

Molecular docking analysis of CDK-1 inhibitors from *Chrysophyllum cainito* leaves

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Abstract:

It is of interest to document the molecular docking analysis of Cyclin-dependent kinase 1 (CDK-1) inhibitors from *Chrysophyllum cainito* leaves towards the treatment of tumors using the known structure of PDB ID: 5HQ0. Data shows that molecules such as 8-(Dimethylamino)-7-(3-(4-ethylphenoxy)-2d, ethyl 6-oxo-5-propylheptanoate, 2,3-dihydro-3, 5-dihydroxy-6-methyl-4h-pyran-4-one, 1,2,3-benzenetriol and 1,4-benzenediol 2,5-bis (1,1-dimethylethyl) identified in methanolic extract of *C. cainito* have binding features with CDK1 for further consideration.

Keywords: CDK-1; Oral squamous cell carcinoma; *Chrysophyllum cainito*; Schrodinger

Background:

The sixth most common cancer is oral squamous cell carcinoma (OSCC), which affects 90% of people worldwide [1]. The mortality rate is high and the 5-year survival rate of OSCC cases remains low despite improvement in multidisciplinary treatment [2]. Dysregulation of CDK1 is frequently observed in many cancers, including OSCC patients. Because of this rationale, the relative 5-

year survival rate of OSCC cases remains within 50–55% and lack disparity even after multidisciplinary treatment strategies including radiation therapy, surgery, and chemotherapy or combined therapy [3]. Paclitaxel, an effective anti-cancer drug well known for the treatment of breast, neck, ovarian and lung cancer, is isolated from the tree bark of *Taxus brevifolia* [4].

Many medicinal plants with indigenous anti-cancer properties have been identified, but the underlying molecular mechanism is not well explored. In this way, the tropical tree *Chrysophyllum cainito* (*C. cainito*), is well recognized with anti-cancer effects using its stem extract, but the active agent responsible for exerting anticancer properties in the human liver cancer cell line is unresolved [5-6]. Schrodinger suite is used for molecular docking in this study. Therefore, it is of interest to find out the phytochemical profile of *C. cainito* leaf extract. And the anti-CDK1 inhibitory potential of bioactive compounds found in the methanolic extract was revealed through the molecular docking approach.

Materials and methods:

Plant material:

The healthy fresh plants of *C. cainito* were collected from latitude 11.01° N, longitude: 76.95° E of Coimbatore District, Tamil Nadu, India. The plant species were identified and authenticated by the Botanical Survey of India (voucher number: BSI/SRC/5/23/2020/Tech/808), Tamilnadu Agricultural University campus, Coimbatore. The voucher specimen was provided with a scientific name and deposited for their future references.

Simultaneous distillation and extraction from plant material:

C. cainito leaves were crushed to a fine powder after instant washing of leaves in tap water and distilled water, dried in the shade at room temperature for one week. Then the dried plant leaves were pulverized and stored in a jar until needed. The 100 grams of powdered *C. cainito* leaves were subjected to methanolic extractions (at 1:10 ratio) using the soxhlet apparatus at 65°C and proceeded for 12 hours over boiling percolation. The residual compounds of methanol extract were obtained by solvent evaporation by placing them in a hot air oven for two days at 50°C. The dark brown colour residues were then collected and used for further analysis.

Phytochemical analysis using GC-MS:

The phytochemical analysis of a methanolic extract from *C. cainito* leaves was performed using GC-MS equipment (Thermo MS DSQ II, Thermo Fisher Scientific, USA). Before analysis, the samples were filtered using a 0.22 µm nylon syringe filter (Himedia, India). The instrumentation analysis employed through the following conditions such as DB 35-MS capillary non-polar column with dimensions 30 mm × 0.25 mm ID × 250 nm film thickness were used. Helium gas was used as a carrier, which is set at a flow rate of 1.0 mL/min. The injector temperature was operated at 250°C and

the GC oven temperature was programmed from 60°C for 15 min, with a gradual increase of 12°C/min up to 280°C which is maintained and ending at 3 min. Finally, the mass spectra data were interpreted by comparing their analyzed retention indices of unknown components, with the known components of the NIST and Wiley spectral library databases [7]. Active site residues for the CDK-1 protein structure (5HQ0) were identified using the CASTp server. The residues are TYR 15, GLU 81, PHE 82, LEU 83, ASP 86, HIS 120, ARG 123, VAL 124, LEU 125, GLN 132, GLN 136, ASP 146, ARG 151, PHE 153, GLY 154, GLU 173, SER 178, ARG 180, TYR 181, SER 182, THR 183, PRO 184, ILE 187, TRP 228, PRO 229, GLU 230, VAL 231, LEU 234, ASP 271, PRO 272, ALA 273, ARG 275, ILE 276, SER 277, GLY 278 respectively.

Molecular Docking:

A molecular docking study was performed using the Maestro module with Schrodinger docking suite to predict an interaction between specific ligand molecules and the binding sites of desired protein (5HQ0). [8]. In specific, the interaction between receptor CDK-1 (PDB ID: 5HQ0) and active molecules of *C. cainito* was anticipated using the Glide score [9]. There are two modes of docking calculations: XP (Extra Precision) and an SP (Standard Precision) method. Thus concerning the accuracy, the Glide module of XP visualizer connected with OPLS-2005 force field was used in this study to estimate the binding affinity. Table 1 describes the molecular docking interactions of *C. cainito* onto the receptor 5HQ0 (Table 3).

Preparation of Protein:

The crystal structure of a CDK-1 domain was obtained from the Protein Data Bank (PDB) website (<https://www.rcsb.org/>), ensures with PDB ID: 5HQ0. The target protein was prepared using the protein preparation wizard tool (Schrodinger Suite, 2018). Briefly, for docking studies, the input protein molecule (CDK-1) were prepared with respective wizard applications such as deletion of unwanted chains and waters, fixing the orientation of hetero groups which are incorporated into the raw PDB structure. The generated 3D structure of CDK-1 protein was shown in (Figure 1). The 3D structures of input ligand molecules were retrieved from the PubChem database based on GCMS findings, and the structure was prepared using the LigPrep module [10] in Schrodinger Suite 2018. LigPrep tools contain options for default parameters such as tautomers, selective ionization states, stereo chemistries, tautomeric combinations, low energy structure and correct chiralities, ring conformations, the addition of hydrogen atoms, and versatile filters to create entirely customizable ligand libraries that are tailored for

compounds at its amino acid residues GLN132, ASP86 which better attained a bonding distance between 1.71 Å and 2.27 Å. Hence these ligand-5HQ0 interaction reveals good inhibitory activity against CDK-1 domain, becomes appropriate molecule in controlling OSCC progression.

Gscore of ensuing four ligands as follows: ethyl 6-oxo-5-propylheptanoate, 2,3-dihydro-3,5-dihydroxy-6-methyl-4h-pyran-4-one, 1,2,3-benzenetriol and 1,4-benzenediol 2,5-bis(1,1-dimethylethyl) were -6.9, -6.53, -6.45 and -6.28. Oxygen bond of ethyl 6-oxo-5-propylheptanoate dichotomously found to be interacted on the complex of 5HQ0, remarkably at the residues of

ASP 146 as well as an LEU 83 on hydrogen atom with the bond length of 1.97 Å and 2.06 Å. Following ligand 2,3-dihydro-3,5-dihydroxy-6-methyl-4h-pyran-4-one hydrogen as well as oxygen bonds have found to possess the feasibility to interact simultaneously on the LEU 83 residue of the complex over oxygen and hydrogen bonds at the bond length of 2.12 Å 1.94 Å. Similarly, 1,2,3-benzenetriol and 1,4-benzenediol 2,5-bis(1,1-dimethylethyl) have also found to interact with LEU 83 and GLN 132 residue with the bond length of 2.08 and 1.82.

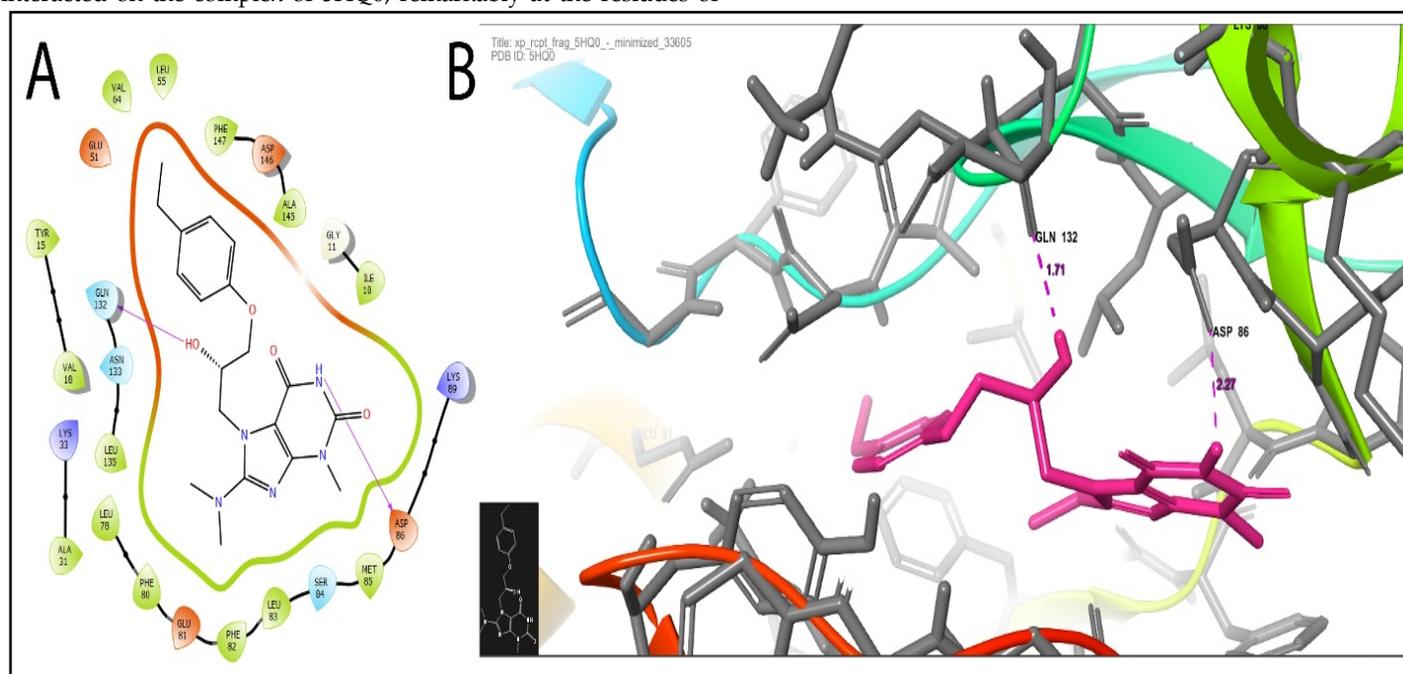


Figure 3: (A) displays the interaction of 8-(Dimethylamino)-7-(3-(4-ethylphenoxy)-2d over CDK-1 (PDB ID: 5HQ0) is shown. Hydrogen bonds specified as purple dash in individuals images. (B) The schematic representation of molecular interaction of an 8-(Dimethylamino)-7-(3-(4-ethylphenoxy)-2d over the CDK-1 protein (PDB ID: 5HQ0) is displayed.

Table 1: ADMET properties of *C. cainito* phytocompounds are given.

Phytocompounds	mol_MW	Donor HB	Accept HB	QP log S	QPlog BB	Human oral absorption	Percent human oral absorption
1,2,3-benzenetriol	126.112	3	2.25	-0.313	-0.73	2	73.973
1,2,3-propanetriol	92.094	3	5.1	0.092	-0.84	2	66.473
1,4-benzenediol, 2,5-bis(1,1-dimethylethyl)	222.327	2	1.5	-3.369	-0.16	3	100
2,3-dihydro-3,5-dihydroxy-6-methyl-4h-pyran-4-one	144.127	2	5.2	-0.667	-0.617	2	71.123
6-octen-1-ol, 3,7-dimethyl	156.267	1	1.7	-2.479	-0.276	3	100
8-(dimethylamino)-7-(3-(4-ethylphenoxy)-2d	387.438	2	7.95	-4.694	-1.58	3	86.697
ethyl 6-oxo-5-propylheptanoate	214.304	0	4	-3.085	-0.721	3	100

cyclopropylmethanol	72.107	1	1.7	-0.205	0.027	3	91.866
benzoic acid, 4-[(trimethylsilyl)amino]	281.501	1	3	-5.645	-0.05	3	100

Table 2: GCMS analysis of a methanolic extract of *C. cainito* is shown. Data with underline indicate the phyto chemical compounds, which hold good interactions with the CDK-1 protein.

Peak report TIC										
Peak #	R. Time	I. Time	F. Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	2.533	2.517	2.708	64736	0.36	16664	0.97	3.88		Cyclopropylmethanol
2	2.752	2.708	2.825	190977	1.05	62953	3.66	3.03		1,2,3-Propanetriol
3	3.408	3.375	3.658	80115	0.44	11434	0.66	7.01		Formic Acid, 2-Propenyl Ester
4	4.3	4.25	4.533	146182	0.8	24982	1.45	5.85	MI	<u>Ethyl 6-Oxo-5-Propylheptanoate</u>
5	5.208	4.958	5.292	80724	0.44	7047	0.41	11.46	MI	Butyl Alcohol-1-D1
6	5.594	5.533	5.667	134719	0.74	43498	2.53	3.1		<u>2,3-Dihydro-3,5-Dihydroxy-6-Met</u>
7	7.384	7.275	7.558	47152	0.26	6427	0.37	7.34	MI	Cyclopropa[3,4]Pentaleno[1,2-D][1,3]Dioxo
8	11.463	11.317	12.125	13822279	75.99	842131	48.94	16.41	S	<u>1,2,3-Benzenetriol</u>
9	15.345	15.292	15.408	141709	0.78	54014	3.14	2.62		Undecanoic Acid, Methyl Ester
10	15.884	15.825	16.158	47548	0.26	6933	0.4	6.86	MI	Isoamyl Nitrite
11	16.284	16.2	16.442	45358	0.25	10996	0.64	4.12	MI	Tridecanoic Acid
12	19.967	19.7	20.317	70449	0.39	16573	0.96	4.25	MI	Nonanoic Acid, Methyl Ester
13	22.674	22.625	22.733	66286	0.36	26262	1.53	2.52		1,1'-Bicyclopentyl, 2-Hexadecyl
14	24.137	24.092	24.2	105115	0.58	38854	2.26	2.71		Heptadecanoic Acid, Methyl Es
15	27.277	27.242	27.325	78772	0.43	30976	1.8	2.54	V	3-Tetradecen-5-Yne, (Z)-
16	27.715	27.658	27.783	136177	0.75	50965	2.96	2.67		6-Octen-1-ol, 3,7-Dimethyl-
17	27.929	27.858	27.983	97268	0.53	34978	2.03	2.78		Heptadecanoic Acid, Methyl Es
18	42.49	42.283	42.508	103278	0.57	7588	0.44	13.61	V	1,2-Cinnolinedicarboxylic Acid, 1,2,3,5,6,7
19	42.886	42.867	43.158	142036	0.78	14334	0.83	9.91	V	Heptasiloxane, 1,1,3,3,5,5,7,7,9,9,11,11,13
20	43.65	43.625	43.708	76131	0.42	16974	0.99	4.49		2',6'-Dihydroxyacetophenone, Bis(Trimethyl
21	43.725	43.708	43.9	177318	0.97	20400	1.19	8.69	V	<u>8-(Dimethylamino)-7-(3-(4-Ethylphenoxy)-</u>
22	44.071	43.9	44.1	153613	0.84	15486	0.9	9.92	V	Cyclodecasiloxane, Eicosamethyl-
23	44.835	44.817	44.85	86444	0.48	47591	2.77	1.82	V	<u>1,4-Benzenediol, 2,5-Bis(1,1-Dimethylethyl</u>
24	44.875	44.85	44.9	194471	1.07	67935	3.95	2.86	V	3-Ethoxy-1,1,1,5,5,5-Hexamethyl-3-(Trimet
25	44.939	44.9	45.017	756655	4.16	102882	5.98	7.35	V	Benzoic Acid, 4-[(Trimethylsilyl)Amino]-, Tri
26	45.033	45.017	45.317	1143921	6.29	141999	8.25	8.06	V	GC Stationary Phase P1895
				18189433	100	1720876	100			

Table 3: Energy data for ligands interacting with CDK-1 are listed

S.No	Plant molecule (Ligand)	GScore	DScore	HBond
1	8-(dimethylamino)-7-(3-(4-ethylphenoxy)	-7.2	-7.2	-1
2	ethyl 6-oxo-5-propylheptanoate	-6.9	-6.9	-1.33
3	2,3-dihydro-3,5-dihydroxy-6-methyl-4h-pyran-4-one	-6.53	-5.37	-2.07
4	1,2,3-benzenetriol	-6.45	-6.45	-3.2
5	1,4-benzenediol, 2,5-bis(1,1-dimethylethyl	-6.28	-6.28	-0.7
6	1,2,3-propanetriol	-5.49	-5.49	-3.36
7	6-octen-1-ol, 3,7-dimethyl	-5.22	-5.22	-0.7
8	cyclopropylmethanol	-4.72	-4.72	-1.25
9	benzoic acid, 4-[(trimethylsilyl)amino]	-4.28	-4.28	-0.53

Table 4: Residue data for ligands interacting with CDK-1 are listed

S. No	Plant molecule (Ligand)	Interacting residues	Bond length
1	8-(dimethylamino)-7-(3-(4-ethylphenoxy)	GLN 136, ASP 86	1.71, 2.27
2	ethyl 6-oxo-5-propylheptanoate	ASP 146, LEU 83	1.97, 2.06
3	2,3-dihydro-3,5-dihydroxy-6-methyl-4h-pyran-4-one	LEU 83	2.12, 1.94
4	1,2,3-benzenetriol	LEU 83	1.91, 2.11, 2.08
5	1,4-benzenediol, 2,5-bis(1,1-dimethylethyl	GLN 132	1.82
6	1,2,3-propanetriol	LEU 83	2.07, 1.79, 1.95
7	6-octen-1-ol, 3,7-dimethyl	ASP 146	1.93
8	cyclopropylmethanol	GLU 81, PHE 82	1.88, 2.12
9	benzoic acid, 4-[(trimethylsilyl)amino]	TYR 15	2.2

Conclusion:

We document the molecular binding features of 8-(Dimethylamino)-7-(3-(4-ethylphenoxy)-2d with the CDK-1 protein for further consideration.

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Conflict of interest:

Authors declare no conflict of interest in this manuscript.

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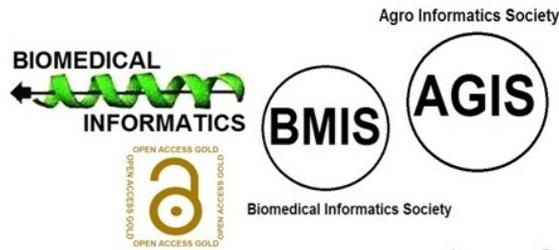
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