining the flexibility and behavior of molecules for bioactive conformation.

➢ ***Quantitative Structure Activity Relationships (QSAR)***

Quantitative Structure-Activity Relationship (QSAR) is a useful technique for drug design, which is a crucial step in the process of finding novel medications. Using characteristics known as molecular descriptors, QSAR is a statistical method that connects a molecule's structure to its biological activity. Because of this, QSAR is a useful technique for creating medications that work. Density Functional Theory (DFT)-based chemical characteristics are used by QSAR to investigate compounds.

Since they describe the molecular characteristics associated with activities, selecting the appropriate descriptors from a wide range of alternatives is a major challenge. To enhance the study of these activities, new
QSAR techniques have been created.[8]

 Different Descriptors:

- ✓ Topological descriptor
- ✓ Geometrical descriptor
- ✓ Molecular descriptor
- ✓ Thermodynamic descriptor
- ✓ Constitutional descriptor
- ✓ Electronic descriptor

III. MOLECULAR DOCKING

➢ ***Aim:***

The main objective of molecular docking is to predict the most stable interaction between a ligand and a target receptor by identifying the best possible binding orientation at the active site. The technique helps in determining how a drug molecule fits into the binding pocket of a protein while maintaining minimum energy conditions for stable complex formation. Molecular docking is widely used to estimate binding affinity, binding position, and molecular interactions between the receptor and ligand. It plays a significant role in modern drug design and discovery by helping researchers identify potential drug candidates, understand mechanisms of action, and optimize the effectiveness of therapeutic compounds before laboratory experimentation. Therefore, molecular docking serves as an important computational tool in the development of safer and more effective medicines.

➢ ***Objective:***

- Ligand-protein docking is an optimization issue that relies on ligand energy position prediction.
- Single-objective and multi-objective methods are typically used to solve molecular docking problems to decrease the binding with the lowest binding energy in the receptor's active site.
- A novel multi-objective formulation that considers the binding (intermolecular) energy and the Root Mean Square Deviation (RMSD) variation in ligand coordinates as two objectives to assess the quality of the ligandprotein interactions.
- Using multi-objective algorithms to identify a group of representatives.

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- The performances have been evaluated using two primary quality indicators designed to gauge front variety and convergence.

- Additionally, AutoDock, a reference single-objective evolutionary method for molecular docking, is compared with LGA.
- In silico docking investigations to choose novel anticancer drugs for therapeutic targets that are multidrug resistant, this new multi-objective approach demonstrates an improvement over the ligand-protein docking predictions that may be promising. [10]

➢ ***Scope***

Molecular docking and computer-aided drug design (CADD) offer a quick and economical way to find and refine possible therapeutic candidates prior to laboratory testing. By predicting how tiny molecules interact with biological targets, these techniques enable early screening of drugs with attractive pharmacokinetic profiles and high binding affinities. Docking makes it possible to compare several pharmacological compounds for target specificity, identify important binding residues, and visualize ligand–protein interactions. Supporting lead optimization, ranking compounds for synthesis, cutting down on experimental burden, and expediting the entire drug development process are all included in the scope.

When combined, CADD and docking provide a potent platform for logical drug design, target validation, and the identification of promising therapeutic compounds for additional in-vitro, in-vivo, and clinical testing.

➢ ***Principles of Molecular Docking***

One of the main issues in structural biology is molecular recognition. Almost every biological event involves the interaction of molecules, whether they are large macromolecules or tiny ligands. Medicinal chemists have been working to precisely alter these interactions for over a century. To create therapeutic drugs more quickly, we need to be able to both understand and anticipate the structural characteristics of recognition events. If we had a complete understanding of the basis for complementarity, we could make predictions for the purpose of drug design. In recent years, molecular docking has become an essential part of computer simulation-based drug development.

This method entails forecasting the atomic-level interactions between a protein and a small molecule. By examining the actions of tiny substances, like nutraceuticals, inside the target binding site, researchers can better comprehend proteins and the basic metabolic mechanism underlying this interaction. The strategy is effective. The method relies on the target protein structure, which must be obtained in a high-resolution, three-dimensional format using technology. Xray crystallography, NMR spectroscopy, and cryo-EM7 are examples of analysis methods.

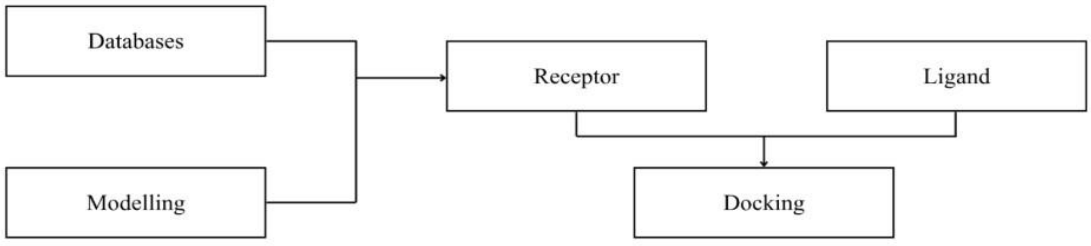

Figure 3: Basic Molecular Docking Procedure [9]

 Docking Types Include:

1. Rigid docking (lock and key): Where a ligand and receptor have rigid geometries.
2. Flexible docking: In this kind of docking, molecules rotate with each rotation.

The characteristics of assessed docking programs

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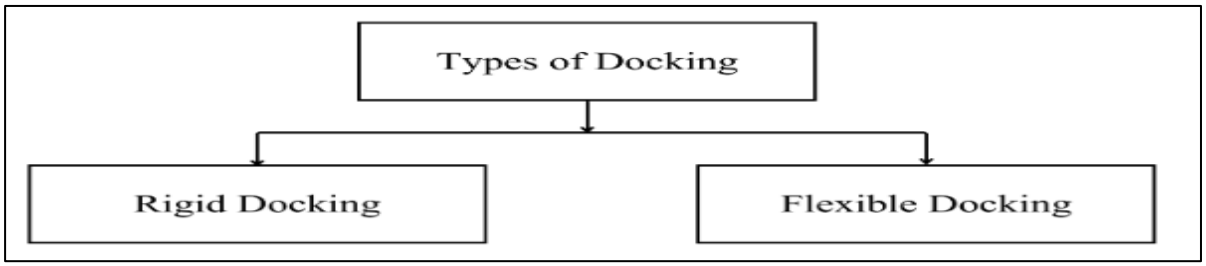

Figure 4: Types of Docking

 Docking Can be Between:

- ✓ Protein- ligand.
- ✓ Protein- protein.
- ✓ Protein- nucleotide.

 Types of Interactions:

- ✓ Electrostatic forces.
- ✓ Electrodynamics forces.
- ✓ Steric forces.
- ✓ Solvent related forces.

 Key Stages in Docking

- ✓ Target selection and preparation
- ✓ Ligand selection
- ✓ Docking-Evaluating docking result [10]

➢ *Various Docking Approaches:*

- *The Monte Carlo Method:*

This method works well for creating a ligand's initial orientation at the active site with translation and random conformation rotation. It has the ability to score both the initial orientation and a newly generated arrangement. The ability of a new configuration to be retained can be assessed using a metropolis criterion. The Metropolis criterion is predicated on accepting new solutions right away, but only if they are superior to the preceding one. If a configuration is determined not to be novel, a Boltzmann-based probability function is used.

- *Fragment-Based Approach:*

As the name implies, this approach primarily relies on the division of ligands into fragments or little protons, which is then followed by the docking process and, lastly, the joining of docked fragments.

- *Distance Geometry:*

Intramolecular or intermolecular distances have been used to communicate information about the structure. This geometry first calculates the distance and then the consistency of 3-d structures is calculated with these distances.

- *Matching Approach:*

The complementarity between the ligand and the protein serves as the fundamental foundation of the matching strategy. This method creates the ligand-receptor configuration by positioning the ligand atom at the optimal location within the protein. This configuration may need to be further optimized.

- *Ligand Fit Strategy*:

This strategy is based on the shape of similarity between the active regions of proteins and ligands. As a result, it helps with quick and precise techniques for docking ligands of smaller molecules into protein active sites.

- *Point Complementarity Approach:*

This method seeks to assess the chemical complementarity and shape of the molecules that create interactions.

- *Blind Docking:*

This docking technique is used to identify potential binding locations. Additionally, the targeted proteins' entire surface can be scanned to determine the peptide ligand's fashion.

- *Inverse Docking:*

This docking process makes use of computer techniques to identify the side effects and toxicity of small molecular protein targets. The comprehension of these proteins' capabilities

➢ *Application of Molecular Docking:*

- *Hit Identification:*

When paired with a scoring system, docking provides rapid in silico screening of a wide range of potential treatments to identify compounds that can bind to a single target of interest

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• *Lead Optimization:*
Docking, also referred to as the binding mode or pose, is a method for estimating the exact position and separation of a ligand's attachment to a protein. The previously supplied data can be used to create mimics that are more potent and accurate.

• *Drug Discovery:*
By forecasting how small molecules will bind to a polypeptide or receptor, molecular docking is utilized to identify possible pharmacological replacements. To improve a lead compound's binding affinity and selectivity, its structure can also be changed

• *ADMET Prediction:*
Molecular docking may be able to mimic small molecule characteristics such Shock Absorption, Distribution of Benefit, Metabolism or Flushing, and Neurotoxicity (ADMET, which stands).

• *Clarification of structure:*
Molecular docking can help confirm the structures of antibodies with ambiguous geometries.

• *Target Fishing:*
Molecular docking can be used to identify particular proteins that the drug may work through.

• *Nutraceutical Research:*
Molecular docking can be used to better define the cellular targets of nutraceuticals for medical usage.

• *Bioremediation:*
Molecular docking can be used to identify enzymes and how they are activated. Finding connections between proteins is also crucial. The restoration treatment is used to
electronically examine molecules. [8]

IV. MATERIALS AND METHODS

The method entails studying the intermolecular interactions between two molecules, such as a ligand and receptor, in silico. The protein receptor is a macromolecule, and the ligand is a macromolecule that functions as an inhibitor. The method includes:

➢ ***Step I: Identification of Molecular Target***
The crystal structures of the molecular targets were selected based on an extensive literature survey. DHPS [1EYE] were retrieved from the RCSB Protein Data Bank for further analysis.

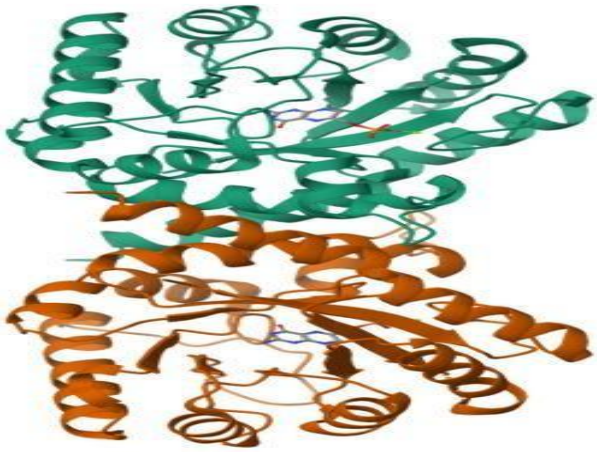

Figure 5 : Structure of protein [1EYE]

➢ ***Step II: Target Protein Preparation***
The target protein crystal structure was loaded into UCSF ChimeraX for preprocessing after being obtained from the RCSB Protein Data Bank (PDB). All non-standard residues and heteroatoms were selected and deleted. The processed protein structure was then saved as protein.pdb for further docking studies.

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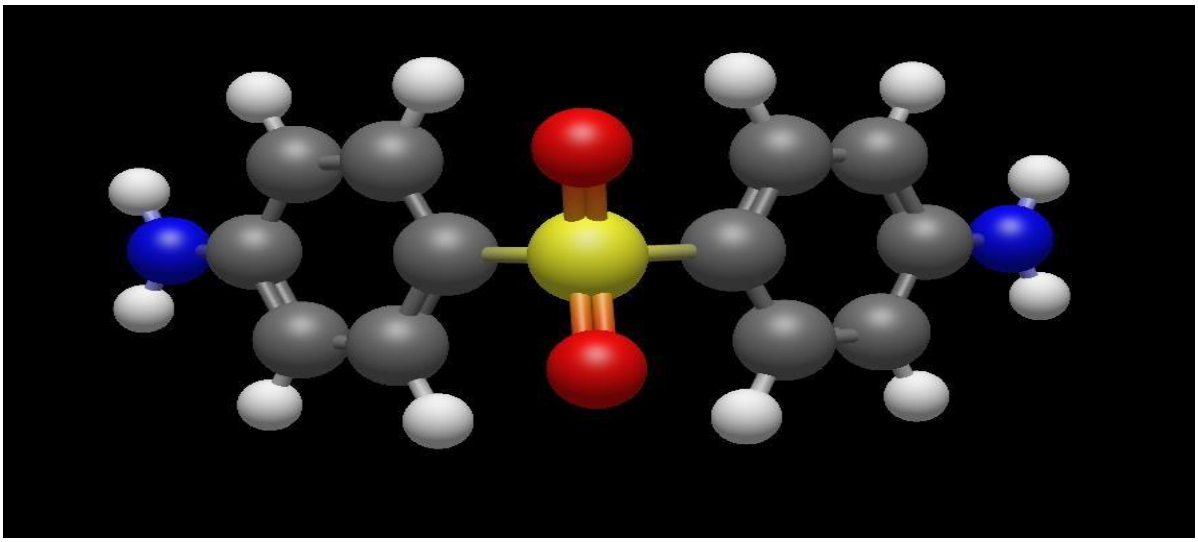

Figure 6: Ligand Preparation of Dapsone

➢ ***Step III: Ligand Selection and Preparation***

The ligand was selected from the PubChem database and downloaded in 3D SDF format. It was then opened in Avogadro, where hydrogens were added, and geometry optimization was performed until the structure stabilized. The optimized ligand was saved in ligand.mol2 format for further use.

➢ ***Step IV: Docking*** *:*

The prepared ligand (ligand.mol2) and target protein (protein.pdb) were subjected to docking using AutoDock.

The resulting docked complexes were analyzed, and the best binding conformation was selected based on the lowest binding energy for studies.

➢ ***Step V: Prediction of Active Site:***

Active site prediction and interaction analysis for the Dihydropteroate synthase [DHPS] proteins were performed using AutoDock and visualized with AutoDockTools (ADT).

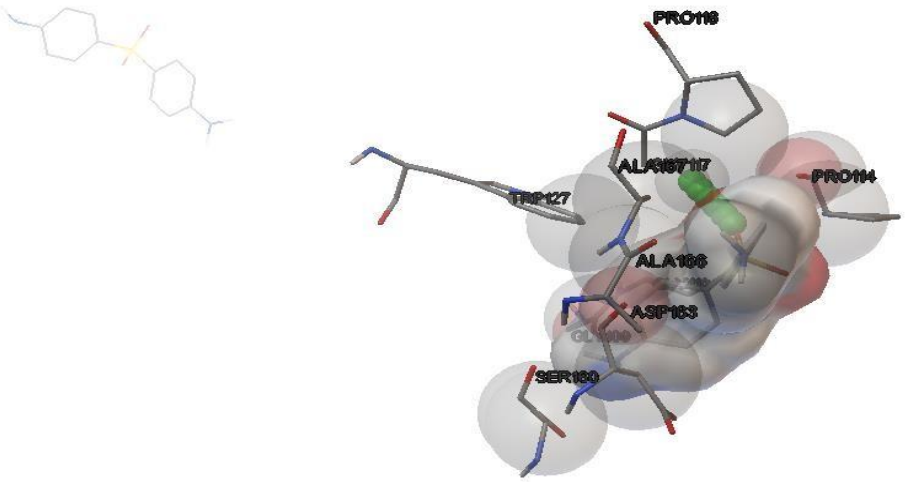

Figure 7: Binding modes of Ligands with DHPS [1EYE]

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For *DHPS [PDB ID:1EYE*], the active site was defined by *PRO118, TRP127, GLY117, ALA167, PRO114, ALA166, ASP163, SER16, GLY110 and GLY109.*

	Key Features	Website
UCSF ChimeraX	Protein preparation, visualization, and analysis of molecular interactions.	https://www.cgl.ucsf.edu/chimera/
Avogadro	Ligand structure building, optimization, and energy minimization.	https://avogadro.cc/
MGL Tools (Auto Dock)	Molecular docking and binding affinity prediction.	https://ccsb.scripps.edu/mgltools/
BIOVIA Discovery Studio Visualizer	Visualization of docked complexes and interaction analysis.	https://discover.3ds.com/discovery-studio-visualizer-download
Swiss ADME	Prediction of pharmacokinetic and drug-likeness properties (ADME).	http://www.swissadme.ch/
Pro Tox-II	Toxicity prediction and LD_{50} estimation of compounds.	https://tox-new.charite.de/protox_II/

Table No.1 Docking Tools

V. ADMET PREDICTION

This compound ($C_{12}H_{12}N_2O_2S$; MW 248.3 g/mol) seems to be a tiny, completely aromatic molecule with good oral drug-like qualities based on its physicochemical features. Its balanced hydrogen-bonding capacity (2 donors, 2 acceptors) and moderate polarity (TPSA = 94.6 Å²) promote good permeability through the gastrointestinal tract, which is consistent with the expectation of high GI absorption. The moderate lipophilicity indicated by the consensus logP of 1.55 offers a good trade-off between water solubility and membrane permeability. In fact, depending on the model, the projected water solubility varies from soluble to moderately soluble, which is typically beneficial for oral formulations. Because of its relatively high polarity and minimal lipophilicity, the chemical is not expected to penetrate the blood–brain barrier. Additionally, it is not a substrate of P-glycoprotein, which allays worries about efflux-related bioavailability problems. Furthermore, there is no anticipated inhibition of the main CYP450 isoforms, indicating a low risk of drug-drug interactions related to metabolism

From the perspective of medicinal chemistry, the chemical has a typical bioavailability score of 0.55, indicating favorable oral drug potential, and it fulfills all main drug-likeness filters (Lipinski, Veber, Egan, Ghose, and Muegge). The synthetic accessibility score (1.92) indicates that the molecule should be simple to manufacture, and there are no PAINS alarms. The sole structural issue that has been raised is the presence of an aniline moiety, which occasionally presents toxicity or metabolic problems and may need more research. The compound's entirely aromatic, flat structure (Csp^3 = 0.00) may limit three-dimensionality, however this can be adjusted during optimization, and it is marginally smaller than what some criteria consider ideal for a lead. All things considered, the profile points to a potential, easily adjustable early-stage lead with favorable oral characteristics and low ADME liabilities aside from the aniline alert and lack of CNS exposure.

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Table 2 ADME Analysis

Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-7.13 cm/s

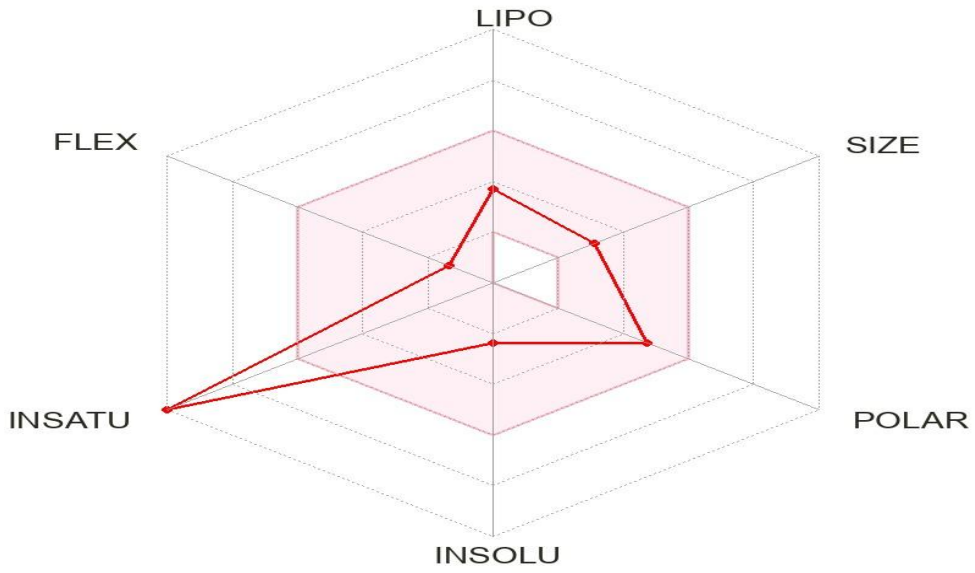

Figure 8 : Bioavailability Radar plot for dapsone calculated using the SwissADME web tool

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Toxicity Prediction :

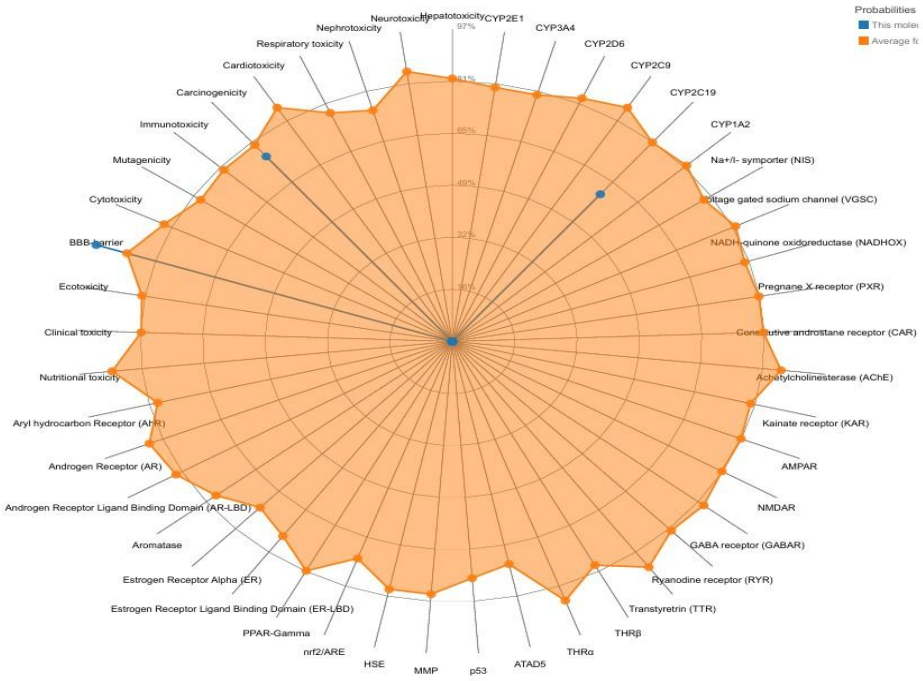

Fig9: Toxicity radar chart of drugs showing organ and endpoint predictions generated using ProTox-II

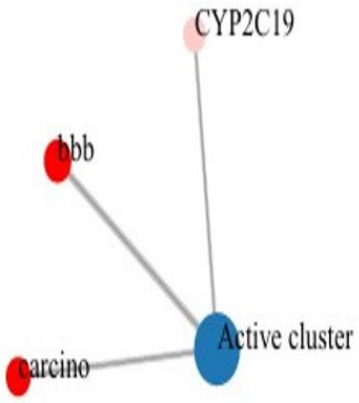

Figure 10 : Network chart of drugs predicted toxicity targets generated using ProTox-II

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VI. RESULTS

AutoDock 4.2.6 was used to perform molecular docking investigations of the target proteins dihydopteroate synthase [DHPS]: Dapsone, Clofazimine. Each chemical's docking results were examined using binding affinity (kcal/mol) and inhibition constant (Ki).

Rank	Run	Binding Energy
1	5	-5.79
2	10	-5.61
2	4	-5.43
3	6	-5.03
4	7	-4.90
5	3	-4.79
6	8	-4.69
7	2	-4.64
8	9	-4.36
9	1	-4.22

Table 3 : Molecular Docking results of Dapsone with DHPS

DISCUSSION :

Molecular Docking Studies:

The docking results validate dapsone's known function in interfering with folate production by confirming that it binds firmly to the active site of DHPS in Mycobacterium leprae. Its efficacy in contemporary multidrug therapy is explained by the anticipated interactions, primarily hydrogen bonds and hydrophobic contacts. Variations in dapsone's binding to mutant DHPS models point to the potential role that structural alterations in the enzyme may play in drug resistance.

The sulfone and amine groups, which are crucial for binding and can serve as building blocks for the creation of better analogues, are two more important chemical characteristics of dapsone that are highlighted in this work. Docking gives useful insights that can direct additional computational screening and experimental validation, despite the fact that it only presents a simplified, static representation of the drug–target interaction. Overall, the results show how computational tools can help uncover improved leprosy therapies and underscore the significance of DHPS as a therapeutic target.

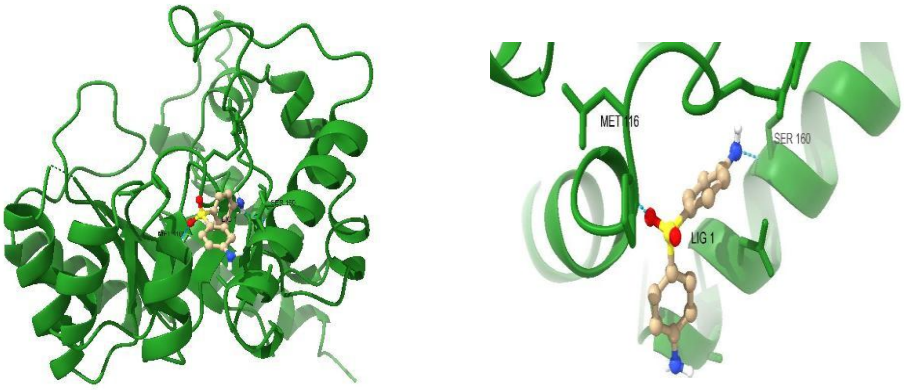

Figure 11 : 3D visualisation molecular docking of dapsone with target DHPS [1EYE]

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VII. FUTURE PROSPECTIVES:

The present study lays the basis for creating better leprosy treatments by proving the use of molecular docking and computational drug design in studying the relationship between dapsone and DHPS. To gain a better understanding of binding mechanisms and resistancerelated effects, future studies can use sophisticated molecular dynamics simulations to examine the stability and conformational flexibility of the dapsone–DHPS complex under dynamic settings. Including free-energy calculations, like MM-PBSA or alchemical techniques, can help prioritize interesting analogues and improve the accuracy of anticipated binding affinities. Comprehensive virtual screening of natural compounds, synthetic sulfonamide derivatives, and FDA-approved medications may identify new scaffolds with enhanced pharmacokinetics, decreased toxicity, and increased potency.

To get over resistance brought on by DHPS mutations, dapsone can be rationally modified using structural insights from docking, such as bioisosteric substitutions and aromatic ring modifications. Further, multi-target drug design strategies that target DHPS in addition to other crucial enzymes like RNA polymerase, DHFR, or fatty acid synthases may increase efficacy and lower the risk of resistance development. One effective way to speed up drug discovery is to use artificial intelligence and machine learning models to anticipate binding affinities, create new compounds, and improve drug-like qualities.

Early in the screening process, ADMET and toxicity predictions can assist in choosing safer, drug-like candidates, while complementary homology modeling of other M. leprae proteins can increase the pool of verified targets. To turn these discoveries into useful treatments, in vitro and in vivo research will be necessary to experimentally validate computer predictions. Future studies have great potential to generate next-generation anti-leprosy medications with increased efficacy, decreased resistance potential, and better patient outcomes by integrating these computational techniques with focused experimental research.

VIII. CONCLUSION:

The molecular basis of action of dapsone against Mycobacterium leprae is elucidated by molecular docking studies and computational drug design. Its well-established mechanism as a competitive inhibitor of folate metabolism is supported by the studies, which consistently demonstrate that dapsone has sustained binding interactions with major enzyme targets involved in folate synthesis, most notably dihydropteroate synthase.

Dapsone has a long history of clinical use, and its excellent oral bioavailability, sufficient solubility, and modest expected CYP inhibition are further supported by physicochemical and ADME predictions. Dapsone's efficacy as an efficient chemotherapeutic treatment for leprosy is further supported by its strong docking affinity, dependable binding modalities, and lack of significant structural warnings. All things considered, these computer results support current pharmacological understanding and demonstrate dapsone's ongoing significance. They also offer a foundation for the logical creation of better analogs with increased potency or decreased toxicity.

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