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Research Article

MOLECULAR DOCKING AND QSAR STUDIES ON PLANT DERIVED BIOACTIVE COMPOUNDS AS POTENT INHIBITORS OF DEK ONCOPROTEIN

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ABSTRACT

The DEK proto-oncogene has been associated with human carcinogenesis-either as a fusion with the CAN nucleoporin protein or when transcriptionally upregulated. DEK is frequently upregulated in aggressive human tumors such as glioblastoma, melanoma and bladder carcinoma. A molecular docking of nine plants derived bioactive compounds with the oncoprotein DEK was performed using ArgusLab 4.0.1 and the differences in their binding modes were investigated. QSAR toxicity analysis has been performed for a series of plant derived nine bioactive compounds using FAF Drugs ADME/tox filtering server. Considering the molecular properties of the ligands, higher inhibitory activity is associated with reduced molecular flexibility, as measured by lower polar surface area (TPSA), LogP, lower hydrogen bond counts, confirming the capability of the bioactive compounds for binding at the active site of the receptor.

Key words: DEK oncoprotein, Bioactive compounds, Docking, ArgusLab 4.0.1, QSAR.

INTRODUCTION

The human DEK proto-oncogene was originally identified as a fusion with the CAN/NUP214 nucleoporin in a subset of acute myeloid leukemia patients[1].

Since its discovery, DEK has also been found to be transcriptionally upregulated in a number of aggressive human tumors such as bladder carcinoma, hepatocellular carcinoma, glioblastoma, melanoma, and acute myeloid leukemia types that do not exhibit the above translocation[2].

DEK is abundantly expressed in proliferating cells, and a majority of the protein is bound to chromatin, whereas a small fraction is bound to RNA[3]. More recently, DEK has also been linked to the resistance of malignant cells to apoptotic inducers. Interestingly, a fraction of DEK can also bind RNA and affect alternative splicing, further illustrating the pleiotropic roles that this protein may exert in cancer cells[4].

Human DEK is an abundant nuclear protein of 375 amino acids that occurs in copy numbers of more than a million/nucleus. Most nuclear DEK protein is bound to chromatin throughout the cell cycle[5]. DEK has two DNA-binding domains.

A first domain is located in a central peptide that includes a conserved sequence element, the SAF (scaffold attachment factor) or SAP (after SAF-A/B; acinus; Pias) box. A second DNA-binding domain is in the C-terminal region of DEK and overlaps with most of the identified phosphorylation sites[6].

Natural products have historically and continually been investigated for promising new leads in pharmaceutical development[7]. New anticancer drugs derived from research on plant, antitumor agents will be continuously discovered.

The activities of bioactive compounds and the synergistic action shown by them with other drugs make them ideal in alternative cancer therapies[8].Molecular docking is an application, wherein molecular modeling techniques are used to predict how a protein interacts with small molecules (ligand)[9].

The concept of docking is important in the study of various properties associated with protein-ligand interactions such as binding energy, geometry complementarity, electron distribution, hydrogen bond donor acceptor properties, hydrophobicity and polarizability[10]. Elucidation of ligand binding mechanisms is the necessary step to obtain more selective and potent drugs for this new potential target[11].

MATERIALS AND METHODS

Preparation of protein structure

The crystal structure of the DEK oncoprotein (PDB ID: 1Q1V) has been obtained from RCSB Protein Data Bank (http://www.pdb.org). All water molecules were removed and on the final stage hydrogen atoms were added to the target protein molecule.

Preparation of ligand structures

All the compounds used for docking study were selected from the literature[12 -17]. ChemSketch, chemically intelligent drawing interface freeware developed by Advanced Chemistry Development, Inc., (http://www.acdlabs.com) was used to construct the structure of the ligands. Using draw mode of Chemsketch, the ligands were generated and three dimensional optimizations were done and then saved in .mol file. Geometry optimizations of the ligands were performed according to the Hartree-Fock (HF) calculation method by ArgusLab 4.0.1 software.

Binding site detection

Q-SiteFinder (http://www.bioinformatics.leeds.ac.uk/qsitefinder) is one of the tools for binding site prediction. It uses the interaction energy between the protein and a simple Vander Waals probe to locate energetically favourable binding sites. Here, Q-site finder server was analysed further for the identification of the most potential active site where the ligand can bind and interact with target protein.

Protein-ligand interaction using ArgusLab 4.0.1

Argus Lab is the electronic structure program that is based on the quantum mechanics, it predicts the potential energies, molecular structures; geometry optimization of structure, vibration frequencies of coordinates of atoms, bond length, bond angle and reactions pathway[18].

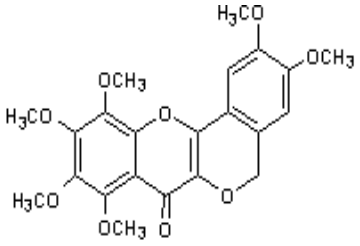
DEK protein was docked against the obtained nine ligands using ArgusLab 4.0.1 (Mark A. Thompson, Planaria Software LLC, Seattle, WA, USA, http://www.arguslab.com) to find the reasonable binding geometries and explore the protein ligand interactions. Docking of the protein ligand complex was mainly targeted only on to the predicted active site. Docking simulations were performed by selecting "ArgusDock" as the docking engine. The selected residues of the receptor were defined to be a part of the binding site.

Table 1: Bioactive compounds from plants taken for docking analysis

COMPOUND CLASS AND NAME	SOURCE
Flavonoids	
1. Crotoncaudatin	*Croton caudatus*
2. 8-hydroxyethyl-7,2′,4′-trihydroxyflavone	*Morus mongolica*
3. (±)-7-methoxy-8-hydroxyethyl-2′,4′-dihydroxyflavane	*Morus mongolica*
4. 2R*,4R*-8-hydroxyethyl-7,4′-dihydroxy-4,2′-epoxyflavane	*Morus mongolica*
5. 2′E-3′-(4′-hydroxyisopentenyl)-2,4,2′,4′-tetrahydroxychalcone	*Morus mongolica*
6. 2-(2, 4-Dihydroxy-phenyl)-3, 6, 8-trihydroxy-chromen-4-one	*Plumbago zeylanica*
7. 4'-hydroxy-8,3'- dimethoxy-6-acroleinylflavan-3,4-diol	*Premna fulva*
Alkaloid	
8. 1-(4'-methoxyphenyl)-aziridine	*Abies webbiana*
9. (-)-N-methylguattescidine	*Fissistigma latifolium*

Table 2: Chemical Structures of the Ligands

(1)



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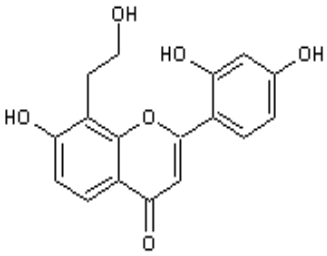

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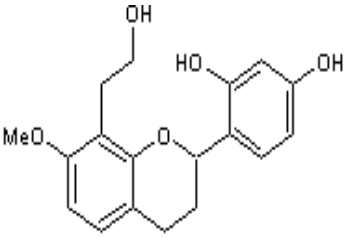

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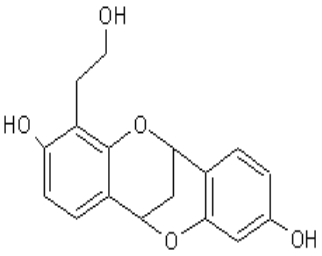

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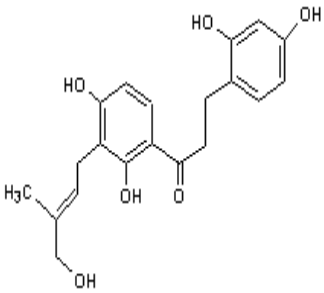

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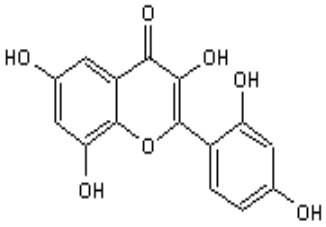

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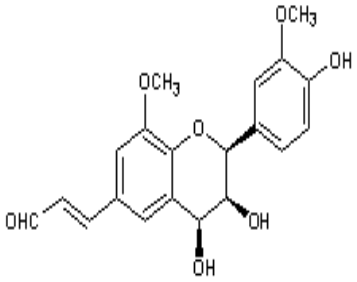

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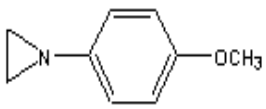

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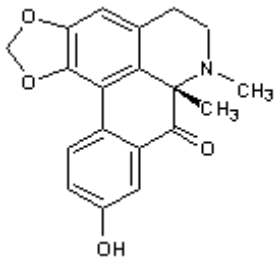

Table 3: Docking score and molecular properties of the ligands

Compounds	Energy value (kcal/mol)	MW	HD (OH+NH)	HA (O+N)	LogP	TPSA
1	-5.91	430.2	0	9	2.28	90.91
2	-7.16	314.2	4	6	2.12	107.22
3	-7.69	315.2	3	5	2.40	79.15
4	-7.40	300.2	3	3	2.14	79.15
5	-7.19	358.2	5	6	2.15	118.22
6	-6.24	302.2	5	7	2.39	127.45
7	-7.11	372.2	3	7	1.98	105.45
8	-6.39	149.1	0	2	1.94	101.24
9	-8.65	323.2	1	5	2.59	59.00

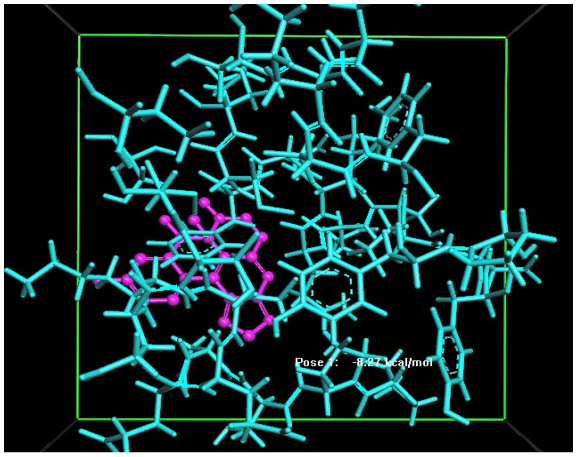

Fig. 1: Crucial Interaction between compound 9 (pink) and dek (blue).

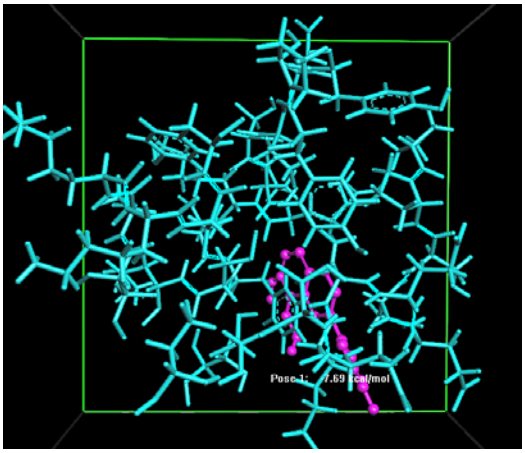

Fig. 2: Crucial Interaction between compound 3 (pink) and dek (blue)

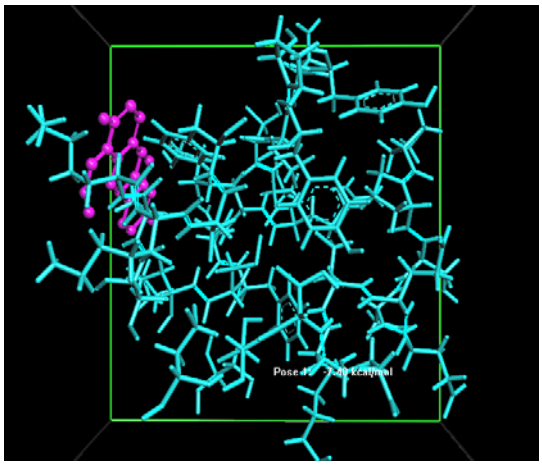

Fig. 3: Crucial Interation Between Compound 4 and dek. The protein in shown in stick model.

A spacing of 0.4 Å between the grid points was used and an exhaustive search was performed by enabling "High precision" option in Docking precision menu, "Dock" was chosen as the calculation type, "flexible" for the ligand and the AScore was used as the scoring function. At maximum 150 poses were allowed to be analyzed, binding site box size was set to 20 x 20 x 20 angstroms so as to encompass the entire active site.

The AScore function, with the parameters read from the AScore.prm file was used to calculate the binding energies of the resulting docked structures.

All the compounds in the dataset were docked into the active site of DEK oncoprotein, using the same protocol.After completion of docking, the docked protein (protein-ligand complex) was analyzed to investigate the type of interactions. The docking poses saved for each compound were ranked according to their dock score function. The pose having the highest dock score was selected for further analysis.

Ligand screening and QSAR studies

FAF-Drugs is an online absorption, distribution, metabolism, excretion and toxicity prediction tool based on Frowns chemoinformatics tool kit[19]. It was used to calculate molecular descriptors like LogP, drug likeliness, polar surface area, molecular weight, number of hydrogen atoms and donors for all the inhibitors taken for the docking analysis.

RESULTS AND DISCUSSION

In the present study, to understand the interactions between the ligands and DEK protein and to explore their binding mode, docking study was performed using ArgusDock section available under ArgusLab 4.0.1.

The crystal structure of the DEK protein (1Q1V) was derived from PDB and used as a target for docking simulation. The compounds selected from the literature were listed in Table 1. Ligands were created and prepared for the docking procedure using ChemSketch and ArgusLab. The structures of the ligands obtained from the ChemSketch were shown in Table 2.

Binding site of the protein

The detection of ligand-binding sites is often the starting point for protein function identification and drug discovery[20]. In our study, Q-site Finder predicted active site of the protein DEK with a higher average precision.

The active site of DEK comprises of amino acid residues such as PRO 319, PRO 320, THR 321, ASP 322, GLU 323, GLU 324, LEU 325, LYS 326, GLU 327, THR 328, ILE 329, LEU 332, ILE 346, CYS 347, LYS 348, LYS 349, VAL 350, TYR 351, TYR 354, PRO 355, TYR 357, ASP 358, LEU 359, THR 360, GLU 361, ARG 362, LYS 363, ASP 364, PHE 365, ILE 366, LYS 367 and THR 369. As most of the amino acid residues in the active site are hydrophobic so they are the main contributors to the receptor-ligand interaction.

Interaction studies

The goal of ligand-protein docking is to predict the predominant binding model(s) of a ligand with a protein of known three-dimensional structure[21]. To study the binding modes of bioactive compounds in the binding site of human DEK oncoprotein, intermolecular flexible docking simulations were performed and energy values were calculated from the docked conformations of the DEK-inhibitor complexes. Docking studies yielded crucial information concerning the orientation of the inhibitors in the binding pocket of the target protein. Several potential inhibitors have been identified through the docking simulation.

The majority of the ligands had a greater binding affinity with the target protein DEK. Inhibition was measured by the binding energy of the best ligand pose measured in kcal/mol.

The docking scores were the highest for (-)-N-methylguattescidine with -8.65 kcal/mol followed by (±)-7-methoxy-8-hydroxyethyl-2′,4′-dihydroxyflavane with -7.69 kcal/mol, 2R ❋,4R ❋-8-hydroxyethyl-7,4′-dihydroxy-4,2′-epoxyflavane with -7.40 kcal/mol, 2″E-3′-(4″-hydroxyisopentenyl)-2,4,2′,4′-tetrahydroxychalcone with -7.19 kcal/mol, 8-hydroxyethyl-7,2′,4′-trihydroxyflavone with -7.16, 4'-hydroxy-8,3'- dimethoxy-6-acroleinylflavan-3,4-diol with -7.11 kcal/mol, 1-(4'-methoxyphenyl)-aziridine with -6.39 kcal/mol, 2-(2, 4-Dihydroxy-phenyl)-3, 6, 8-trihydroxy-chromen-4-one with -6.24 kcal/mol and Crotoncaudatin with -5.91 kcal/mol.

The interactions were stronger (energetically lesser) for 3 out of 9 compounds which are used for docking simulation. Figure 1-3 shows the crucial interaction between best 3 compounds (compound 9, 3 and 4) with DEK.

Analysis of ligand binding interaction with the DEK oncoprotein can be useful for new preventive and therapeutic drug for cancer. The results obtained from this study would be useful in both understanding the inhibitory mode as well as in rapidly and accurately predicting the activities of new inhibitors on the basis of docking scores.

Validation of ligands by QSAR studies

QSAR techniques are widely used in lead optimization-like processes[22]. In the present study, QSAR studies were performed using FAF Drugs: ADME/Tox filtering server for the determination of the inhibitor's molecular properties such as LogP (partition coefficient), TPSA (topological polar surface area), Molecular weight, hydrogen bong acceptors and donors.

Several physicochemical properties of drug molecules such as aqueous solubility, partition coefficient, distribution coefficient (logD), ionization constant (pKa), topological polar surface area, etc., play an important role and undesirable physicochemical properties point to the potentially undesirable pharmacokinetic behaviour[23].

TPSA, captured as the Vander Waals surface area of all nitrogen and oxygen atoms and their attached hydrogen atoms, was considered as an indicator for number of HB donors and acceptors. These descriptors neither describe the strength of the hydrogen bond nor accounts for the possibility of internal hydrogen bonds[24].

Calculated molecular properties and docking scores of all the compounds were shown in Table 3. The results show that the Lipinski's rule[25] is respected for all the compounds and that these molecules are accepted to be orally bioavailable.

(-)-N-methylguattescidine which is an alkaloid found in the bark of Fissistigma latifolium, when analyzed showed a docking energy of -8.65 kcal/mol and very low TPSA value of 59.00. Thus with the least binding energy, least TPSA and LogP at all ensures this ligand to be a good drug that can act in an effective way against the DEK protein.

CONCLUSION

In this study, the molecular docking was applied to explore the binding mechanism and to correlate its docking score with the activity of plant derived compounds.

The results of our present study can be useful for the design and development of novel compounds having better inhibitory activity against several type of cancer. These potential drug candidates can further be validated in wet lab studies for its proper function.

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