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Docking Studies on Ligand Molecules of Neem, Phyllanthus and Garlic against Dipeptidyl Peptidase IV - A Diabetic Mellitus Target

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Abstract: ***Molecular docking is a process by which two molecules bind to each other in a 3D space where the target site, receptor are responsible for the pharmaceutical effect .Docking of a ligand with the desired protein is a method of approaches for tackling the needs for drug discovery through CADD (Computer aided drug discovery). Diabetes type 2 is a chronic condition that affects the way the body processes blood sugar (Glucose).With type 2 diabetes, the body either doesnot produce enough insulin, or it resists insulin. The aim of this present study is to examine the docking efficacy of bioactive compounds from Neem, Phyllanthus and Garlic against Dipeptidyl Peptidase IV – A Diabetic Mellitus Target using ArgusLab. ArgusLab reveals the docking energy value of each bioactive compound after docking with the target. Ligand binding values are negative for all ligands except Azadirachtin. Allicin showed highest interaction with the target followed by Nimbin, Malvidin and Phyllanthin.***
Keywords: Docking, Diabetes mellitus, Dipeptidyl peptidase, Neem, Phyllanthus, Garlic, ArgusLab

I. INTRODUCTION

Diabetes mellitus (DM) is also known as Madhumeha [1]. It is a chronic metabolic disorder characterized by persistent hyperglycemia [2]. It may be due to impaired insulin secretion, resistance to peripheral actions of insulin, or both. According to the International Diabetes Federation (IDF), approximately 415 million adults between the ages of 20 to 79 years had diabetes mellitus in 2015 [3] . DM is proving to be a global public health burden as this number is expected to rise to another 200 million by 2040. Type 2 diabetes mellitus (T2DM) accounts for around 90% of all cases of diabetes. In T2DM, the response to insulin is diminished, and this is defined as insulin resistance. During this state, insulin is ineffective and is initially countered by an increase in insulin production to maintain glucose homeostasis, but over time, insulin production decreases, resulting in T2DM. T2DM is most commonly seen in persons older than 45 years. Still, it is increasingly seen in children, adolescents, and younger adults due to rising levels of obesity, physical inactivity, and energy-dense diets [4]. Dipeptidyl peptidase-4 (DPP4), also known as adenosine deaminase complexing protein 2 or CD26 (cluster of differentiation 26) is a protein that, in humans, is encoded by the DPP4 gene .DPP4 plays a major role in glucose metabolism. It is responsible for the degradation of incretins such as GLP-1 [5].

A. Diet and Diabetes

India have listed around 45,000 plant speciess out of 7500 species of plants have medicinal value. Large number of plant and plant products have been scientifically tested and reported to possess the ability to decrease blood sugar levels of normal and/or diabetic animals. Medicinal plants exhibits hypoglycemic and antidiabetic activity as a result of the presence of certain very important active principles and minerals in these plants that include terpenoids, alkaloids, phenolics, flavonoids, saponins, carbohydrates, cardiac glycosides, copper, zinc and manganese [6] [7] [8]. The cornerstone of therapy is diet and exercise for both type 1 and type 2 diabetes [9] [10] [11]. A diet low in saturated fat, refined carbohydrates, fructose corn syrup, and high in fiber and monounsaturated fats needs to be encouraged.

Azadirachta indica, locally named as neem which belongs to family Meliaceae. It is available in India and Burma [12]. It contain bioactive compounds nimbin and azadirachtin. Ethanolic and aqueous extract of *Azadirachta indica* shows reduction in blood glucose level in high dose. It can be combined with allopathic drugs in type 2 diabetic patients whose diabetes is not maintained by allopathic drugs only [13]. Worldwide large numbers of patients are treated by natural neem tablets. Its extract improves the blood circulation by enlarging the blood vessels and useful in reducing the blood glucose level in the body [14].

Phyllanthus niruri commonly known as Phyllanthus is a genus of flowering plant used in herbal medicine. Phyllanthus contain bioactive compounds such as Phyllanthin and malvidin which can reduce glycemia. Phyllanthus can also interact with drugs used to treat diabetes, potentially enhancing their effects and causing an adverse drop in blood sugar (hypoglycemia). It may also have a similar effect when used with anti-hypertensive medications, leading to an adverse drop in blood pressure (hytension) [15].

Allium sativum It is locally name as garlic belongs to Liliaceae, a family of Allium sativum [12]. Ethanolic extract of garlic (10 ml/kg/day) frequently shows hypoglycemic activity [13]. Extract of garlic was more efficient than anti diabetic drug glibenclamide [16]. Garlic shows various therapeutic effect such as anti platelet, antibacterial, lowering the blood pressure and lowering the cholesterol level in the body [17].

II. MATERIALS AND METHODS

A. *Protein Preparation (Target Prepartion)*

The Protein Data Bank (PDB) is a database for the three-dimensional structural data of large biological molecules, such as proteins and nucleic acids 0btained through X-Ray crystallography and NMR experiments. The PDB is a key in areas of structural biology, such as structural genomics. The crystal structure of dipeptidyl peptidase iv in complex with inhibitor was obtained from RCSB PDB. Complexes such as Non essential water molecules and hetero atoms are removed and Energy minimization was carried out using SWISS PDB VIEWER [18].

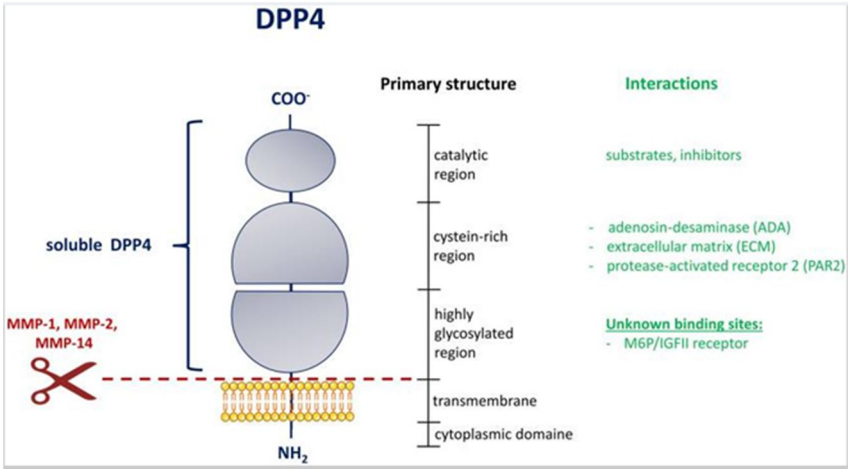

Fig. 1 Protein domain structure of Dipeptidyl peptidase IV

B. *Ligand Preparation*

Ligands such as Nimbin, Azadirachtin, Allicin, Phyllanthin and Malvidin were retrieved from pubchem.ncbi.nlm.nih.gov in SDF format and converted them into PDB format using Open Babel software. Lead validation is done using SwissADME Website which is used to predict ADME parameters , Pharmacokinetic properties and drug like nature of selected ligands. These ligands are then opened in ArgusLab for docking studies.

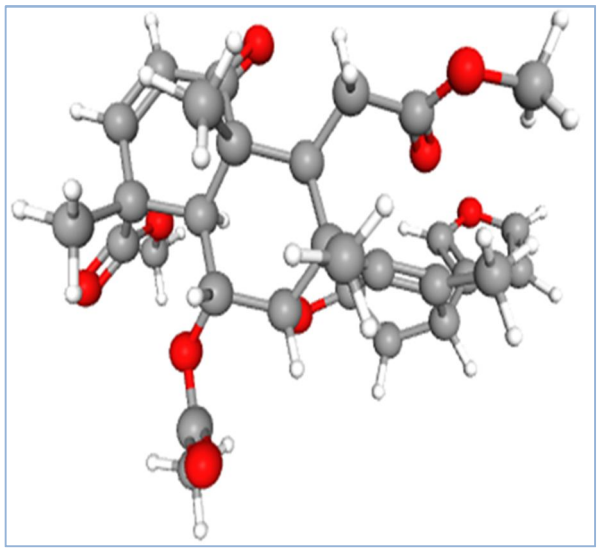

Fig. 2 3D structure of nimbin retrieved from Pubchem

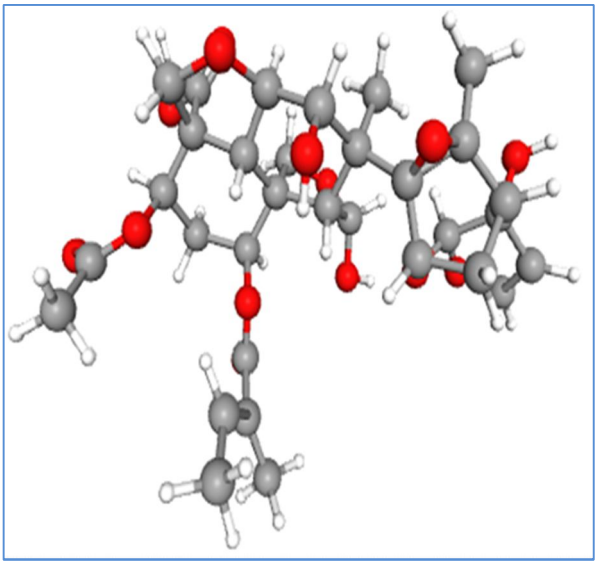

Fig. 3 3D structure of Azadirachtin retrieved from Pubchem

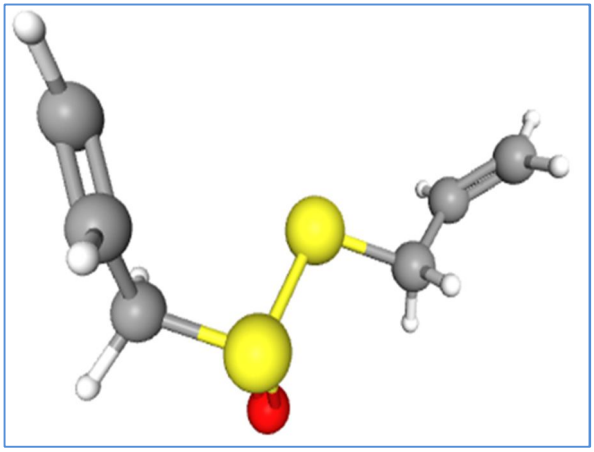

Fig. 4 3D structure of Allicin retrieved from Pubchem

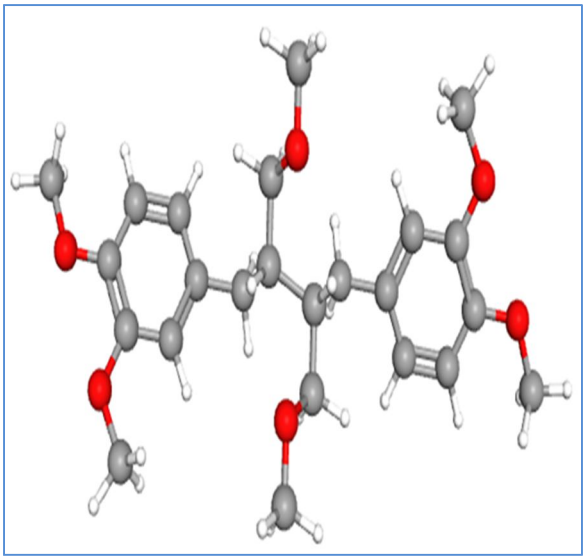

Fig. 5 3D structure of Phyllanthin retrieved from Pubchem

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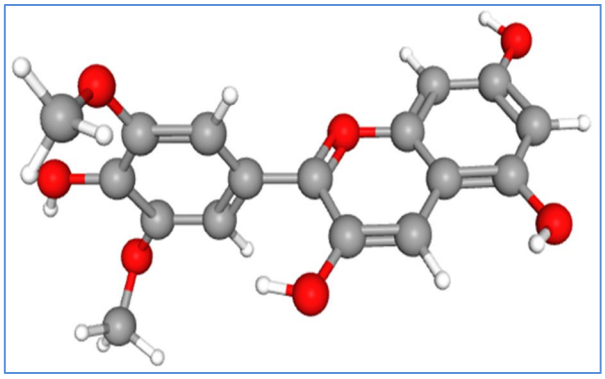

Fig. 6 3D structure of Malvidin retrieved from Pubchem

C. Ligand-Receptor docking

ArgusLab is a molecular modeling, graphics, and drug design program for Windows operating systems. It is a very useful, highly-featured and easy-to-use molecular modeling, graphics, and drug design program. This program is specially recommend as an effective teaching tool to demonstrate molecular docking.

Phytochemicals such as Nimbin and Azadirachtin from Neem, Allicin from Garlic and Phyllanthin and Malvidin from Phyllanthus were docked with the diabetic drug target, Dipeptidyl peptidase IV (PDB ID 3F8S).

III. RESULT AND DISCUSSION

Docking is used to predict the binding of small candidate drugs to their protein targets. Molecular docking is one of the most frequently used methods in structure-based drug design, due to its ability to predict the binding-conformation of small molecule ligands to the appropriate target binding site. Candidate ligands used are plant conctituents present in neem such as Nimbin and Azadirachtin, Garlic such as Allicin and Phyllanthus such as Phyllanthin and Malvidin.

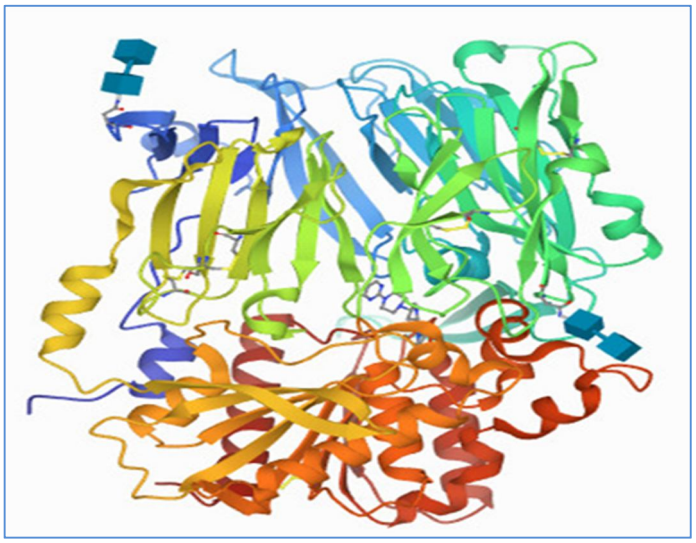

Fig. 7 Crystal structure of dipeptidyl peptidase IV in complex with inhibitor (PDB ID 3F8S).

Dipeptidyl-peptidase (DPP) IV, which is also known as CD26, is a ubiquitously expressed glycoprotein of 766 amino acids and 110 kDa. DPP-IV is a critical enzyme that regulates a wide variety of physiological processes including eating, digestion, immune function, pain perception, growth, infection, and many others. It is a complex enzyme that exists as a membrane-anchored cell surface peptidase that transmits intracellular signals. The DPP4 protein consists mainly of 4 domains: a short cytoplasmic domain (1–6), a transmembrane domain (TMD) (7–28), a flexible stalk segment (29–39), and the extracellular domain (40–766), which can be further separated by a highly glycosylated region, the cysteine-rich region, and the catalytic region. The energy minimization was done by removing water molecules and adding hydrogen using SWISS PDB VIEWER.

TARGET	PDB ID	AREA (SA)	VOLUME (SA)
4	3F8S	4966.818	10153.932

Table. 1 CASTp result of Target expressed in SA - Richard's Solvent Accessible unit

CASTp (http://cast.engr.uic.edu) is an online tool that locates and measures pockets and voids on 3D protein structures. New version of CASTp includes annotated functional information of specific residues on the protein structure. The updated CASTp web server can be used to study surface features, functional regions and specific roles of key residues of proteins.

Molecule	Molecular Weight (g/mol)	Hydrogen Bond Acceptor	Hydrogen Bond Donor	Log P_3	GI Absorption	Lipinski
Nimbin $C_{30}H_{36}O_9$	540.6	9	0	3.95	High	Yes
Azadirachtin $C_{35}H_{44}O_{16}$	720.7	16	3	3.90	Low	No
Allicin $C_6H_{10}OS_2$	162.3	1	0	1.95	High	Yes
Phyllanthin $C_{24}H_{34}O_6$	418.5	6	0	4.26	High	Yes
Malvidin $C_{17}H_{15}O_7^+$	331.3	7	4	-1.80	High	Yes

Table. 2 Energy scored for docking of each ligands with target Crystal structure of dipeptidyl peptidase IV in complex with inhibitor (PDB ID 3F8S).

Swiss ADME software is used to compute physico chemical descriptors as well as to predict ADME parameters, pharmacokinetic properties, druglike nature and medicinal chemistry friendliness of one or multiple small molecules to support drug discovery. The results obtained from Swiss ADME implies that all compounds except Azadirachtin obey Lipinski rule so that they can act as drug molecule.

A. Interaction Studies of Docking

Docking is an essential tool for calculation of binding interactions of ligands to the protein target. Docking studies predicts whether the molecule fits to the active site and also minimum enegy for interaction [19]. Phytoconstituents such as Nimbin, Azadirachtin, Allicin and Phyllanthin binds with the Target dipeptidyl peptidase IV. All of their ligand binding values are negative, i.e, all the compounds shows greater affinity towards the target. These compounds can be used effectively in antidiabetic studies and they will decrease the emergence of secondary disease.

SL NO	TARGET	LIGAND	BEST LIGAND POSE ENERGY
1	3F8S	Nimbin	-6.63375 kcal/mol
2		Azadirachtin	0
3		Allicin	-7.20579 kcal/mol
4		Phyllanthin	-6.22102 kcal/mol
5		Malvidin	-6.239 kcal/mol

Table. 3 Best Ligand Pose Energy of Selected Ligands Docked with Target 2 (pdb id 3F8S)

Allicin showed highest interaction with the target (-7.20579kcal/mol). Followed by Allicin, Nimbin showed highest interaction (-6.63375 kcal/mol) then Malvidin (-6.239 kcal/mol) and Phyllanthin (-6.22102 kcal/mol).

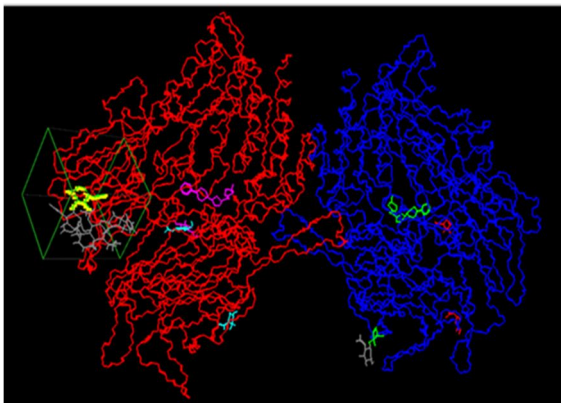

Fig. 8 Structure of Docking of Nimbin with target Dipeptidyl peptidase IV (3F8S) in ArgusLab

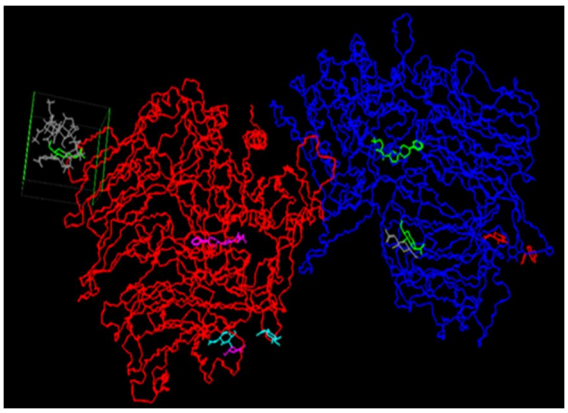

Fig. 9 Structure of Docking of Azadirachtin with target Dipeptidyl peptidase IV (3F8S) in ArgusLab

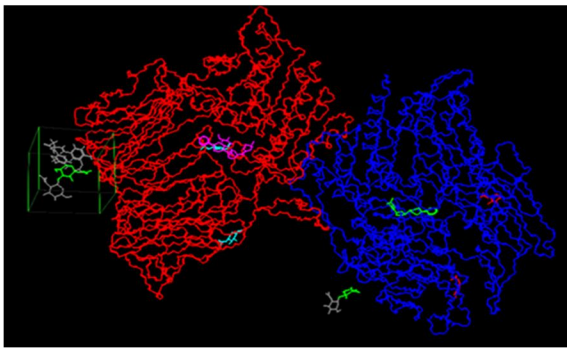

Fig. 10 Structure of Docking of Allicin with target Dipeptidyl peptidase IV (3F8S) in ArgusLab

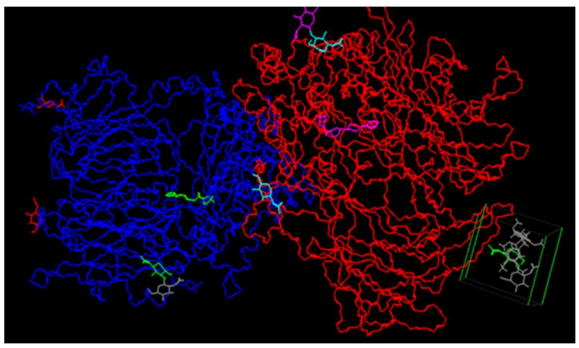

Fig. 11 Structure of Docking of Phyllanthin with target Dipeptidyl peptidase IV (3F8S) in ArgusLab

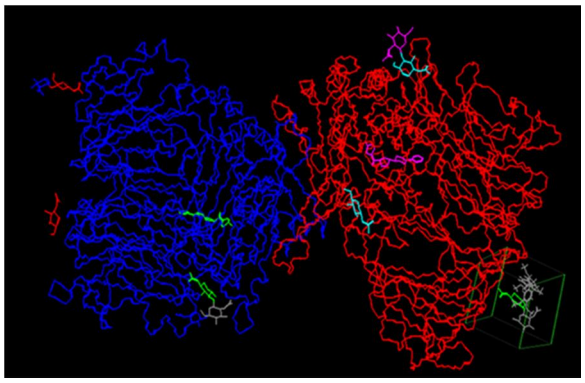

Fig. 12 Structure of Docking of Malvidin with target Dipeptidyl peptidase IV (3F8S) in ArgusLab

IV. CONCLUSION

Diabetes Type 2 is a major metabolic, multi-causal and heterogenous disorder causing significant morbidity & mortality. The no of death due to T2DM highlights the insufficiency of the currently available drugs [20]. Bioactive compounds from natural plants have anti-diabetic activity & these compounds can be used as alternative therapy. Long term diabetic treatment with certain anti-diabetic plant could result in better control of blood glucose. Bioinformatics provides more efficient target discovery and validation approaches, thus to help to ensure that more drug candidates are successful during the approval process and making it more cost-effective. The results of the current study have revealed that the plant compounds selected for this study act as potential inhibitor for Dipeptidyl peptidase IV, a diabetic drug target. Thus validated the possibility of Neem, Garlic and Phyllanthus plant extract as alternative therapy to the existing diabetic approaches. These Bioactive compounds isolated from different natural resources play very important role to design medicine and treat hyperglycemic problem in diabetes mellitus which have low side effect and wide range of bio activity and do not require laborious pharmaceutical synthesis seems highly attractive.

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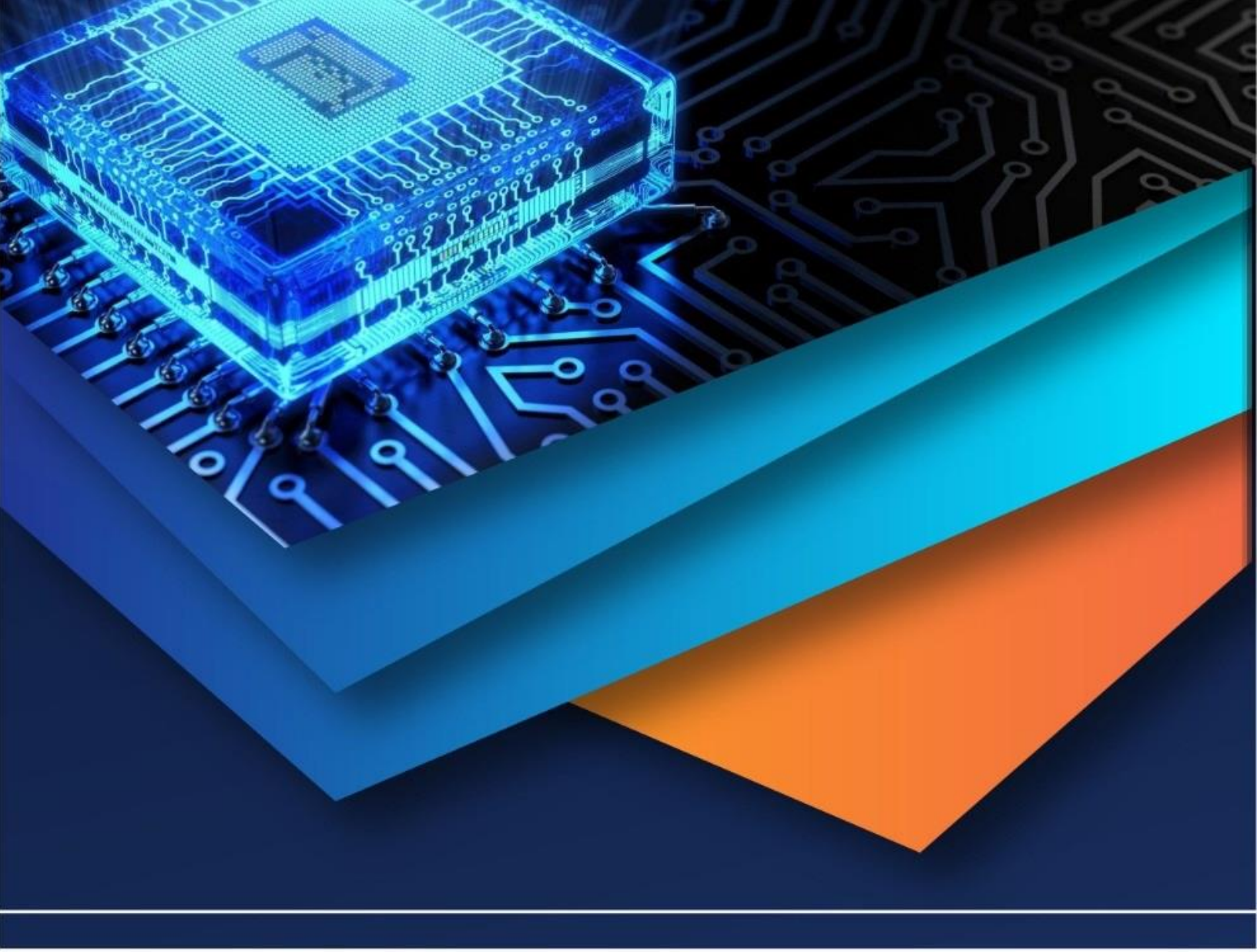

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