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The Treatment of Alzheimer's Disease through Molecular Docking Studies using Phyltetralin against Kallikrein_6: A Bioinformatic Approach

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Abstract: ***Background: Alzheimer's disease (AD) is a neurodegenerative disease that generally begins leisurely and gets worse with time. Alzheimer's disease (AD) dementia is the specific beginning of age-related declination of cognitive abilities and function, which eventually leads to death. Alzheimer's disease (AD) is one of the neurodeteriorating disorders which is one of the mostcritical complications that our current health care system faces. The phenomenon of molecular docking has progressively become a strong tool in the field of pharmaceutical research including drug discovery. The aim of the presentin silico study was to inhibit the expression of KLK-6 (kallikrein-6) which is a target or receptor protein by its interaction with three distinct secondary metabolites for treating Alzheimer's disease (AD) through molecular docking.***
Methods: The in-silico study was based on molecular docking. Docking was executed amidst ligands- Quercetin (CID: 5280343), Ricinoleic Acid (CID: 643684), Phyltetralin (CID: 11223782), and the target or receptor protein Kallikrein-6 (PDB ID: 1LO6). The protein and the ligands were downloaded in the required format. Through PyRx, the ligands were virtually screened after importing them in the PyRx window. The results of PyRx and SwissADME were analyzed and the best ligand was finalized. Among the three, Phyltetralin was the best ligand contrary to KLK-6 having minimum binding energy and it was following Lipinski's five rules along with 0 violations. Results: The final docking was carried out between Phyltetralin and KLK-6 through AutoDock Vina. The outcome showed 9 poses with distinct binding energy, RSMD LB (root mean square deviation lower bound) and RSMD UB (root mean square deviation upper bound). With the help of PyMOL which is an open-access tool for molecular visualization, the interaction amidst Phyltetralin and KLK-6 can be visualized.
Conclusion: Based on this in silico study it can be concluded that KLK-6 (kallikrein-6) which is responsible for causing AD can be inhibited by ligand Phyltetralin and for the treatment of AD, phyltetralin might act as a potential drug. Thus, in future studies, Phyltetralin from natural sources can prevent Alzheimer's disease and can be proved as a promising and efficient drug for treating Alzheimer's disease.
Keywords: Alzheimer's disease, AutoDock Vina, KLK-6, Molecular docking, Phyltetralin

I. INTRODUCTION

Alzheimer's disease (AD) is also known as Alzheimer's. AD is a disease that is neurodegenerative that generally begins leisurely and gets worse with time. [1]. Alzheimer's disease (AD) dementia is the specific beginning of age-related declination of cognitive abilities and function, which eventually leads to death [2]. In 1906, Alzheimer's disease was mainly introduced or described as intensifying and neurodeteriorating disease by Alois Alzheimer. Alzheimer's disease (AD) is one of the neurodeteriorating disorders which are one-off the critical complications that our current health care system faces. From the preliminaries of the 21st century, Alzheimer's disease is acknowledged as the most widespread type of dementia among elderly or aged people [3]. The most frequent source of dementia is Alzheimer's disease (AD), accounting for nearly 60 to 80% of all cases of dementia globally [4]. Continuous deprivation of neurons in the central nervous system (CNS), functions of the brain, function of cognition, are some major characteristics through which Alzheimer's disease can be distinguished [5]. Alzheimer's disease is one of the progressive-growing diseases which is mostly linked with the neurofibrillary tangles composed of phosphorylated tau protein (P-tau), formation of aggregates of misfolded proteins that form in the spaces between nerve cells i.e. beta-amyloid plaques, loss of synapse, and degeneration of neurons [6].

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Risk factors of AD include- age, genetics, family history, and some potentially modifiable risks such as physiological factors (educational attainment, cognitive activity, and bilingualism, social engagement, depression, and stress), pre-existing diseases (diabetes, hypertension, obesity, dyslipidemia, cardiovascular diseases, traumatic brain injury, etc.), and lifestyle (physical activity, sleep disturbances, smoking, excessive alcohol consumptions, diet, coffee, and tea).Alzheimer disease mainly characterized by;

1) Senile plaques (SP), continuous formation of aggregates of β-amyloid (Aβ) proteins occurring in the spaces between nerve cells [7].
2) Neurofibrillary tangles (NFTs), aggregates of highly-phosphorylated tau protein (P-tau) found inside the brain's cells [7].
3) Acetylcholine's level declination- Ach is a chief neurotransmitter amalgamated from the brain's cholinergic neurons having a major role in the transmission of signals and messages delivery in the brain [7], [8], [9].

More than 36.5 million people are having Alzheimer's disease, as of today. There might an increase in the number of people to 65.7 million in 2030 and 115.4 million in 2050. WHO (World Health Organization) projected that in most developing countries more than fifty percent (50%) of persons are affected by Alzheimer's disease (AD) and by 2025 it can increase up to 70% [10]. By mid-century, it is estimated that the number of Alzheimer's dementia patients will accomplish 152 million globally, additionally, there is an expectance of maximum increment in the countries having middle and low revenues [11].In America, the number of AD patients of age 65 and older might increase greatly from 6.2 million to 7.2 million by 2025 and is estimated to reach 13.8 million by 2060 [12], [13].

Natural products from different sources are very beneficial for our wellbeing and also, they provide help in reducing the development and symptoms of various diseases which also include AD i.e., Alzheimer's. Natural compounds are rising as very promising agents for therapy of Alzheimer's disease (AD). A variety of advantageous pharmacological activities like anticholinesterase, anti-amyloidogenic, antioxidant, and activity against inflammation are shown by a lot of compounds like flavonoids, polyphenols, sterols, lignans, alkaloids, triterpenes, and tannins [14].

The phenomenon of molecular docking has progressively become a strong tool in the field of pharmaceutical research including drug discovery. The method of molecular docking is a kind of bioinformatics modeling. At the atomic level, molecular docking helps in predicting the intermolecular framework established between a protein and a small molecule. In the binding site of the target protein, the characterization of the nature or role of a small molecule is enabled to us by this prediction. Additionally, it also enables us to exemplify essential chemical processes occurring in living organisms i.e. biochemical processes [15].To form a steady complex, molecular docking predicts the ligand's preferential orientation contrary to receptor (Protein) [16]. The binding affinity or strength of interaction between ligand and receptor (protein) can be anticipated through preferential confirmation by using functions of scoring. To anticipate the drug's affinity and the drug's activity, docking is usually employed to predict the binding orientation of candidates of drugs contrary to the target protein. Thus, in the process of drug designing and drug discovery, molecular docking has a very significant role [17].

The procedure of molecular docking involves:-

a) Protein selection and preparation
b) Ligand selection and preparation
c) Autodocking
d) Result evaluation

II. METHODOLOGY

A. *Protein Identification*

For the selected ligand, Kallikrein-6 (KLK-6) was utilized as a receptor. Human kallikrein-6 (hK6) is a serine protease having 223 residues of AA (amino acid). In the family of *Homo sapiens* KLK gene, hK6 (human kallikrein-6) is a novel member which is determined. Neurosin [20], Protease M [19], or Zyme [18] are the synonyms or other names of Human kallikrein-6 (hK6). It has been demonstrated that the continuous growth of AD, hK6 is likely to engage [21], [20], [18], [22].

From the RCSB Protein Data Bank (PDB)[https://www.rcsb.org], the structure of the selected protein i.e. kallikrein-6 (KLK-6) (PDB Id- 1LO6)was fetched and the protein molecule was evaluated for its resolution. The downloaded structure of KLK-6 protein molecule must be in .pdbformat.

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B. Ligands Retrieval

The three natural compounds were utilized as ligands in the study- Quercetin, Ricinoleic Acid and Phyltetralin.

1) *Quercetin:* Quercetin is a flavonol, naturally occurring polyphenolic compounds present in various vegetables such as onions, radish leaves, carpers, etc, fruits like apples, berries, etc. It can also be found in red wine and green tea. Quercetin decreased the imbalance of free radicals and antioxidants in the body i.e. oxidative stress and enhanced the impairments of cognition and memory of an Alzheimer's disease (AD) model, this was shown by the studies done in vivo [23]. Besides this, there is evidence recommended by the in vitro studies that quercetin destabilizes beta-amyloid fibrils and suppresses the formation of beta-amyloid fibrils [24], restricts the accumulation of beta-amyloid (Aβ) [25].
2) *Ricinoleic acid (RA):* RA (12-hydroxy-9-cis-octadecenoic acid) is a high-value or potent hydroxyl fatty acid having significant relevance in industries [26]. The chief source of ricinoleic acid is the seed oil of the castor plant (*Ricinus communis*). In castor oil, about 90% of the content of fatty acid is the triglyceride formed from ricinoleic acid [27]. Ricinoleic acid relieves pain specifically through analgesic effects and also reduces inflammation by having activity against inflammation [28].
3) *Phyltetralin:* Phyltetralin is a type of lignan which is extracted from the Phyllanthus genus. Evaluation of phyltetralin has been done for a broad range of biological actions. Phyltetralin is a biologically active intermediate of naturally occurring metabolism reactions i.e. metabolites. Analysis and report illustrating different pharmacological and biological effects encompassing modulating and potentiate the immune system, keeping it prepared for threat i.e. immunomodulatory effects [29].

With the help of PubChem (https://pubchem.ncbi.nlm.nih.gov), which is a public chemical database, distinct ligands were downloaded. The ligands were downloaded in a three-dimensional (3D) structure and .sdf format. Further, the conversion of downloaded ligands from .sdf to. pdb format was done with the help of an online SMILES Translator (https://cactus.nci.nih.gov/translate). After the successful conversion in the .pdb format, the converted files of these ligands were downloaded.

C. Virtual Screening of Ligands

PyRx is open-source software that is used for the virtual screening of compounds contrary to potential drug targets. With the help of PyRx, virtual screening of the ligands was done through which the binding energies and affinities of the ligands were illustrated. The software PyRx runs in a specific format i.e. .pdbqt format. The process of virtual screening through PyRx begins with the loading of our protein molecule retrieved in .pdb form it as shown in **Figure 1**. From the .pdb format, the protein molecule was transfigured into .pdbqt format. After that, the importing of downloaded ligands in .sdf format was done. Before the conversion of ligands (from .sdfto .pdbqt), the ligand's energies were reduced. Subsequently, the ligands were transformed in desired .pdbqt format from .sdf format. Amidst target protein and ligand docking was executed and the outcome was examined based on the binding affinity of ligands.

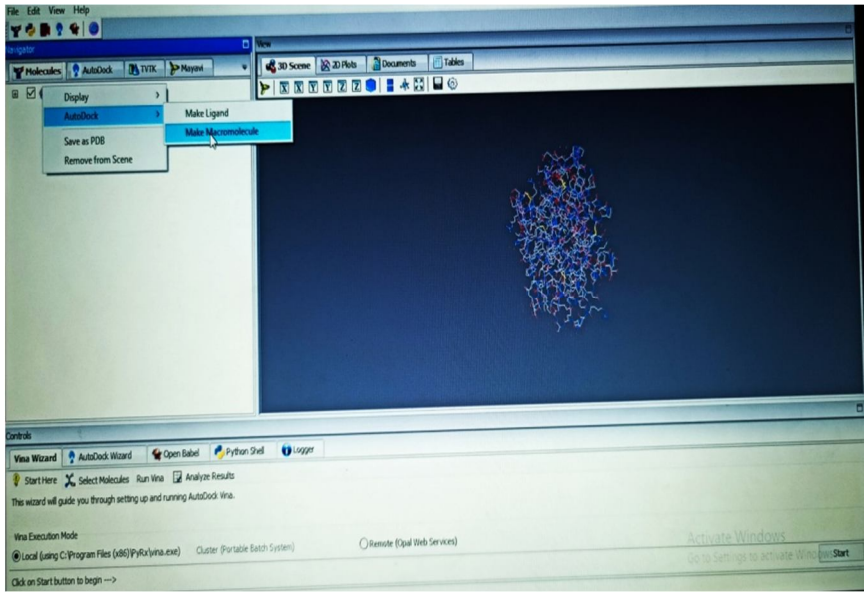

Figure1: Protein molecule loaded in PyRx window

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D. Drug Likeliness Property Analysis

SwissADME is an online server for drug likeliness property analysis. The ligands having minimum binding affinity which were screened through PyRx were validated for their drug likeliness property with the help of the online server SwissADME (http://www.swissadme.ch/). The analysis is done for Lipinski's rule of five. From the public chemical database i.e. PubChem, the canonical smiles of the screened ligands were copied and pasted on swissADME for the screening of ligands based on five rules of Lipinski. Lipinski's five rules as follows [30] :-

1) The molecular weight must be < 500 Da.
2) Hydrogen bond acceptors should be < 10.
3) Hydrogen bond donors ought to be < 5.
4) Partition coefficient LogP should be < 5.
5) The number of violations should be either 0 or 1 and should not be more than 1.

The ligands following all the Lipinski's five rule were finalized for the final docking through AutoDock Vina.

E. Final Docking Between Target Protein (PDB Id-1LO6) and Phyltetralin through AutoDock Vina

AutoDock Vina is an open-source program for executing molecular docking between the ligand and the target protein. The best ligand was selected and it was further taken forward against the receptor protein i.e. KLK-6 for executing the final with the help of AutoDock Vina. Firstly, on the graphical window of AutoDock Vina, the target protein was loaded. After loading the protein, deletion of molecules of water (H2O), the addition of polar hydrogen atoms, and then the addition of Kollman charges were done. Further the protein was transformed from .pdb format into .pdbqt format. Then the ligand molecule i.e. Phyltetralin was imported into the software followed by its conversion from .pdb format to .pdbqt form. For the region to be docked the grid box's boundaries were calibrated by adjusting its dimensions as per requirement. Utilizing the command (cmd) prompt, molecular docking was carried out and the analysis of results was done.

F. Visualization of Structure through PyMOL

PyMOL is an open-access tool for molecular visualization. With the help of the structure visualization tool PyMOL, the results of docking were visualized. On the graphical screen of PyMOL, the protein molecule in .pdbqt format was loaded accompanied by the output .pdbqt file. Then visualization and examination of the interaction between the protein and ligand or the docked structure were done. After this, conversion of a molecule into "molecular surface" from the option "shown as" was done.

III. RESULT AND DISCUSSION

From the PDB (Protein Data Bank), the structure of KLK-6 (Kallikrein-6) was downloaded as depicted in **Figure 2**. The protein belongs to the hydrolase class with a resolution of 1.56 A. The R-value observed was 0.197 while the R-value free was 0.223. The three-dimensional (3D) structure of the ligands namely- Quercetin (CID: 5280343), Ricinoleic Acid (CID: 643684), and Phyltetralin (CID: 11223782) were retrieved through PubChem in .sdf format as depicted in **Table 1**. Then it was converted into .pdb format with the help of an online SMILES translator.

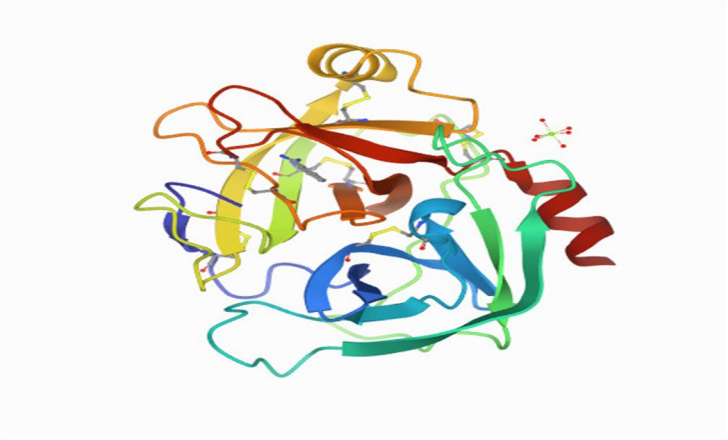

Figure 2: 3D structure of KLK-6 (PDB ID: 1LO6) protein.

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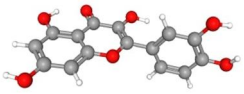
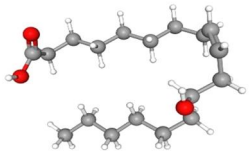
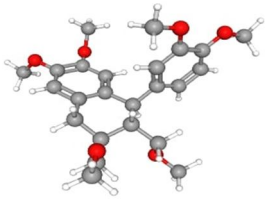
Table 1- Structure of ligands in 3D form

Ligands	Structure	PuChem CID	Molecular Weight	Molecular Formula
Quercetin		5280343	302.23 g/mol	$C_{15}H_{10}O_7$
Ricinoleic Acid		643684	298.5 g/mol	$C_{18}H_{34}O_3$
Phyltetralin		11223782	416.5 g/mol	$C_{24}H_{32}O_6$

The ligands were virtually screened with the help of an open-source software PyRx. The ligands were screened based on their binding energies. The binding affinity of Quercetin was -5.7, Ricinoleic Acid was -6.6 and Phenyltetralin was -8.2 as illustrated in **Table 2**. The ligands Phyltetralin and Ricinoleic Acid were finalized based on the results of PyRx.

Table 2- The binding affinitiy, root mean square deviation lower bound (RMSD LB) and root mean square deviation upper bound (RMSD UB) of the ligand molecules contrary to the KLK-6 (PDB ID: 1LO6) protein.

S No.	Ligand Molecules	Binding Affinity	Mode	RMSD Lower Bound	RMSD Upper Bound
1.)	Quercetin	-8.2	0	0	0
2.)	RicinoleicAcid	-5.7	0	0	0
3.)	Phyltetralin	-6.6	0	0	0

The ligands selected through virtual screening i.e.Ricinoleic Acid and Phyltetralin having the best minimum energy were taken forward for their drug likeliness property analysis. This analysis of drug likeliness property was done with the help of SwissADME. The ligands were analyzed and screened based on five rules of Lipinski as depicted in **Table 3**. The results of SwissADME were analyzed and finally, best ligand molecule was selected. Phyltertalin was the best molecule having minimum binding energy with the KLK-6 protein molecule as well as it was following all the five rules of Lipinski.

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Table 3- Drug Likeliness Property Analysis

S No.	Ligand Molecules	Molecular weight < 500 k da	Number of H bond acceptors < 10	Number of H bond donors < 5	Log Po/w (MLOGP) < 5	Violations
1.	Ricinoleic Acid	298.46 g/mol	3	2	3.69	Yes; 0 violation
2.	Phyltertalin	416.51 g/mol	6	0	2.03	Yes; 0 violation

The best ligand screened through SwissADMEi.e.Phyltetralin (CID: 11223782) was subjected to final docking against the target protein i.e. KLK-6 (kallikrein-6) with the help of AutoDock Vina which is open-source software for molecular docking. The outcome showed 9 poses with distinct binding energy, RSMD LB (root mean square deviation lower bound) and RSMD UB (root mean square deviation upper bound) as illustrated in Table 4**.**

Table 4- Results of AutoDock Vina

Mode	Affinity (kcal/mol)	Dist from best mode	
		RSMD LB	RSMD UB
1	-5.5	0.000	0.000
2	-5.4	23.205	25.091
3	-5.2	2.071	5.430
4	-5.2	29.121	32.896
5	-5.2	24.601	26.170
6	-5.2	24.773	27.152
7	-5.1	22.463	25.669
8	-5.1	1.986	4.910
9	-5.1	20.230	23.464

The results of AutoDock Vina proved that the ligand Phyltetralin (CID: 11223782) has a strong binding affinity with the target protein KLK-6. With the help of PyMOL which is an open-access tool for molecular visualization, the interaction amidst Phyltetralin and KLK-6 can be visualized as depicted in Figure 3**.**

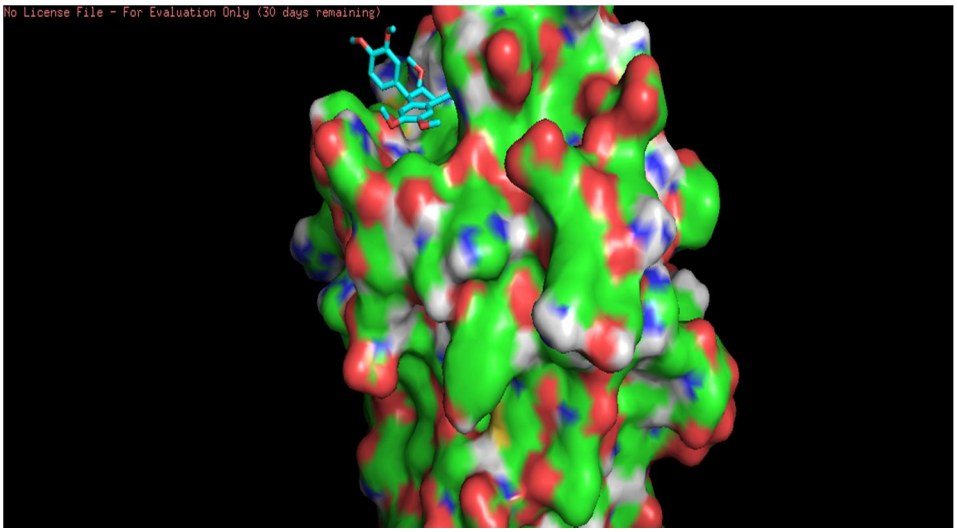

Figure 3- PyMOL Result of Interaction of KLK-6 (PDB ID: 1LO6) with Phyltetralin (CID: 11223782)

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IV. CONCLUSION

Alzheimer's disease (AD) is a prominent neurodegenerative disorder. It is a continuous neurodeteriorating disarray which has an adverse effect on cognitive function as well as on the functioning of the brain. Molecular docking is a very significant computer-based tool for the discovery of drugs and due to its usefulness, it is becoming a popular approach in pharmaceutical research. Molecular docking predicts the interaction between a target molecule i.e. protein and a drug candidate i.e. ligand. In this *in silico* study, molecular docking was performed to examine the interaction of distinct natural compounds (ligand molecules) with target protein i.e. kallikrein-6. The study predicted that the ligand molecule i.e.Phyltetralin (CID: 11223782) has a strong binding affinity with the receptor or target protein i.e. Kallikrein-6 (KLK-6) (PDB ID: 1LO6) and its potential as a drug against Alzheimer's disease (AD) is conformed. After PyRx and SwissADME analysis, the only compound with the best minimum binding energy was Phyltetralin. Also, it was following all the five rules of Lipinski along with 0 violations. Hence, based on this *in silico* study, KLK-6 (kallikrein-6) which is responsible for causing AD can be inhibited by ligand Phyltetralin and for the treatment of AD, phyltetralin might act as a potential drug. Thus, in future studies, phyltetralin from natural sources can prevent Alzheimer's disease and can be checked as a promising and efficient drug for treating Alzheimer's disease.

V. ACKNOWLEDGEMENT

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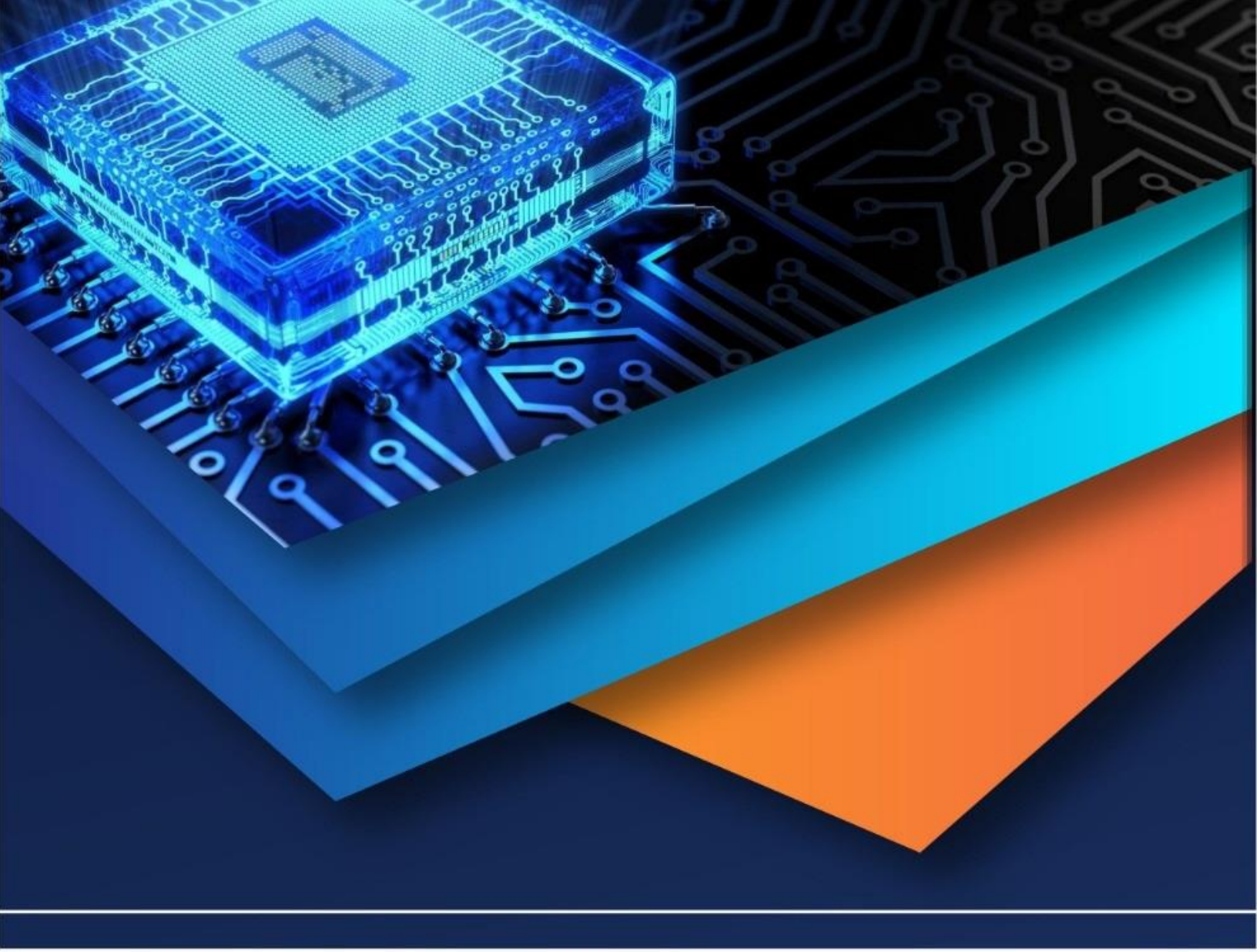

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