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Effect of Harmine against Parkinson's Disease Protein (PARK7) through Molecular Docking Studies

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Abstract: Parkinson's disease (PD) is a common known neurodegenerative disorder with unknown etiology. It was estimated about 0.3% prevalence in the U.S population and enhance to 4 to 5% in older than 85 years. All studies were depending on the molecular docking where all ligands and protein PARK7 (PDB ID: 2RK3) were interacted by docked process. Some natural compounds was selected such as Harmine, Alloxan, Alpha spinasterol, Myrcene, and Vasicinone and PARK7 (PDB ID: 2RK3) protein. According to the PyRx and SWISS ADME result, Harmine was the only ligand which was showing minimum binding affinity. AutoDock Vina software was used for docking process between ligand (Harmine) and receptor protein PARK7 (PDB ID: 2RK3). The result was visualized under PyMol. Harmine was inhibiting the activity of PARK7 (PDB ID: 2RK3) and it may be used for the treatment of PD in future prospect after its in vitro and in vivo studies.
Keywords: Parkinson's disease, Harmine and PARK7.

I. INTRODUCTION

Parkinson disease (PD) is a simply long-term degenerative disorder of the central nervous system which affects the motor system [1]. The PD was expands from 1817, when a British apothecary James Parkinson was published "An Essay on the Shaking Palsy" while in 20th century occur greatly improved knowledge of the disease and its treatments and describe their name PD [2]. It was a paralysis and PD was coined by William Sanders in 1865 and later popularized by French neurologist Jean Martin Charcot [3]. An Ayurvedic medical treatise describes a disease evolvement with tremor, lack of movement, drooling and other symptoms of PD from 10th Century B.C [4, 5]. In 19th century a positive effect of tremor of anticholinergic alkaloids was obtained by belladonna plant and described by Charcot, Erb and others. The mid-20th century Levopoda was firstly synthesized and identified by Casimir Funk in 1911 which received little attention. Later in 1968 improvements was show in PD affecting people. It was a revolution in the management of PD [6, 7].

The PD was showing symptoms usually worsens, non-motor symptom [8, 9] and early symptoms are difficulty with walking, tremor rigidity and slowness of movement and cognitive behavioral problems has been shown with anxiety, apathy and depression in many people of PD [6]. PD dementia is an advanced step of the disease. Coffee, tea and tobacco smokers can reduce their risk [9, 10]. The neuropathological features can characteristics of this disease are the Dopaminergic Neurons in Nigra Substantia and their existence of eosinophilic intracytoplasmic inclusions (Lewy Bodies) which showing residual dopaminergic neurons [11]. Basic characteristics of PD may include tremor, stiffness, bradykinia, and balance of interference; Depression is also present in patients, affecting the quality of life [12].The pathogenic mechanism may include oxidative stress, mitochondrial dysfunction, protein dysfunction, infammatic, autophagy, and apoptosis [13].

II. MATERIALS AND METHODS

A. Identification Of Protein

PARK7 (likewise called DJ-1 or Parkinsonism related deglycase) is a simply type of pleiotropic protein with the peptidase C56 family. The human protein deglycase DJ-1 was consisting 189 amino acids residue through 7 β-strands and nine α-helices in total [14-16].This protein having 20kDa in size. It controlling of androgen receptor-subordinate record activity, redox-delicate chaperone pathways, sensor for oxidative pressure system, and clearly secures neurons against oxidative pressure and cell passing activity. Dysfunctions in PARK7 are identified with autosomal latent beginning stage Parkinson illness 7 and disease structures. This protein present in tissues and organs, including the brain.

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1) *Harmine:* Harmine(HM) is also known as banisterine, hallucinogenic Alkaloid which is found seeds of a Peganum Harmala plant of the Mediterranean region from Middle East at the time of South American vine (Banisteriopsis caapi). It is a natives Mountains of the Andes which prepared a drug for religious and medicinal use. Chemically, the armination is a type of in dole hallucinogen which blocks the activity of serotonin in their brain tissue. The studies have shown that HM displays important antitumor activities in vitro and in vivo [17], including inhibitory proliferation, Promote apoptosis [18] and prevent Tumor genesis.
2) *Alpha Spinasterol:* Alpha-Spinasterol, is like a α-spinasterol or bessisterol, which classified like organic compounds which act as stigmastanes and derivatives. These are sterol lipids which supported the stigmastane skeleton and consist of a cholestane moiety ethyl at the atom C24. Thus, alpha-spinasterol has a sterol lipid molecule which hydrophobic molecule was insoluble (in water), and comparatively neutral. The Preceding observe has been uncovered that α-spinasterol Elicits exact anticancer interest in opposition to breast and Ovarian most cancers cells with minimum impact on normal Cells viability or proliferation.
3) *Alloxan:* In 1818, Italian physicist Luigi V. Brugnatelli was separates an alloxan; he orchestrated it by means of nitric corrosive oxidative debasement of uric corrosive. Soon after Friedrich Wöhler found that urea can be produced using inorganic materials in 1828, he and Justus von Liebig found alloxan in human discharges, showing that it likewise can be biosynthesized. Presently, alloxan is set up from barbituric corrosive or alloxantin; the article of trade is the monohydrate.
4) *Vasicinone:* Vasicinone is shown the activity of cytotoxic and antiproliferative movement in a few tumor cell lines. Vasicinone, is a type of oxidation result of vascinine is a strong bronchodialator. Vasicinone could be used in substitute enemy of asthmatic treatment, since it assumes an essential part in searching Nitric oxide which could forestall the bronchial aggravation in asthmatic patients.
5) *Myrcene:* Myrcene, or β-myrcene, is an alkene herbal hydrocarbon and may exactly categorize as a monoterpene. Monoterpenes are dimers of isoprenoid precursors, and myrcene is an extensive factor of the vital oil of various floras. There chemical formula is C10H16 with 0.794g/cm3 Density. All the herbal compounds had been elected on the groundwork of literature. These regular mixtures were recovered from PubChem online data set https://pubchem.ncbi.nlm.nih.gov/ [20]. The mixtures were downloaded in SDF design. Every one of these compounds were changed over from .sdf organization to .pdb design by Online SMILES Translator https://cactus.nci.nih.gov/interpret/ [21], the .pdf records of the ligands were downloaded in .pdb design.

B. Protein Preparation

The protein PARK7 was playing an important role in cell protection against oxidative stress and cell death acting as oxidative stress sensor and redox-sensitive chaperone and protease. The PARK7 protein was searching by Uniprot online server and clicks on the option of structure and download the RCSB PDB less resolution file in .pdb format and saved for further process. The structure of PARK7 [PDB ID 2RK3] was obtained by Protein Data bank (PDB) https://www.rcsb.org/ [19].

C. Screening Through PyRx

PyRx software was utilized for the virtual screening of the ligands. The PyRx software was showing the restricting partiality and restricting energy of every ligand through their virtual screening. The protein molecule was uploaded in PyRx window and was changed over from .pdb configuration to .pdbqt form. The ligand atoms were likewise imported in .sdf format. The energies of the ligands were minimized and were converted from .sdf format to .pdbqt format.

D. Drug Likeness Properties

The herbal compounds were chosen for drug likeliness property analysis. Ligands were screened on the basis of Lipinski's rule of five. Lipinski's rule of five are as follows:

1) Molecular mass less than 500 Da;
2) High lipophilicity (expressed as LogP less than 5);
3) It should be check only 5 hydrogen bond donors;
4) May should be 10 hydrogen bond acceptors not more;
5) Not more than 1 violate.

Drugs likeliness property examination was done through online tool SwissADME https://cactus.nci.nih.gov/translate/ [22]. Canonical SMILE annotations were copied by PubChem and were run into SwissADME online web server.

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E. Docking Through Autodock Vina

The protein file of .pdb format was loaded in AutoDock Vina graphical windows. The protein .pdb file was prepared by deleting the water molecules, adding Kollman charges to their protein molecule, adding hydrogen polar bond and further it was saved in ". pdbqt" file. The ligand molecule was loaded in .pdb format in AutoDock Vina and was converted to". pdbqt" format.

F. Preparation Of Grid

Grid maps were prepared by changed the value of 0.375 Å for the ligand restricting in grid box. The grid measurement was changed in accordance with 40 × 40 × 40 npts. AutoDock Vina was used to interacting with docking maps and values were calculated by Auto Grid. The selected protein of interaction energy was assigned at every one point of the grid and calculated their ligand affinity. The minimum energy of ligands was converting the .sdf file to ". pdbqt" format. The results were analyzed based on their binding affinity.

G. Structure Visualisation Through Pymol

Pymol 2.4 is a free and handy software. The structure was visualized under Pymol 2.4 tool. The ".pdbqt" file of protein was load in PyMOL 2.4 graphical screen and output. Pdbqt file was also uploaded in Pymol 2.4 tool screen. The docked structure was visualized and analysed.

III. RESULTS AND DISCUSSION

The PARK7 was obtained by Uniprot database The resolution of this Protein was 1.05 Å and belongs to chaperone class. Harmine (CID: 5280953), Alpha spinasterol (CID: 5281331), Myrcene (CID: 31253), Alloxan (CID: 5781), Vasicinone (CID: 442935) were downloaded in 3D Structure in .sdf format as shown in Figure 1 and Figure 2.

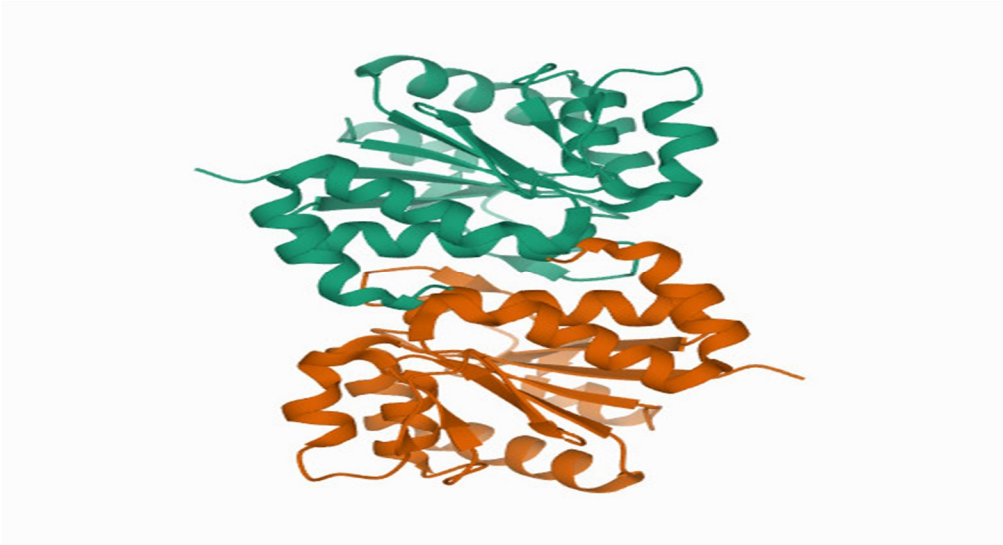
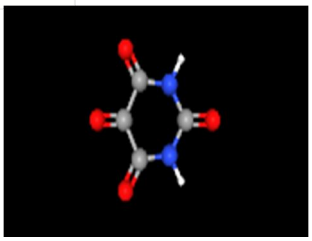


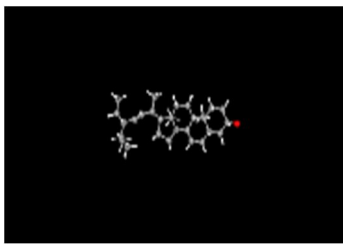
Figure 1: The crystal structure of Human PARK7 [2RK3].

PROTEIN NAME	: PARKINSON DISEASE PROTEIN 7
GENE	: PARK7
PROTEIN DATABASE NO	: 2RK3
CLASSIFICATION	: CHAPERONE
ORGANISM (S)	: HOMOSAPIENS (HUMAN)
EXPRESSION SYSTEM	: ESCHERICHIA COLI BL21 [DE3]
MUTATION	: YES
SEQUENCE LENGTH	: 197

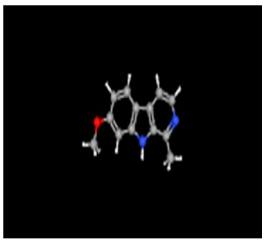
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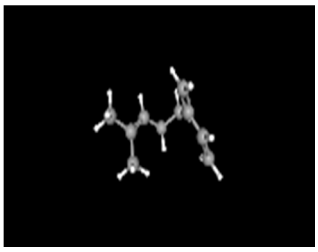
ALLOXAN CID - 5781 MF - C4H2N2O4 MW - 142.07



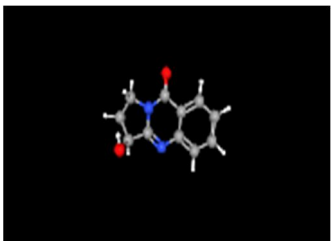
ALPHA SPINASTEROL CID - 5281331 MF - C29H48O MW - 412.7



HARMINE CID - 5280953 MF - C13H12N2O MW - 212.25



MYRCENE CID - 31253 MF - C10H16 MW - 136.23



VASICINONE CID - 442935 MF - C11H10N2O2 MW - 202.21

Figure 2: 3D Structure of Ligands

Virtual screening of the ligand molecules were alalyzed by PyRx software. According to the minimum binding energy ligands were screened. The binding affinity of Harmine was -4.9, Alpha spinasterol was 1..4, Alloxan was -4.3, Myrcene was -4.2 and Vasicinone was -4.7 as shown in Table 1 and Table 2. The ligands which were selected after PyRx result were Alpha spinasterol, Harmine, Myrcene and Alloxan. These ligands were further analyzed for drug likeliness property analysis

Table 1 : Interaction between Target Protein and Ligands (PyRx Result)

Compound	Ligand	Binding Affinity	Mode	RMSD lower Bound	RMSD upper Bound
Alloxan	PARK_5781_mmff94_E=69.31	-4.3	0	0	0
		-3.9	1	18.68	17.27
Alpha Spinasterol	PARK_5781_mmff94_E=94.11	1.4	0	0	0
		1.5	1	8.441	3.544
Harmine	PARK_5781_mmff94_E=29.12	-4.9	0	0	0
		-4.7	1	2.381	1.202
Myrcene	PARK_5781_mmff94_E=23.90	-4.2	0	0	0
		-3.9	1	2.737	1.207
Vasicinone	PARK_5781_mmff94_E=17.45	-4.7	0	0	0
		-4.7	1	30.897	28.896

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Table 2: Binding Energies of different Ligands			
Sr.no.	Compound	CID	Binding Energy
1	Alloxan	5781	-4.3
2	Alpha Spinasterol	5281331	1.4
3	Harmine	5280953	-4.9
4	Myrcene	31253	-4.2
5	Vasicinone	442935	-4.7

Drug likeliness property analysis was analyzed from SwissADME and ligands were screened according to Lipinski's Rule of Five as shown in Table 3. Harmine was the only molecule qualifying all the properties of Drug.

Table 3: Result of SWISS ADME via (Drug Likeliness Property Analysis)						
Ligands	Binding Affinity	M.W <500 k da	No. of Hydrogen Bond Acceptors	No. of Hydrogen Bond Donors	Log Po/w [MLOGP]	Violation
Alloxan	-4.3	142.07g/mol	4	2	-2.36	Yes, 0 violation
Alpha Spinasterol	1.4	412.69g/mol	1	1	6.62	Yes, 1 violation
Harmine	-4.9	212.25g/mol	2	1	1.56	Yes, 0 violation
Myrcene	-4.2	136.23g/mol	0	0	3.56	Yes, 0 violation

The protein target PARK7 (PDB ID: 2RK3) and Harmine (CID: 5280953) were docked through AutoDock Vina software. The ligand was showing result in 9 poses through command prompt with different binding affinity in table 4. All molecules interaction was further visualized under PyMol as shown in figure 3.

Table 4 Autodock Vina Result			
		Dist. From best Mode	
Mode	Affinity (Kcal/mol)	RMSD L.B	RMSD U.B
1	-6.3	0.000	0.000
2	-6.0	26.05	27.08
3	-6.0	27.08	27.99
4	-5.9	2.652	5.562
5	-5.8	26.037	26.858
6	-5.7	26.723	28.439
7	-5.6	2.99	6.60
8	-5.5	3.138	6.823
9	-5.4	4.416	6.185

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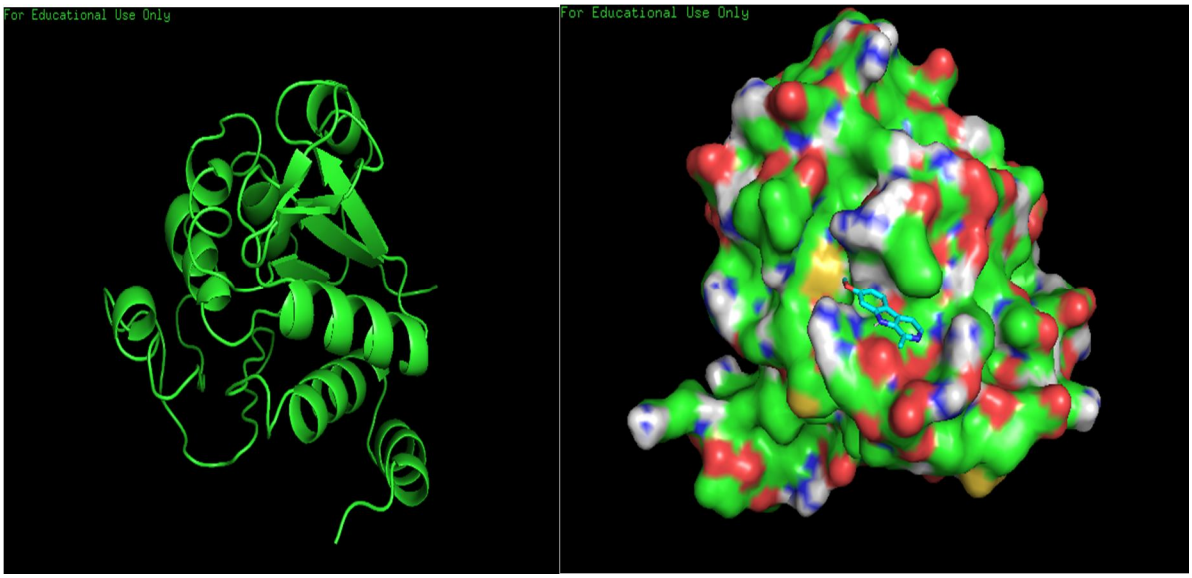


Figure 3: Interaction of PARK7 with Harmine through PyMOL visualizer.

Harmine showed a strong binding affinity with target drug and was shown their visualized structure in Figure 3 by PyMOL. The Harmine act like as an inhibitor which can used for making the drug and control the PD. Thus, this drug can performed better result for prevention of PD and will used in drug purpose for the treatment of PD.

IV. CONCLUSION

According to molecular docking the interaction of the Harmine, Alpha spinasterol, Myrcene, Alloxan, Vasicinone with the target protein PAARK7 (PDB ID: 2RK3) were analysed and the best-docked ligand was further docked through Autodock Vina. According to the results, Harmine was acting like a good ligand with minimum binding affinity and it followed Lipinski's rule of five with zero violations. Harmine may be used as a drug for the treatment of PD and may inhibit the activity of PARK7 protein. Harmine is a natural sources which may be used to prepare a drug for the treatment of PD.

A. Conflict Of Interest

The authors declare that there is no conflict of interest.

V. ACKNOWLEDGEMENT

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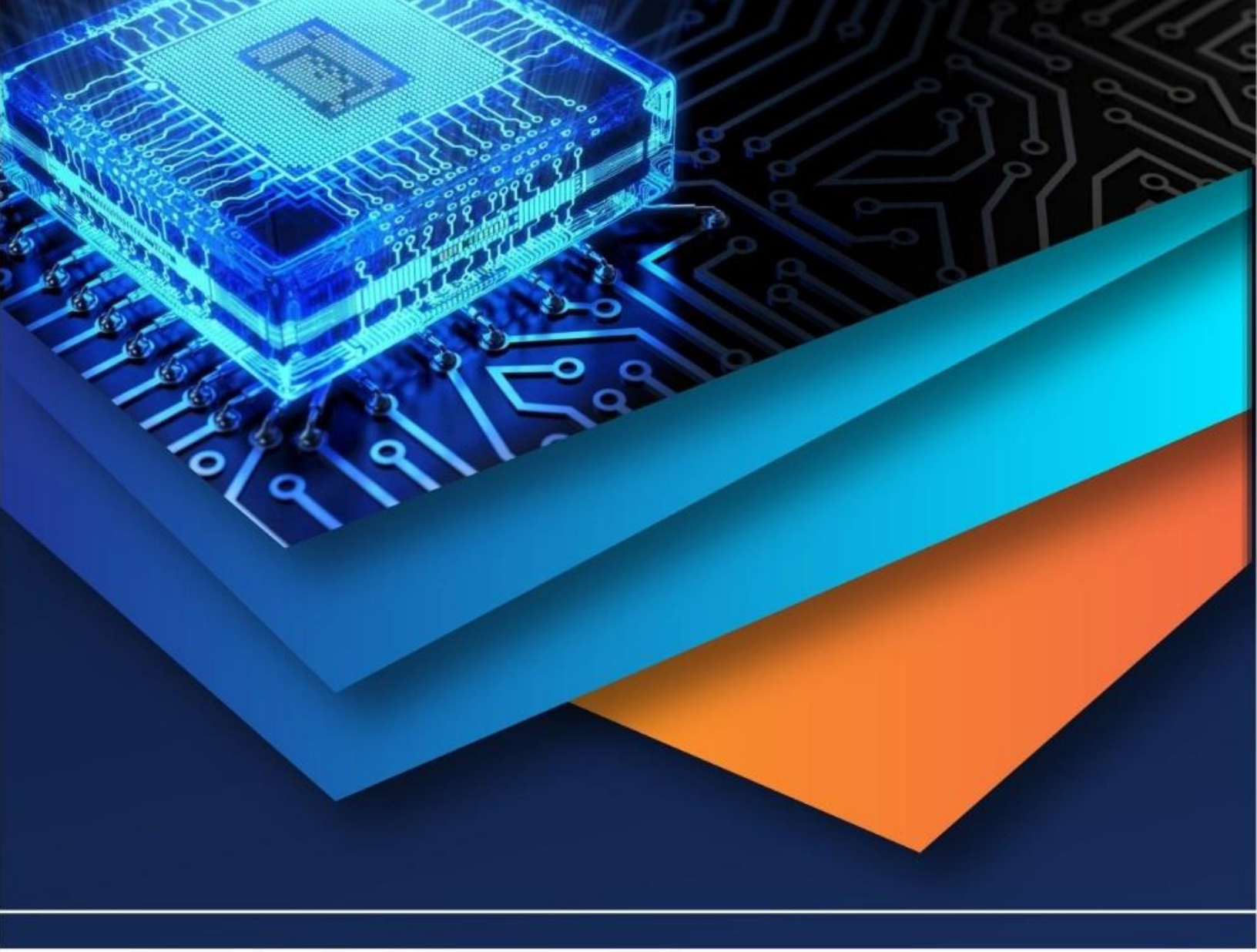
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