iJRASET
International Journal For Research in Applied Science and Engineering Technology

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 9 **Issue:** VI **Month of publication:** June 2021

DOI: https://doi.org/10.22214/ijraset.2021.35932

www.ijraset.com

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International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.429
Volume 9 Issue VI Jun 2021- Available at www.ijraset.com

A Possible Role of Pulegone against Glypican-1 for the Treatment of Alzheimer's Disease through *In-Silico* Approach

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Abstract: ***Background: Alzheimer's disease (AD) dementia is a type of neurodegenerative disease, refers to a distinct arrival and certainly functional and mental decline which is linked with age which eventually leads to death. This current study was to demonstrate the role of pulegone against Glypican-1 for the treatment of Alzheimer's disease through an in-silico approach.***
Methods: All the information and studies were gleaned from molecular docking. With the use of docking software, Docking was implemented between the target protein GPC1 (PDB ID: 4YWT) and the entire ligands. We preferred GPC1 (PDB ID: 4YWT) as a target protein and several natural compounds such as Rosmarinic acid, Allo ocimene, and Pulegone as ligands. When the preparation of protein is done, in PyRx software we introduced the entire ligand for the process of virtual screening. As reported by the result of PyRx and Lipinski's Rule of Five, the finest compound against GPC1 with its smallest amount of binding energy was Pulegone. Results: For the procedure of molecular docking between the receptor protein GPC1 (PDB ID: 4YWT) and Pulegone a software called AutoDock Vina was used. The outcome showed 9 poses with distinct binding energy, RMSD LB (Root means square deviation Lower Bound), RMSD UB (Root mean square deviation Upper Bound). Through PyMol (an open-access tool for the visualization of the molecule), the interaction amidst Pulegone and GPC1 can be visualized.
Conclusion: The merely compound which can restrain the activity of GPC1 (PDB ID: 4YWT) was Pulegone, based on the in-silico approach. Therefore in the advanced studies, Pulegone can be a capable medicine acquired from natural sources for dealing with Alzheimer's disease.
Keywords: Alzheimer's disease, Pulegone, Molecular docking, Autodock vina, GPC1.

I. INTRODUCTION

Alzheimer's disease (AD) dementia is a type of neurodegenerative disease, which refers to a distinct arrival and certainly functional and mental decline which is linked with age which eventually leads to death [1]. The disease was first reported in 1906 by Alois Alzheimer, he narrated the case of a 51-year-old woman, Auguste Deter who was suffered from perplexity, hallucination, cognitive trouble, and other communicative or interactive transitions and she died 4.5 years later in the year of 1906. Fastidious modifications in cortical cell clusters and disperse brain atrophy showed by Alzheimer's neuropathologic evaluation. In a session 'on the peculiar disease process of the cerebral cortex, he described his conclusion [2]. Post-mortem evaluation of brain tissue, through cerebrospinal fluid (CSF) and positron emission tomography (PET), are required for the ultimate diagnosis of AD, also the PET biomarkers linked with more than a few moderately new scientific basis can assist diagnosis in living patients [3]. Cholinesterase inhibitors are generally available for patients of AD as a current treatment in fact with whichever phase of AD dementia and memantine for the public with moderate to cruel AD dementia. The quality of life of AD patients, as well as a caregiver, can be improved by these medications when given at the suitable instance during disease; nevertheless, they do not modify the rate of decline [4].
Alzheimer's disease is the most general cause of dementia [5], [6]. Dementia is a type of medical condition or a syndrome distinguish by continuing decrease in two or more cerebral domains, including language, memory, supervisory function, and visuospatial function means the component of working memory responsible for handling visual and spatial information, also behavior and personality, which fails incapacity to achieve normal actions of daily life. For determining the stage of dementia, the Diagnostic and Statistical Manual of Mental Disorders (DSM) may pass on via Physicians to direct them in identifying if a person has dementia, and, if so then what might be the reason. Dementia is classified as a chief neurocognitive disease that is predicated on the most recent DSM criteria [7]. It is identified as a kind of foremost neurocognitive disorder for the reason that it obstructs cognitive tasks as well as doing actions daily. verbal communication, remembrance, decision making, communication, way of thinking potential, these activities are coming under Cognitive function and examples of everyday activities are paying bills, traveling to a market to buy something, and making food.

Alzheimer's disease (AD) reports for up to 80% of all dementia diagnoses [8]. In 1984, medical diagnostic fundamentals for AD dementia were rationalized, and to identify the utilization of biomarkers it further developed in the year 2011 and 2018 and also with the new ability to characterize preclinical stages of the disease [9], [10], [11], [12]. Post-mortem evaluation of brain tissue, through cerebrospinal fluid (CSF) and positron emission tomography (PET), are required for the ultimate diagnosis of AD, also the PET biomarkers linked with more than a few moderately new scientific basis can assist diagnosis in living patients [3].
Cholinesterase inhibitors are generally available for patients of AD as a current treatment in fact with whichever phase of AD dementia and memantine for the public with moderate to cruel AD dementia. The quality of life of AD patients, as well as caregivers, can be improved by these medications when given at a suitable instance during disease; nevertheless, they do not modify the rate of decline [4].
Natural products have been used for the management of various diseases and are becoming an important research area for drug discovery. Natural compounds are growing as extremely capable agents for the treatment of Alzheimer's disease (AD). The natural compounds play a very noteworthy function in the prevention of Alzheimer's disease. Medicinal plants play an important role to reduce the development and symptoms of AD [13]. To scrutinize the property of entire medicinal plant extracts on AD and also to isolate and recognize the lively compounds involved in it a lot of studies have been conducted [14]. A range of valuable pharmacological activities was shown by numerous compounds, including flavonoids, triterpenes, lignans, alkaloids, tannins, and sterols for example anticholinesterase, anti-inflammatory, antioxidant, and anti-amyloidogenic [13].
Molecular docking is defined as a procedure in which the binding of a ligand to a particular protein of interest takes place. On the other hand, 'hand-in-glove' correlation is further suitable than 'lock-and-key because mutually the protein and the ligand are flexible [15]. Molecular docking can envisage the binding-conformation of small-molecule ligands to the suitable target binding site and because of this ability, molecular docking is generally a commonly used method in structure-based drug design. To illuminate elementary biochemical procedures, the representation of the binding behaviour is significant. Also, it plays an essential role in the rational design of drugs [16], [17]. The research done on Molecular docking gives attention to computationally bracing the molecular recognition progression. Its focus to minimize the free energy of the overall system by optimizing the conformation of both the protein and ligand as well as the relative adjustment between them. Molecular docking is one of the most commonly used methods in Structure-Based Drug Design (SBDD) because some reasons like its capability to forecast, with a significant degree of accurateness, the arrangement of small-molecule ligands inside the suitable target binding site [18]. Additionally, molecular docking algorithms categorize docked compounds based upon the ligand-receptor complexes' binding affinity and carry out the assessable prognostication of binding energetic [19], [20].

II. MATERIALS AND METHODS

A. *Identification of protein*

A protein named Glypican-1 is encoded by the *GPC1* gene and found in humans [21], [22]. There is a presence of a center protein in the members of the GRIPS (glypican-related integral membrane proteoglycan family). This center protein is attached to the cytoplasmic membrane through a linkage named glycosylphosphatidylinositol. In managing growth regulation and cell division these proteins play an essential role [21]. The interaction of Glypican 1 with SLIT2 has been demonstrating [23]. The clinical significance of Glypican-1 is that in the cell membrane the misfolding of usual prion proteins to the infectious prion appearance [24]. GPC-1 is composed of a protein with 558 AA. Along with this, at S490, S488 and S486 respectively, there is an addition of three chains of Heparan Sulfate. GPC-1 has two forms: the first one is secreted in a form that is soluble and the second is a form that is embedded in a membrane [25]. The cleavage can be done by Notum [26], [27]. GPC-1 is primarily expressed in embryonic development in the skeletal system and the central nervous system, and in adults, it is expressed in the majority of tissues [28]. GPC-1 functions through the binding of enzymes, growth factors, viral proteins, cytokines, and further factors with its HS side chains [29], [30], [31], [32].

B. *Identification of Ligands*

Rosmarinic acid (*Rosmarinus officinalis*), Allo ocimene (*2,6-dimethyl-2,4,6-octatriene)* and Pulegone *((R)-5-Methyl-2(1-methylethylidine)cyclohexanone)* were the three natural compounds that were used as ligands in the study.
Rosmarinic acid is a type of chemical compound that is available in a range of many plants. It was isolated and distinguished in 1958 from rosemary (*Rosmarinus officinalis*) by the Italian chemists M. L. Scarpatti and G. Oriente [33]. When inspected *in vitro*, this chemical compound show signs of photoprotective effect against ultraviolet C (UVC) damage [34].

Rosmarinus officinalis is a forested, everlasting herb with odorous, narrow leaves and pink, white, blue, or purple flowers, inhabitant to South Europe and the Mediterranean area [35].

The desiccated and new leaves of rosemary are used as herbs in conventional Mediterranean gastronomy for their extreme bitter and pungent flavor or taste in many dishes. In aromatherapy, rosemary extracts are moreover used to treat anxiety-related circumstances and increase awareness [36].

Allo ocimene is a member of the class of compounds known as acyclic monoterpenoids. It can be written as 2,6-dimethyl-2,4,6-octatriene. Allo ocimene can be found mainly in saliva. Acyclic monoterpenoids are the monoterpenes that don't include a cycle. 2,6-dimethyl-2,4,6-octatriene can be found in tarragon, parsnip, and sweet basil, which makes 2,6-dimethyl-2,4,6-octatriene a probable biomarker for the utilization of these foodstuffs [37].

Pulegone is an organic compound present in nature. It is isolated from certain plants like *Mentha piperita, pennyroyal,* and *Nepeta cataria* (catnip) [38], [39]. Pulegone is also known as a crucial compound in Schizonepeta essential oil. It also has the ability of anti-inflammatory activity [40]. Pulegone has a wide range of pharmacological roles, like as medicines that fight against bacterial infections i.e. anti-biotic, antidepressant, anti-ulcer, and anti-oxidant, property [41]. Pulegone is also used as a defoliant or an insecticide [42]. It is also classified as a monoterpene. Pulegone has a pleasing aroma similar to camphor, pennyroyal, and peppermint and is a clear monochrome oily fluid. The compound is used in many functions like aromatherapy, flavoring agents, and perfumery. Also when the chemical is consumed in a large quantity then it is sometimes poisonous to rats [43], [44].

C. Protein Preparation

The Protein Data Bank (PDB) is a database for the three-dimensional (3D) structural data of biological molecules larger in size, for example, proteins and nucleic acids [45]. The structure of the selected protein was pick up from the Protein Data Bank (PDB), and the protein molecule was estimated for its resolution. The structure of the protein molecule must be downloaded in .pdb format.

D. Ligands Retrieval

The compounds named Rosmarinic Acid, Allo ocimene, and Pulegone were selected from the literature and were used for the docking procedure. The selection of every Ligand was done from the phytochemical components of different plants. Different ligands were downloaded with the help of PubChem (public chemical database). The ligands were downloaded in .sdf format with a three-dimensional (3D) structure. Moreover, the alteration of downloaded ligands from .sdf to.pdf format was completed.

E. Virtual Screening

PyRx software was used for the virtual screening of the ligands. The PyRx software demonstrated the binding affinity and binding energy of each ligand via the virtual screening. The protein molecule was loaded in PyRx window as shown in **Figure 1**, and was converted from .pdb format to. pdbqt format. 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.

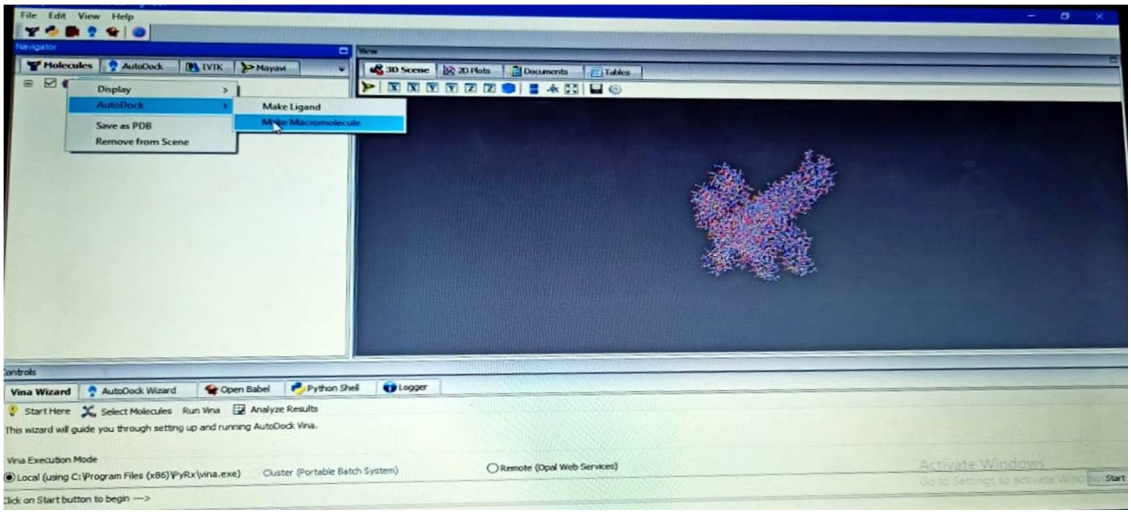


Figure 1. Protein molecule loaded in PyRx window

F. Drug likeliness property analysis

The natural compounds were selected for final molecular docking studies by screening those ligands which were having drug like properties. According to the Lipinski's rule of five the ligands were screened. Lipinski's rule of five states the following [46] :

1) High lipophilicity (expressed as LogP less than 5).
2) The molecular mass should be below 500 Da.
3) Smaller than 10 hydrogen bond acceptors.
4) Lesser than 5 hydrogen bond donors.
5) More than one rule shouldn't violate.

The Lipinski's rule of five was analyzed using online web server SwissADME http://www.swissadme.ch/. From the PubChem the SMILE notations of the ligands molecules were copied. Then the pasting of these notations on SwissADME for the analysis of Lipinski's rule of five.

G. Docking through AutoDock Vina by using MGL tools

The loading of the protein target was carried out on the graphical window. After the loading of the target protein deletion of a water molecule from the target, the protein was done followed by the addition of polar hydrogen atoms and Kollman charges to it. The protein was further converted into. pdbqt format. The ligand molecule was imported and was converted into. pdbqt format. Both the protein and ligand molecules were loaded on the graphical screen. After preparation of protein and ligand molecule docking was launched from command prompt and the results were analyzed.

H. Structure visualization

PyMol software was used for the visualization of protein and ligand interaction. After AutoDock Vina the output file was automatically saved in the selected folder with the name output. pdbqt file. The protein. pdbqt and output. pdbqt files were loaded on the graphical screen of PyMol. The interaction between the protein and ligand was visualized and analyzed.

III. RESULTS AND DISCUSSION

From Protein Data Bank the crystal structure of GPC1**(**PDB ID: 4YWT) in .pdb format was retrieved as revealed in **Figure 2.** The protein resolution was 2.38 Å.Rosmarinic acid (CID: 5281792), Allo ocimene (CID: 5368821), Pulegone (CID: 442495) were downloaded in 3D structure in .sdf format as shown in **Table 1.**

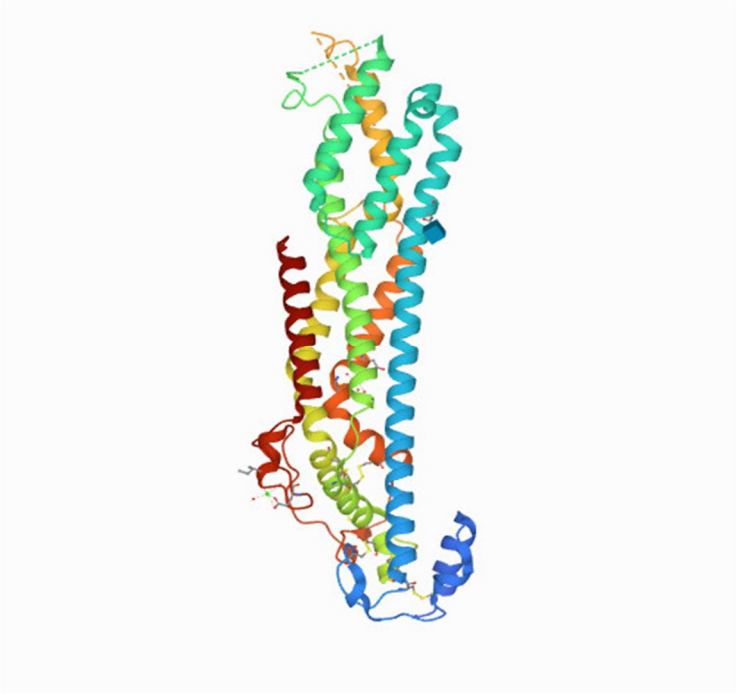
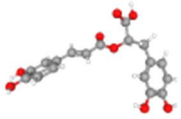
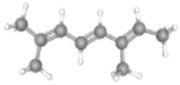
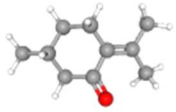


Figure 2. 3D structure of GPC1(PDB ID: 4YWT) Protein

ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.429
Volume 9 Issue VI Jun 2021- Available at www.ijraset.com

Table 1. 3D Structure of Ligands

		
ROSMARINIC ACID CID: 5281792 MF : $C_{18}H_{16}O_8$ MW: 360.3 g/mol	**ALLO OCIMENE** CID: 5368821 MF:$C_{10}H_{16}$ MW: 136.23 g/mol	**PULEGONE** CID: 442495 MF: $C_{10}H_{16}O$ MW: 152.23 g/mol

Virtual screening of the ligand molecules was done through PyRx software. According to the minimum binding energy, ligands were screened. As shown in **Table 2,** Rosmarinic acid binding affinity was -5.6, -7.8 for Allo ocimene and the binding affinity of Pulegone was -6.5. Ligand which was selected after PyRx result was Pulegone. The ligand was further analyzed for drug likeliness property analysis.

Table 2. Result of PyRx

Ligand Molecules	Binding Afinity	Mode	RMSD upper Bond	RMSD lower Bond
Pulegone	-6.5	0	0	0
Rosmarinic Acid	-5.6	0	0	0
Allo ocimene	-7.8	0	0	0

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

Table 3. Result of SwissADME

Ligands	Molecular weight	Number of H-bond acceptors	Number of H-bond donors	Log *Po*/w (MLOGP)	Violation
Pulegone	152.23 g/mol	1	0	2.20	Yes, 0 violation
Allo ocimene	136.23 g/mol	0	0	3.56	Yes, 0 violation

ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.429
Volume 9 Issue VI Jun 2021- Available at www.ijraset.com

The protein target GPC1 (PDB ID: 4YWT) and Pulegone (CID: 442495) were docked through AutoDock Vina software. The outcome showed 9 poses with distinct binding energy, RMSD LB (Root means square deviation Lower Bound), RMSD UB (Root mean square deviation Upper Bound). Through PyMol (open-access tool for the visualization of the molecule), the interaction amidst Pulegone and GPC1 can be visualized as shown in **Table 4.**

Table 4. AutoDock Vina Results

Mode	Affinity (kcal/mol)	Dist from best mode	
		RMSD LB	RMSD UB
1	-7.1	0.000	0.000
2	-5.9	39.107	39.682
3	-5.8	39.383	39.106
4	-5.3	38.960	39.594
5	-5.1	9.142	10.784
6	-4.8	37.943	38.816
7	-4.7	10.314	11.729
8	-4.6	11.765	13.052
9	-4.6	10.512	12.096

The interaction was further visualized under PyMol as shown in Figure 3.

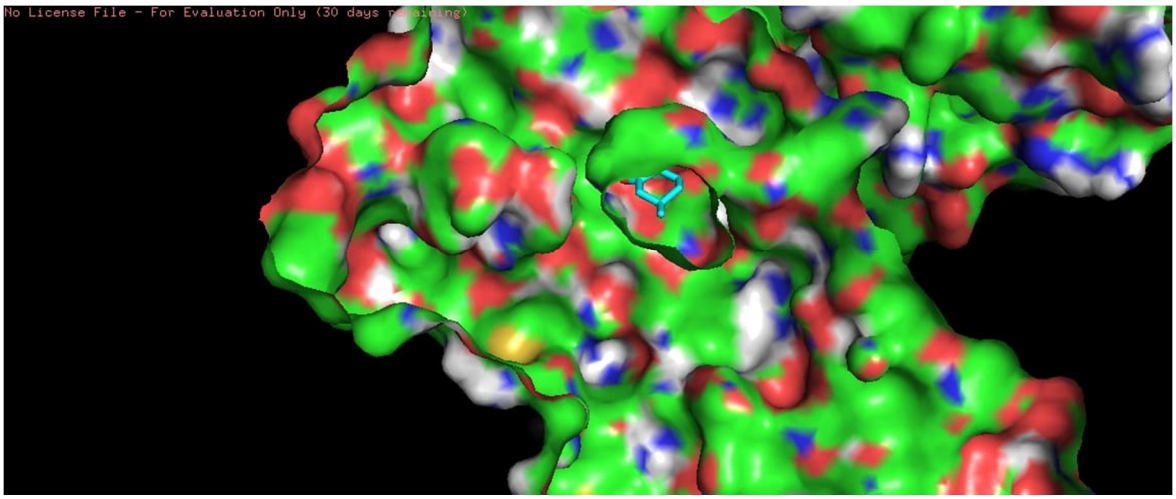


Figure 3. Interaction of GPC1 (PDB ID: 4YWT)with Pulegone (CID: 442495)through PyMOL visualizer

IV. CONCLUSION

In this study, to investigate the potential of ligand molecules against the selected protein Glypican 1, GPC1 (PDB ID: 4YWT) the molecular docking technique was used. Based on this molecular docking, pulegone was the only ligand having the best minimum binding energy. It was also following all five rules of Lipinski. By prohibiting the target protein (Glypican 1), Pulegone can be a potential drug candidate for treating AD. In the understanding of the structural features required to enhance the inhibitory activities the results which are obtained are advantageous. Hence in future studies, Pulegone from natural sources can prevent Alzheimer's disease and can be checked as an effective drug for treating AD.

V. ACKNOWLEDGEMENT

The authors acknowledge the help provided by Department of Biotechnology, Faculty of Life sciences, Institute of Applied Medicines and Research, Ghaziabad, India.

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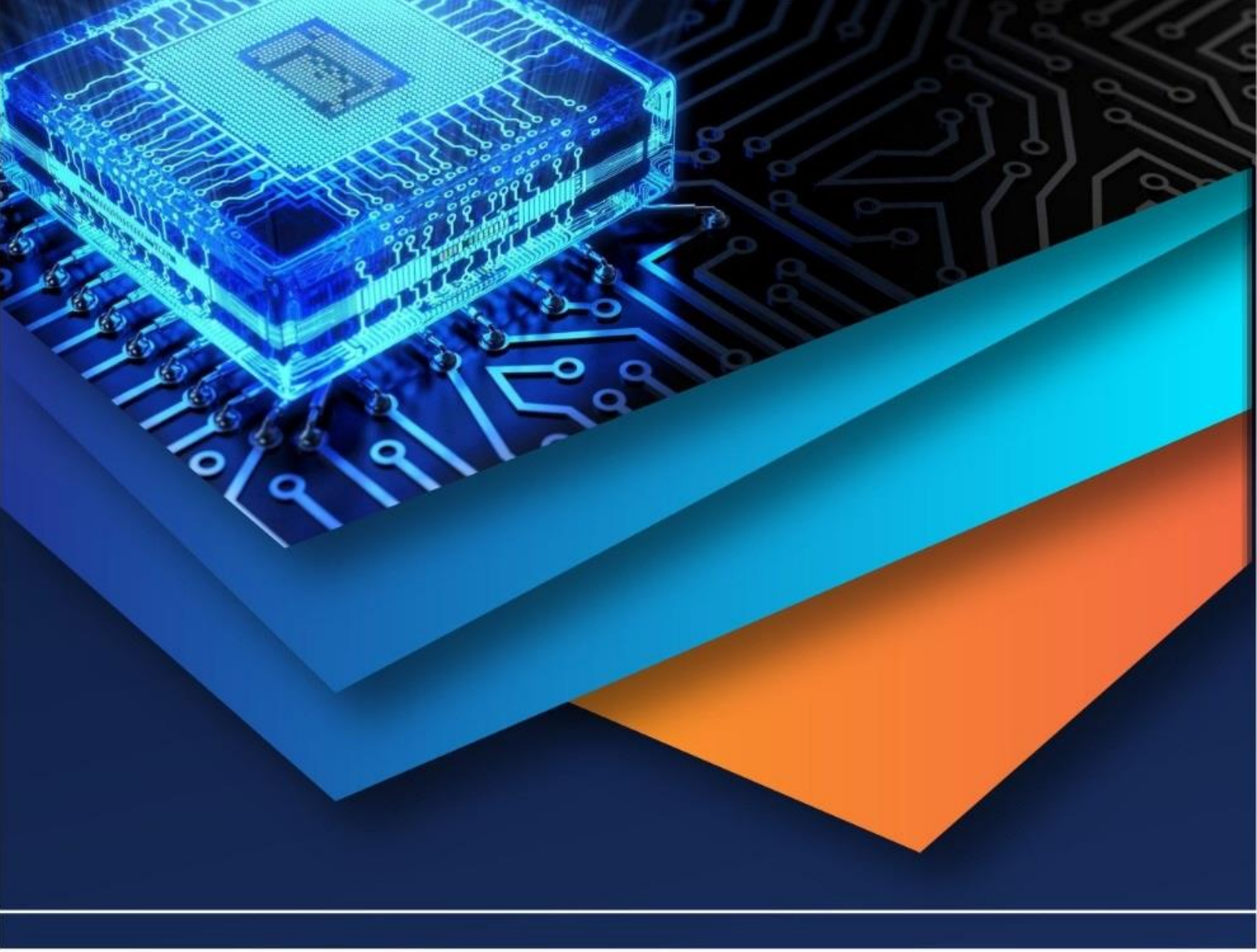

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