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Favipiravir Derivatives as Potential Inhibitors for NS3 Protease of West Nile Virus

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Abstract: ***West Nile Virus (WNV) belongs to* Flavivirus *genus and transmitted by Culex mosquitoes between its avian hosts and occasionally in mammalian hosts. It was first isolated in 1937 from Uganda's West Nile area. The outbreak of WNV into New York in 1999, and its continued spread throughout the north America contaminating more than nineteen thousand individuals and causing more than seven hundred fatalities. Presently, there is no effective antiviral treatment available for human WNV infection. NS3 protease of WNV has potential to work as drug target protein since it was involved in fundamental of viral replication. Inhibition of protease could be considered as a strategy for treatment of WNV infection. In this study, we performed molecular docking analysis of antiviral drug Favipiravir and its derivatives against NS3 Protease (PDB Id: 3E90) of WNV using Autodock 4.2 Autodock 4.2 and ArgusLab 4.0.1 program. Favipiravir is an antiviral drug, which shown to protect mice against experimental infection with a lethal dose of West Nile virus. Favipiravir has shown binding affinity of -5.11 kcal/mol at active site region of the NS3 protease. Active site region of NS3 Protease was predicted by CASTp Server. Based on the properties of Favipiravir, more similar compounds were retrieved from PubChem database and a structure-based virtual screening was carried out by AutoDock4.2 and ArgusLab 4.0.1 tool. we got two potent compound CID22674959 and CID135001386 of them with optimal binding energy-5.48, -5.61 kcal/mol with AutoDock and -5.43, -5.67 kcal/mol with ArgusLab, respectively, which were lower than Favipiravir (-5.11 kcal/mol). The docked complex structures were optimized by molecular dynamics simulation. Observations made in this study may extend an assuring platform for developing anti-viral competitive inhibitors against WNV.***
Keywords: Favipiravir, West Nile Virus, NS3 protease, CASTp, Autodock, ArgusLab

I. INTRODUCTION

West Nile virus belong to *Flavivirus* genus, which contains numerous noteworthy human pathogens, including dengue infection, Japanese encephalitis infection and yellow fever infection, and was first isolated in 1937 from Uganda's West Nile area[1]. WNV has thusly been found in areas of Africa, the Middle East, Europe, Russia, western Asia, and Australia and most as of late in North America[2]. WNV is transmitted by Culex mosquitoes from avian supply hosts to vertebrate deadlock has, including people and stallions. Human contamination is by and large asymptomatic or causes a gentle febrile malady, West Nile fever[2]. Notwithstanding, later contaminations of WNV have additionally been related with higher rates of serious neurological sickness and fatalities, especially among the elderly. Since the presentation of WNV into New York in 1999, the infection has spread quickly all through North America, contaminating more than 19,000 individuals and causing more than 700 fatalities (www.cdc.gov/ncidod/dvbid/westnile/index.htm)[3]. Right now there is no immunization or antiviral treatment for the aversion or treatment of human WNV contamination. WNV is a little, wrapped infection with a solitary stranded, positive sense 11-kb RNA genome, which encodes a solitary polyprotein forerunner. This polyprotein must be cut co-and post-translationally to create 10 utilitarian proteins: three basic (C, prM, and E) and seven nonstructural (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5)[4]. NS3 is a multifunctional protein, the protease containing the N-terminal third and nucleotide triphosphatase, RNA triphosphatase, and helicase parts involving the rest of NS3protease is a potential helpful target since it is fundamental for viral replication[5].

Drug discovery process is a serious issue in the pharmaceutical industry since it is a very costly and time consuming process to produce new drug potentials and enlarge the scope of diseases incurred[6]. The process of drug development targets towards the identification of compounds with pharmacological interest to assist in the treatment of diseases[7]. Drug development for West Nile infection has been in advance for quite a few years. In this study, we docked Favipiravir and its derivatives with West Nile virus NS3 Protease using AutoDock4.2 and ArgusLab 4.0.1 tool[8]. The docked complex structures were optimized by molecular dynamics simulation for 5 ps with the CHARMM-22 force field using NAMD incorporated in VMD 1.9.2 and then evaluating the stability of complex structures by calculating RMSD. Further, Favipiravir derivatives were screened from pubchem compound database using similar compound, score >=99 and docked with NS3 Protease. Again docked complexes stability was evaluated by molecular dynamics simulation.

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II. MATERIALS AND METHODS

A. Protein Target Structure

The 3D coordinates of the West Nile virus NS2B-NS3 protease in complexed with inhibitor Naph-KKR-H (PDB Id: 3E90) was retrieved from Protein Databank (http://www.rcsb.org/). This is used as a target model for flexible docking. The structure was optimized using the chimera tool[9].

B. Binding Site Analysis

CastP server uses the weighted Delaunay triangulation and the alpha complex for shape measurements. This software allows the identification and measurements of surface accessible pockets as well as interior inaccessible cavities of protein structures and other molecules[10].

C. Inhibitors Dataset

The 3D structures of Favipiravir and derivatives were subjected to energy minimization using the HyperChem software (HyperChem, Release 7.5)[11].

D. Molecular Docking

Docking of Favipiravir and its derivatives against NS3 Protease structure was done using molecular docking program AutoDock 4. 2 and ArgusLab 4. 0. 1.[12] During the docking procedure a Lamarckian Genetic Algorithm (LGA) were used for flexible ligand rigid protein docking calculation[13].

E. Molecular Dynamics Simulations

Molecular dynamics simulations were done using the NAMD (NAnoscale Molecular Dynamics program; v2.7) graphical interface module incorporated visual molecular dynamics (VMD 1.9.2)[14][15]**.** After the simulations, the results were analyzed in VMD by calculating the Root mean square deviation (RMSD) of the complex and was accessed in Microsoft excel.

III. RESULTS AND DISCUSSION

A. Binding Site Analysis

CASTp Server predicted binding site residues of NS3 Protease consist of residues LYS73, GLU74, ARG76, GLN86, HIS87, LYS88, TRP89, THR118, PRO119, GLU120, GLY121, GLU122, ILE123, GLY124, ILE147, ASN152, ALA164, ILE165, VAL166, GLN167, GLY168, LYS169 as shown in figure 1 in red color space fill model. Molecular surface area and volume are 378.834 and 493.576, respectively.

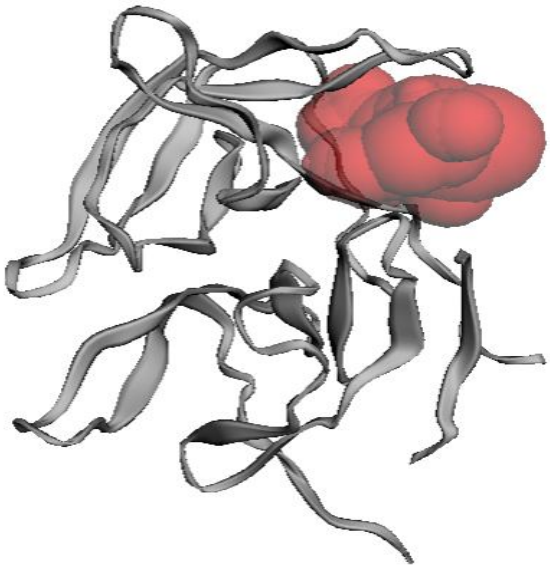

Figure 1: Predicted ligand-binding site. The predicted binding site residues were shown with red color in space fill model and backbone of protein is represented by gray color in ribbon model.

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B. Molecular Docking by AutoDock

Docking studies prophesied the interaction of ligands with protein and residues involved in binding. After that, the ligands were allowed to run using GA algorithm and a Score scoring function complex. Optimal interactions and the best score were used as criteria to interpret the best conformation among the 10 conformations, generated by AutoDock program. The docking results of Favipiravir and its derivatives with NS3 Protease were shown in table 1.

Table 1: Docking result of Favipiravir and its derivatives with NS3 Protease

Sl. No.	Pubchem CID/drug	BE	IME	IE	TorE	VdwE	EE
1	Favipiravir	-5.11	-5.41	-0.48	0.3	-5.31	-0.1
2	294642	-5.15	-5.44	-0.57	0.3	-5.28	-0.16
3	22674959	-5.48	-5.78	-0.17	0.3	-5.5	-0.28
4	67534452	-5.08	-5.38	-0.66	0.3	-5.26	-0.12
5	71812190	-5.11	-5.41	-0.49	0.3	-5.08	-0.28
6	72188728	-5.11	-5.41	-0.53	0.3	-5.27	-0.13
7	72201087	-5.17	-5.47	-0.05	0.3	-5.4	-0.07
8	76973015	-5.15	-5.44	-0.41	0.3	-5.32	-0.13
9	76973021	-5.14	-5.44	-0.48	0.3	-5.3	-0.13
10	76973034	-5.2	-5.49	-0.48	0.3	-5.35	-0.14
11	76973035	-5.09	-5-38	-0.49	0.3	-5.27	-0.12
12	76973036	-5.36	-5.66	-0.21	0.3	-5.39	-0.28
13	76973037	-5.12	-5.42	-0.49	0.3	-5.28	-0.14
14	89869520	-4.84	-5.13	-0.48	0.3	-5.07	-0.07
15	123273976	-4.45	-5.05	-1.29	0.6	-3.98	-1.07
16	135001386	-5.61	-6.21	-0.38	0.6	-6.06	-0.14
17	135395256	-5.16	-5.46	-0.49	0.3	-5.32	-0.14

BE: Binding Energy; IME: Intermolecular Energy;IE: Internal Energy; TorE: Torsional Energy; VdwE:Vdw-lbDesolv Energy; EE: Electrostatic Energy.

C. Docking Studies by ArgusLab

The WNV NS3 Protease protein was downloaded into ArgusLab program and binding site was made by choosing “Make binding site for this protein” option. The inhibitors were chosen, centered and added hydrogens. In next step, the ligands were allowed to run using GA (Genetic Algorithm) dock to compare with AutoDock 4.2. In Argus lab tool, docking calculation type was set to “Dock” and “Flexible” ligand docking mode and used for each docking run.

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Table 2: Binding energy of Favipiravir and its derivatives from AutoDock 4. 2 and ArgusLab 4. 0. 1.

Sl. No.	Pubchem CID/drug	Binding Energy (Kcal/mol) from AutoDock	Binding Energy (Kcal/mol) from ArgusLab
1	Favipiravir	-5.11	-5.02
2	294642	-5.15	-5.12
3	22674959	-5.48	-5.43
4	67534452	-5.08	-5.02
5	71812190	-5.11	-5.16
6	72188728	-5.11	-5.18
7	72201087	-5.17	-5.12
8	76973015	-5.15	-5.11
9	76973021	-5.14	-5.10
10	76973034	-5.20	-5.24
11	76973035	-5.09	-5.13
12	76973036	-5.36	-5.38
13	76973037	-5.12	-5.18
14	89869520	-4.84	-4.88
15	123273976	-4.45	-4.41
16	135001386	-5.61	-5.67
17	135395256	-5.16	-5.12

From the study, the docking results with AutoDock 4.2 and ArgusLab 4.0.1 were compared in table 2. Both programs show almost similar results.

Docking poses of the best conformation of Favipiravir and its derivative CID22674959 and CID135001386 with WNV NS3 Protease were analysed by Python molecular viewer were shown in figure 2 to 4.

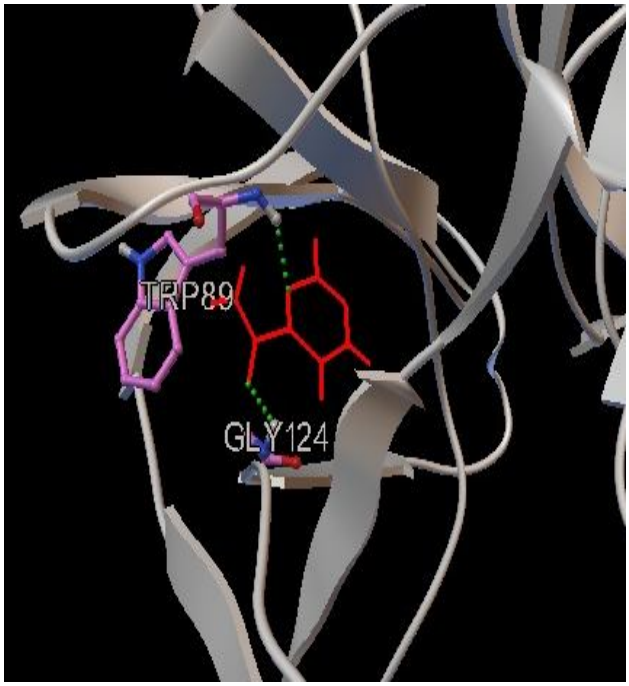

Figure 2: Docking orientation of Favipiravir with NS3 Protease. Complex depicting compound formed two H-bond with GLY124 and TRP89 of protein. Compound Favipiravir is represented as lines and colored as red.

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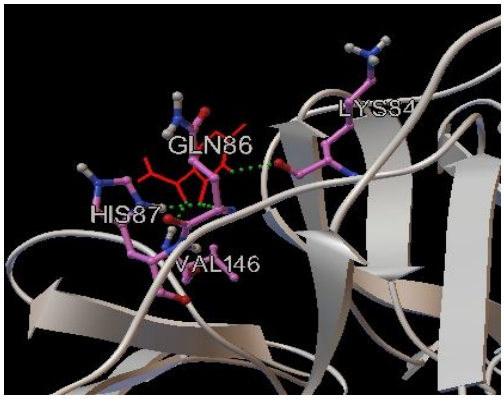

Figure 3: Docking orientation of Compound CID22674959 with NS3 Protease.Complex depicting compound formed four H-bond with GLN86, LYS84, HIS87 and VAL146 of protein. Compound CID22674959 is represented as lines and colored as red.

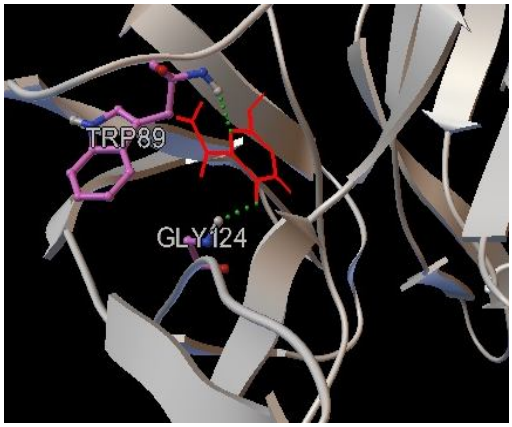

Figure 4: Docking orientation of Compound CID135001386 with NS3 Protease. Complex depicting compound formed two H-bond with GLY124 and TRP 89 of protein. Compound CID135001386 is represented as lines and colored as red.

Docking activity gives proteins the ability to promote or inhibit chemical reactions and to accelerate or prevent the processes that keep cells alive and maintain a balanced micro environment. More over the specific effects of a drug could depend on the structure of the molecular aggregates formed. Favipiravir derivatives were screened from pubchem compound database were further dock and verified by ArgusLab with NS3 Protease.

D. Molecular Dynamics Simulations

RSMD, a crucial parameter to analyze the equilibration of MD trajectories, is estimated for backbone atoms of the compounds CID22674959 and CID135001386 with NS3 Protease complex (shown in figure 5 to 7). Measurements of the backbone RMSD for the complex provided insights into the conformational stability.

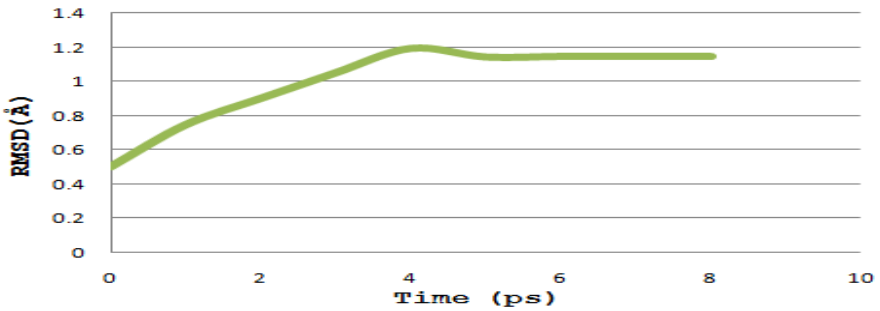

Figure 5: Graph displaying root mean square deviation (RMSD) of the backbone atoms of docked complex (CID22674959 - NS3 Protease) versus time at 310 K, resulted in highest peak at 1.19 Å.

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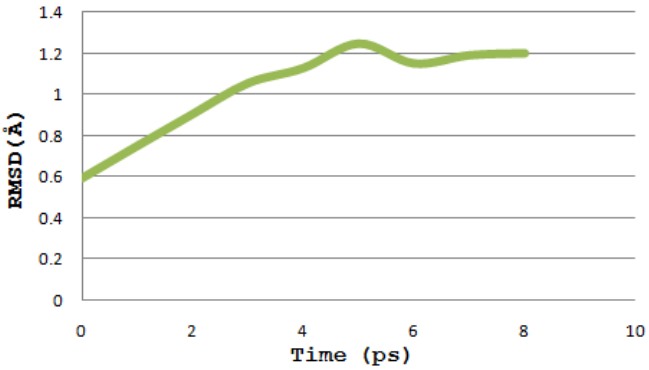

Figure 6: Graph displaying root mean square deviation (RMSD) of the backbone atoms of docked complex (CID135001386 - NS3 Protease) versus time at 310 K, resulted in highest peak at 1.24 Å.

IV. CONCULUSION

We used Favipiravir and its derivatives for docking studies against WNV NS3 Protease. We used AutoDock and ArgusLab for docking studies in this work. Both the tools were used Lamarckian Genetic Algorithm for docking calculation. Thus from Favipiravir derivatives, which were docked, we got two compound CID22674959 and CID135001386 of them with optimal binding energy-5.48, -5.61 kcal/mol with AutoDock and -5.43, -5.67 kcal/mol with ArgusLab, respectivley. Both the docking tool predicts almost same binding energy. Anaysis of best-docked complex using Python Molecular Viewer shows Compound CID22674959 formed four H-bond with GLN86, LYS84, HIS87 and VAL146 of NS3 Protease. And compound CID135001386 formed two H-bond with GLY124 and TRP 89 of NS3 Protease. Optimizatin of docked protein - inhibitor complexes shows its stability.

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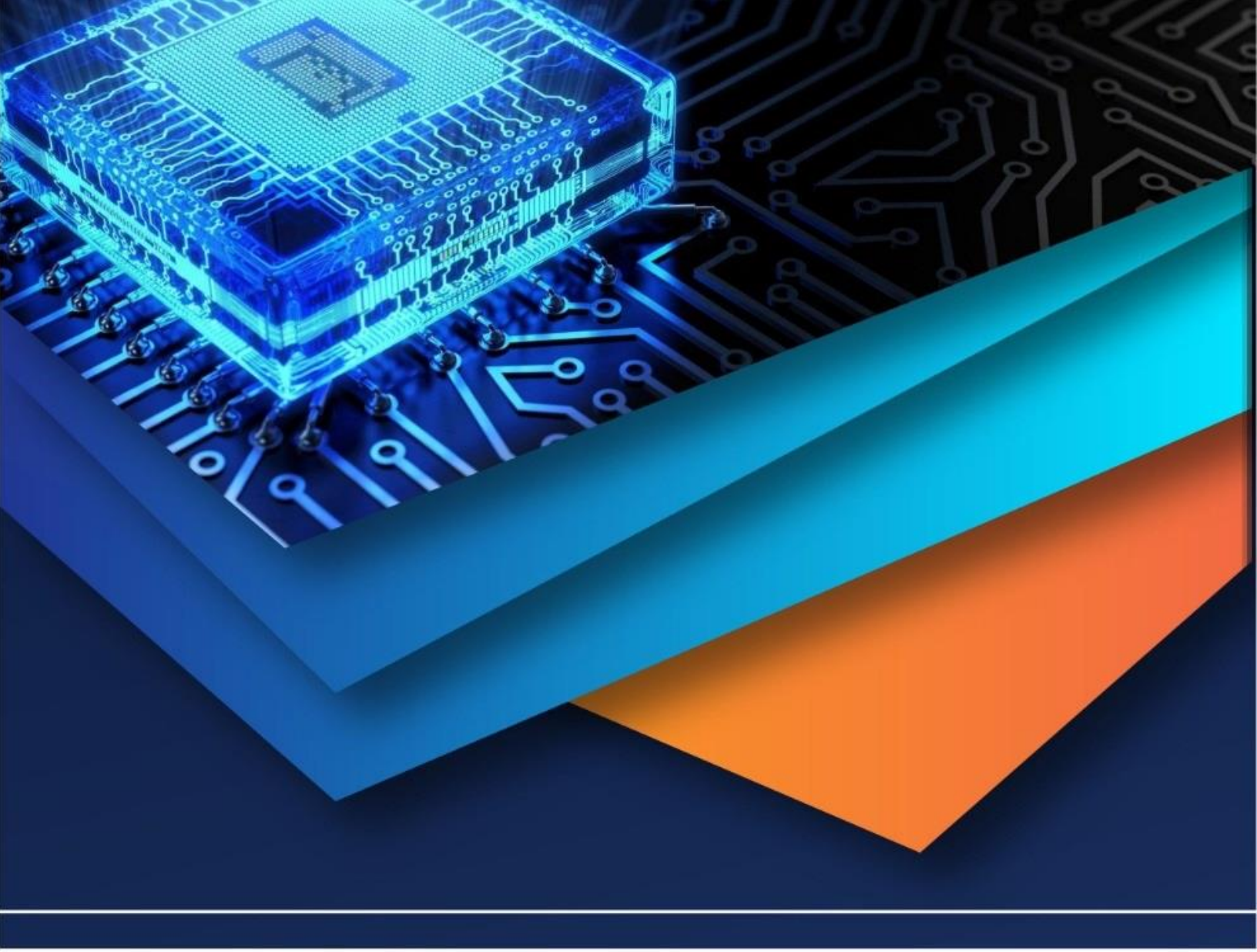

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