AN IN SILICO MOLECULAR DOCKING AND ADMET ANALYSIS OF NATURALLY DERIVED ANTI-CANCER HERBAL BIOACTIVE COMPOUND FOR THE TREATMENT OF CANCER

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***Abstract*- There is a continuous research need to develop new, effective, and affordable anticancer phytopharmaceutical drugs. Plant-derived medicine is a valuable and alternative approach to finding a novel antitumor agent. Our research aims to identify the anticancer compound from the plant source using a bioinformatics approach (molecular docking). The database was used from different sources such as Scopus, Pub Med, goggle scholar, etc. Molecular docking studies were done through InstaDock software and ADME was investigated using the Swiss ADMET model. On the basis of our outcomes molecular docking demonstrated the selected herbal bioactive molecules have a better binding affinity with cyclin-dependent kinase 2 (CDK2). Furthermore, all the selected compounds satisfy the ADME characteristics and have no violence of Lipinski's rule of five. A total of 2 compounds were chosen for further research as per our findings. This research will aid in this search for new cyclin dependent kinase 2 inhibitor alternatives. Our study suggests that the resultant compound from plant sources may be useful for cancer treatment after successful and effective investigation using In-vitro and In-vivo studies.**

Keywords: **ADMET Molecular docking studies, anti-cancer drug, ligand preparations, cyclin depended kinase 2 PDB, virtual screening.**

INTRODUCTION:

CANCER: Cells are the fundamental units that make up the human body. Cells grow and start divide to make new cells as per body needs. Cells die when they get too old or damaged. Then, new cells take their place. Cancer starts when genetic changes interfere with orderly process. Cells begins to grow uncontrollably, these cells forms a mass called it tumor. A tumor can be cancerous or benign. A cancerous tumor is malignant, meaning it can grow and spread to other parts of the body. A benign tumor means the tumor can grow but will not spread some types of cancer do not form a tumor. These are leukemia's, most types of lymphoma, and myeloma.

HERBAL DRUG: Medicinal plants have been used for thousands of years in folk medicines in Asian and African populations and many plants are consumed for their health benefits in developed nations. According to the World Health Organization (WHO) some nations still reply of plant-based treatment as their main source of medicine and developing nations are utilizing the benefits of naturally sourced compounds for therapeutic purposes 13. Compounds which have been identified and extracted from terrestrial plants for their anticancer properties include polyphones, brassin osteroids and taxols.

IN SILICO DRUG DESIGN: In silico medicine (also known as "computational medicine") is the application of in silico research to problems involving health and medicine. It is the direct use of computer simulation in the diagnosis, treatment, or prevention of a disease. More specifically, in silico medicine is characterized by modeling, simulation, and visualization of biological and medical processes in computers with the goal of simulating real biological processes in a virtual environment

Material and Methods:

Molecular docking studies
Ligand preparation
Protein preparation
ADMET analysis

A number of 20 molecules were drawing by using pub cam sketcher v 2.4 databases, and the structure drugs SIMILES was copy and pest in pub cam structure v 2.4, export the mole file of our anticancerherbal bioactive from for this purpes insta dock software used for legend preparation. By this softer MOLE file converted into the PDB file and finally the energy minimized by the soft ware outomaticatley and this PDB file converted into PDBQT files. Anticancer herbal bioactive from this purpes insta dock software by used for legend preparation. By this softer MOLE file converted into the PDB file and finally the energy were minimized by the soft ware outomaticatley and this PDB file converted into PDBQT files.

Crystal structure of the cyclin dependend kinase 2 (PDB 5JQ8) protein was retrieved from the protein data bank (PDB). The protein preparation the protein was done by the soft ware insta dock, hydrogen atom per added to the polar atom , water molecules were deleted, Finally, the grid was set up at the well-known active site of the kinase protein Molecular docking. Molecular docking was performed with the insta dock software. The best docking poses with the Insta dock score were chosen for the atomic level of interaction studies. The Pymol software was used to visualize and interpret atomic-level interaction.

ADMET ADMET analysis of molecules was performed using the Swiss ADMET models. The molecules which satisfy the recommended values were selected for further analysis Molecular docking-based virtual screening of a library of 20 compounds with 5JQ8 target was performed to predict their binding affinity and detailed interactions. The docking was performed using Insta Dock, a single click molecular docking tool that atomizes the entire process of molecular docking-based virtual screening. The binding affinities between the ligand and protein were calculated using the Quick Vina-W Modified Auto Dock Vina program which uses a hybrid scoring function (empirical + knowledge-based) in docking calculations and a blind search space for the ligand. The p*Ki*, the negative decimal logarithm of inhibition constant [4] was calculated from the Δ*G* parameter while using the following formula:

$$\Delta G = RT$$

$$(\text{Ln } Ki_{pred})\ Ki\text{pred} = e\ (\Delta G/RT)\ pKi = -\log\ (Ki_{pre}$$

Where Δ*G* is the binding affinity (kcal mol^{-1}), R (gas constant) is 1.98 cal*(mol*K)$^{-1}$, T (room temperature) is 298.15 Kelvin, and Ki_{pred} is the predicted inhibitory constant. Ligand efficiency (LE) is a commonly applied parameter for selecting favorable ligands by comparing the values of average binding energy per atom. The following formula was applied to calculate LE:

$$LE = -\Delta G/N$$

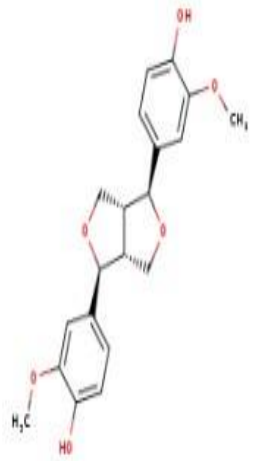
RESULTS

All 20 compounds were subjected to docking analysis and presented a binding affinity within therange of 4.0 kcal/mol to 8.8 kcal/mol towards 5JQ8 target. Please refer to the CSV file givenin the central directory for the binding affinities and other docking parameters of each compoundused in this study, where the highest binding affinity was observed in the case of NPACT00013 as 8.8.

Name of the ligand	Binding FreeEnergy (kcal/mol)	pKi	Ligand Efficiency (kcal/mol/non-H atom)	Tensional Energy
NPACT00013	-8.8	6.45	0.1375	2.8017
NPACT00011	-8.4	6.16	0.1135	3.4243
NPACT00008	-8.3	6.09	0.3192	1.2452
Conformer3D_CID_72281	-8.3	6.09	0.3773	1.5565
Conformer3D_CID_60838	-7.8	5.72	0.1814	1.8678
NPACT00012	-7.7	5.65	0.1878	2.1791
Conformer3D_CID_36462	-7.6	5.57	0.181	2.4904
NPACT00001	-7	5.13	0.1591	2.8017
Conformer3D_CID_442015	-6.9	5.06	0.2654	0.6226
Conformer3D_CID_64971	-6.8	4.99	0.2061	1.2452
Conformer3D_CID_72326	-6.7	4.91	0.2094	1.2452
Conformer3D_CID_5280343	-6.7	4.91	0.3045	1.8678
Conformer3D_CID_5318889	-6.5	4.77	0.3095	0.9339
ZINC000096006020	-6.4	4.69	0.1032	4.3582
Conformer3D_CID_68094	-6.1	4.47	0.4067	0

NPACT00002	-6.1	4.47	0.2905	1.8678
NPACT00004	-6	4.4	0.1579	3.4243
NPACT00007	-6	4.4	0.1395	3.4243
NPACT00003	-5.7	4.18	0.1295	3.4243
Conformer3D_CID_74335503	-4	2.93	0.3333	1.8678

Molecule 1



SMILES COc1cc(ccc1O)[C@H]1OC[C@H]2[C@@H]1CO[C@@H]2c1ccc(c(c1)OC)O

Physicochemical Properties	
Formula	C20H22O6
Molecular weight	358.39 g/mol
Num. heavy atoms	26
Num. arom. heavy atoms	12
Fraction Csp3	0.40
Num. rotatable bonds	4
Num. H-bond acceptors	6
Num. H-bond donors	2
Molar Refractivity	94.90
TPSA	77.38 Å²

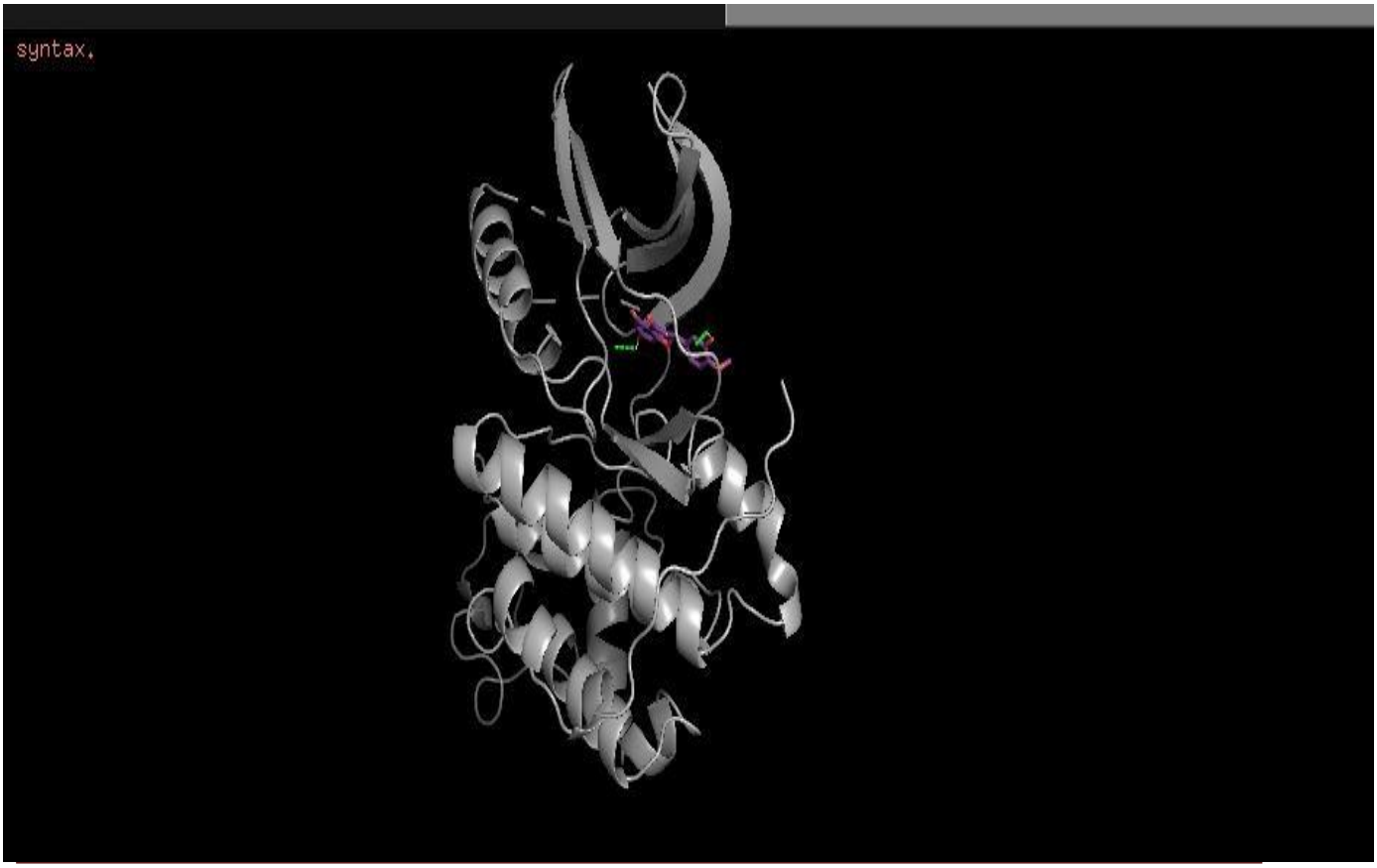
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	2.67
Log $P_{o/w}$ (XLOGP3)	2.28
Log $P_{o/w}$ (WLOGP)	2.54
Log $P_{o/w}$ (MLOGP)	1.17
Log $P_{o/w}$ (SILICOS-IT)	2.66
Consensus Log $P_{o/w}$	2.26

Water Solubility	
Log S (ESOL)	-3.58
Solubility	9.52e-02 mg/ml ; 2.66e-04 mol/l
Class	Soluble
Log S (Ali)	-3.54
Solubility	1.03e-01 mg/ml ; 2.87e-04 mol/l
Class	Soluble
Log S (SILICOS-IT)	-4.19
Solubility	2.29e-02 mg/ml ; 6.40e-05 mol/l
Class	Moderately soluble

Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-6.87 cm/s

Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55

Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 1 violation: MW>350
Synthetic accessibility	3.99



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