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Molecular Docking of Rosmarinic Acid against DNMT1 to Treat Breast Cancer

Debasray Saha[1], Noopur Khare[2], Abhimanyu Kumar Jha[3*]
[1, 3]*Department of Biotechnology, Faculty of Life Sciences, Institute of Applied Medicines and Research, Ghaziabad, Uttar Pradesh, India.*
[2]*Institute of Technology and Management, Meerut, Uttar Pradesh, Affiliated to Dr. A.P.J. Abdul Kalam Technical University, Lucknow, Uttar Pradesh, India*
[2]*Shri Ramswaroop Memorial University, Barabanki, Uttar Pradesh, India*
[*]*Corresponding Author: Email address- abhimanyujha630@gmail.com*

Abstract: ***Breast Cancer (BC) is one of the most common types of malignancies in women worldwide. Breast tumorigenesis is unrecognized because of a diversity of risk factors in context to bio-molecular dynamics. This present study was to inhibit the expression of the DMNT1 by a secondary metabolite with the help of molecular docking for the treatment of Breast Cancer. The rational drug design together with structure-based modeling and rapid screening tools or potential for the reason that characteristic and developing lead malignant tumor molecules. Thus, the molecular docking method plays an important role in screening a large set of molecules based on their free binding energies and proposes structural hypotheses of how the molecules can inhibit the target.***

Therefore, it is of interest to screen DNMT1 (PDB ID 4WXX) target protein with known ligand compound using computer aided molecular modeling and docking tools. The DNMT1 (PDB ID 4WXX) structure model was constructed using different online server followed by molecular docking of Rosmarinic acid; one known ligand compound with PDB ID 4WXX protein model predicted by AutoDock Vina and Biovia Discovery studio Visualizer and Client Server. The screening exercise shows that rosmarinic acid (with binding free energy of -7.4 kcol/mol), a ligand compound derived from DNMT1 (Breast cancer) has the top binding properties. Thus, it is of interest to consider the compound for further validation. So, in the further studies, Rosmarinic acid can be a promising drug for the treatment and management strategies of Breast Cancer (BC) after its in vitro and in vivo studies.

Keywords: AutoDock Vina, Breast tumorigenesis, DMNT1, Ligand, Molecular docking, Secondary metabolite

I. INTRODUCTION

Cancer is one of the serious threats to humans, causing deaths worldwide in spite of substantial advances in research for its diagnosis and treatment. Almost 20 million new cases are predicted by the year 2020. Disturbingly, the proportion of new cases from the developing countries like India is expected to rise around 70% [1]. Breast cancer is that the most ordinarily occurring cancer in women's and therefore the second most typical cancer overall. BC ranks first among the cancers diagnosed in women between 20 and 59 years of age [2].

During the past 30 years, BC mortality in Chinese females has followed a gradual upward trend, making it the fifth most common cause of cancer death in females [3]. BC is also a huge financial burden and source of pain in patients' daily lives [4]. The clinical outcome of BC is immensely variable, ranging from complete curability to a time span of 10 years post-surgical Z different secondary metabolites to inhibit the protein activity.

DNMTs are overexpressed in various type of tumor in cancer, including breast cancer [10-12]. Remarkably, DNMT1 and DNMT3a were overexpressed in only 5 and 3% of breast tumorigenesis [11]. Consequently, DNMT3b plays the predominant role over DNMT3a and DNMT1 in breast tumorigenesis. This is consistent with a recent study in breast cancer cell lines, which demonstrated a strong correlation between total DNMT activity and overexpression of DNMT3b, but not with the expression of DNMT3a or DNMT1 [11].

Molecular docking is a crucial tool in structural biology as well as computer-assisted drug design (CADD). The goal of ligand—protein docking is to predict the predominant binding mode(s) of a ligand with a macromolecule (protein) of well-known three-dimensional (3-D) structure. Victorious docking strategies search high-dimensional areas effectively and use an evaluation operate that properly ranks candidate dockings. Docking will be accustomed perform virtual screening on giant libraries of compounds, rank

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the results, and propose structural hypotheses of however the ligands inhibit the target, that is valuable in lead optimization. Molecular docking methodologies will be accustomed establish the interaction between a little ligand and a target molecule and to work out whether or not they could behave together because the binding site of two or a lot of constituent molecules with a given structure. The comparison of docking molecules for proteins, alternative drug-like molecules, or perhaps fragments from the initial molecule allows a pool of distinguished candidates to be calculated with recorded values

The objective of the current study is to analyze the domain and active sites of the DNMT1 protein, to perform docking of the chemical compounds and determine their active sites and compound docking so that their potentiality as a therapeutic agent against DNMT1 is assessed.

II. MATERIALS AND METHODS

A. *Identification of Protein*

Disease causing protein was retrieved through various literature. The structure of protein molecule of DNA (cytosine-5)-methyltransferace1 (DNMT1) (PDB ID: 4WXX) which was a Breast Cancer causing protein was obtained from RCSB Protein Data Bank (PDB) (http://www.rcsb.org/.) [13,14]. Protein molecule structure was retrieved in ".pdb" format. All water molecules were removed and on the final stage hydrogen atoms were added to the target protein molecule. Finally, the stability of protein molecule was checked through Rampage (http://mordred.bioc.cam.ac.uk/~rapper/rampage.php) [15,16].

The PDB was recognized in the year 1971, which is the universal archive of structural data of biological macromolecules, established by Brookhaven National Laboratories [14].

B. *Identification of Ligands*

Rosmarinic Acid, Allo ocimene and Pulegone compounds were used for docking study were selected from the literature. All Ligands were selected from phytochemical constituents of different plants. These ligand molecules were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/) [17,18]. The ligands were retrieved in 3D structure in ".sdf" format. Further, all the downloaded structures of ligands were converted into ".pdb" format through online SMILES Translator (https://cactus.nci.nih.gov/translate/) [19]. The converted files were downloaded in ".pdb" format. These ".pdb" files were used to run different tools and software's [20].

C. *Protein Preparation Through Biovia Discovery Studio Visualizer*

The preparations of protein molecule were done by Biovia Discovery Studio Visualizer. This software suite for analyzed and missing atoms in incomplete residues, modeling missing loop regions, deleting alternate conformations (disorder), removing waters, standardizing atom names, and protonating titratable residues use predicted pKs [21]. The docked molecule structure can be viewed during this software. The present software was used to prepare the protein molecules through removing the water and additional ligands if attached to their active site. Firstly, the protein molecule was loaded in the graphical windows and under view option its hierarchy was analyzed. The water molecules and attached ligand molecules were deleted by selecting the atoms. The crystal structure of the protein molecule was further saved in .pdb format. This protein molecule was used for docking.

D. *Preparation of Grid Parameter File*

Grid maps were generated and spacing was adjusted to 0.375 Å to enable ligand binding. The grid dimension was adjusted to 40 × 40 × 40 points. AutoDock Vina uses interaction maps for docking. Prior to the actual docking run, these maps were calculated by Auto Grid. For each ligand atom type, the interaction energy between the ligand atom and receptor was calculated for the entire binding site, which is discretized through a grid. The interaction energy of the protein was assigned at each grid point and the affinity for each of the ligand was calculated.

E. *Virtual Screening Through PyRx*

Screening of ligands were done through PyRx software [22]. This software was used to screen those ligands which were having minimum binding energy with the protein target. Ligands which were found to be having minimum binding energy were screened for the drug likeliness property analysis.

PyRx runs on. pdbqt format. The procedure of PyRx starts with loading of protein molecule, which was first converted from ".pdb" to ". pdbqt" format and then ligands were imported from the specific folder in .sdf format. The energy of ligands was minimized followed by the conversion of .sdf file to ". pdbqt" file. Docking was performed between protein target and ligand molecule, and according to minimum binding energy ligands were screened.

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F. Drug Likeliness Property Analysis

Drug likeliness property analysis was done through online server i.e. SwissADME. The screened ligands were analyzed for its drug property. SMILE notations of screened ligands were copied from PubChem and were pasted on online web server SwissADME [23]. Drugs were analyzed for Lipinski rule of five. Lipinski rule of five states the following points: -

1) Hydrogen bond donors should be less than 5 (< 5).
2) Hydrogen bond acceptors should be less than 10 (< 10).
3) The molecular weight should be less than 500 Dalton.
4) Partition co-efficient LogP should be less than 5 (< 5).
5) Not more than 1 rule can be violated.

The ligands which followed the above Lipinski rule of five were selected for final docking through *AutoDock Vina* and *Biovia Discovery Studio Client 2020.*

G. Docking Through AutoDock Vina

The protein target in .pdb was loaded on graphical windows of AutoDock Vina [24]. The protein target in .pdb format was prepared for docking by deleting water molecules, adding hydrogen polar atoms and by adding Kollman charges to the protein molecule and finally protein was saved in ". pdbqt" format. Ligand molecule was imported in .pdb format and was converted to ". pdbqt" format. After that grid box was selected for the region to be docked. Using command prompt AutoDock Vina was executed and results were analyzed [25].

H. Docking through Biovia Discovery Studio Client 2020

The Biovia discovery studio client 2020 was well-known dock the overall protein target with the very best ligand molecule. The protein molecule was prepared for the docking observed by the ligand molecule [26]. Both the protein .pdb format file and ligand format file were loaded on graphical window and then a charges were added. The best docked molecule showed the interaction of amino acids between protein and ligand. The absolute energy, clean energy, Confg Number, Mol_Number, Relative energy and pose number were analyzed as a result.

I. Structure Visualization through PyMOL

Structure visualization was done through the tool *PyMOL 2.4*. *PyMOL 2.4* is freely available tool. The protein molecule in ". pdbqt" form was loaded on *PyMOL 2.4* graphical screen followed by output ". pdbqt" file. The docked structure was visualized and under "shown as" option molecule was converted into "molecular surface".

III. RESULTS AND DISCUSSION

The crystal structure of human DNMT1 in .pdb format was retrieved from Protein Data Bank as shown in Figure 1 along with additional details of DNMT1 in Figure 2. DNMT1 belongs to transferase class, the resolution of protein was 2.62Å, R- value free was 0.245, R-value work was 0.205, R- value observed was 0. 207 and method was X-ray diffraction. The stability of protein was analyzed through Rampage as shown in Figure 3. Secondary metabolites from different plants were retrieved from PubChem online database. The structures of Rosmarinic acid, Allo ocimene, Pulegone were downloaded in ".sdf" and 2-D or 3D structure format as shown in Figure 4 (a), (b), (c) and Figure 5 (a), (b), (c) and Table 1. Finally, the downloaded structure was converted into ".pdb" format.

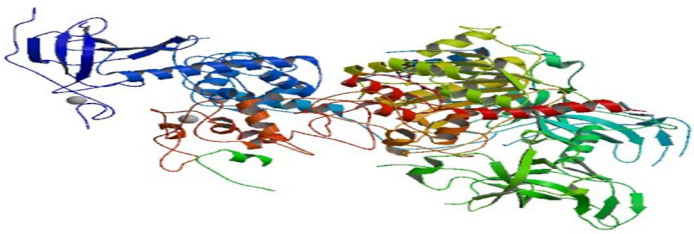
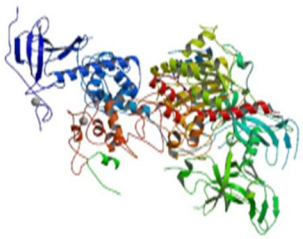


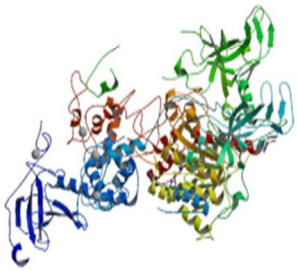
Figure 1: The crystal structure of human DNMT1(4wxx)

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- **Protein Name** – DNA(cytosine-5)-methyltransferase
- **Gene** – DNMT1
- **Protein database No** – 4WXX
- **Classification:** TRANSFERASE
- **Organism(s): Homo sapiens**
- **Expression System:** Escherichia coli
- **Mutation(s):** No
- **Sequence Length:**1256



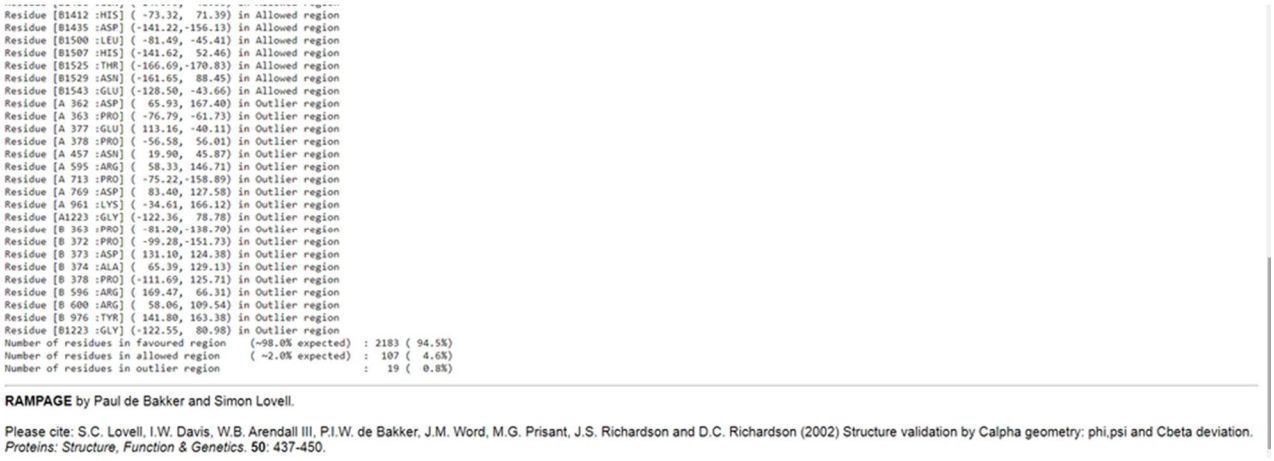
Biological Assembly 1



Biological Assembly 2

Figure 2: Additional details of Protein molecule (DNMT1) from Protein Data Bank

Number of residues in favoured region (~98.0% expected)	: 2183 (94.5%)
Number of residues in allowed region (~2.0% expected)	: 107 (4.6%)
Number of residues in outlier region	: 19 (0.8%)



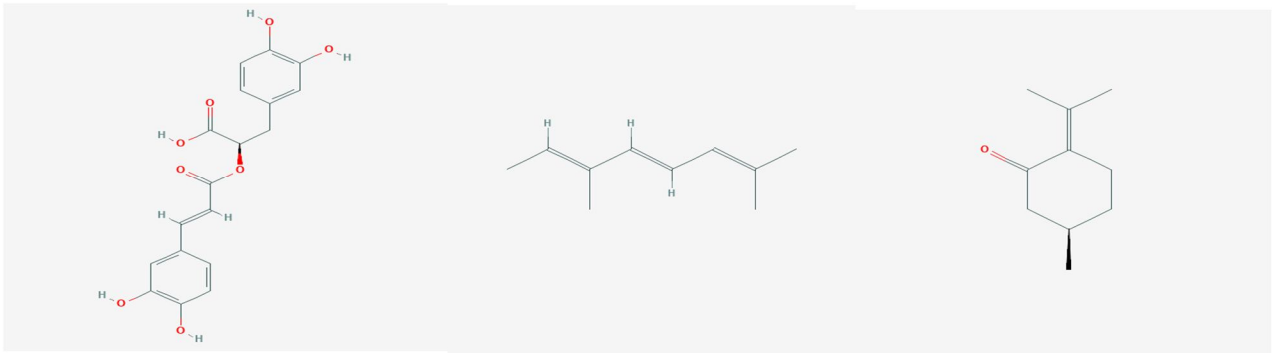
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Residue [B1412 :HIS] ( -73.32,  71.39) in Allowed region
Residue [B1435 :ASP] (-141.22,-156.13) in Allowed region
Residue [B1500 :LEU] ( -81.49, -45.41) in Allowed region
Residue [B1507 :HIS] (-141.62,  52.46) in Allowed region
Residue [B1525 :THR] (-166.69,-170.83) in Allowed region
Residue [B1529 :ASN] (-161.65,  88.45) in Allowed region
Residue [B1543 :GLU] (-128.50, -43.66) in Allowed region
Residue [A 362 :ASP] (  65.93, 167.40) in Outlier region
Residue [A 363 :PRO] ( -76.79, -61.73) in Outlier region
Residue [A 377 :GLU] ( 113.16, -40.11) in Outlier region
Residue [A 378 :PRO] ( -56.58,  56.01) in Outlier region
Residue [A 457 :ASN] (  19.90,  45.87) in Outlier region
Residue [A 595 :ARG] (  58.33, 146.71) in Outlier region
Residue [A 713 :PRO] ( -75.22,-158.89) in Outlier region
Residue [A 769 :ASP] (  83.40, 127.58) in Outlier region
Residue [A 961 :LYS] ( -34.61, 166.12) in Outlier region
Residue [A1223 :GLY] (-122.36,  78.78) in Outlier region
Residue [B 363 :PRO] ( -81.20,-138.70) in Outlier region
Residue [B 372 :PRO] ( -99.28,-151.73) in Outlier region
Residue [B 373 :ASP] ( 131.10, 124.38) in Outlier region
Residue [B 374 :ALA] (  65.39, 129.13) in Outlier region
Residue [B 378 :PRO] (-111.69, 125.71) in Outlier region
Residue [B 596 :ARG] ( 169.47,  66.31) in Outlier region
Residue [B 600 :ARG] (  58.06, 109.54) in Outlier region
Residue [B 976 :TYR] ( 141.80, 163.38) in Outlier region
Residue [B1223 :GLY] (-122.55,  80.98) in Outlier region
Number of residues in favoured region    (~98.0% expected)  : 2183 ( 94.5%)
Number of residues in allowed region     ( ~2.0% expected)  :  107 (  4.6%)
Number of residues in outlier region                        :   19 (  0.8%)

RAMPAGE by Paul de Bakker and Simon Lovell.

Please cite: S.C. Lovell, I.W. Davis, W.B. Arendall III, P.I.W. de Bakker, J.M. Word, M.G. Prisant, J.S. Richardson and D.C. Richardson (2002) Structure validation by Calpha geometry: phi,psi and Cbeta deviation.
Proteins: Structure, Function & Genetics. 50: 437-450.
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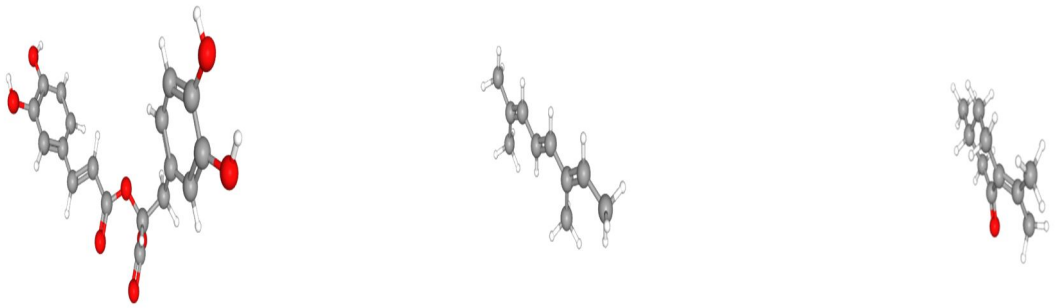
Figure 3: Rampage Result of DNMT1 (PDB ID: 4WXX)

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(a) (b) (c)

Figure 4: 2 D Structures of (a) Rosmarinic acid (b) Allo ocimene (c) Pulegone.



(a) (b) (c)

Figure 5: 3 D Structures of (a) Rosmarinic acid (b) Allo ocimene (c) Pulegone.

S. NO	Name of Ligand	Alternative Name	PubChem CID	M. weight	M. formula	LogP3	H-Bond Donor	H-Bond Acceptor
1.	Rosmarinic acid	Rosemary acid (R)-rosmarinic acid Rosmarinate	5281792	360.3 g/mol	$C_{18}H_{16}O_8$	2.4	5	8
2.	Allo ocimene	2,6-Dimethyl-2,4,6-octatriene 673-84-7 trans, trans-Alloocimene	5368821	136.23 g/mol	$C_{10}H_{16}$	4.2	0	0
3.	Pulegone	(+)-Pulegone (R)-Pulegone d-Pulegone (R)-(+)-Pulegone	442495	152.23 g/mol	$C_{10}H_{16}O$	2.8	0	1

Table 1: Ligand molecule details from PubChem

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All the three ligands Rosmarinic acid, Allo ocimene, Pulegone were subjected for virtual screening through PyRx software. The results are shown in Table 2 and Table 3. The binding affinity of Rosmarinic acid was -7.3 Kcal/mol, root mean square deviation lower bound was 1.928 (RMSD) and upper bound was 5.021(RMSD) in Mode 7 and root mean square deviation lower bound was 1.836 (RMSD) and upper bound was 6.276 (RMSD) in Mode 8. The binding affinity of Allo ocimene was -4.9 Kcal/mol, root mean square deviation lower bound was 4.133 (RMSD) and upper bound was 5.758 (RMSD) in Mode 8. The binding affinity of Pulegone was -5.8 Kcal/mol, root mean square deviation lower bound was 2.082 (RMSD) and upper bound was 4.541 (RMSD) in Mode 7 and root mean square deviation lower bound was 16.343 (RMSD) and upper bound was 18.116 (RMSD) in Mode 8 as shown in Table 2. The binding energy of Rosmarinic acid was -7.4, Allo ocimene was -4.9 and Pulegone was -5.8 as depicted in Table 3.

Table 2: The Binding affinity, Mode, RMSD lower bound and RMSD upper bound of different ligands with protein molecules.

Ligand molecule	CID Value	Binding affinity (Kcal/mol)	Mode	RMSD lower bound	RMSD upper bound
Rosmarinic acid	5281792	-7.3	1	1.928	5.021
Allo ocimene	5368821	-4.9	1	4.133	5.758
Pulegone	442495	-5.8	1	2.082	4.541

Table 3: The Binding energy of different ligands with protein molecules.

Ligand molecules	Binding energy
Rosmarinic acid	-7.4
Allo ocimene	-4.9
Pulegone	-5.8

According to PyRx results it was concluded that Rosmarinic acid, Allo ocimene and Pulegone showed minimum binding energy. The screened molecules Rosmarinic acid, Allo ocimene and Pulegone were analysed for drug likeliness property analysis. The screened three ligands were analysed by SwissADME online web server. Further the ligands were screened on the basis of qualifying Lipinski's Rule of five. The ligands were analysed for the its Molecular weight, Hydrogen bond donor, Hydrogen bond acceptor, Partition coefficient and Lipinski's rule violation as shown in **Table 4**. It was analysed that Rosmarinic acid was having minimum binding energy with protein molecule and it was also qualifying Linpinski's rule of five.

Table 4: Drug likeliness Property Analysis

Compound Name	Molecular weight	H-bond Donor	H-bond Acceptor	Partition co-efficient MlogP	Violation
Rosmarinic acid	360.3 g/mol	5	8	0.90	Yes; 0
Allo ocimene	136.23 g/mol	0	0	3.56	Yes; 0
Pulegone	152.23 g/mol	0	1	2.20	Yes; 0

The screened ligand Rosmarinic acid was docked with protein target through AutoDock Vina and Biovia Discovery Studio Client 2020. Through AutoDock Vina software, ligand showed minimum binding energy, and through Biovia Discovery Studio Client 2020 the result was same. Rosmarinic acid was considered as the best binding ligand against protein target through AutoDock Vina as shown in Table 5. The results of Biovia Discovery Studio Client 2020 can be depicted in Table 6.

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Table 5: AutoDock Vina Result

Mode	Affinity (kcal/mol)	Dist from best mode	
		Rmsd l.B.	Rmsd U.B.
1	-7.4	0	0
2	-7.3	11.43	12.98
3	-7.0	1.105	3.473
4	-6.8	1.393	2.653
5	-6.6	0.821	0.983
6	-6.4	1.662	4.116
7	-6.3	0.155	0.890
8	-6.0	7.032	8.588
9	-5.8	0.763	3.934

Table 6: Result of *Biovia Discovery Studio Client 2020*

Rosmerimic Acid	Absolute energy	Clean energy	ConfNumber	Mol_Number	Relative energy	Pose_Number
1.	-7.3	-7.1	126	1	2.89645	1
2.	-7.2	-7.0	45	1	2.87672	2
3.	-6.8	-6.9	62	1	1.65490	3

Rosmarinic acid showed a strong binding affinity with the drug target. The interaction of ligand and the target protein was visualized through PyMOL as shown in Figure 6. In this in silico study, Rosmarinic acid may act as an inhibitor and it may be used in a form of drug which may control breast cancer. Thus, this drug can prevent cancer and may form effective drug for the treatment of breast cancer.

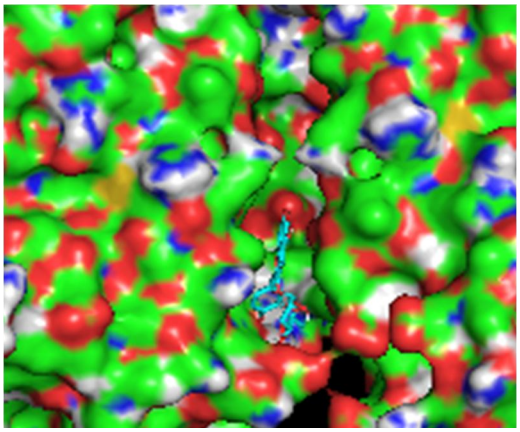


Figure 6: Interaction of DNMT1 with Rosmarinic acid through PyMOL visualizer

IV. CONCLUSION

The crystal structure of human DNMT1 was elucidated earlier by molecular modelling associated with dynamics and was used in the docking studies. Docking studies showed that the strong affinity of Rosmarinic acid toward breast cancer related protein, especially protein kinases and apoptosis- related protein. Thus, according to the *in-silico* study, Rosmarinic acid may act as an inhibitor and it may be used in a form of drug which may control breast cancer and also can be used as a promising anticancer agent for the treatment of breast cancer. Thus, this drug may prevent cancer and may form effective drug for the treatment of breast cancer.

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A. Conflict of Interest Statement

The authors declare that there is no conflict of interest.

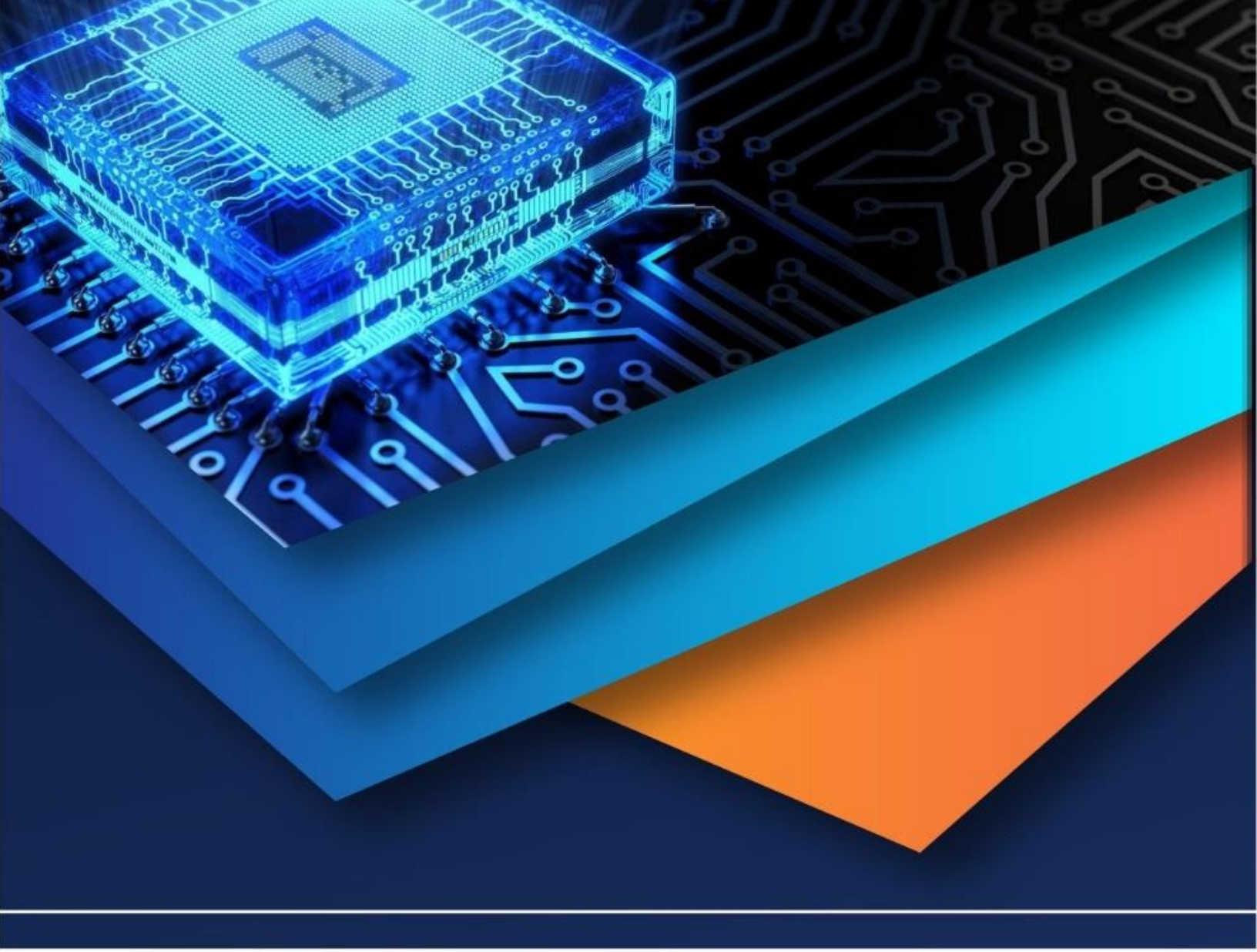
V. ACKNOWLEDGMENTS

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