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Molecular Docking Analysis for the Compounds of *Ziziphus jujuba* – An Indian Medicinal Plant

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A B S T R A C T

Molecular docking plays a major role in drug discovery. Right from the past, docking studies among the particular compound against particular disease served as a pool proof in the medical field to struggle against the many dread full diseases. The compounds identified from many natural resources played a predominant role in treating the human disorders at the earliest. In such a way, *Ziziphus jujuba* – an Indian medicinal plant was analyzed briefly at the molecular level to find out the active biological compound against the most predominant cause of cancer. Thus, the compounds identified from different solvent extracts were exposed in this present study. Twenty-seven compounds identified from different solvent extracts were docked against Human Cyclin Dependent Kinase II. This study concluded that, among all those different compounds, only three compounds like Stigmast-5-en-3-ol, Campesterol and Eicosanoic acid showed better binding activity against human cyclin dependent kinase II when compared to all other compounds. Thus, the present investigation revealed an understandable knowledge about the compounds present in *Ziziphus jujuba* for the future research work.

***Key words*:** Molecular docking, *Ziziphus jujuba*, Binding affinity, Active compounds

As the technology was improved and modernized the analytical method named molecular docking was considered as a powerful tool for remodeling the compound as an effective drug for treating the human disorders. At the earlier stage, docking method was compared with the lock and key model projected by Fischer, as that in the same way the ligand binds with the docking receptor [1]. In the docking analysis the binding affinity and the scoring function plays a major role in determining the activity of the particular compound against the docking receptor [2]. Though lot of development was discovered among the medical field the usage of natural compound obtained from the Indian medicinal plants were become a leading source in treating various diseases. Even though, more medicinal plants were available in our day-to-day life, studying about the phytochemical compounds along with its effective pharmacological properties were not properly retrieved. Among different medicinal plants, *Ziziphus jujuba* – an Indian medicinal plant plays a multipurpose role in curing many ailments.

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Ziziphus jujuba belongs to the family of Rhamnaceae and scattered around the subtropical regions throughout the world. Each and every part of this plant served as an excellent source of medicine for treating the human disorders [3]. The fruits and seeds of this species possess numerous pharmacological properties and the dried powder of its seed was used as a component of folk medicine in eastern part of Asia [4]. The seeds of this fruit were mainly used in the treatment of insomnia and also used as a tremendous sleeping dosage by the Chinese people for the past 200 years [5-6]. On account of its medicinal properties, the compounds were identified from the leaves, fruits and seeds of this particular species and allowed for molecular docking against the human cyclin dependent kinase II in this present study. Thus, the present research work was focused on establishing the biologically active phytochemical compounds from the Indian medicinal plant.

MATERIALS AND METHODS

Target selection

The X-ray Crystal Structure of Human cyclin dependent kinase 2 was selected as target protein and retrieved from Protein Databank. Using PyRx, the protein in PDB format was converted into PDBQT file and used for further Docking studies.

Ligand selection

The 2D structures of all the 27 phytochemical compounds of *Ziziphus jujuba* plant were sketched by using ACD Chemsketch and saved in mol format. The mol files are converted into 3D structures and saved as PDBQT format, which includes atomic partial charges by using Open Babel tool.

Binding site prediction

The amino acid residues in binding site of human cyclin dependent kinase 2 protein is defined by using the reference Ligand of human cyclin dependent kinase 2 complexed with the cdk4 inhibitor. The binding site of natural ligand in the receptor proteins were considered as grid points and the grid is constructed around the binding pocket in autodock vina using PyRx. This grid configuration is used for further docking studies.

Virtual screening

In PyRx, the ligands and grid values with accurate grit size and position were used in docking. The probability of performing local search on an individual in the population was set to 0.06. Unbound target and unbound ligands were both treated as rigid.

Prediction of ligand- receptor interactions

The interactions between the plant compounds and the receptors as docked complex were analyzed in terms of binding affinity (Kcal/mol) and their interactions were visualized by using Ligand interactions module in Discovery studio V2.5.

RESULTS AND DISCUSSION

Effective phytochemical compounds from all the three samples of *Z. jujube* like seeds, fruits and seeds were identified using different parameters and 27 common compounds present in all the parts of *Z. jujube* were taken for further investigation. Thus, the common compounds were analyzed using bioinformatics tools to find out its molecular interaction and its docking affinity towards the Human Cyclin dependent kinase which is mainly involved in regulation of cell cycle (Table 1). The Cyclin-dependent kinases are mainly involved in controlling the cell cycle. Thus, the protein structure of Human cyclin dependent kinase 2 complexed with the cdk4 inhibitor (PDB ID: 1GII) (Figure 1) was retrieved from Protein Databank and used as receptor for further docking studies. The 27 Phytochemical compounds extracted from *Z. jujube* were used as ligand to explore their anticancer activities while estimating their binding affinities against the CDK2 protein through virtual screening.

Table 1 List of phytochemical compounds and their docking scores

S. No.	Phytochemical compounds	Binding energy (kcal/mol)
1.	1-hexacosanol	-8.2
2.	1-tetradecanol	-7.5
3.	2_3h_-furanone	-4
4.	5.2_5-furandione	-4.5
5.	2-furancarboxaldehyde	-4.1
6.	2-pyrrolidinone_	-4.2
7.	4-methyl_itaconate	-4.9
8.	5-acetoxymethyl-2-furaldehyde	-5
9.	7_9-di-tert-butyl-1-oxaspiro_4_5_deca-6_9-diene-2_8-dione	-7.1
10.	9_12-octadecadienoic_acid_	-7.9
11.	Azelaic_acid	-6.8
12.	Behenic_alcohol	-8.2
13.	Campesterol	-9.5
14.	Docosane	-8.2
15.	Dodecanoic_acid	-7.3
16.	Eicosanoic_acid	-8.4
17.	Heptadecanoic_acid_	-8
18.	Hexadecanoic_acid	-7.9
19.	Hexatriacontane	-8.1
20.	Methyl_stearate	-8.1
21.	Octadecanoic_acid	-8.2
22.	Oleic_acid	-6.9
23.	Palmitoleic_acid	-8
24.	Pentadecanoic_acid	-7.8
25.	Stigmast-5-en-3-ol	-11.3
26.	Tetracosane	-8.2
27.	Tetradecanoic_acid	-7.7

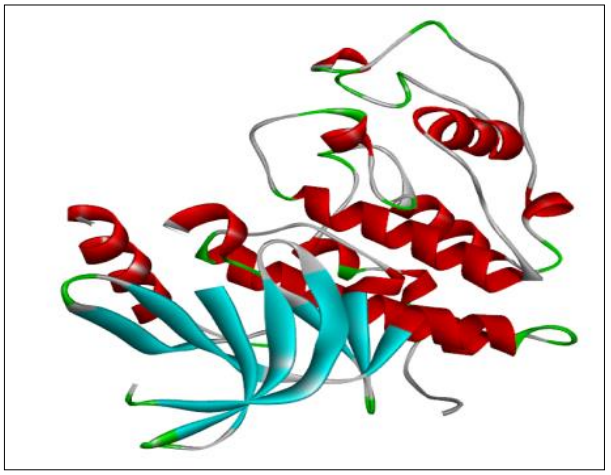

Fig 1 The X-ray crystal structure of human cyclin dependent kinase 2 (PDB ID: 1GII)

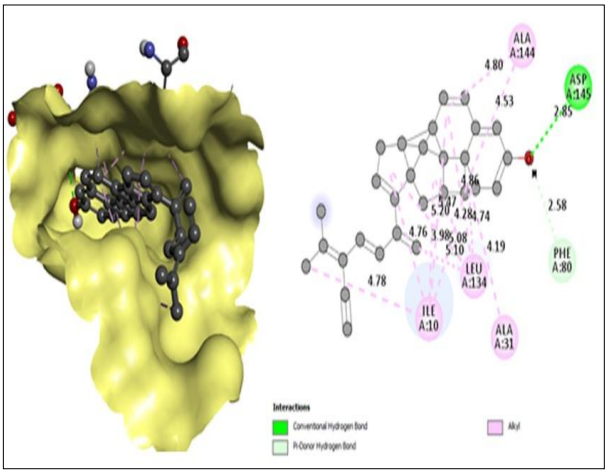

Fig 2 Docking complex and interaction of CDK-2 and Stigmast-5-en-3-ol (Binding affinity: -11.3 kcal/mol)

It is observed that all the 27 compounds exhibited theoretically encouraging docking scores. However, it is observed that the compound Stigmast-5-en-3-ol showed relatively better binding affinity with the binding affinity of-11.3 kcal/mol. While, the compound 2-furancarboxaldehyde exhibited relatively poor binding affinity of -4.1 kcal/mol. The binding affinities among CDK2 and best three phytochemical compounds such as Stigmast-5-en-3-ol, Campesterol and Eicosanoic acid that exhibited higher binding affinities were discussed. While the remaining compounds binding affinities were shown in (Table 1). The docking interactions of Stigmast-5-en-3-ol are favoured by H bonds (Asp145 and Phe80) and alkyl type non-bonded interactions (Ile10, Ala31, Leu134 and Ala144) with binding affinity of -11. 3 kcal/mol) (Figure 2). The docking interactions of Campesterol is favoured by Phe80 (Pi-sigma), Pi-alkyl (Ile10, Val18, Ala31, Lys33, Val64, Leu134, Ala144) with binding affinity of (-9.5 kcal/mol) (Fig 3). The docking interactions of Eicosanoic_acid is favoured by Hbonds (Asp145 and Phe80) and no Non-bonded interactions with binding affinities of (-8.4 kcal/mol) (Fig 4).

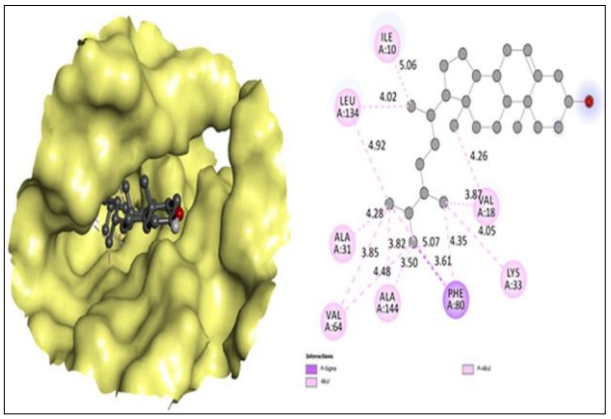

Fig 3 Docking complex and interaction of CDK-2 and Campesterol (Binding affinity: -9.5 kcal/mol)

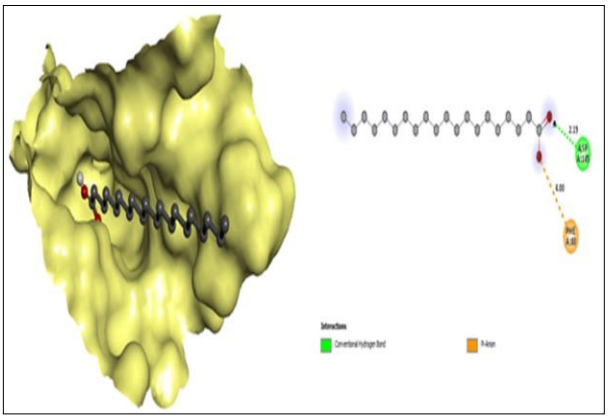

Fig 4 Docking complex and interaction of CDK-2 and Eicosanoic_acid (Binding affinity: -8.4 kcal/mol)

Nowadays, novel method called molecular docking plays a vital role in drug discovery [7]. The molecular docking is also known as Virtual Screening (VS) method from which most of the active Phytochemical compounds from the plant sources were screened with suitable docking receptor to establish the binding nature of the particular compound [8-10]. Right from the past, the Virtual Screening method was considered as cost effective and time-consuming method for the innovation of new drugs while comparing with the other experimental methods [11-13]. Thus, in the present study also the same Virtual Screening method was used to predict the docking score range for the compounds identified from *Z. jujuba.*

The molecular docking analysis was used to predict the interaction that takes place in between the small molecules and protein at molecular level which helps to characterize the nature of binding molecules with the target protein structure [14]. It was retrieved from the studies of Shaik and their coworkers that the compounds identified and docked from 97 plant species were found to have glycoside derivatives, Flavanoids and alkaloids with high docking score [15]. A recent report states that a compound named Berberine, a derivative of alkaloid was possessed to have potent inhibitory activity against docked compound with high docking score while comparing with all other compounds in the above study [16]. Thus, in the present study also it was clear that the compound docked with the docking receptor was a derivative of glycosides.

The fatty acid substances present in different herbal plant species may have a potent anticancer and anti-inflammatory activity. A recent survey states that the derivatives of fatty acids may also involve in the discovery of new drugs against life threatening disease like HIV, Tuberculosis, cancer and diabetes [17-18]. It was also

proved from the present research work that the fatty acid derivative called Eicosanoic acid may also possessed to have high docking score against Human Cyclin Dependent Kinase II. Thus, it was proved that the same compound was found to present in *Z. jujuba* species and also found to have high molecular activity against cancer cells.

The author named Khwaza from his research findings proved that the pentacyclic triterpenoid quantified from rosemary and olive was possessed to have several medicinal activities such as anti-inflammatory, anticancer, antioxidant and hepatoprotective activity [19]. The same compound and its derivatives like oleic acid were found to have potent antiviral activity against several viruses such as HIV, influenza and Hepatitis virus at the earlier stage [20]. Thus, the present docking analysis also proved that the same compound oleic acids were found to show moderate docking score against Human Cyclin Dependent Kinase II.

CONCLUSION

Thus, the docking studies implies that the conserved amino acids such as Aspartic Acid (D) and Phenyl alanine (F) in the binding pockets of CDK-2 are vital in posing the better binding interaction with these phytocompounds. These docking interactions also envisages that the =O (keto group) present in the compounds and -NH (amino group) on the amino acids favors the H-bond interactions. Hence these findings clearly picture that phytochemical compounds, Stigmast-5-en-3-ol, Campesterol and Eicosanoic_acid could significantly possess better anti-cancer activity and could be an alternative therapeutic agent to replace the drugs with severe side effects. However, this research also suggests that its worth to explore more number of Alkaloids and Flavonoids from the medicinal plants for their anti-cancer activity.

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