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Molecular Docking Studies of Secondary Metabolites against Sequestosome-1 to Treat Parkinson Disease

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Abstract: Parkinson's disease (PD) is one of the major progressive neurological disorders. It occurs due to a low level of a chemical substance in the brain known as Dopamine, which controls the muscle movements of the body. In many cases, PD occurs due to a low level of dopamine. PD generally appears in persons between the ages of 50 & 60. Some common symptoms of Parkinson's are slow movements, tremors, change in voice, depression, anxiety, hallucinations, psychosis, etc. Diagnosis of PD is done by CAT (Computerized Axial Tomography) scan or MRI (Magnetic Resonance Imaging, and DAT (Dopamine Transporter) scan. No specific cure for PD but Medication, Surgery, Adequate rest, exercise, and a balanced diet, and Several different drugs may help to relieve Parkinson's Disease (PD). According to the in silico study, we found that Rosmarinic Acid (RA) was the compound, which may inhibit the activities of Sequestosome-1. After in vitro and in vivo studies, Rosmarinic Acid may be an effective drug to control Parkinson's disease (PD).

Keywords*: Parkinson's, Neurological, Dopamine, Rosmarinic Acid, In silico.*

I. INTRODUCTION

Parkinson's disease (PD) is one of the major progressive disorders of the Central Nervous System (CNS) [1]. The muscle movements of the body are made possible by a chemical substance in the brain known as dopamine, which is produced in a part of the brain known as the Substantia Nigra. In Parkinson's patients, the cells of the substantia nigra start to die. This condition happens, when dopamine levels are dropped. Symptoms of Parkinson's start to appear, when dopamine level dropped 60 to 80 percent. The first signs of (PD) results in the problem with movement [2], [3], [4], [5], [6], [7], [8], [9], [10]. PD creates problems in the sleep and sensory system of Parkinson's disease (PD) patients [1].

A. Symptoms of Parkinson's disease

1) *Some Early Symptoms Of Parkinson's Disease (Pd) Appear Before Motor Problems Such As:* Small, cramped handwriting, Change in voice, constipation, Loses ability to smell (anosmia), stooped posture, etc. Early signs of PD are generally unrecognized. The movement difficulties begin with these warning signs by the body which may try to alert you.
2) *Some Major Motor Problems Such As:* Slow movements, tremor (shaking that occurs at rest), problems with balance and tendency to fall, stiffness of arms, legs, and trunk
3) *Some Other Symptoms Include:* Possibility to fall backward, problem in speech, changes in facial expression, and swallowing, etc.
4) *More Severe, Symptoms May Include:* Problems with attention and memory, depression, anxiety, more chances of skin cancer, hallucinations, psychosis, difficulty with visual-spatial relationships, problem in sleep, and problem in talking, etc.

B. Causes of Parkinson's Disease (PD)

The main causes of Parkinson's are unknown. Parkinson's disease (PD) may have both environmental components & genetic. Low levels of dopamine & norepinephrine, a substance that regulates dopamine, have been linked with PD.

C. Diagnosis of Parkinson's Disease

No specific test for diagnosing Parkinson's disease (PD), but diagnosis is made based on like History of Health, Neurological &physical exam, and review of signs & symptoms.

D. Imaging Tests

MRI (Magnetic Resonance Imaging) or CAT (Computerized Axial Tomography) scan, and DAT (Dopamine Transporter) scan may be used.

E. Treatment

Exercise, Medication, Surgery, Rest, Healthy diet , and some drugs etc are used for PD treatment [2], [3], [4], [5], [6], [7], [8], [9], [10]. The effect of the selected compound against the protein for the treatment of Parkinson's disease was checked through Molecular Docking (MD). Nowadays, the population is running towards herbal compounds, because herbal compounds have no side effects [11]. Approximately 50-55% of all the drugs form used in the clinical fields are produced from the compounds which are extracted from plants [12]. Traditional drugs were time & resource-consuming, but nowadays, bioinformatics has played an important role in research, which saves both time and resources. Molecular docking is a technique used to screen drugs based on structure-based drug designing. The small molecules' interaction with the target protein is analyzed in docking. Structural-Based Drug Designing (SBDD) uses the molecular docking (MD) method that is used to check the ligand-binding sites with a protein of known (3-D) three-dimensional structure [13]. Docking helps in the screening of a large set of compounds based on their proposed structural hypotheses and free binding energies, and how the molecules could inhibit the target [14]. In our study, some natural compounds were collected from different plant sources such as Rosmarinic Acid, Quercitrin, Isoquecitrin, Nirurin, and Rutin. The research aimed to study the interaction of selected natural compounds against Sequestosome-1 for the treatment of Parkinson's disease with the help of molecular docking.

II. MATERIALS & METHODS

A. Identification of Protein

Structure of Sequestosome-1 (Protein) (PDB ID: 5YP7) was retrieved from Protein Data Bank (PDB) https://www.rcsb.org/ [15]. After it, the Sequestosome-1 (PDB ID: 5YP7) protein was downloaded in .pdb format.

B. Identification of Ligands

Rosmarinic Acid, Quercitrin, Isoquercitrin, Nirurin, *and* Rutin were the five natural compounds that were used as ligands in the study. All the natural compounds were selected based on the literature. These natural compounds were retrieved from PubChem's online database https://pubchem.ncbi.nlm.nih.gov/. After it, the compounds were downloaded in .sdf format. After it, all these compounds were converted into .pdb format from .sdf format by Online SMILES Translator (OST) https://cactus.nci.nih.gov/translate/, and the ligands were downloaded in .pdb format [11].

C. Virtual Screening through PyRx

The *PyRx* software was used for the virtual screening of the ligands. The *PyRx* software demonstrated the binding affinity & binding energy of each ligand via the virtual screening. The protein molecule was loaded in *PyRx* software and was converted from .pdb format to. pdbqt format. After it, the ligand molecules were also imported in .sdf format. All the energies from the ligands were minimized and all the ligand compounds were converted from .sdf format to. pdbqt format. The results were analyzed based on their binding affinity [11].

D. Drug Likeliness Property Analysis

The natural compounds were selected for final molecular docking studies by screening, which was having drug-like properties. Screening of the ligands was done based on Lipinski's rule of five or Lipinski's rule.

Following points of Lipinski's rule of five such as [16]: -

1) Not more than one rule should violate.
2) Less than 10 (<10) hydrogen bond acceptors.
3) Less than 5 (< 5) hydrogen bond donors.
4) Molecular Mass less than 500 (<500) Dalton.
5) High Lipophilicity (LogP less than 5(<5)).

Lipinski's rule of five was analyzed using the online web server SwissADME http://www.swissadme.ch/. The canonical SMILE formula of the ligands was copied from PubChem and was pasted on SwissADME for the analysis of Lipinski's rule of five.
Which ligands was followed Lipinski's rule were selected for final docking via *AutoDock Vina* [17].

E. Docking via AutoDock Vina

Protein the target was loaded on the *AutoDock Vina* window in .pdb format. After it, the water molecules were deleted from the protein molecule. After it, polar hydrogen atoms & Kollman charges were added to the protein molecule. After it, the protein was further converted into .pdbqt format. After it, the ligand molecule was imported & it was converted into .pdbqt format. After this, both the protein & ligand molecule were loaded on the *AutoDock Vina* screen. The boundaries of the grid box were set as shown in **Figure 1**. After preparation of protein and ligand molecule docking was launched from command prompt & the results were analyzed [11].

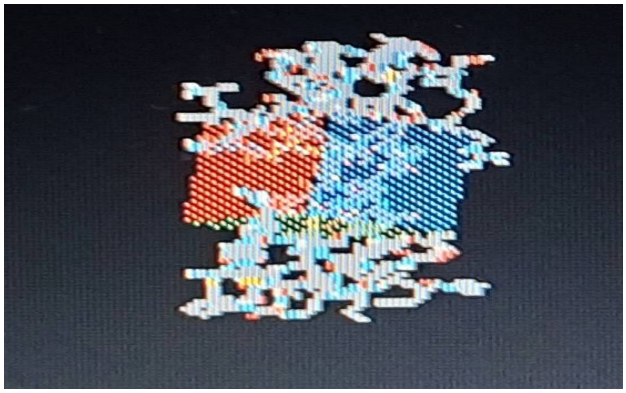


Figure 1: The Grid Box

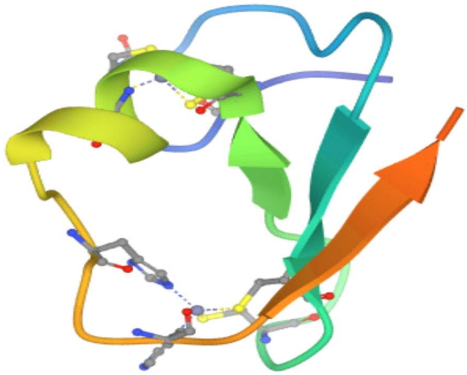
F. Structure Visualization through PyMOL

The *PyMol* software was used for visualization structure of protein & ligand interaction. After completion of *AutoDock Vina,* the output file was automatically saved in the selected folder with the name output.pdbqt file. Both protein .pdbqt & output.pdbqt files were loaded on the PyMOL software screen. The protein & ligand interactions were visualized and analyzed by PyMOL software. [11]

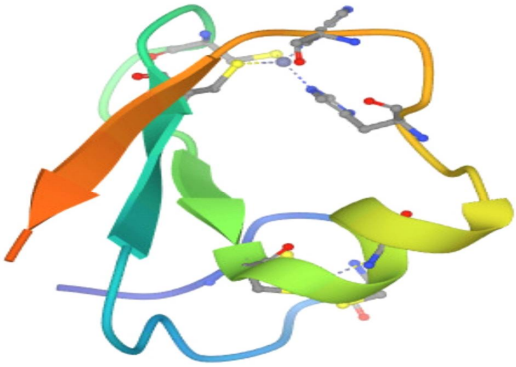
III. RESULTS & DISCUSSION

Sequestosome-1(Protein) (PDB ID: 5YP7) was obtained from Protein Data Bank as shown in Figure 2. The resolution of the protein was 1.42 Å and belongs to the Signaling Protein class. *Rosmarinic Acid* (CID: 5281792), *Quercitrin* (CID: 5280459), *Isoquercitrin* (CID: 5280804), *Nirurin* (CID: 2112061), *Rutin* (CID: 5280805) were downloaded in 3D structure in .sdf format as shown in Table A. 2 D (2 Dimension) & 3 D (3 Dimension) structure of selected compounds shown in Figure 3 & Figure

Protein Name - Sequestosome-1
Gene - SQSTM1
Protein database No. - 5YP7
Classification: Signaling Protein
Organism(s): *Homo sapiens (*Human)
Expression System: (*E.coli*) *Escherichia coli* BL21
Mutation(s): No
Sequence Length: 55

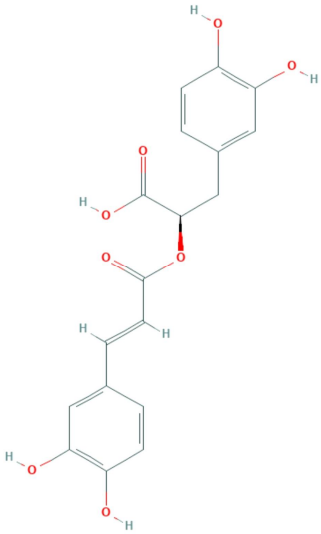


(A) Biological Assembly 1

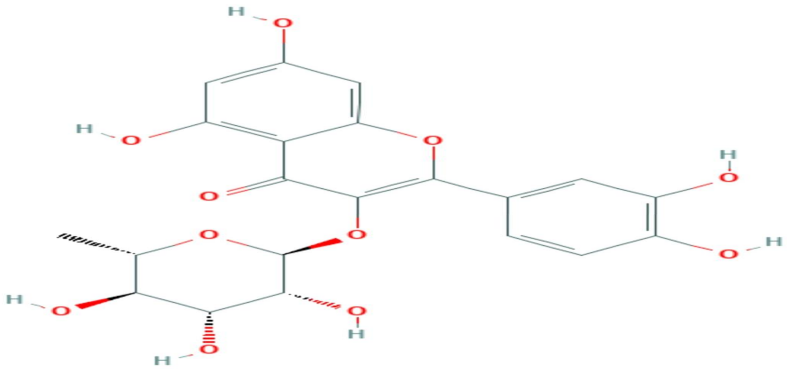


(B) Biological Assembly 2

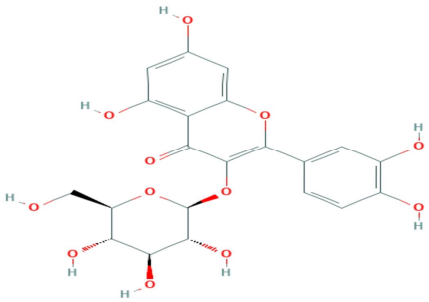
Figure 2: Structure of Sequestosome-1 (A) Biological Assembly 1(B) Biological Assembly 2



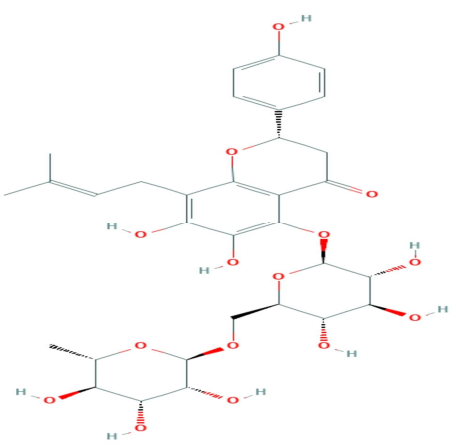
(A) *Rosmarinic Acid*

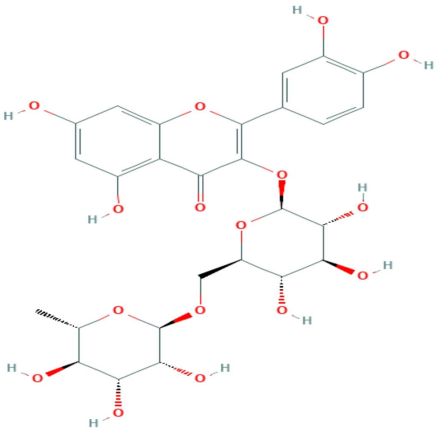


(B) *Querctrin*



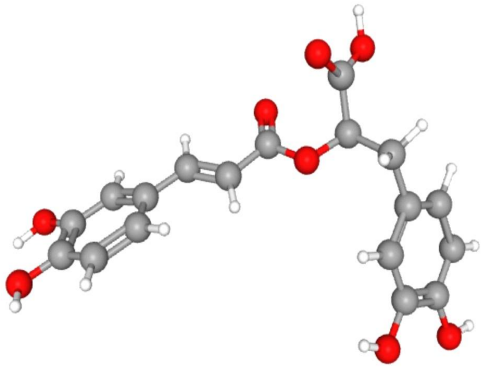
(C) *Isoquercitrin*

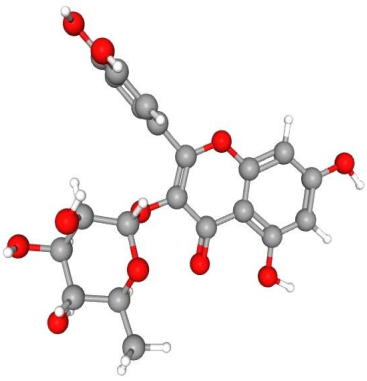




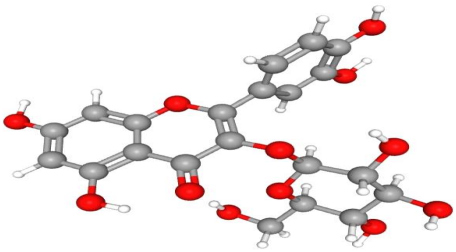
(D) *Nirurin* (E) *Rutin*

Figure 3: 2 D (2 Dimension) Structrue (A) *Rosmarinic Acid* (B) *Quercitrn* (C) *Isoquercitrin* (D) *Nirurin* (E) *Rutin*

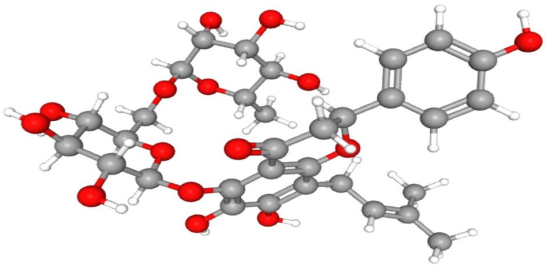




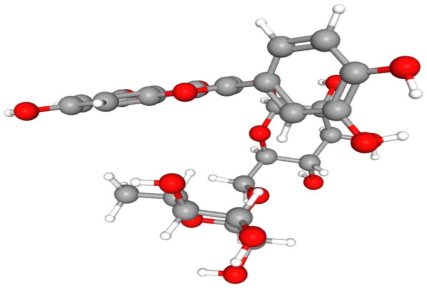
(a) *Rosmarinic Acid* (b) *Quercitrin*



(c) *Isoquercitrin*



(d) *Nirurin*



(e) *Rutin*

Figure 4: 3 D (3 Dimension) Structure (a) *Rosmarinic Acid* (b) *Quercitrin* (c) *Isoquercitrin* (d) *Nirun* (e) *Rutin*

Table A: Ligand molecule details from PubChem

Sr. NO.	Name of Ligands	Alternative Names	PubChem CID:	M. Weight in g/mol	M. Formula	LogP3 value	H-Bond Donor	H-Bond Acceptor
1.	Rosmarinic ac	Rosmarinate Rosemary acid (R)-rosmarinic acid	5281792	360.3	$C_{18}H_{16}O_8$	2.4	5	8
2.	Quercitrin	Quercitroside Quercetrin Quercimelin	5280459	448.4	$C_{21}H_{20}O_{11}$	0.9	7	11
3.	Isoquercitrin	Isoquercetin Quercetin 3-glucoside Hirsutrin	5280804	464.4	$C_{21}H_{20}O_{12}$	0.4	8	12
4.	Nirurin	(2S)-6,7-Dihydroxy-2-(4-hydroxyphenyl)-8-(3-methylbut-2-enyl)-5-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-[[(2R,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxymethyl]oxan-2-yl]oxy-2,3-dihydrochromen-4-one	21120611	664.6	$C_{32}H_{40}O_{15}$	0	9	15
5.	Rutin	Rutoside Phytomelin Quercetin 3-rutoside	5280805	610.5	$C_{27}H_{30}O_{16}$	-1.3	10	16

Virtual screening of the ligand molecules was done by *PyRx* software. According to the minimum binding energy, ligands were screened. The binding affinity of *Rosmarinic Acid* was -6.5, *Quercitrin* was -6.6, *Isoquercitrin* was -6.6, *Nirurin* was -7.2 and *Rutin* was -7.1 as shown in **Table B** and the Binding energies of *Rosmarinic Acid* was -6.5, *Quercitrin* was -6.6, *Isoquercitrin* was -6.6, *Nirurin* was -7.2 and *Rutin* was -7.1 as shown in **Table C.** The ligands which were selected after *PyRx* result were *Rosmarinic Acid, Quercitrin, Isoquercitrin, Nirurin,* and *Rutin.* All these ligands were further analyzed for drug likeliness property analysis.

Table B: The Binding affinity, Mode, RMSD Upper Bound & RMSD Lower Bound of different ligands with protein molecules.

Ligand molecules	PubChem CID:	Binding Affinity (Kcal/mol)	Mode	RMSD Upper Bound	RMSD Lower Bound
Rosmarinic acid	5281792	-6.5	0	0	0
Quercitrin	5280459	-6.6	0	0	0
Isoquercitrin	5280804	-6.6	0	0	0
Nirurin	21120611	-7.2	0	0	0
Rutin	5280805	-7.1	0	0	0

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

Ligand molecules	Binding energy
Rosmarinic acid	-6.5
Quercitrin	-6.6
Isoquercitrin	-6.6
Nirurin	-7.2
Rutin	-7.1

Drug likeliness property analysis was done by SwissADME & ligands were screened according to Lipinski's Rule of Five as shown in **Table D.** *Rosmarinic Acid* was the only molecule that follows all the properties of the Drug.

Table D: Drug Likeliness Property Analysis

Compound Name	Molecular Weight in g/mol	H-bond Acceptors	H-bond Donors	Partition Coefficient MlogP	Violation
Rosmarinic acid	360.3	8	5	0.90	Yes; 0
Quercitrin	448.38	11	7	-1.84	No; 2
Isoquercitrin	464.4	12	8	-2.59	No; 2
Nirurin	664.6	15	9	-2.35	No; 3
Rutin	610.5	16	10	-3.89	No; 3

The protein target Sequestosome-1 (PDB ID: 5YP7) & *Rosmarinic Acid* (CID: 5281792) were docked via *AutoDock Vina* software. The result showed in 9 Columns with different (BA) Binding Affinity, (RMSD LB) (Root Mean Square Deviation Lower Bound) and (RMSD UB) (Root Mean Square Deviation Upper Bound) as shown in **Table E:**

Table E: AutoDock Vina Result

Mode	Affinity in (kcal/mol)	Dist. From Best Mode	
		RMSD Lower Bound	RMSD Upper Bound
1	-6.9	0	0
2	-6.7	1.912	4.906
3	-6.6	2.320	3.834
4	-6.6	1.498	4.438
5	-6.4	1.719	2.268
6	-6.4	3.061	5.778
7	-6.4	2.680	5.306
8	-6.3	2.946	7.921
9	-6.2	2.832	6.092

The *Rosmarinic Acid (*RA*)* showed a strong (BA) binding affinity with the drug target. The ligand & the target protein interaction structure was visualized via *PyMOL* as shown in **Figure 5**. According to this, *in silico* study, *Rosmarinic acid* may act as an inhibitor & *Rosmarinic acid* may be used as a drug that may control Parkinson's disease. Thus, it may form an effective drug that can prevent Parkinson's disease (PD).

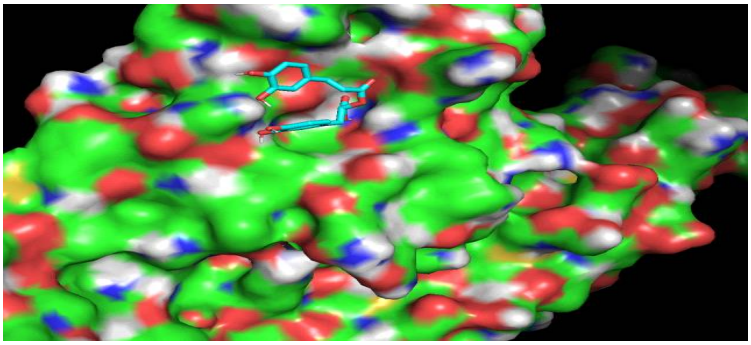


Figure 5: Structure of Interaction of Sequestosome-1 with *Rosmarinic acid* via *PyMOL* visualizer.

IV. CONCLUSION

According to the *in silico* study, the docking technique was used to examine the potential of natural compounds which were selected as a ligand against the selected protein target. According to this docking, the interaction of the ligand (*Rosmarinic Acid*, *Quercitrin, Isoquercitrin, Nirurin,* and *Rutin*) with the target protein Sequestosome-1 (PDB ID: 5YP7) was predicted in *in silico* study. *Rosmarinic Acid* was found with the best binding energy and it also followed Lipinski's rule with zero violations. *Rosmarinic Acid* may act as a drug for the treatment of Parkinson's by inhibiting Sequestosome-1 protein. The obtained results may be very useful to understand the structural features required to enhance the inhibitory activities against the protein. In future studies, extracted Rosmarinic Acid from natural sources may be a promising drug for the treatment of Parkinson's disease (PD).

V. CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

VI. ACKNOWLEDGEMENT

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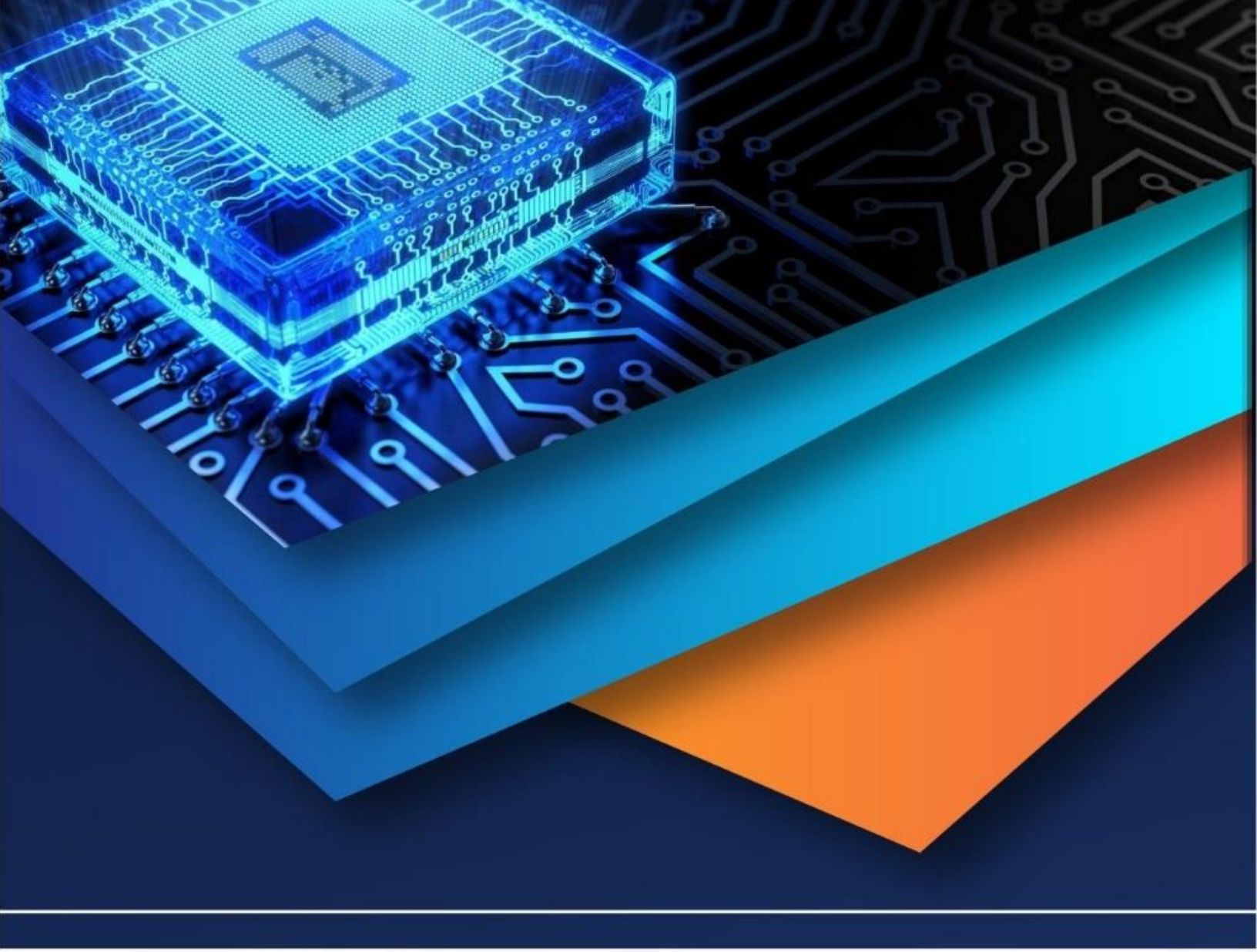

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