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Structure based Docking of Secondary Metabolites against DrpE1 to Treat Tuberculosis

Vikas Singh[1], Noopur Khare[2], Monika Bajpai[3], Abhimanyu Kumar Jha[4]
[1, 3. 4]*Department of Biotechnology, Faculty of Life Sciences, Institute of Applied Medicines & Research, Ghaziabad ,U P, India.*
[2] *Shri Ramswaroop Memorial University, Barabanki, Uttar Pradesh, India.*

Abstract: Background: Tuberculosis (TB) is one of the most infectious diseases in the current scenario, triggered when the body detects Mycobacterium tuberculosis. Since tuberculosis is a communicable disease or transferable disease, it is easily transmitted via the inhalation cycle of air droplets carrying the particular bacteria to another person who remains in contact with the infected person. The in silico study was conducted with the help of molecular docking to treat tuberculosis to inhibit the activity of DrpE1 by drug molecule.

Methods: All the studies were based on docking with molecules. Docking was done with the aid of docking software between all the ligands and the target protein DrpE1 (PDB ID: 4FDN). We picked several natural compounds, such as Thiophenes, Sulfonamides, Benzimidazole, Lidamycin and protein target as DrpE1 (PDB ID: 4FDN). After Biovia Discovery Studio Visualizer 's protein preparation we imported all of the ligand for virtual screening into PyRx software. Benzimidazole was the strongest compound against DrpE1, with its low binding strength, according to the PyRx test and Lipinski 's Rule of Five.

Results: For molecular docking between Benzimidazole and the DrpE1 receptor protein (PDB ID: 4FDN) the Biovia Discovery Studio Server 2020 and AutoDockVina applications were used. The test revealed 9 poses with different binding affinities, Root means Lower Bound (RMSD LB) square deviation, and Upper Bound (RMSD UB) mean square deviation. Via Biovia Discovery Studio Client 2020 the same molecules were further docked, and the interaction was visualized under PyMol.

Conclusion: According to the in silicostudy, Benzimidazole was the only compound which can inhibit the activity of DrpE1 (PDB ID: 4FDN). So in the further studies, Benzimidazole can be a promising drug for the treatment of tuberculosis after its in vitro and in vivo studies.

Keywords: Tuberculosis, Mycobacterium tuberculosis, Benzimidazole, DrpE1

I. INTRODUCTION

Tuberculosis (TB) is one of the most infectious diseases in the current scenario that is caused when the body finds *Mycobacterium tuberculosis*[1]. Since tuberculosis is a communicable disease or transferable disease, it is easily transmitted via the inhalation cycle of air droplets carrying the particular bacteria to another person who remains in contact with the infected person. Tuberculosis affects primarily the lungs but it can also affect other organs. Once this bacteria meets inside the body, the immune cells check and track pathogen. Nevertheless, this disease remains latent but can become active at any time after a few years when the adaptive immune system becomes active[2]. The bacterium is thought to have originated in eastern Africa. As early humans left East Africa and settled in Europe and Asia, TB infection spread with them and continued to wreak havoc in the known world for centuries [3].

Mycobacterium tuberculosis is a soil-borne Pathogen. When inhaled, droplets containing the mycobacteria pool all over the airways. Most of the bacilli are trapped in the upper parts of the airways where there are the goblet cells which secrete the mucus. The mucus attracts the invading bacilli, and the cilia on the surface of the cells are continually undulating to push the mucus upwards and capture foreign particles for removal[4]. This method gives the body initial physical protection which prevents infection in most people exposed to tuberculosis [5]. *Mycobacterium tuberculosis* is a large, non-motile, aerobic bacterium which is having slow growth. This has a predilection for the oxygenated atmosphere of the upper lobes of the lungs as an essential aerobe[6]. *M. Tuberculosis* has a doubling duration of 18 hours, and it may take about 6–8 weeks for clinical cultures. This is resistant to dehydration, and can thus exist in expectorated sputum. Morphologically, the bacterial cell wall contains a range of complex lipids such as mycolic acids, long-chain fatty acids that promote acid-fast characteristics; wax D; and phosphatides that lead to the clinically important features of caseating necrosis [7]. Bioinformatics plays a significant role in the search for targets and compounds for the disease treatment. Computational docking is widely used to study the interactions between protein-ligand, and to discover and construct drugs. The procedure usually starts with a well-known target structure, like the crystallographic structure of a medicinal interest catalyst. The tying up is then used to predict small molecular conformation and bind free energy to the target. Single docking experiments are useful in testing target efficiency, and virtual screening is also used to classify new drug development inhibitors when an outsized compound library is docked and rated [8].

II. METHODOLOGY

A. Identification and Selection of Target Protein

The literature identified disease causing protein. The protein molecule structure DrpE1 (PDB ID: 4FDN) which is a protein-causing tuberculosis has been downloaded from the Protein Data Bank (PDB) (http:/www.rcsb.org/). The structure of the protein molecules was retrieved in the format of .pdb[9]. Protein molecule stability was tested via Rampage (http:/mordred.bioc.cam.ac.uk/~rapper / rampage.php).

B. Selection of Ligand Molecules

Ligands were selected from various phytochemical constituents of the plants. Such ligand molecules were obtained by PubChem (https:/pubchem.ncbi.nlm.nih.gov/). The ligands were downloaded as 3D structure in.sdf format[10]. All downloaded ligand structures were further translated into.pdb format through the online SMILES Converter (https:/cactus.nci.nih.gov / translate/). The converted files are downloaded in the .pdb format. These .pdb files were used to run different resources and applications.

C. Preparation of Protein Molecule

Biovia Discovery Studio Visualizer made the general protein molecule preparations. This software measured the different properties of the protein molecule. The protein was loaded in.pdb format and analyzed by choosing water molecules and ligands to analyze its hierarchy. The bound ligand molecules were isolated from the protein molecule, and also removed from water molecules. The structure of protein crystals was further saved in the format of.pdb.

D. Virtual Screening of Ligands

Ligand screenings were conducted via PyRx software. This device was used to screen several ligands that had insufficient energy binding to the target protein. Ligands found to have minimal binding energy have been tested for an examination of drug likeliness property properties. PyRx runs in the .pdbqt format. PyRx's procedure starts with the loading of protein molecule, which was first translated from.pdb into.pdbqt format, and then imported ligands from the specific folder in.sdf format. The energy of Ligands was reduced, with the conversion of file.sdf to file.pdbqt. The docking was carried out between the protein target and the ligand molecule, and the minimum binding energy ligands were screened [11].

E. Drug Likeliness Property Analysis

Analysis of the properties of drug likeliness was done via online server i.e. SwissADME. The ligands screened were analyzed for their property on drugs. SMILE screened ligand notations were copied from PubChem and pasted on SwissADME online web server [12]. Drugs for the five-fold Lipinski law were analyzed. Lipinski rule of five states the following points:-

1) Hydrogen bond donors should be less than 5.
2) Hydrogen bond acceptors should be less than 10.
3) The molecular weight should be less than 500 Dalton.
4) Partition coefficient LogP should be less than 5.
5) Not more than 1 rule can be violated.

The ligands which followed the above Lipinski rule of five were selected for final docking through AutoDockVina and Biovia Discovery Studio Client 2020.

F. Final Docking Through AutoDockVina and Biovia Discovery Studio Client 2020

The best selected ligand was selected for final docking through AutoDockVina and BioviaDiscovery Studio Client 2020.

1) *AutoDockVina*- The protein target in.pdb has been loaded to graphical windows of AutoDockVina. The protein target was prepared for docking in.pdb format by removing water molecules, adding polar hydrogen atoms and attaching Kollman charges to the protein molecule, and finally saving protein in.pdbqt format. Ligand molecule has been imported into.pdb format and translated to .pdbqt format. After that grid box the area was selected for docking. AutoDockVina was executed and the results were analyzed using the command prompt [13].
2) *Biovia Discovery Studio Client 2020*- Biovia Discovery Studio Client 2020 also conducted ligand docking of protein targets. The target protein (DNMT1) was loaded onto the platform and the ligand (Benzimidazole) in.pdb format followed. Protein molecule was added to the charges, and the ligands minimized energy. All the protein molecule and the ligand molecule were able to dock. The results were analyzed after docking based on Absolute Energy, Confg Number, Mol Number, Relative Energy

and Pose Number. Under the visualisation tool of the structure, i.e. Biovia Discovery Studio Visualizer and PyMol, analysed the relationship between the protein and the ligand molecule.

G. Structure Visualization through PyMOL

Structure visualization was done with the PyMOL method. PyMOL is an open-access instrument. The protein molecule in the form of.pdbqt was loaded on PyMOL 's graphical screen, followed by the output of the .pdbqt file. The docked structure was visualised and converted to "molecular surface" under the option "shown as"[14].

III. RESULTS AND DISCUSSION

The crystal structure of DrpE1 in .pdb format was retrieved from Protein Data Bank as shown in Figure 1. DrpE1 belongs to oxidoreductase class, the resolution of protein was 2.65Å, R- value free was 0.198, R- value observed was 0.173.The stability of protein was analyzed through Rampage as shown in Figure 2. Secondary metabolites from different plants were retrieved from PubChem online database. The structures of Thiophenes, Sulfonamides, BenzimidazoleandLidamycinwere downloaded in .sdf format as shown in Table 1.The downloaded structure were converted into .pdb format.

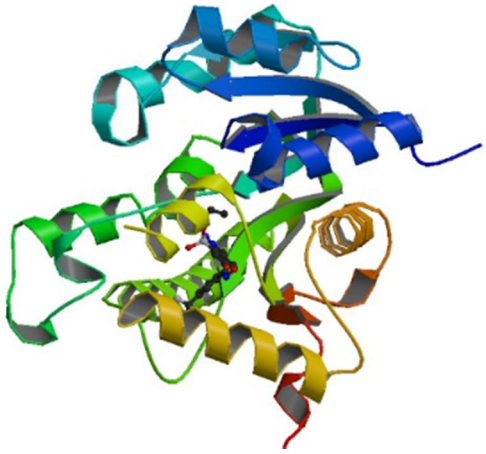
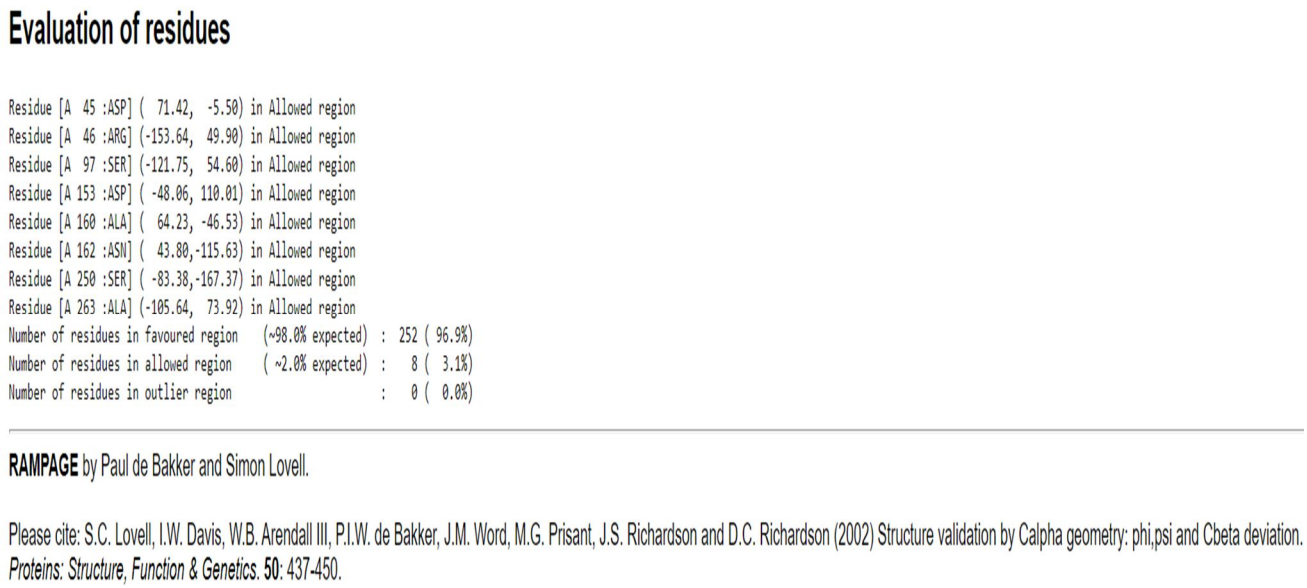


Figure 1: The crystal structure of human DrpE1



Evaluation of residues

Residue [A 45 :ASP] (71.42, -5.50) in Allowed region
Residue [A 46 :ARG] (-153.64, 49.90) in Allowed region
Residue [A 97 :SER] (-121.75, 54.60) in Allowed region
Residue [A 153 :ASP] (-48.06, 110.01) in Allowed region
Residue [A 160 :ALA] (64.23, -46.53) in Allowed region
Residue [A 162 :ASN] (43.80,-115.63) in Allowed region
Residue [A 250 :SER] (-83.38,-167.37) in Allowed region
Residue [A 263 :ALA] (-105.64, 73.92) in Allowed region
Number of residues in favoured region (~98.0% expected) : 252 (96.9%)
Number of residues in allowed region (~2.0% expected) : 8 (3.1%)
Number of residues in outlier region : 0 (0.0%)

RAMPAGE by Paul de Bakker and Simon Lovell.

Please cite: S.C. Lovell, I.W. Davis, W.B. Arendall III, P.I.W. de Bakker, J.M. Word, M.G. Prisant, J.S. Richardson and D.C. Richardson (2002) Structure validation by Calpha geometry: phi,psi and Cbeta deviation. *Proteins: Structure, Function & Genetics.* **50**: 437-450.

Figure 2: Rampage Result

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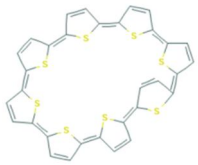
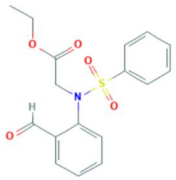
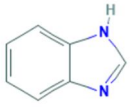
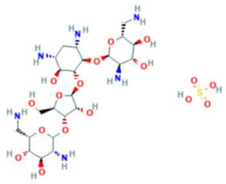
Table 1: Structure of Ligands

Structure	Ligand	PubChem ID
	Thiophenes	CID: 102188099
	Sulfonamides	CID: 91392493
	Benzimidazole;	CID: 5798
	Lidamycin	CID: 62403

All the seven ligands Thiophenes, Sulfonamides, Benzimidazoleand Lidamycin were subjected for virtual screening through PyRx software. The binding affinity of Thiophenes was -7.5Kcal/mol, root mean square deviation lower bound was 2.577 (RMSD) and RMSD upper bound was 7.636, Sulfonamideswas -6.1Kcal/mol, root mean square deviation lower bound was 0.053 (RMSD) and RMSD upper bound was 1.94, Benzimidazolewas -7.5Kcal/molroot mean square deviation lower bound was 1.954 (RMSD) and RMSD upper bound was 4.469, Lidamycin was -11.8Lcal/molroot mean square deviation lower bound was 1.965 (RMSD) and RMSD upper bound was 3.422Table 2. The binding energy of Thiophenes was -7.2, Sulfonamides was -6.1, Benzimidazolewas -7.8, Lidamycinwas -11.8 as depicted in Table 3.

Table 2: The Binding affinity, RMSD lower bound and RMSD upper bound of different ligands with protein molecules.

Ligand molecule	Pub chem ID	Binding energy from docking result	Binding affinity (kcal/mol)	RMSD lower bound	RMSD upper bound
Benzimidazole	5798	-7.6	-7.5	1.954	4.469
Sulfonamides	91392493	-6.1	-6.1	0.053	1.94
Lidamycin	42593	-11.8	-11.8	1.965	3.422
Thiophenes	102188099	-7.3	-7.1	2.577	7.636

Table 3: The Binding energy of different ligands with protein molecules.

Ligand Molecule	Binding energy (from docking result)
Benzimidazole	-7.6
Sulfonamides	-6.1
Lidamycin	-11.8
Thiophenes	-6.4

According to PyRx results it was concluded that Quinolone, Benzimidazole; ,Lidamycinand Thiophenesshowed minimum binding energy. The screened molecules Quinolone, Benzimidazole;, Lidamycinand Thiophenes were analysed for drug likeliness property analysis. The screened three ligands were analysed by SwissADME online web server. Further the ligands were screened on the basis of qualifying Lipinski Rule of five. Theligands were analysed for the its Molecular weight, Hydrogen bond donor, Hydrogen bond acceptor, Partition coefficient and Lipinski rule violation as shown in Table 4.It was analysed that Benzimidazole was having minimum binding energy with protein molecule and it was also qualifying Lipinski's rule of five.

Table 4: Drug Likeliness Property Analysis

Compound name	Molecular weight (g/mol)	Hydrogen donor	Hydrogen Acceptor	Partition coefficient	Violations
Benzimidazole	118.14	1	1	0.98	0 violations
Sulfonamides	347.39	0	5	-1.64	0 violations
Lidamycin	533.95	5	10	-0.85	Yes; 1 violation: MW>500
Thiophenes	656.99	0	0	6.43	No; 2 violations: MW>500, MLOGP>4.15

The screened ligand Benzimidazole was docked with protein target through AutoDockVina and Biovia Discovery Studio Client 2020. Through AutoDockVina software, ligand showed minimum binding energy, and through Biovia Discovery Studio Client 2020 the result was same. Benzimidazole was considered as the best binding ligand against protein target through AutoDockVinas as shown in Table 5.Theresults of Biovia Discovery Studio Client 2020 can be depicted in Table 6.

Table 5: AutoDockVina Result

Mode	Affinity	RMSD L.B	RMSD U.B
1	-7.8	0.000	0.000
2	-7.4	3.144	7.893
3	-7.3	11.022	15.358
4	-7.2	2.593	6.898
5	-6.9	10.950	15.195
6	-6.5	2.821	4.270
7	-6.4	4.183	8.053
8	-6.2	0.966	2.320
9	-6.0	3.676	7.534

Table 6: ResultBiovia Discovery Studio Client 2020

Benzimidazole	Absolute energy	Clean energy	ConfNumber	Mol_Number	Relative energy	Pose_Number
1.	-7.6	-7.5	82	1	4.55098	1
2.	-7.3	-7.4	91	1	4.32189	2
3.	-6.8	-7.2	44	1	3.12674	3

Benzimidazole showed a strong binding affinity with the drug target. The interaction of ligand and the target protein was visualized through PyMol as shown in **Figure 3**. In this *in silico* study, Benzimidazole may act as an inhibitor and it can be used in a form of drug which may control tuberculosis. Thus this drug can prevent tuberculosis and may form effective drug for the treatment of tuberculosis.

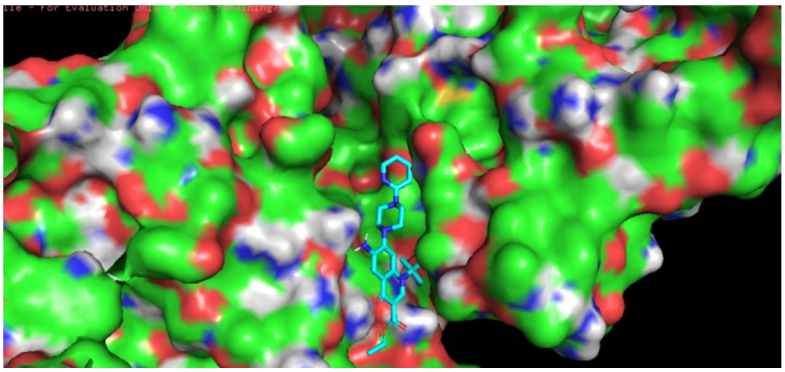


Figure 3: Interaction of DrpE1 with Benzimidazole

IV. CONCLUSION

The disease of Tuberculosis is an airborne illness caused by M. Tuberculosis: Tuberculosis The vaccine called Bacillus Calmette Guerin was one of the most effective therapies in humans for preventing tuberculosis. Tuberculosis is treated with various forms of antibiotics. Several experimental methods are being used to develop the tuberculosis vaccines to protect the body from the experience of these bacterias. Molecular docking was performed to determine the interactions between the different compounds and the target protein. Studies of docking have shown that Benzimidazole has a strong affinity to tuberculosis-related protein. Benzimidazole can thus act as an inhibitor according to the *in-silico* analysis and can be used in a type of drug that can regulate tuberculosis and can be used as a potential antituberculosis agent for the treatment of tuberculosis. Therefore, this medication can prevent tuberculosis and can form an important medication for tuberculosis treatment.

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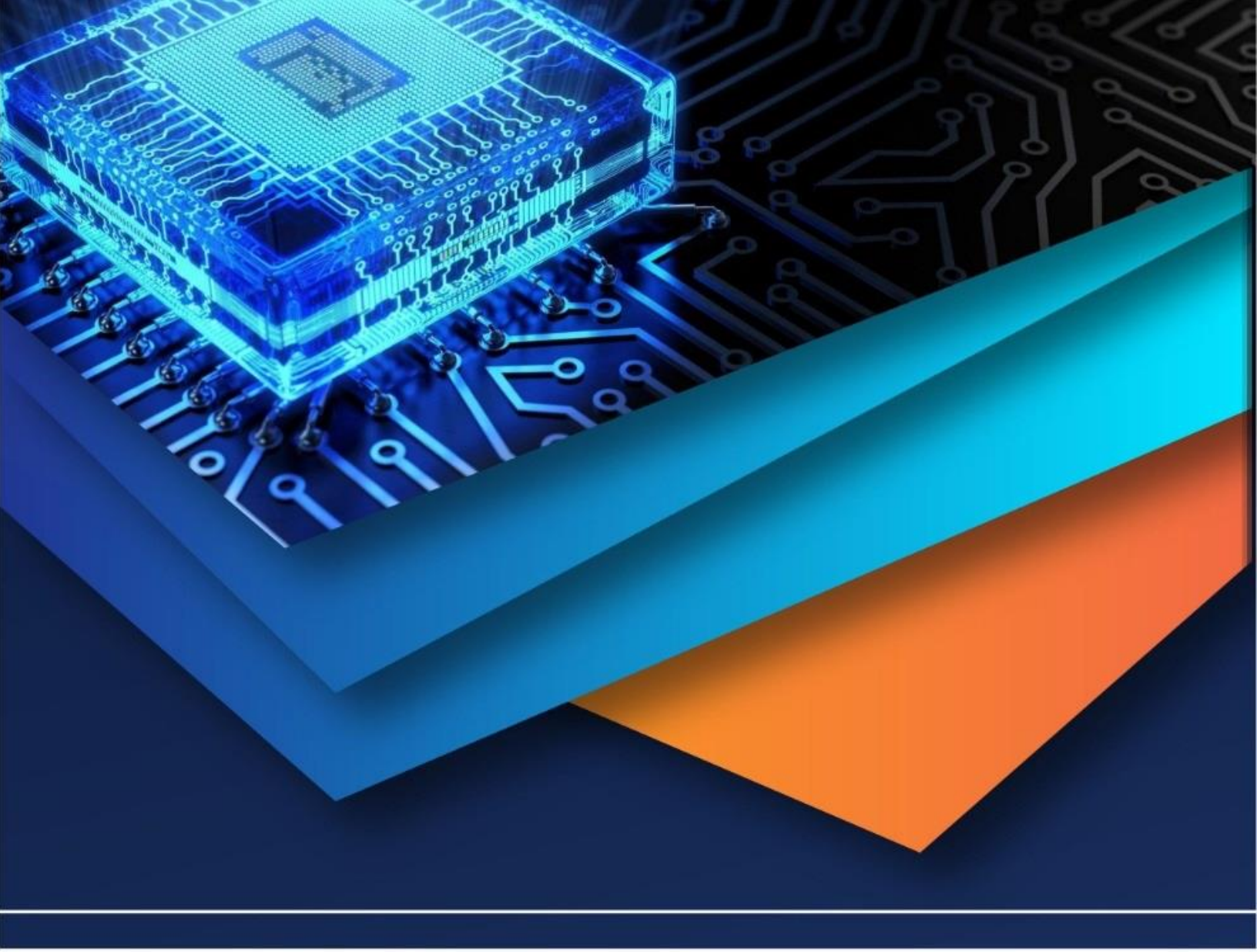

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