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Effect Of Vasicinone Against DNMT1 to Treat Cancer: An *In-Silico* Approach

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Abstract

Cancer is a group of diseases involving irregular cell division in the human body. Cancer is the name given to a collection of related diseases. Tumors are a group of abnormal cells that form lumps or growths. According to World Health Organization (WHO) in 2019, cancer has the third rank in a further 23 century and cause of death before the age of 70 years. There were an estimated 19.3 million new cases and 10 million cancer deaths worldwide in 2020. DNMTs (DNA (cytosine-5)-methyltransferase) are overexpressed in various types of cancer. High expression of DNMT1 (DNA (cytosine-5)-methyltransferase 1) has been observed in a variety of tumors and is a characteristic change of tumor cells. DNA methylation patterns are generated during development and DNMT1 is an important methyltransferase that maintains methylation during cell proliferation. Molecular docking has a vital role in drug discovery. The molecular docking technique is used for observing the interaction between ligands and a target protein-making drug. The PDB was recognized in the year 1971 for all protein data collected in a particular platform, which is the universal archive of structural data of biological macromolecules, established by Brookhaven National Laboratories. PubChem is an open platform for chemical structures and their biological results. It was launched in September 2004 as part of a research program under the NIH Molecular Libraries.

Keywords
DNMT1, PubChem, Molecular docking, Uniprot, Drug discovery

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INTRODUCTION

Cancer is a group of diseases involving irregular cell division in the human body. Cancer is the name given to a collection of related diseases. In cancer disease, body cells start dividing without stopping and spread surrounding tissue [1]. Cancer can grow mostly all over the human body, which is made up of trillions of cells. Normally, human cells grow and divide to form new cells as the body needs them. When cells grow old or become damaged, they die, and new cells take their place. Tumours are groups of abnormal cells that form lumps or growths.

A human adult comprises about 1015 cells; scores of them divide and differentiate to refurbish organs and tissues, which require cell turnover [2]. According to World Health Organization (WHO) in 2019, cancer has the third rank in a further 23 century and cause of death before the age of 70 years. Cancer's rising

prominence as a leading cause of death partly reflects marked declines in mortality rates of stroke and coronary heart disease, relative to cancer, in many countries [3]. There were an estimated 19.3 million new cases and 10 million cancer deaths worldwide in 2020.

DNMTs are overexpressed in various types of cancer [4-5]. The coding exons of the *DNMT1* gene were mutated in 7% of human colorectal cancers tested, which was the first evidence that *DNMT1* is mutated in human cancer [6]. High expression of DNMT1 has been observed in a variety of tumors and is a characteristic change of tumour cells. 20 pancreatic cancer cell lines were analysed and found that 16 of them had DNMT1 expression more than twice that of normal cells [7]. DNA methylation patterns are generated during development and DNMT1 is an important methyltransferase that maintains methylation during cell proliferation. Furthermore, DNMT1 has *de novo* activity in human cancer cells and plays also an important role in maintaining genome stability [8-9].

Molecular docking has a vital role in drug discovery. Molecular docking is a technique that is used for determining the interaction between the ligands and a target protein to prepare the drug. [10]. Molecular docking involves basic two steps: calculation of compound confirmation as well as its position and orientation within these sites and assessment of the binding affinity. This study is to analyse the active site of the DNMT1 protein with some compounds for the treatment of cancer, and it was observed observed that the compound has a potential against DNMT1 protein as a therapeutic agent for treat cancer disease.

METHODOLOGY:

1. **Download protein (Uniprot)**

The protein was downloaded from Uniprot. The structure of protein molecule of DNA - methyltransferace1 (DNMT1) (PDB: 5WVO) was retrieved in .pdb format. The protein was downloaded from Uniprot (RCSB) of the lowest resolution power of Protein Data Bank (PDB) [11-12]. The PDB was recognized in the year 1971 for all protein data collected in a particular platform, which is the universal platform of biological protein structural data. It was established by "Brookhaven National Laboratories" [13]. In the "Uniprot" all protein data are found in one platform.

2. **Download of Ligands (pubchem)**

"PubChem" (http://pubchem.ncbi.nlm.nih.gov) is an open platform in which all chemical structures and their biological results of compounds are found. Pubchem was launched in September 2004 as part of a research program under the NIH Molecular Libraries.PubChem contains three databases: Substance, Compound, and BioAssay. *Fisetin glucoside, Nirurin, Kaempferol rhamno pyranoside,* and *Vasisinone* all-natural compounds used in docking. All-natural compounds extracted from different plants. All compounds were downloaded by PubChem [14].

3. **Conversion of Ligand molecules from .sdf to .pdb format**

The ligand molecules were converted from .sdf format to.pdb format with the help of "SMILES Translator and Structure File Generator".

4. **Initial docking with PyRx software**

The ligand molecules were screened using PyRx software. This software was used to observe the binding energy of ligands with the protein target. The protein molecule in .pdb format was loaded, after that protein molecule was converted from ".pdb" to ".pdbqt" format. The ligands were imported in ".sdf" format from the folder where it was saved. All ligands were converted from".sdf" format to ". pdbqt" format. The ligands with the lowest binding affinity were screened and further screened molecules were checked for drug likeliness property analysis.

5. **Drug Likeliness Property Analysis (Swiss ADME)**

Drug likeliness property analysis was observed by "Swiss ADME". The ligands were screened to analyse their drug properties. Steps involved were as follows:

· Copied "CANONICAL SMILE" structures of ligands from "PubChem".

· It was pasted in "SwissADME" [15].

· Drugs were analyzed for Lipinski's rule of five. Lipinski rule of five states the following points:

1. Molecular weight (MW) = Not more than 500 Dalton.
2. Hydrogen bond donors (HBD) = Not more than 5 (< 5).
3. Hydrogen bond acceptors (HBA) = Not more than 10 (< 10).
4. Partition co-efficient (MLogP) = Not more than 5 (< 5).
5. Violation (Lipinski) = Not more than 1.

6. **Final docking of ligand and protein by Autodockvina**

The target protein was uploaded in ".pdb" format [16]and the protein was prepared by deleting the water molecules from the target protein, by adding the hydrogen polar atoms in the target protein, adding the Kollman charges in the target protein. After that protein was saved in ".pdbqt" format. Ligand was loaded in ".pdb" format, which was further converted into"pdbqt" format. By using

Command prompt AutoDockVina (cmd) was observed, and the results were analyzed [17].

7. **Visualization of structure through PyMol**

After the AutodockVina the structure visualization of protein and ligand by the tool *PyMOL 2.4.*, is freely available. Steps involved in PyMOL are:

1. The output was visualized using PyMol software.
2. The structure was converted from "molecular surface" by the "shown as" option of the molecule.

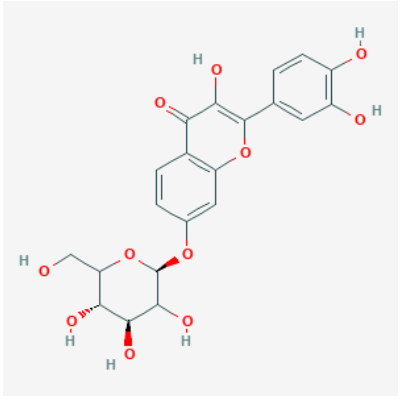
RESULTS AND DISCUSSION

The crystal structure of Homo sapiens DNMT1 in ".pdb" format was downloaded from Uniprot (PDB) as shown in Figure 1 and biological assembly structure Figure 2. The resolution power of DNMT1 protein was 2.00Å, it is the lowest resolution power, and some other values are given below:

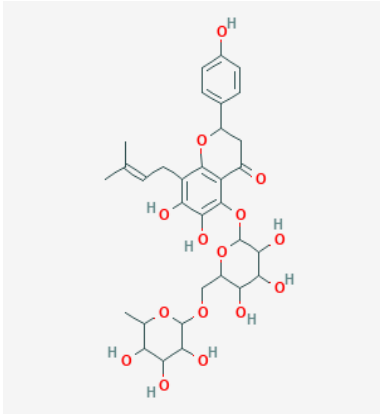
- Resolution free value: 0.239
- Resolution work value: 0.196
- Resolution observed value: 0.198
- Method of protein download: X-ray diffraction

Compounds from different plants were downloaded from PubChem. The structures of compounds *Fisetin glucoside, Nirurin, Kaempferol rhamno pyranoside, and Vasicinone* downloaded in ".sdf" format and also download in 2-D or 3-D structure from Pubchem as shown in Figure 3 (a), (b), (c), (d) and Figure 4(a), (b), (c) and Table 1. The downloaded structure of all ligands was converted into ".pdb" format by "SMILES Translator and Structure File Generator".

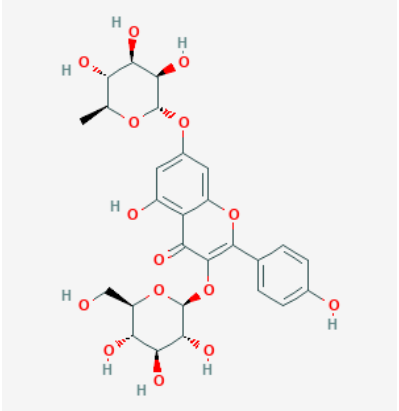
Figure1: The crystal structure of human DNMT1(5wvo)



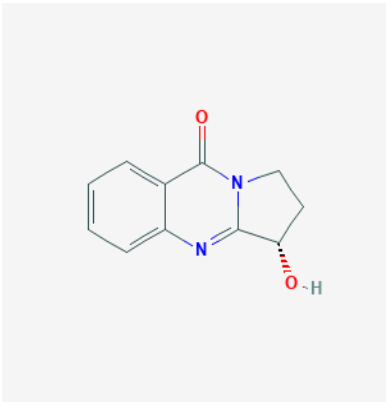
(a)



(b)

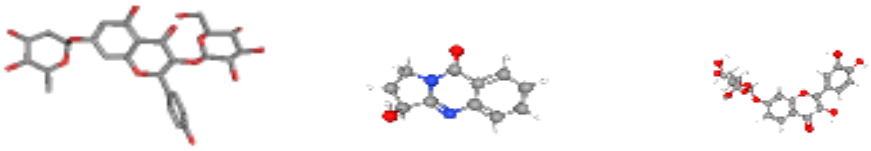


(c)



(d)

Figure 2: 2D Strutures of (a)*Fisetin (b)Nirurin (c) kaempferol rhamnopyranoside (d) Vasicinone*



(a) **(b)** **(c)**

Figure 3:3D Structure (a) *kaempferol rhamnopyranoside (b)Vasicinone (c)Fisetin glucoside*

Table1: Ligand molecule detail

S.no	Names of ligands	PubchemCID no.	Molecular weight	MlogP	Hydrogen bond donor	Hydrogen bond acceptor
1.	***Fisetinglucoside***	44258680	448.38 g/mol	-2.10	7	11
2.	***Nirurin***	125896	664.65 g/mol	-2.35	9	15
3.	***Kaempferol Rhamnopyranoside***	21606527	594.52 g/mol	-3.43	9	15
4.	***Vasicinone***	442935	202.21 g/mol	0.78	1	3

MOLECULAR DOCKING

In the Molecular docking study four ligands *Fisetinglucoside, Nirurin, KaempferolRhamnopyranoside, and Vasicinone* were virtually screened through PyRx software. The binding affinity values of compounds are as shown in table 2

Table 2: The Binding affinity, Mode value, RSMD upper bound value and RSMD lower bound value

S.no	Name of Ligands	Pubchem CID	Binding affinity	Mode	RMSD lower bound value	RSMD upper bound value
1.	***Fisetinglucoside***	44258680	-5.2	0	0.0	0.0
2.	***Nirurin***	125896	-4.6	0	0.0	0.0
3.	***Kaempferol Rhamnopyranoside***	21606527	-4.8	0	0.0	0.0
4.	***Vasicinone***	442935	-7.6	0	0.0	0.0

In PyRx docking, it was observed that *Fisetin glucoside, Nirurin, Kaempferol Rhamnopyranoside, and Vasicinone* all ligands having lowest binding affinity. So, all ligands *Fisetin glucoside, Nirurin, Kaempferol Rhamnopyranoside, and Vasicinone* were analyzed for drug likeliness property analysis. All four ligands were analyzed the Drug likeliness Property Analysis by SwissADME. The Drug likeliness Property Analysis analyzed its Molecular weight, Hydrogen bond acceptor, Hydrogen bond donor, Partition coefficient (MlogP), and Lipinski's violation value as shown in table no. 3. This property analyzed that *Vasicinone* was having minimum binding energy with targeted protein molecule, and it was also qualifying all Lipinski's rule of five.

Table3: Drug likeliness Property Analysis

S.no	Name of Ligands	Molecular weight	Hydrogen bond Acceptor	Hydrogen bond Donor	MlogP	ipinski's Violation
1.	***Fisetinglucoside***	448.38 g/mol	11	7	-2.10	No ; 2
2.	***Nirurin***	664.65 g/mol	15	9	-2.35	No ; 3
3.	***Kaempferol Rhamnopyranoside***	594.53 g/mol	15	9	-3.43	No ; 3
4.	***Vasicinone***	202.21 g/mol	3	1	-7.6	Yes ; 0

In AutoDockVina observed that the *Vasicinone* ligand-target with protein showed the lowest binding energy. In this docking, *Vasicinone* was considered the best compound. *Vasicinone* was the best binding ligand against the protein target for preparing the drug. It was shown through AutoDockVina as shown in Table 4.

Table 4: AutoDock Vina Result of Vasicinone

Mode	***Affinity value (kcal/mol)***	***Dist from best mode***	
		RSMD lower bond value	***RSMD uper bond value***
1.	-6.6	0.000	0.000
2.	-6.6	2.090	4.458
3.	-6.5	1.789	2.730
4.	-6.4	3.338	5.305
5.	-6.4	1.910	4.550
6.	-6.1	1.770	5.169
7.	-6.1	19.598	20.043
8.	-6.1	20.763	22.328
9.	-6.0	19.287	20.078

Vasicinone shows the best binding affinity with the targeted protein. "PyMOL" software showed the interaction between ligand and the target protein as shown in Figure 4. This in silico study observed that the compound *Vasicinone* may be used in form of a drug for controlling cancer disease. Thus, this drug may form an effective drug for the treatment of cancer and also prevent the side effects in the treatment of cancer because it is a natural compound.

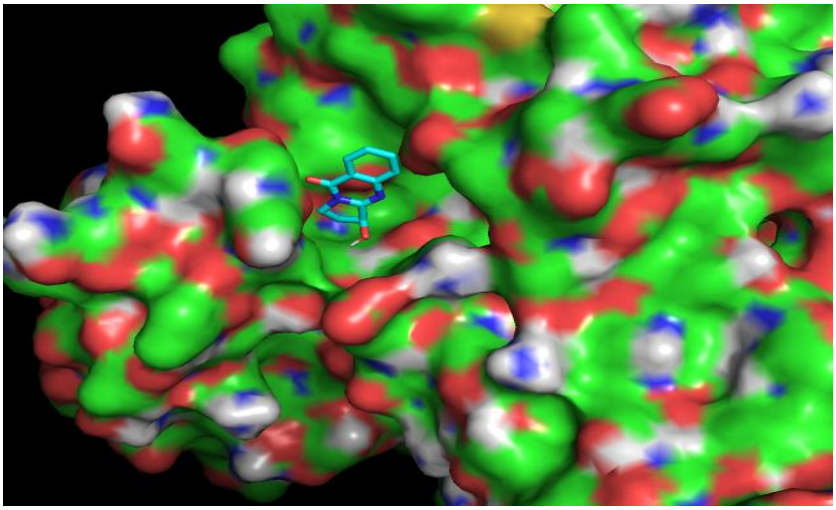


Figure 4: Interaction between DNMT1targeted protein with *Vasicinone* compound through PyMOL

CONCLUSION

The crystal structure of Target protein DNMT1 was studied by molecular docking for drug discovery. This docking study showed the best compound "Vasicinone" towards cancer-related protein. This *in-silico* study showed that *"Vasicinone"* may be used in drugs prepared for treatment of cancer and can be used in the future as an anticancer agent.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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