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Variation of interaction pattern and physico-chemical properties in plant derived compounds and clinical drugs for CDK targets

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Abstract
Cyclin-dependent kinases (CDK) are one of the important drug targets for the inhibition of the cancer cell growth. Numbers of natural compounds from plants possessing CDK inhibitory activity have been reported in NPACT (Naturally Occurring Plant-based Anti-cancer Compound-Activity-Target) database. Compounds derived from plants have higher potency to act as effective drugs due to its reduced nature of toxicity. To understand the molecular interaction of plant derived compounds and clinical drugs reported for target CDK, a comparative analysis have been performed based on the docking and similarity analysis using various bioinformatics software and tools. In similarity analysis, all against all comparison of all the CDK inhibitors was performed based on the tanimoto similarity values. Outcome of the present study would provide a thorough knowledge on the available drugs and plant derived compounds. In addition it would also enhance the vision towards novel CDK drug design strategy.

Keywords: CDK, plant derived compounds, docking, ligand similarity, molecular interaction

Introduction
Cancer is an abnormal growth of cells with the potential to invade to other parts of the body. The cell cycle process is highly conserved in all living organisms. Deregulation of cell cycle leading to unscheduled proliferation is a commonly observed feature of human cancer. Therefore a thorough understanding of the biology of cell cycle plays a key role in developing novel therapeutic methods for the treatment of the deadly disease cancer. Cyclin-dependent kinases (CDKs) play a vital role in regulating the progression of cell cycle [1-6]. In addition to regulation of cell cycle transitions, CDKs which belong to the family of serine/threonine protein kinases also play a crucial role in other biological processes such as transcription, trans, lation, neurogenesis and apoptosis. Among the20 CDKs reported, CDK1, CDK2, CDK4 and CDK6 are involved in the regulation of the transition of phases in the cell cycle while CDKs 7–11 have their role intranscription [7-9]. Regulation of these CDKs in each phase of the cell cycle is imperative for normal cell division and cell growth. Any discrepancy in the regulation of CDKs in any phase of cell cycle results in uncontrolled growth and thus tumor formation. Since deregulation of these kinases, is commonly observed in most of the cancers, CDKs are used as essential targets in developing new anticancer therapeutics [10, 11]. Several *in silico* studies have been carried out for the inhibition of CDKs 1- 9 using inhibitors from different heterocyclic classes. The research findings and strategies employed in these *in silico* studies have been reviewed recently [12]. Although various research works have reported several CDK inhibitors (e.g., flavopiridol, indirubicin, roscovitine, etc.,), these inhibitors were named as pan inhibitors due to their specificity issues. Currently, the drugs palbociclib, abemacicilib and ribociclib have been approved as inhibitors of CDK4 and CDK6 targets. However, design of specific CDK inhibitor still remains a challenge. A comparative analysis of structural differences between ATP binding sites and their inhibitor specificity has been carried out in several CDKs order to develop specific inhibitors [13]. The availability of hundreds of structural studies focused on the intermolecular interactions of CDK with competitive inhibitors has led to the development of new machine learning models to predict binding affinity for CDK [14]. Molecular docking studies of various plant derived natural compounds possessing anticancer properties have been reported to exhibit better binding interactions with CDK than chemically synthesized inhibitors [15]. It has also been reported that phytochemicals namely, proanthocyanidins from grape seeds (GSPs), polyphenols in green tea and honokiol, derived from the *Magnolia* species have proven role in the control of head and neck cancer. Phytochemicals have been used for thousands of years in various traditional systems of medicine.

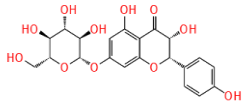
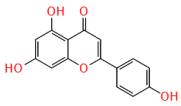
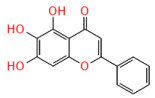
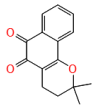
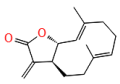
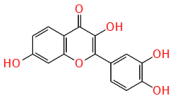
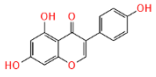
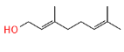
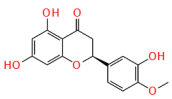
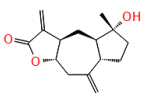
Bioactive non-toxic phytochemicals exists as the primary and promising resource for the development of effective anti-cancer therapeutics [16].

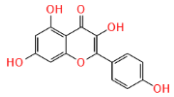
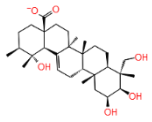
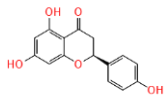
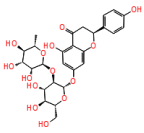
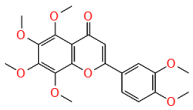
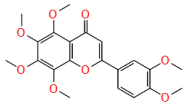
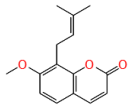
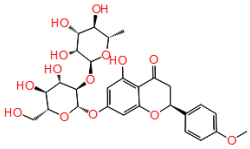
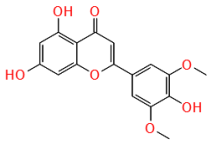
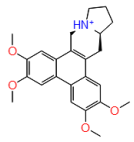
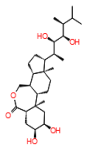
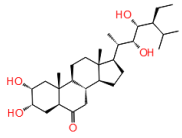
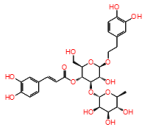
In the present study, we have analyzed the natural plant compounds and clinical drugs based on phtsico-chemical properties and their interaction with CDK protein targets. Docking experiment was performed for the CDK targets viz. CDK1, CDK 2, CDK 4, CDK 6, CDK 7 and CDK 9. NPACT, the curated database of Plant derived natural compounds that exhibit anti-cancerous activity [17] has been used for compiling plant derived CDK inhibitors dataset. Current study focuses mainly to find the similarity and difference between plant derived compounds and clinical drugs by performing docking and similarity studies.

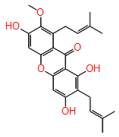
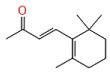
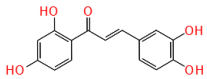
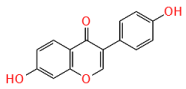
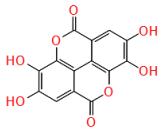
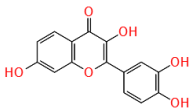
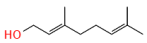
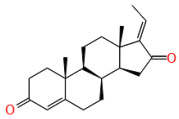
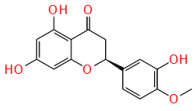
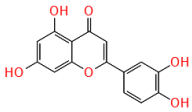
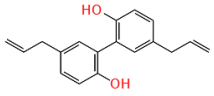
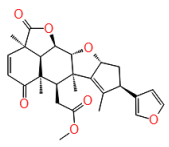
Materials and Methods

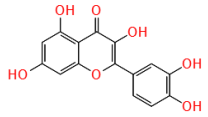
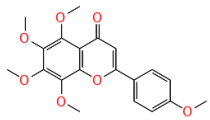
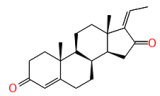
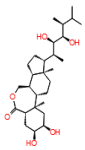
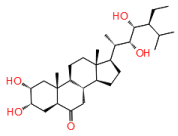
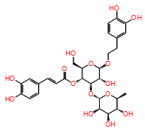
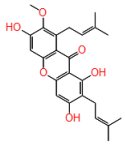
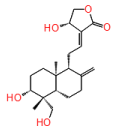
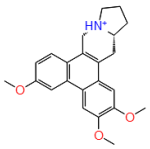
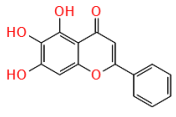
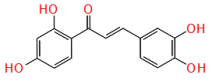
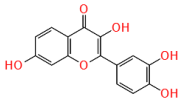
Information regarding the plant derived compounds for the targets CDK1, CDK2, CDK4, CDK6, CDK7 and CDK9 were obtained from the NPACT database (Table 1). Clinical drugs information (Table 2) was obtained from article [18] and their structures were downloaded from the pubchem database. A total of 55 plant derived compounds obtained from the NPACT database were compared with clinical drugs for the target CDKs mentioned above. Glide XP module in the Schrodinger software [19] was used for docking experiment. Protein and ligand preparation was performed using protein preparation wizard and ligand preparation wizard, respectively.

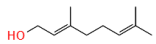
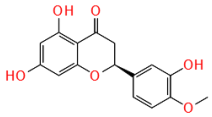
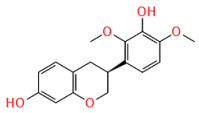
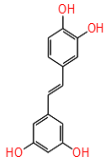
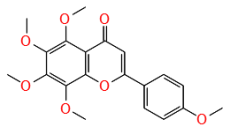
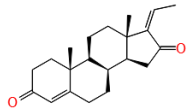
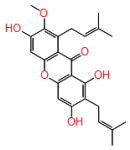
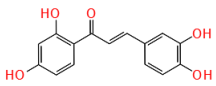
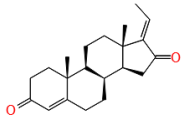
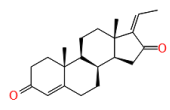
Table 1: Information regarding Plant derived compounds used in this study for the CDK targets

S. No.	Compound ID	Compounds	Molecular Volume	Structure
Target: CDK1				
1	NPACT01486	2-alpha, 3-alpha, 19-beta, 23-beta-tetrahydroxyurs-12-en-28-oic acid	495.49	
2	NPACT00270	Apigenin	224.05	
3	NPACT00301	Baicalein	224.05	
4	NPACT00325	Beta-Lapachone	219.96	
5	NPACT00441	Costunolide	235.47	
6	NPACT00581	Fisetin	232.07	
7	NPACT00605	Genistein	224.05	
8	NPACT00607	Geraniol	175.57	
9	NPACT00659	Hesperetin	255.81	
10	NPACT01237	Inuviscolide	239.14	

11	NPACT00697	Kaempferol	232.07	
12	NPACT00701	Kaempferol-7-O-beta-d-glucoside	370.43	
13	NPACT00798	Naringenin	230.26	
14	NPACT00799	Naringin	486.25	
15	NPACT00800	Narirutin	486.25	
16	NPACT00817	Nobiletin	353.27	
17	NPACT00838	Osthole	231.47	
18	NPACT00878	Poncirin	-8.66	
19	NPACT00994	Tricin	275.14	
Target: CDK2				
1	NPACT01053	(R)-tylophorine	366.15	
2	NPACT00085	24-epibrassinolide	481.23	
3	NPACT00090	28-homocastasterone	390.76	
4	NPACT00212	Acteoside	532.5	

5	NPACT00237	Alpha-mangostin	376.86	
6	NPACT00324	beta-ionone	208.76	
7	NPACT00360	Butein	233.92	
8	NPACT00476	Daidzein	216.03	
9	NPACT00521	ellagic acid	221.78	
10	NPACT00581	Fisetin	232.07	
11	NPACT00607	geraniol	175.57	
12	NPACT00637	guggulsterone	312.85	
13	NPACT00659	Hesperetin	255.81	
14	NPACT00729	Luteolin	232.07	
15	NPACT01258	Magnolol	260.55	
16	NPACT00815	nimbolide	417.03	

17	NPACT00891	Quercetin	240.08	
18	NPACT00967	Tangeretin	327.72	
19	NPACT01032	Z-Guggulsterone	312.85	
Target: CDK4				
1	NPACT00085	24-epibrassinolide	481.23	
2	NPACT00090	28-homocastasterone	390.76	
3	NPACT00212	Acteoside	532.5	
4	NPACT00237	Alpha-mangostin	376.86	
5	NPACT01129	Andrographolide	338.33	
6	NPACT01131	Antofine	340.6	
7	NPACT00301	Baicalein	224.05	
8	NPACT00360	Butein	233.92	
9	NPACT00581	Fisetin	232.07	

10	NPACT00607	geraniol	175.57	
11	NPACT00659	Hesperetin	255.81	
12	NPACT00783	Mucronulatol	271.15	
13	NPACT01294	Piceatannol	214.94	
14	NPACT00967	Tangeretin	327.72	
15	NPACT01032	Z-Guggulsterone	312.85	
Target: CDK6				
1	NPACT00237	Alpha-mangostin	376.86	
2	NPACT00360	Butein	233.92	
3	NPACT00637	guggulsterone	312.85	
4	NPACT01234	Indole-3-carbinol	137.84	
5	NPACT01032	Z-Guggulsterone	312.85	
Target: CDK7				

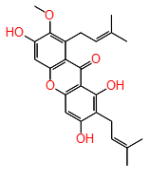
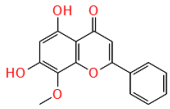
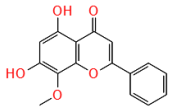
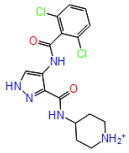
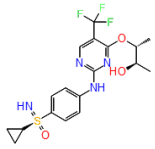
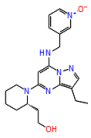
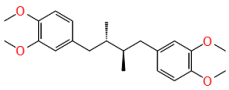
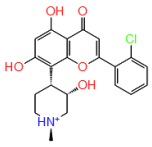
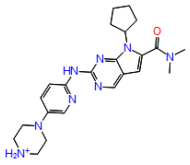
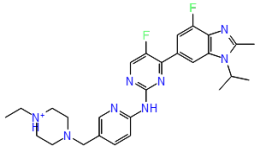
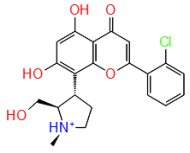
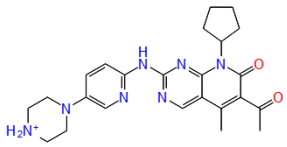
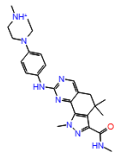
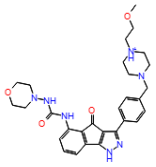
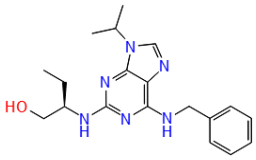
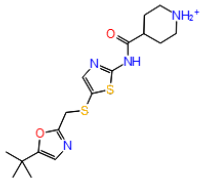
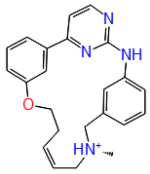
1	NPACT00237	Alpha-mangostin	376.86	
2	NPACT01021	Wogonin	241.58	
Target: CDK9				
1	NPACT01021	Wogonin	241.58	

Table 2: Information regarding clinical drugs used in this study for the CDK targets

S. No.	Clinical Drugs	Volume	Structure
1	AT7519	311.72	
2	BAY-1000394	348.95	
3	Dinaciclib	371.01	
4	EM-1421	358.02	
5	Flavopiridol	340.15	
6	LEE-011	404.38	
7	LY2835219	460.47	
8	P276-00	340.15	

9	PD0332991	410.58	
10	PHA-848125 AC	430.75	
11	RGB-286638	495.64	
12	Roscovitine	338.91	
13	SNS032	337.52	
14	TG02SG1317	353.06	

X-ray crystal structures for all the mentioned CDK targets were retrieved from the Protein Data Bank with high resolution (Table 3). Total of 55 ligands (41 plant derived compounds and 14 clinical drugs) were docked on all CDK subtypes to understand their interaction pattern. Ligand volume and Protein cavity volume were computed using online molinspiration software (www.molinspiration.com) and CASTp server [20] respectively. Protein similarity studies were carried out using PDB e Fold server [21].

Table 3: Structure details of PDB structures for each CDK

S. No	CDK	PDB ID	Resolution	Protein cavity volume Å
1	CDK1	5LQF	2.06 Å	1460.6
2	CDK2	1E1V	1.95 Å	930.2
3	CDK4	2W96	2.3 Å	1323.8
4	CDK6	5L2S	2.27 Å	1372.9
5	CDK7	1UA2	3.02 Å	2408.9
6	CDK9	3BLR	2.8 Å	1248.2

Comparison of similarity of NPACT compounds and clinical drugs for both intra and inter similarities were analyzed using tanimoto coefficient values calculated using Chem Mine tool [22]. Chem Mine Web Tools is an online service for analyzing and clustering small molecules by structural similarities, physicochemical properties. A total of 3025 (55 X 55) tanimoto similarity values were computed and the values have been provided in supplementary information. Percentage similarities of tanimoto coefficient values were calculated as given below:

$$\text{Percentage of similarity} = \frac{\text{number of ligands having greater than 0.7 tanimoto coefficient}}{\text{Total number of ligands}} \times 100$$

Results and Discussion

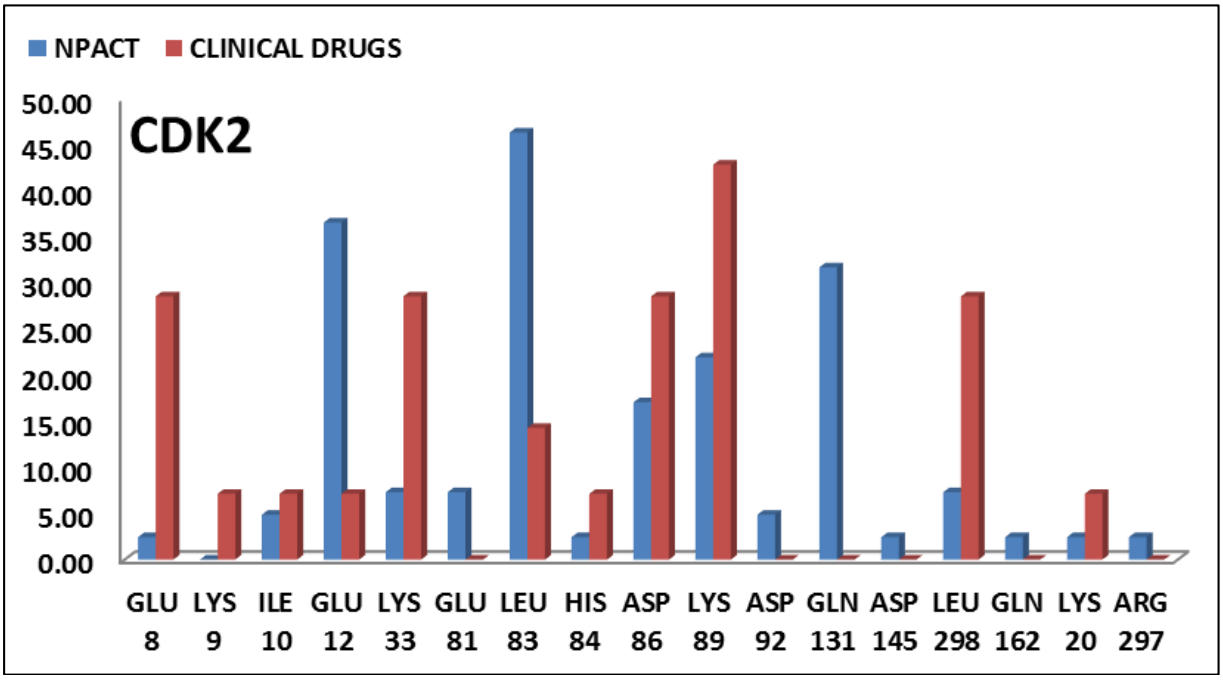
Docking experiment was performed for the CDK targets viz. CDK1, CDK2, CDK4, CDK6, CDK7 and CDK9. Rigid docking scores obtained from the rigid docking undifferentiated the specificity among different CDKs. Overall comparison of docking scores of both drugs and NPACT compounds showed

highest docking score of -12.32 was observed for the NPACT compound naringin for the target CDK6. Lowest value of -1.44 was observed the compound (z)-Guggulsterone for the target CDK-2. All the compounds scored very less for the target CDK-7. Maximum score of -6.99 was obtained for 28-homocastaserone for the target CDK7. Protein cavity volume was observed to be very high for the CDK7 of 2408.9Å which makes ligands to have very less interactions and attain lowest docking score [23]. Ligand volume for NPACT ligands ranged from 140 to 530Å approx. and clinical drugs ranged from 350 to 500Å approx.

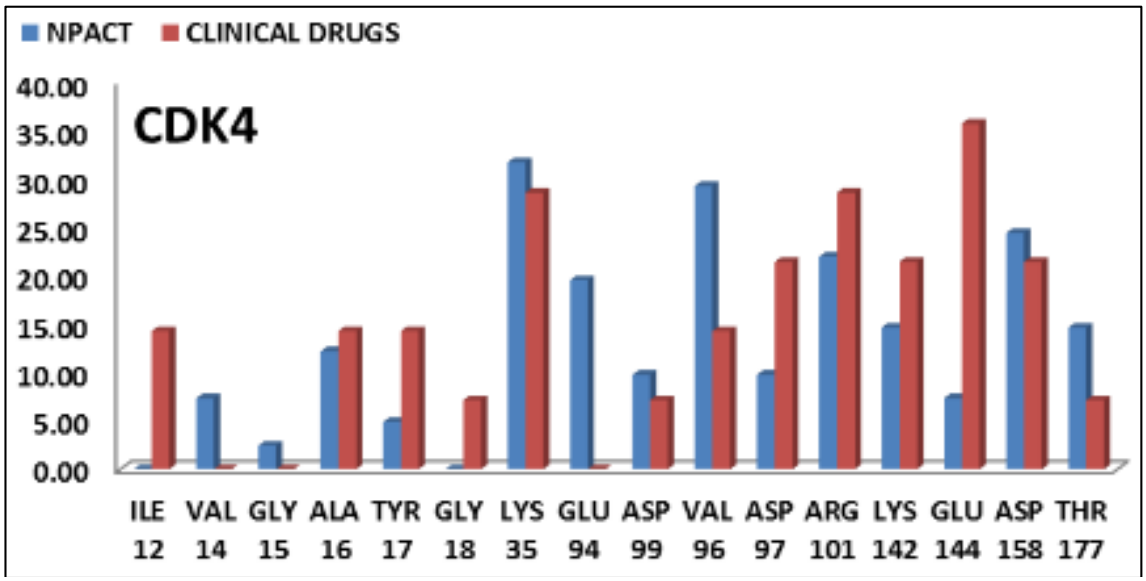
Docking experiment was performed mainly to analyze the hydrogen bond (H-bond) interactions variation observed for plant based compounds and clinically reported drugs. Number of H-bond interactions observed for each binding site residues and the ligand was counted for each CDK. Total number of H-bond interactions observed for each binding site residue was summed up for the NPACT ligands and clinical drugs separately. Variation of H-bond interactions was studied by computing correlation co-efficient value between the total numbers of H-bond interactions observed for NPACT ligands vs clinical drugs for each CDK target. Information regarding binding site residues which exhibit H-bond interactions and the correlation coefficient value (computed between total number of H-bond interactions in plant derived compounds and total number of H-bond interactions in clinical drugs) are provided in Table 4. Almost all the interacting residues for different CDKs reported by Kalra *et al*. 2017 were found to have H-bond interactions with both plant derived compounds and clinical drugs in the present study. Additional residues that possess H-bond interactions in each CDK are also reported here. Co-relation value of 0.9, 0.2, 0.4, 0.9, 0.2 and 0.9 was observed for the targets CDK1, CDK2, CDK4, CDK6, CDK7 and CDK9 respectively. Wide variation in H-bond interactions was observed with CDK2, CDK4 and CDK7 targets respectively (Figure 1).

Table 4: Binding site residues exhibiting H-bond interactions and their correlation coefficient value

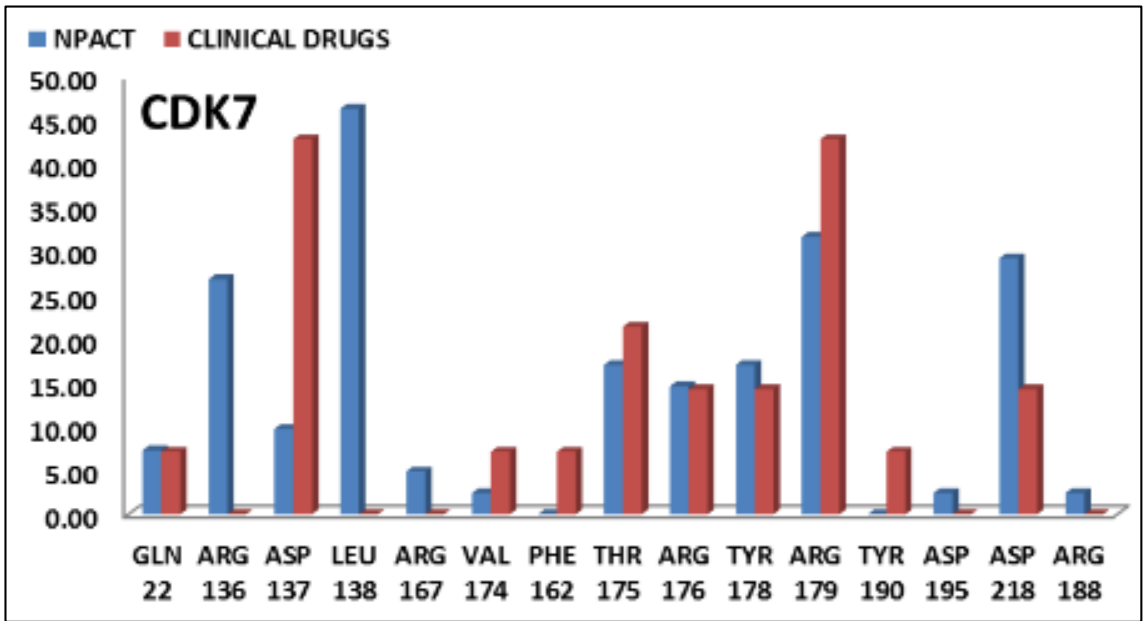
S. No	CDK	Residues showing H-bond interaction	Correlation coefficient (Plant derived compounds vs clinical drugs)
1	CDK1	ILE10, GLU12, LYS33, GLU51, GLU81, LEU83, SER84, ASP86, LYS88, LYS89, LYS180, ASP146, LYS180, GLN132, PHE147	0.9
2	CDK2	GLU8, LYS9, ILE10, GLU12, LYS33, GLU81, LEU83, HIS84, ASP86, LYS89, ASP92, GLN131, ASP145, LEU298, GLN162, LYS20, ARG297	0.2
3	CDK4	ILE12, VAL14, GLY15, ALA16, TYR17, GLY18, LYS35, GLU94, ASP99, VAL96, ASP97, ARG101, LYS142, GLU144, ASP158, THR177	0.4
4	CDK6	GLU18, ILE19, GLU21, TYR24, LYS43, GLU99, HIS100, VAL101, ASP102, ASP104, THR107, LYS147, GLN149, ASP163, ASP110	0.9
5	CDK7	GLN22, ARG136, ASP137, LEU138, ARG167, VAL174, PHE162, THR175, ARG176, TYR178, ARG179, TYR190, ASP195, ASP218, ARG188	0.2
6	CDK9	GLY27, THR29, ASP104, CYS106, GLU017, ASP109, LYS48, ALA153, ASP149, LYS151, ASP154, ASP167, ASN116, THR194	0.9



1a)



1b)

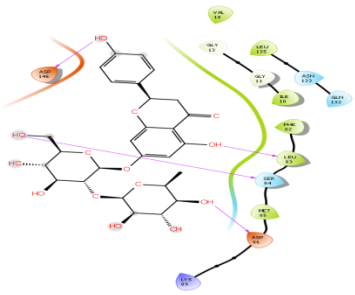
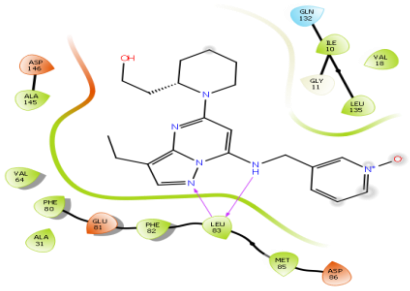
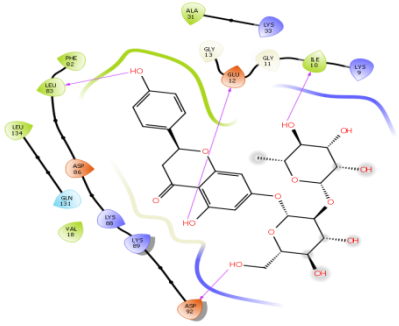
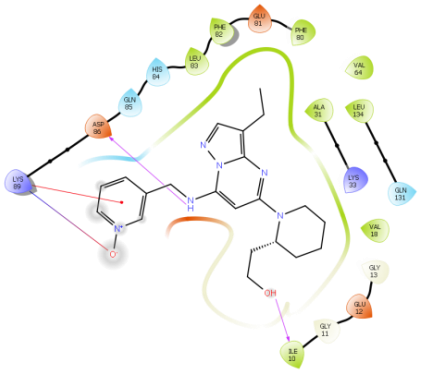
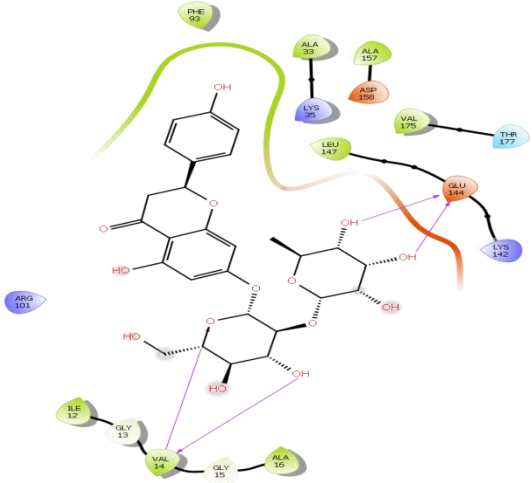
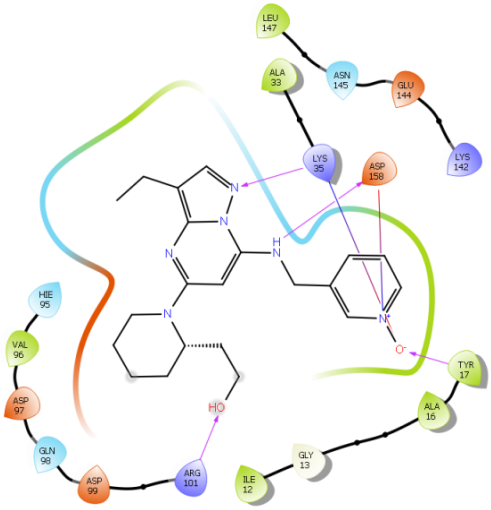
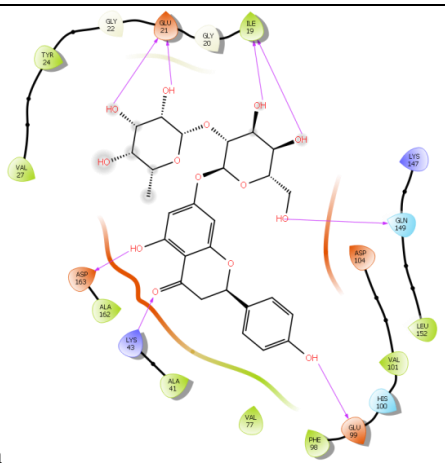
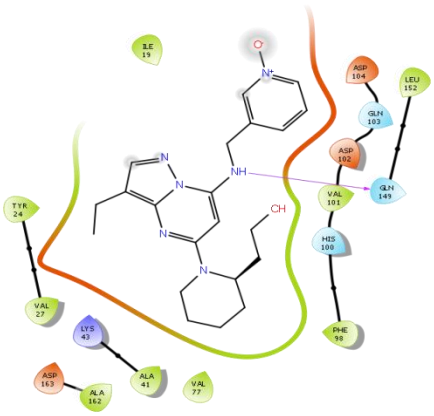


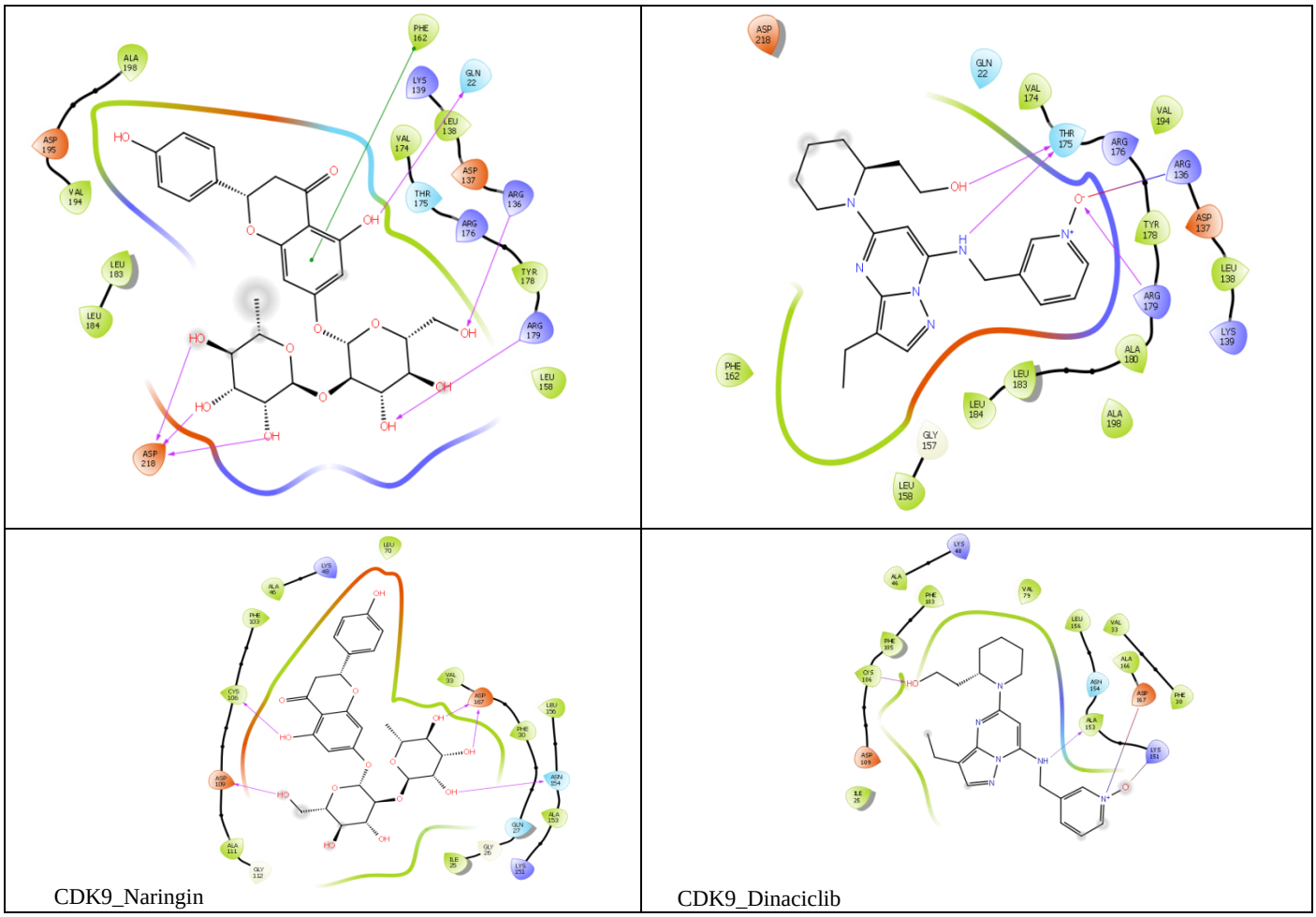
1c)

Fig 1: Variation of H-bond interactions observed between plant derived compounds and clinical drugs for the CDK2 (1a), CDK4 (1b) and CDK7 (1c). Wide difference in interaction pattern is clearly depicted from the figure which had the correlation coefficient of 0.2 (CDK2), 0.4 (CDK4) and 0.2 (CDK7) respectively. LYS35 and ASP158 residues of CDK4 showed similar kind of interaction pattern.

Residues such as GLU8, LYS33, ASP86, LYS89 and LEU298 tend to have more (>10%) interactions in comparison to NPACT ligands for the target CDK2. In order to gain selectivity, ASP86 and LYS89 residues are reported to have considerable importance [23]. Likewise for CDK4, residues such as ILE12, TYR17, ASP97 and GLU144 have higher number of interaction with clinical drugs. GLU144 residue interaction has also been reported by Sridhar *et al* (2006) for its role in CDK4 subtype selectivity. ASP137 and ARG179 are the residues observed to have >10% interactions for CDK7. Table 5 provides docking interaction results of plant derived compound Naringin and clinical drug Dinaciclib for CDK targets. Number of interactions was observed to be higher for Naringin in comparison to Dinaciclib. Table 5 clearly shows that Naringin exhibits higher number of interactions with CDK binding sites when compared to Dinaciclib in all the cases. In addition, Pi-pi stacking interaction was observed only with CDK7-Naringin docked complex.

Table 5: Docking results showing Interactions of plant derived compound Naringin and clinical drug Dinaciclib.

Protein_ligand name	Protein-ligand interaction
 CDK1_Naringin	 CDK1_Dinaciclib
 CDK2_Naringin	 CDK2_Dinaciclib
CDK4_Naringin 	 CDK4_Dinaciclib
 CDK6_Naringin	 CDK6_Dinaciclib
CDK7_Naringin	CDK7_Dinaciclib



For all the CDK targets studied, some of the H-bond interactions were observed only for NPACT ligands and absent in the case of clinical drugs. Table 6 provides the details of residues that have interactions only with NPACT ligands. Those residues which show greater than 10% interactions are alone reported and minimal variations (<10%) are omitted in order to have significant results. Imperative docking studies was useful to differentiate the interacting residues required for specificity for a particular CDK subtype.

Table 6: Residues that possess H bond interaction only with NPACT ligands and absent for the clinical drugs

S. No.	Target	Residues
1	CDK1	GLU12
2	CDK2	GLN 131
3	CDK4	GLU 94
4	CDK6	ASP 163
5	CDK7	ARG 136, LEU 138
6	CDK9	-

How much similar are the NPACT and clinical drugs?

To know the similarity of NPACT compounds and clinical drugs, Tanimoto similarity scores were computed for all the compounds using chem mine tools. Any two compounds possessing tanimoto coefficient value of 1.0 are tend to have identical structure. Comparison was made at three levels, NPACT vs NPACT, clinical drugs vs clinical drugs and NPACT vs clinical drugs by setting two criterias, in which ligands having similarity greater than 0.7 and those with less than 0.25 tanimoto similarities were analyzed. Ligands which shares>0.7 tanimoto coefficient tend to have more similar structure (Suppl. S1). In the present analysis, none of the ligands have >0.7 tanimoto coefficient value. In this study, 95% of the ligands have highly diverse structures. Three plant derived compounds (remaining 5%) were merely similar at the percentage of cdk2_Luteolin (7%), cdk1_kaempferol (10%), cdk2_Quercetin (7%) and cdk1_naringin (10%) respectively. We have also compared 3d structure of all CDK subtypes using the PDB e fold server. 3D structure comparison of all CDKs resulted in the RMSD value of less than 2.5Å. Higher and lower RMSD value of 2.2 Å and 1.2 Å was observed for the structures CDK2 vs CDK1 and CDK9 vs CDK4 respectively.

Conclusion

In the current study, systematic comparison of both NPACT ligands and clinical drugs was performed to understand their interaction pattern variation and similarity. Structural modification of the plant derived compounds for enhancing the inhibitory activity via the interactions would provide the better way to find more lead molecules for the target. As few plant compounds have lesser molecular volume compared to clinical drugs, there exists a broad likelihood to modify the chemical structure to have further interaction points without modifying the core structure.

The tanimoto similarity analysis of 55 ligands has resulted in the identification of highly diverse structures. As plant derived compounds have been reported to be more successful in the development of new drugs, this study can be used for the identification of novel lead molecules for successful drug design strategies. Thus, findings from the present study would provide a way through for the identification of plant-derived natural compounds with improved inhibitory activity against cancer targets.

Conflicts of interest: None Declared

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