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Molecular Docking Evaluation of *Cedrus deodara* Secondary Metabolites as a Potent Anti-ovarian Cancer Agent

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Abstract

Objective: *According to the statistics for the year 2022 it was seen that cancer total cases is 14,61,427. After breast cancer, ovarian cancer is the second most frequent cancer among women. The estrogen receptor (PDB ID: 1X7E), progesterone receptor (PDB ID: 1A28), and Phosphoinositide 3-kinases (PDB ID: 4FJY) can be considered as target protein for ovarian cancer. The plant Cedrus deodara and its phytochemicals were chosen in this study to identify their pharmacological characteristics and the inhibitory effects against the target protein which is said to be involved in ovarian cancer. Infugem and Melphalan are FDA-approved ovarian cancer drugs. This drug is also chosen to compare the inhibitory effect of plant derivatives and the drugs.* ***Methods:*** *In this study, 30 phytochemicals were selected to know their binding affinity towards the protein targets.2 FDA-approved were also docked against all three target proteins. The target proteins were purified, and the missing residue was modeled using BIOVIA Discovery Studio then the protein structure analysis was also performed using PDBsum Generate. Using ADMETlab 2.0 pharmacological studies were performed.* ***Result:*** *The Oleanolic acid and 7beta-Hydroxydehydroabietic acid ligands showed the lowest binding affinity towards all three target proteins. By comparing the docking results of phytochemicals and FDA-approved drugs it is seen that the plant phytochemicals have the best binding affinity, and all the phytochemicals fulfill the criteria of ADMET analysis.* ***Conclusion:*** *According to the result observed from docking we can conclude that the ligands Oleanolic acid and 7beta-Hydroxydehydroabietic acid are showing inhibitory action against all three target proteins. Further In vitro study must be performed.*

Keywords: Molecular docking, ovarian cancer, progesterone receptor, phosphoinositide 3-kinases, *Cedrus deodara*, ADMET analysis

INTRODUCTION

India is recognized for its medicinal plants and for employing these herbs and spices to cure a variety of ailments. The phytochemicals found in these healing herbs and spices have been demonstrated to have a wide range of physiochemical effects, including anticancer, antibacterial, and many more. The prevalence of Ayurveda is ostensibly seen among dietary customs as well as in socially accepted medical procedures [1]. A new study has also determined the effectiveness of herbal remedies because they include antioxidant components that may slow the growth of cancer cells and increase apoptosis in a variety of malignancies, including ovarian cancer [2]. According to the Globocan 2018 Fact sheet, ovary cancer is the eighth most common disease worldwide and the third most prevalent cancer among Indian women, accounting for 3.44%

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(36170) of all cancer cases [3]. High-grade serous ovarian carcinoma, the most prevalent type of ovarian cancer, is formed from epithelial cells [1]. The effectiveness of the treatment in reducing cancer is inversely correlated with the significance of the target in the functioning of cancer cells. Hence, we have selected the progesterone receptor, estrogen receptor, and PI3K.

PI3K plays a crucial role in the control of the cell cycle and functions as an intermediary molecule in the signaling pathway. They are divided into PI3K class I, PI3K class II, and PI3K class III, respectively. They have been identified as a target for cancer, and numerous medications using the small molecule PI3K have been developed, and research on them is ongoing [4]. Estrogen receptor ligands have a significant impact on ovarian cancer. ER signaling is oncogenic because it promotes the growth and survival of cancer cells. The ERα and ERβ subtypes of the estrogen receptor exist. The ovarian cancer cell is seen to exhibit ERα. The nuclear receptors class includes the progesterone receptor (PR), a part of which specifically controls the activation and target genes in relation to hormonal stimuli. Positive chemotherapeutic response is associated with progesterone receptor expression [5].

Infugem and Melphalan are FDA-approved drugs that are used to treat ovarian cancer. Pancreatic cancer, non-small cell lung cancer, breast cancer, and ovarian cancer are all treated with the prescription drug Infugem. You can take Infugem separately or in combination with other drugs. The medication Infugem is a member of the antineoplastic, antimetabolite drug class [6]. Melphalan is also used to treat ovarian cancer. Alkeran is the brand name, and the drug name is Melphalan. This drug is used for the treatment of myeloma and ovarian epithelial cancer. This drug is orally administrated.

Numerous plant-derived treatments are widely used in current medicine. Many people are using these medicinal plants to treat a variety of ailments [7]. Ayurveda, Siddha, Unani, and other local medical traditions are just a few of the numerous medicinal systems in India that employ a range of herbs to treat a wide range of human diseases [8]. Screening phytochemicals from Indian Ayurvedic stores on ovarian tumor target proteins may be done successfully using methods focused on bioinformatics and cheminformatics [9]. Ayurvedic herbs like garlic, ginger, gooseberry, turmeric, saffron, periwinkle, and many more are used for the treatment of cancer [10].

Cedrus deodara is an 85-meter-tall conifer with extending branches, tough, black bark, and dimorphic leaflets that are 2–8 cm long and pointedly needle-like. Pinaceae species have distribution in the tropics and subtropics of *Cedrus*. Most of these genera are used for decoration or they are used as medicine as they have beneficial properties. Flowers blossom from September through October. In very well soil, these trees thrive. For the development of plants, higher humidity levels are advantageous. Young trees may be harmed by cold winds and frosts. Ingestion of *Cedrus deodara* has no harmful effects on the human body. The wood extract is carminative, diaphoretic, as well as antipyretic, but also utilized to cure gastric problems, rheumatism, piles, kidney stones, and pulmonary and bladder disorders, among other things. Bark extraction serves as an astringent and to heal fever, diarrhea, and dysentery. Several in vivo as well as *in vitro* pharmacological actions of *Cedrus deodara* have been observed. These plants have many components including anti-inflammatory, immunomodulatory, antispasmodic, anticancer, antiapoptotic, antibacterial, and more properties [11].

METHODS

Retrieval of Ligands

The Indian Medicinal Plants, Phytochemistry and Therapeutics 2.0 (IMPPAT 2.0) (*https://cb.imsc.res.in/imppat/*) online database was used to select the 30 ligands for the analysis. Further using PubChem, the canonical SMILES and PubChem CID were documented and the ligands were downloaded in SDF format (*https://pubchem.ncbi.nlm.nih.gov/*).

Retrieval of Proteins

The three-dimensional structural information of major macromolecules like protein as well as nucleic acid is stored in a database which is Protein Data Bank (*https://www.rcsb.org/*). The three-dimensional structure of phosphoinositide3-kinases (PDB ID:4FJY), estrogen receptor (PDB ID:1X7E), and progesterone receptor (PDB ID:1A28) was downloaded using the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) in .pdb format.

Purification of Proteins

The missing residue was modeled using BIOVIA Discovery Studio software. The protein was purified using BIOVIA Discovery Studio software and heteroatoms, ligand group, and water molecules were eliminated by only retaining A chain, and a polar hydrogen atom was added to the purified protein. The purified protein structure was further saved as .pdb files and used to obtain Ramachandran plot and secondary structure of a protein using PDBsum Generate (*http://www.ebi.ac.uk/thornton-srv/databases/pdbsum/Generate.html*). The hydrophobicity chart was obtained using BIOVIA Discovery Studio software.

Molecular Docking

The PyRx software assumes the protein is a macromolecule by adding Kollman charges and assigning every atom as AutoDock4 type. Using the Molecular docking engine of the PyRx program, the 30 screened ligands were molecularly docked. Ligands were subjected to energy minimization by the application of a universal force field and the torsions of the ligands were detected. The following grids were generated for each target protein 1A28 center (X: 29.8219, Y: 8.3553, and Z: 67.7776) and dimensions (X: 54.2057Å, Y: 49.4344Å and Z: 50.0111Å), 1X7E centers (X: 24.5074, Y: 20.2783 and Z: 12.6599) and dimensions (X:44.6301Å, Y: 48.9986Å and Z: 57.5595Å) and 4FJY centers (X: 35.3436, Y: 0.1978 and Z: 26.8481) and dimensions (X: 90.6616Å, Y: 81.7223Å and Z: 97.9709Å). The ligands and approved drug (Infugem and Melphalan) were docked with the target proteins and the docking interactions were estimated based on the binding affinity. The 30 ligands and approved drug were docked against the target protein 1A28,1X7E and 4FJY. The degree of binding is evaluated based on the binding affinity. The least binding affinity indicates the best docking confirmations and therefore the top 3 ligands were selected and docked ligand was saved in .pdb format and interaction was visualized in BIOVIA Discovery Studio.

Visualization

The docked structure was saved as .pdb files and it was used to visualize the interaction using the BIOVIA Discovery Studio software. The two-dimensional, three-dimensional structure and non-bond interaction were evaluated.

Pharmacological Studies

Using ADMETlab 2.0 pharmacological properties like lipophilicity, saturation, insolubility, flexibility, size, polarity, and toxicity parameters of ligands were evaluated. The ligands that were common for all three target proteins and had the best binding affinity were further taken for the ADMET analysis which was performed using ADMETlab 2.0 (*https://admetmesh.scbdd.com/*) online server. Then the ligand was evaluated based on Lipinski's Rule of Five and a toxicity study was also performed.

RESULTS

Selection of Ligands

In total 30 *Cedrus deodara* derivatives were chosen from the IMPPAT and they were docked against the target proteins. Based on the docking result, the top 13 ligands were common on all the proteins as listed in Table 1 and had the best binding affinity against all three proteins. Infugem and Melphalan are FDA-approved drugs for the treatment of ovarian cancer the structure of the two drugs was also retrieved from the PubChem database.

Ramachandra Plot Statistics

The Ramachandran plot was produced for all the 3 proteins 1A28,1X7E and 4FJY using the online tool PDBsum Generate as shown in Figure 1(a), Figure 2(a), and Figure 3(c), respectively.

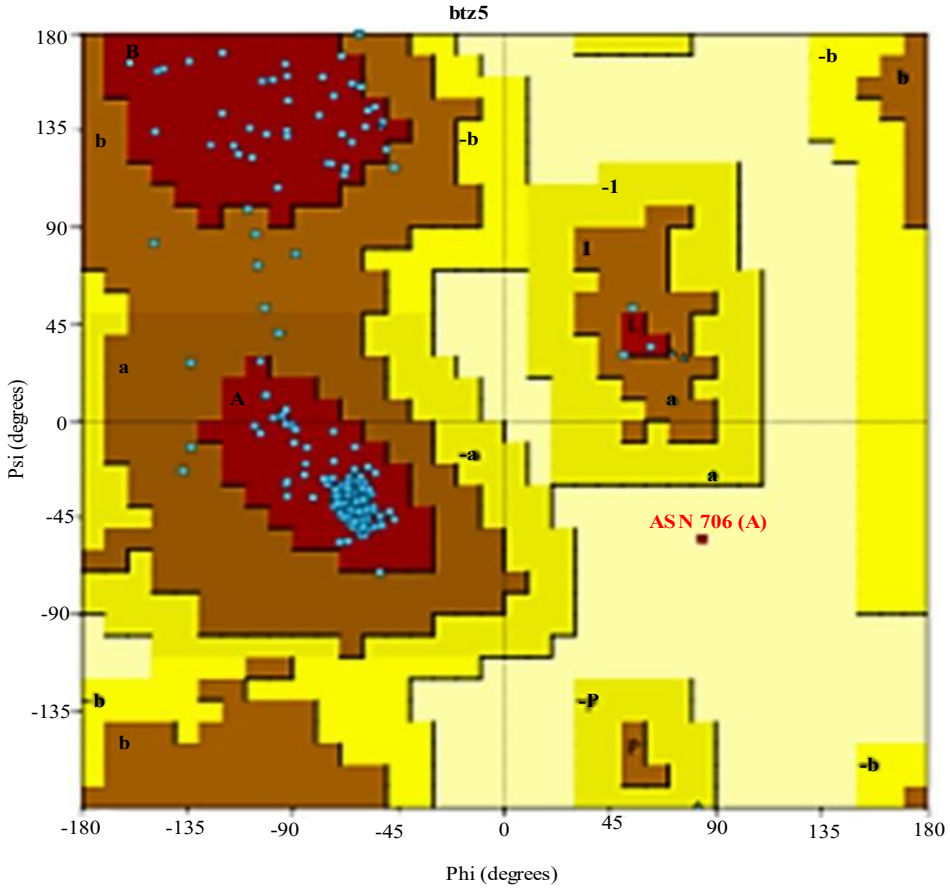
- *1A28:* According to the Ramachandran plot, the 3D structure of protein 1A28 has 93.4% of its residue in the favored region, 6.1% in the additional allowed region, 0.0% in the generally allowed region, and 0.4% in the disallowed region.
- *1X7E:* The 3D structure of protein 1X7E has its residue 85.8% in the favored region,11.1% in the additional allowed region,0.9% in the generally allowed region, and 2.2% in the disallowed region according to the Ramachandran plot.
- *4FJY:* The 3D structure of 4FJY has 91.6% in the favored region of the Ramachandran plot, 8.4% in the additional region, 0.0% in the generally allowed region and 0.0% in the disallowed region according to the Ramachandran plot statistics.

These statistical findings confirm that the 3D structures that were modeled are high-quality models.

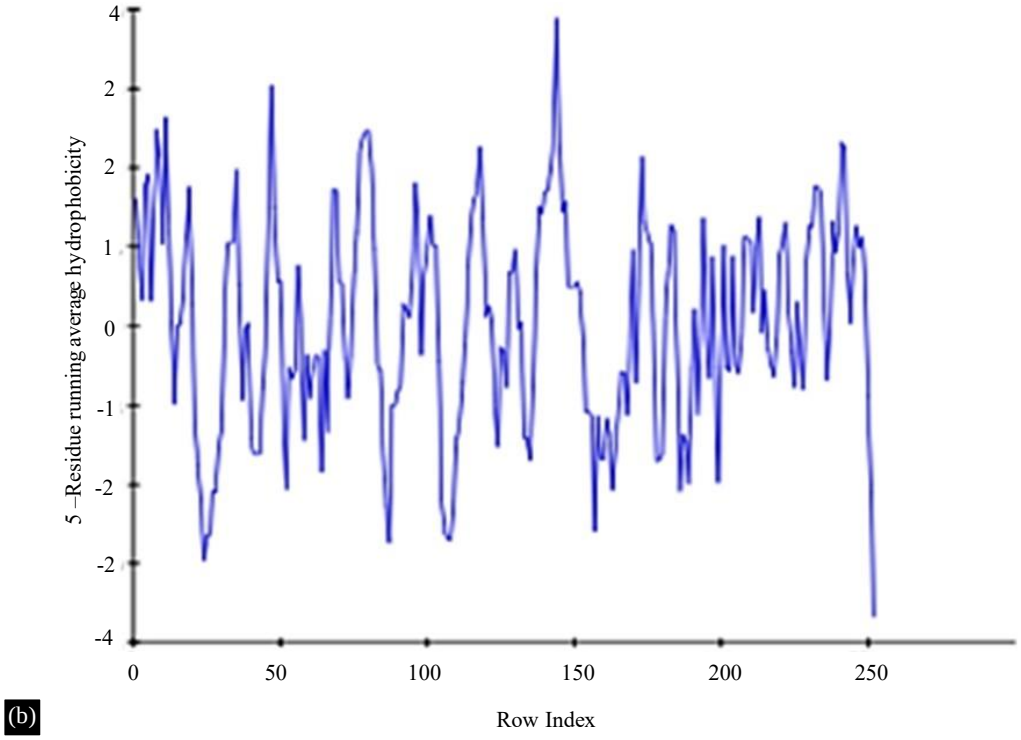
Secondary Structure

PDBsum was utilized to examine the secondary structure of the 3 chosen proteins, namely, 1A28,1X7E, and 4FJY as represented in Figure 1 (c), Figure 2 (c), and Figure 3(a), respectively.

- *1A28:* The PDBsum results for predicting protein secondary structure are it has a total of 252 residue, 2 sheets, 2 beta hairpins, 1 beta bulge, 11 helices, 21 helix-helix interaction, 9 beta turns, and 1 gamma turn.
- *1X7E:* However, the PDBsum data for 1X7E indicates it has 245 residues in total, 1 sheet, 1 beta-hairpin, 1 beta bulge, 2 strands, 10 helices, 20 helix-helix interaction, and 2 gamma turns.
- *4FJY:* The secondary structure prediction of protein is 6 sheets,11 beta hairpins, 10 beta bulges, 25 strands, 39 helices, 75 helix-helix interactions, 56 beta turns, and a total of 903 residues.



(a)



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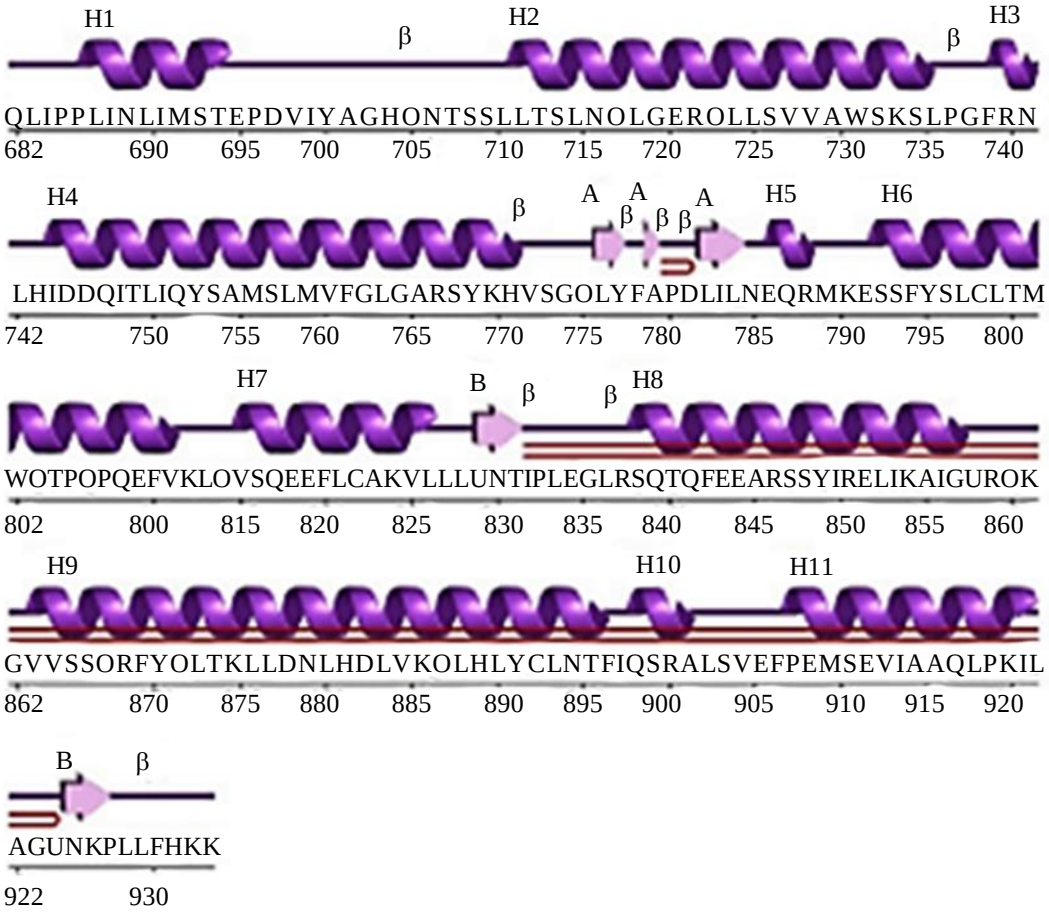
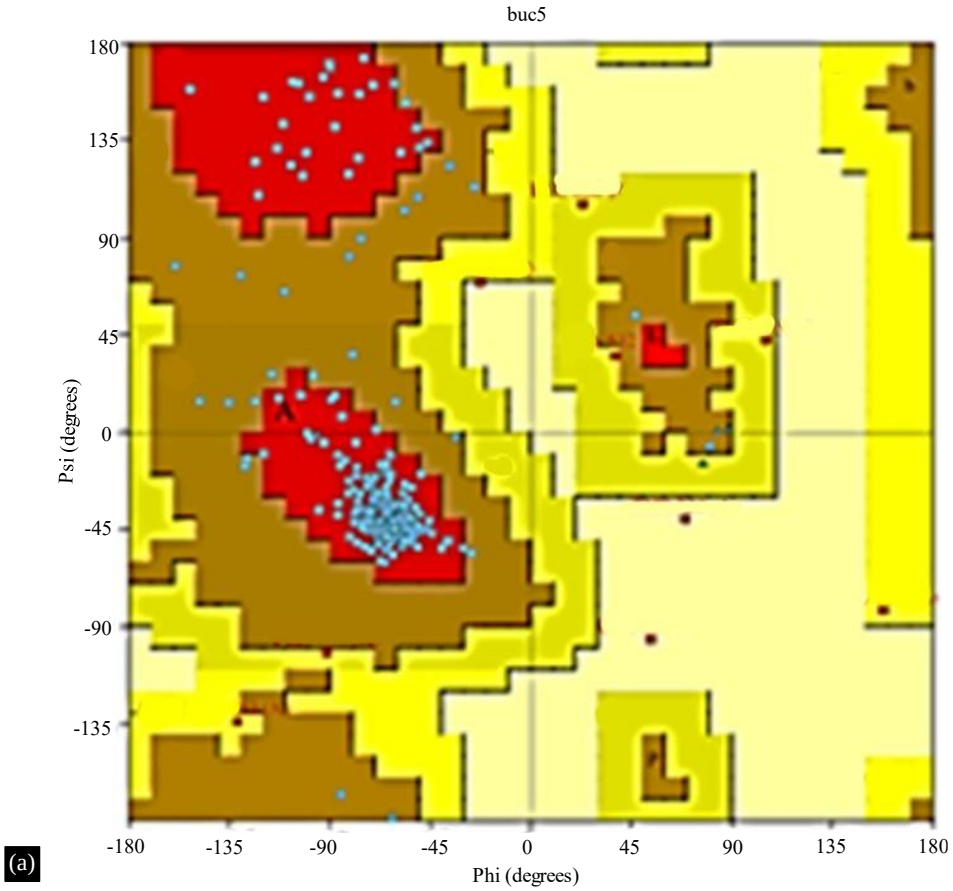
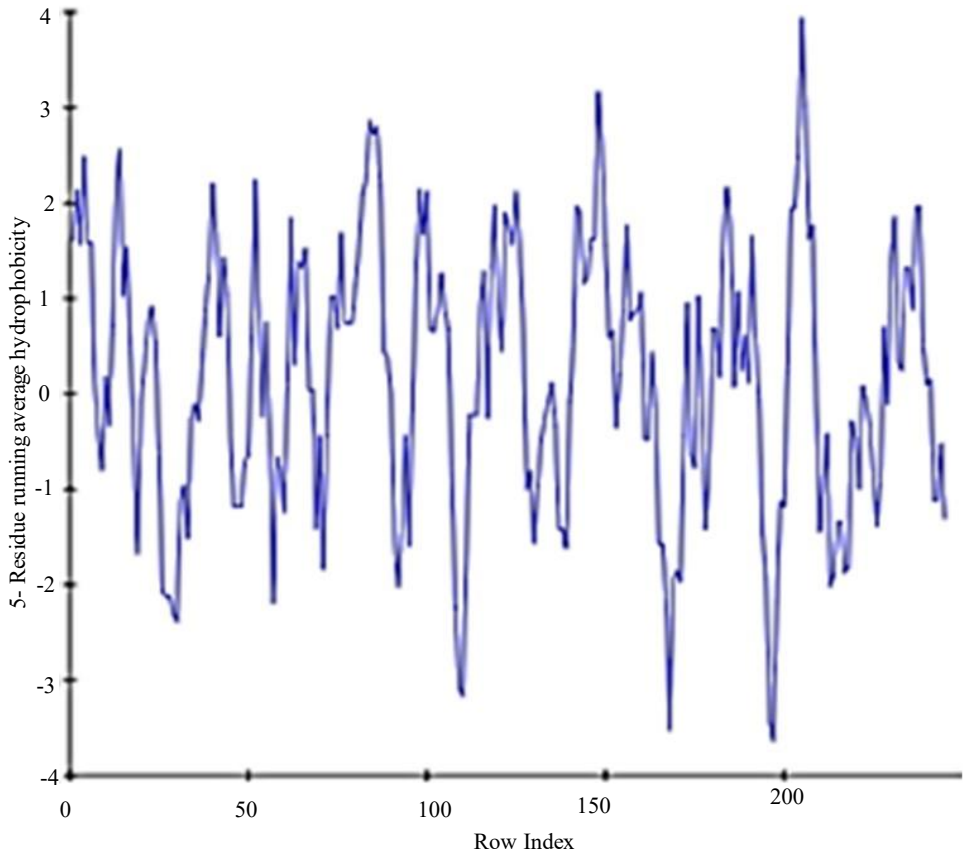


(c)

Figure 1. Structural analysis of progesterone receptor (PDB ID:1X7E) protein. (a) Ramachandran plot, (b) hydropathy plot, (c) secondary structure.



(a)



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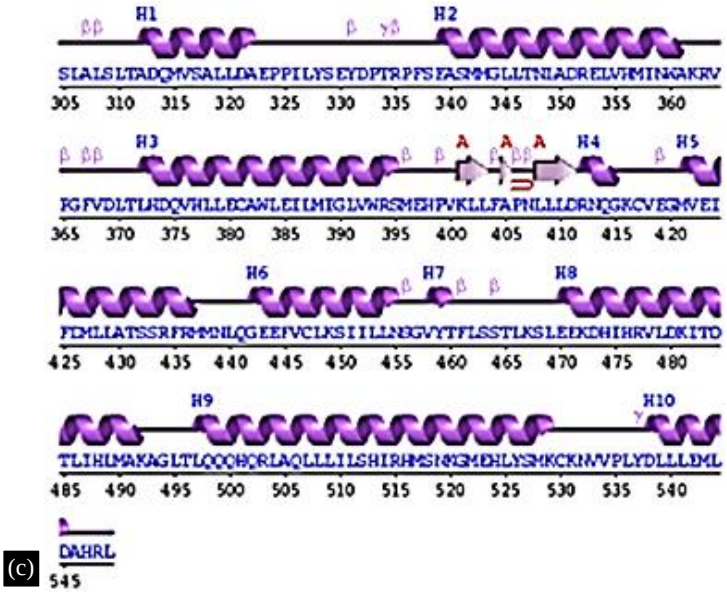
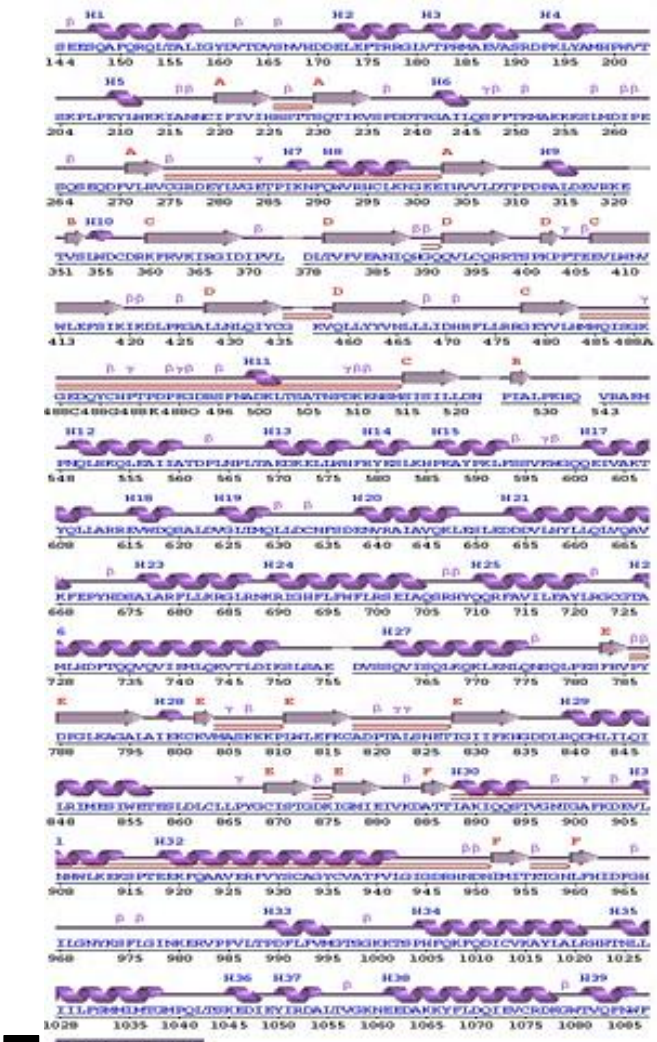
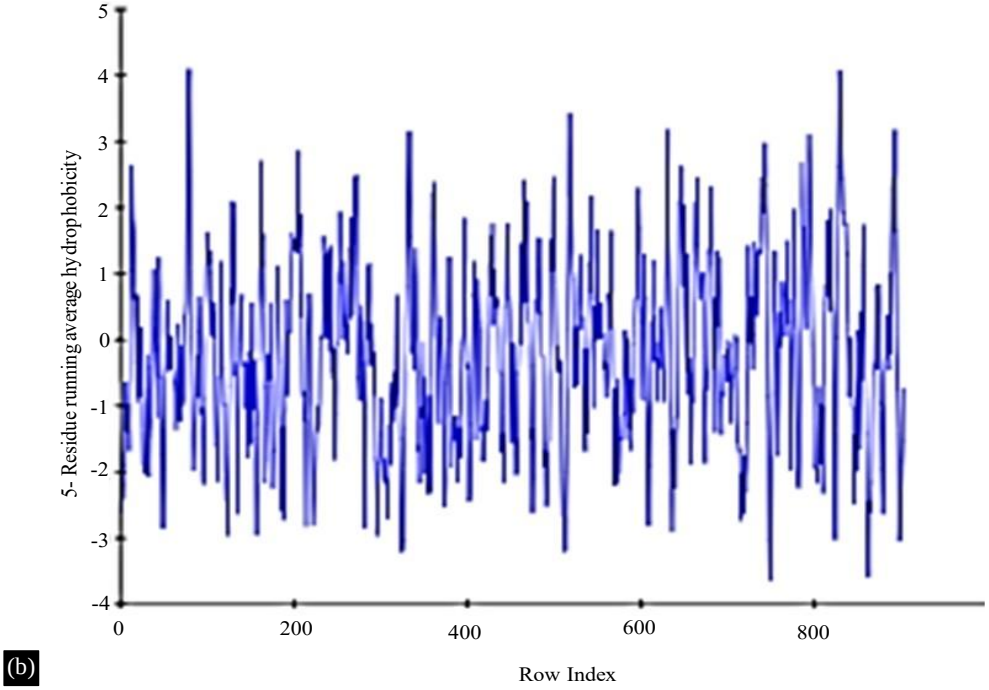


(c)

Figure 2. Structure analysis of estrogen receptor (1X7E) protein. (a) Ramachandran plot, (b) hydropathy plot, (c) secondary structure.



(a)



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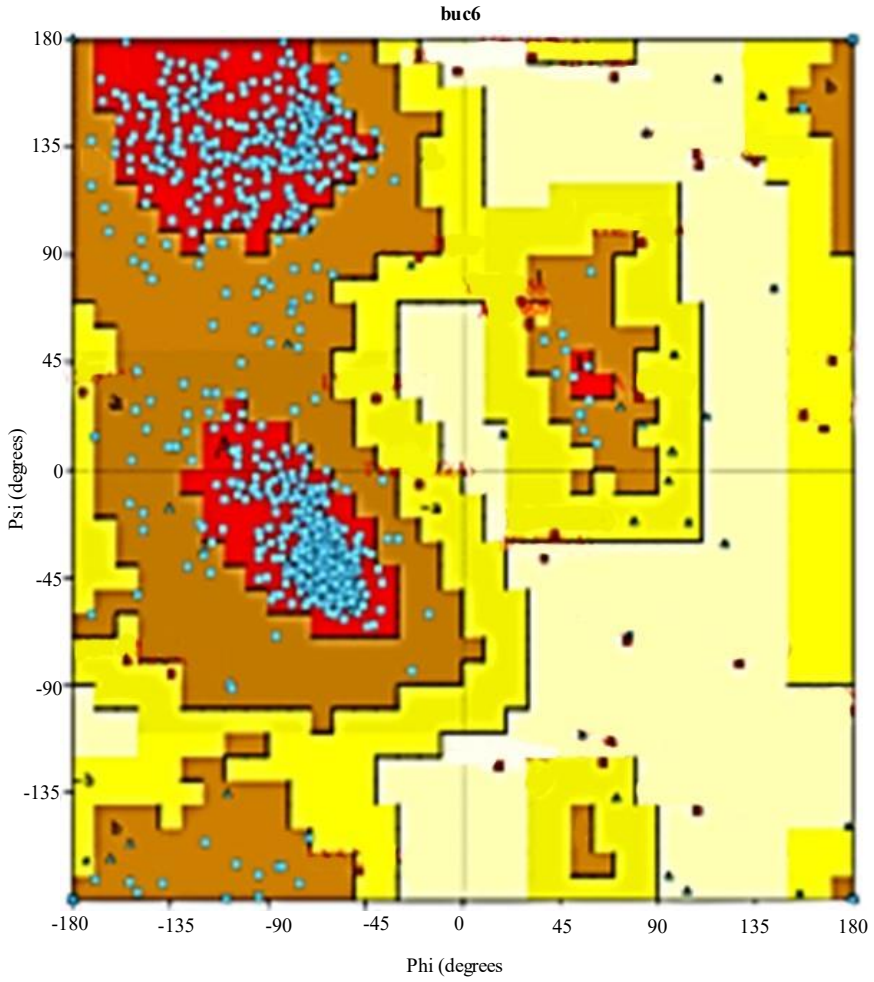


(c)

Figure 3. Structure analysis of PI3K(4FJY) protein. (a) Secondary structure, (b) hydropathy plot, (c) Ramachandran plot.

Hydropathy Plot

The BIOVIA Discovery Studio software was used to create the hydrophobicity plots of the target proteins 1A28,1X7E and 4FJY as shown in Figures 1(b), 2(b), and 3(b), respectively.

Molecular Docking

All the 30 ligands were docked using PyRx software against 3 protein targets 1A28, 4FJY, and 1X7E. Based on the docking result the ligands having the lowest binding affinity and Root Mean Square Deviation (RMSD) were selected as good docking angles for the ligands. Among 30 ligands, the top 13 ligands were selected which have the lowest binding affinity for each protein 1A28,1X7E and 4FJY. The docking was also performed between the approved drug against all 3-target proteins 1A28, 1X7E, and 4FJY. Binding affinity and the RMSD value of these 2 drugs were also documented as shown in Table 1.

Table 1. The binding affinity of *Cedrus deodara* derivatives towards the target proteins.

ligands	**Binding affinity**		
	1A28	***1X7E***	***4FJY***
10494	-15.8	-14.6	-16.3
13370052	-11.9	-12.5	-13.1
643004	-9.1	-7.9	-8.0
439533	-9.0	-7.8	-8.5
5280343	-9.0	-7.8	-8.6
131852604	-9.0	-8.3	-9.1
182026	-8.7	-7.5	-8.9
14657303	-8.1	-9.0	-7.6
932	-7.9	-8.6	-8.5
11830551	-7.6	-8.8	-8.5
577062	-7.6	-8.7	-7.5
13855300	-7.3	-8.1	-7.8
14187089	-7.1	-7.2	-9.1
FDA-approved drug			
Infugem	-6.3	-7.8	-4.4
Melphalan	-6.6	-5.8	-10.5

Visualization

Using Dassault Systems BIOVIA Discovery Studio Visualizer, the chosen ligands were visualized, and three-dimensional models were generated. Additionally, data on the type and category of interactions, as well as the bonding distance for the relevant amino acid residues in the ligand, were also recorded as shown in Figures 4, 5, and 6.

ADMET Analysis

The top 13 ligands namely oleanolic acid (PubChem CID: 10494), 7beta-hydroxydehydroabietic acid (PubChem CID: 13370052), 15-hydroxyabieta-7,13-dien-18-oic acid (PubChem CID: 643004), taxifolin (PubChem CID: 439533), deodarin (PubChem CID: 131852604), naringetol (PubChem CID: 932), (-)-alpha-himachalene (PubChem CID: 11830551), gamma-himachalane (PubChem CID: 577062), himasecolone (PubChem CID: 13855300) and taxifolin 3'-glucoside (PubChem CID: 14187089) were subjected for screening for their physicochemical property, medicinal property, Absorption, Distribution and Toxicity through ADMETlab 2.0 tool as shown in the following Table 2,3,4,5,6 and 7.

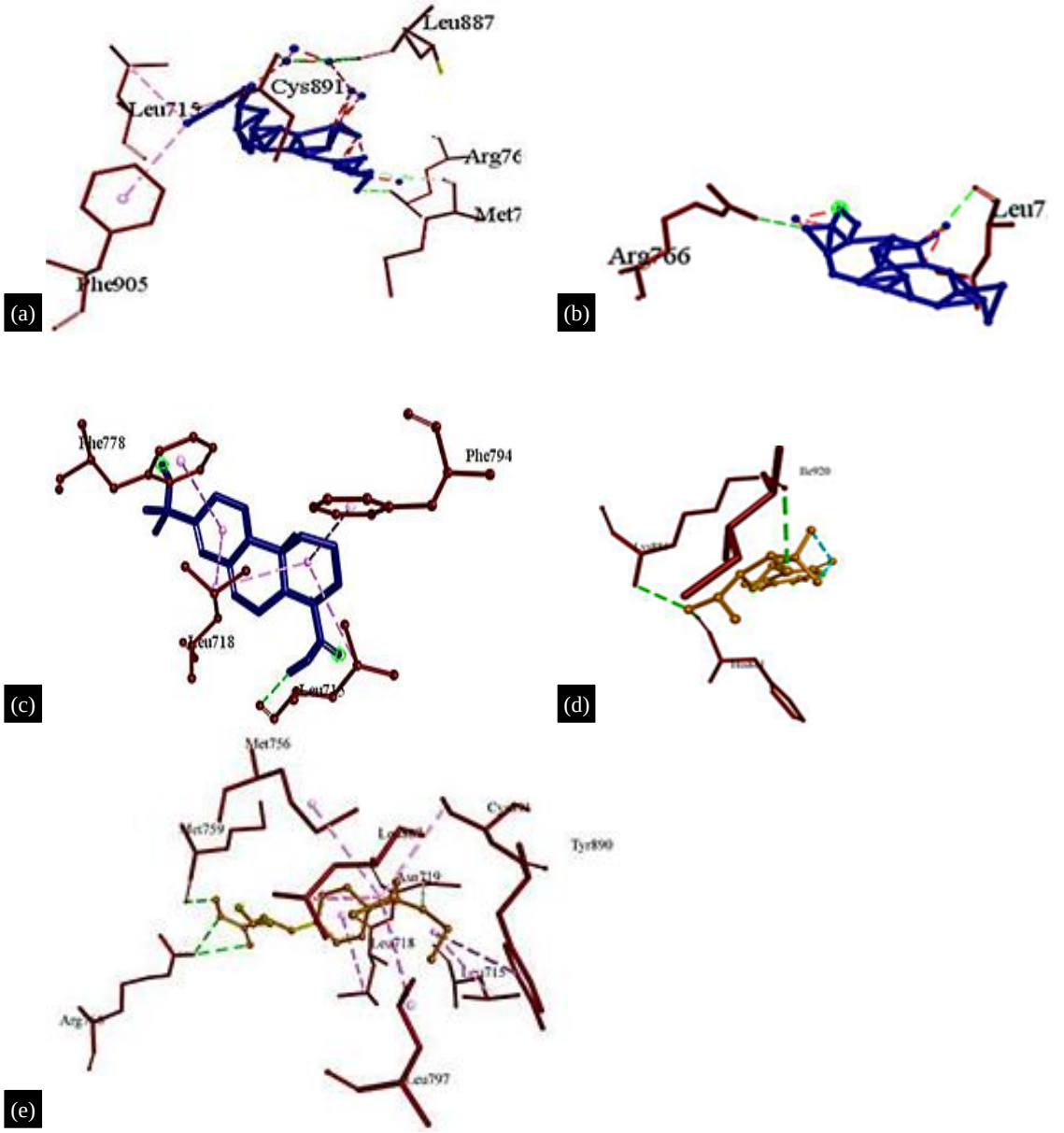
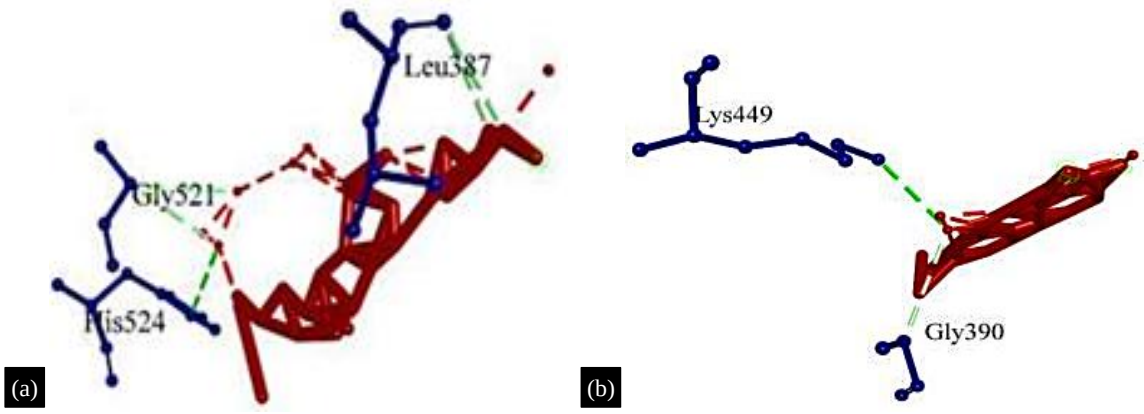


Figure 4. 3D interactions of top ligands with progesterone receptor (PDB ID:1A28). (a) Oleanolic acid, (b) 7beta-hydroxydehydroabietic acid, (c) 15-hydroxyabieta-7,13-dien-18-oic acid, (d) Infugem, (e) Melphalan.



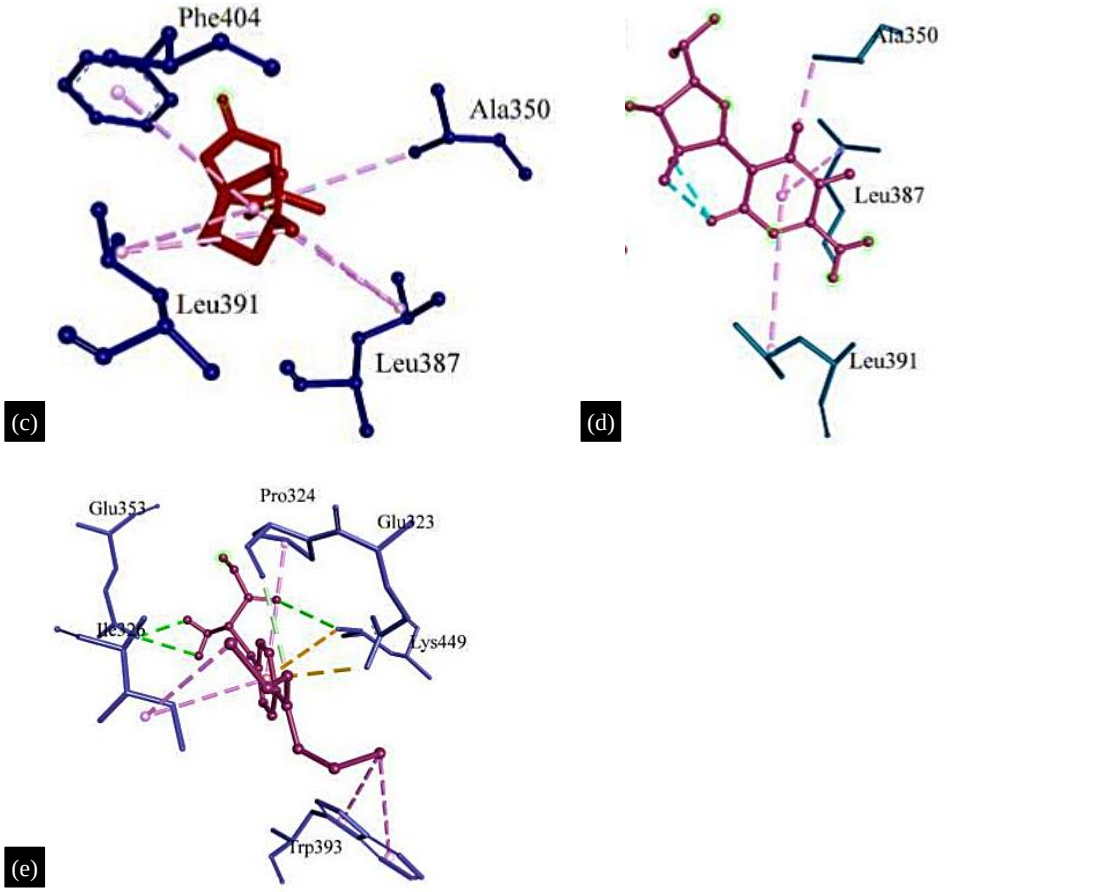
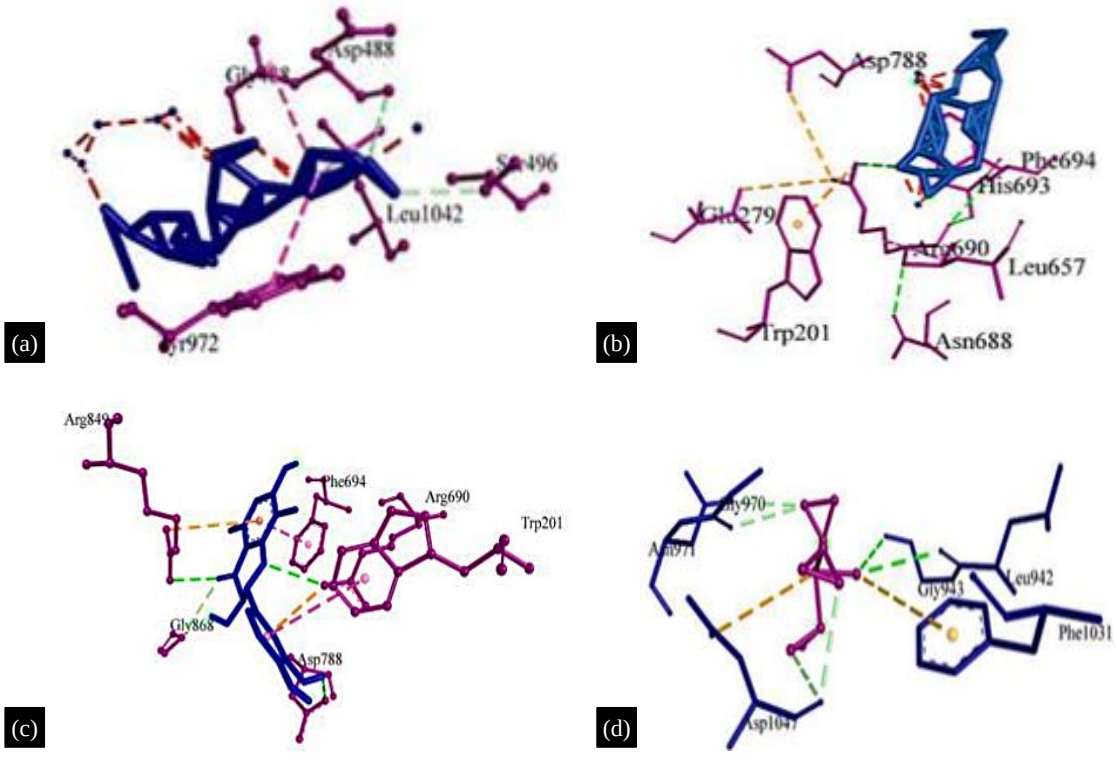
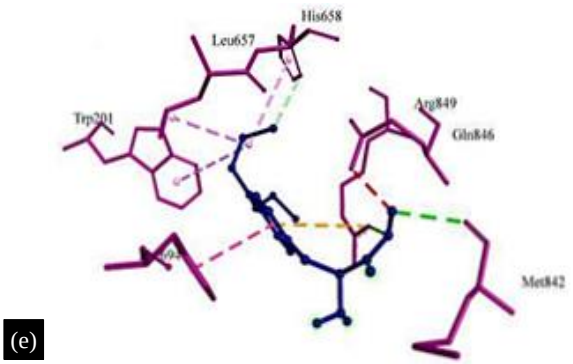


Figure 5. 3D interactions of top ligands interacting with estrogen receptor (PDB ID: 1X7E). (a) Oleanolic acid, (b) 7beta-hydroxydehydroabietic acid, (c) deodarone, (d) Infugem, (e) Melphalan.





(e)

Figure 6. 3D interactions of top ligands interacting with phosphoinositide3-kinases (PDB ID:4FJY). (a) Oleanolic acid, (b) 7beta-Hydroxydehydroabietic acid, (c) deodarin, (d) Infugem, (e) Melphalan.

Table 2. Physicochemical properties of the top *Cedrus deodara* derivatives.

Ligands	MW	Vol	nHA	nHD	nRot	nRing	nHet	fChar	Flex	TPSA	LogS
10494	456.36	505.755	3	2	1	5	3	0	0.037	57.53	-4.066
13370052	316.2	344.632	3	2	2	3	3	0	0.118	57.53	-4.019
643004	318.22	347.268	3	2	2	3	3	0	0.118	57.53	-3.778
439533	304.06	285.403	7	5	1	3	7	0	0,056	127.45	-2.662
5280343	302.04	282.767	7	5	1	3	7	0	0.056	131.36	-3.671
131852604	318.07	302.699	7	5	1	3	7	0	0.056	127.45	-2.945
182026	318.07	302.699	7	5	1	3	7	0	0.056	127.45	-3.496
14657303	236.18	263.191	2	0	1	6	2	0	0.077	26.30	–3.032
932	272.07	267.823	5	3	1	3	5	0	0.056	86.99	-3.876
11830551	204.19	245.61	0	0	0	2	0	0	0.000	0.000	-6.325
577062	204.19	245.61	0	0	0	2	0	0	0.000	0.000	-6.344
13855300	234.16	266.474	2	1	5	1	2	0	0.714	37.3	-3.623
14187089	466.11	424.574	12	8	4	4	12	0	0.167	206.6	-3.425

Table 3. Medicinal chemistry properties of the top *Cedrus deodara* derivatives.

Ligand	QED	Synth	Fsp3	PAINS	Lipinski
10494	0.409	4.589	0.900	0	accepted
13370052	0.850	3.837	0.650	0	accepted
643004	0.797	4.376	0.750	0	accepted
439533	0.501	3.546	0.133	1	accepted
5280343	0.434	2.545	0.000	1	accepted
131852604	0.505	3.717	0.188	1	accepted
182026	0.504	3.462	0.188	1	accepted
14657303	0.650	4.008	0.800	0	accepted
932	0.742	2.825	0.133	0	accepted
11830551	0.501	3.908	0.733	0	accepted
577062	0.501	3.910	0.733	0	accepted
13855300	0.842	2.296	0.533	0	accepted
14187089	0.256	4.344	0.381	1	rejected

Table 4. Absorption properties of the top *Cedrus deodara* derivatives.

Ligand	Caco-2	MDCK	Pgp-inh	Pgp-sub	HIA	F (20%)
10494	-5.300	1.20E-05	0.000	0.000	0.022	0.007

13370052	-4.796	2.24E-05	0.004	0.007	0.004	0.033
643004	-5.031	1.82E-05	0.023	0.000	0.009	0.007
439533	-6.055	4.00E-06	0.005	0.016	0.014	0.892
5280343	-5.204	7.69E-06	0.004	0.005	0.014	0.930
131852604	-5.433	4.18E-06	0.003	0.022	0.008	0.749
182026	-5.972	4.23E-06	0.003	0.001	0.046	0.035
14657303	-4.531	1.96E-05	0.341	0.000	0.005	0.130
932	-4.803	7.23E-06	0.007	0.001	0.018	0.972
11830551	-4.531	1.30E-05	0.321	0.000	0.003	0.812
577062	-4.445	1.13E-05	0.213	0.000	0.004	0.937
13855300	-4.700	1.88E-05	0.590	0.004	0.006	0.941
14187089	-6.541	1.25E-05	0.003	0.071	0.929	0.738

Table 5. Distribution properties of the top *Cedrus deodara* derivatives.

Ligand	BBB	PPB	VDss	Fu
10494	0.694	98.63%	0.896	3.48%
13370052	0.222	94.43%	0.347	6.20%
643004	0.206	93.88%	0.622	5.13%
439533	0.031	85.44%	0.681	15.91%
5280343	0.008	95.50%	0.579	7.42%
131852604	0.019	93.49%	0.555	7.90%
182026	0.021	97.01%	0.464	3.67%
14657303	0.970	86.20%	1.177	11.72%
932	0.042	93.76%	0.502	5.65%
11830551	0.732	95.63%	3.998	3.55%
577062	0.244	96.82%	6.174	2.77%
13855300	0.383	95.04%	1.982	5.70%
14187089	0.271	87.55%	0.588	18.66%

Table 6. Toxicity properties of the top *Cedrus deodara* derivatives.

Ligand	hERG	HHT	DILI	AMES	Carcinogenicity	Respiratory	IGC50	LC50
10494	0.001	0.269	0.007	0.025	0.037	0.969	5.073	5.991
13370052	0.009	0.095	0.023	0.018	0.055	0.573	4.336	4.641
643004	0.012	0.507	0.018	0.006	0.516	0.888	3.112	4.099
439533	0.070	0.176	0.943	0.544	0.039	0.296	4.116	5.581
5280343	0.099	0.100	0.98	0.657	0.050	0.072	4.231	5.222
131852604	0.093	0.187	0.948	0.541	0.043	0.272	4.252	5.832
182026	0.043	0.065	0.928	0.612	0.097	0.057	4.631	5.334
14657303	0.010	0.772	0.307	0.006	0.864	0.031	2.061	2.482
932	0.044	0.098	0.853	0.342	0.576	0.340	4.992	6.165
11830551	0.008	0.265	0.243	0.018	0.104	0.204	4.411	6.267
577062	0.011	0.548	0.129	0.013	0.139	0.177	3.931	5.75
13855300	0.025	0.048	0.035	0.019	0.060	0.196	4.173	4.308
14187089	0.012	0.11	0.956	0.662	0.122	0.019	4.218	5.362

hERG: The human ether-a-go-go related gene; *DILI:* Drug-induced liver injury; *AMES:* The Ames test for mutagenicity; *FDAMDD:* The maximum recommended daily dose, carcinogenicity, and LC_{50} were evaluated.

Table 7. Metabolism and excretion properties of the top *Cedrus deodara* derivatives.

Ligand	CYP1A2-inh	CYP1A2-sub	CYP3A4-inh	CYP3A4-sub	CL
10494	0.007	0.344	0.125	0.228	2.248
13370052	0.036	0.8700	0.053	0.464	0.788
643004	0.016	0.460	0.053	0.255	0.889
439533	0.044	0.101	0.140	0.249	9.517
5280343	0.943	0.115	0.348	0.046	8.284
131852604	0.050	0.121	0.088	0.290	8.529
182026	0.147	0.116	0.286	0.186	9.271
14657303	0.078	0.310	0.132	0.243	12.589
932	0.917	0.177	0.855	0.154	17.388
11830551	0.425	0.748	0.220	0.303	5.016
577062	0.408	0.625	0.272	0.278	9.190
13855300	0.520	0.940	0.158	0.376	6.891
14187089	0.021	0.033	0.274	0.070	2.634

DISCUSSION

A total of 14,61,427 cases of cancer are predicted in India in 2022. One in nine persons will acquire cancer, with breast cancer being the most common type in women and lung cancer in men. Even though cancer was not particularly common a century ago, it has been considerably more common in recent years, most likely as a result of our changing habits, lifestyle, and longer life expectancy [11]. Ovarian cancer is the second most common malignancy in women after breast cancer. Women's ovaries are their reproductive organs. The feminine hormones progesterone and estrogen are mainly produced by the ovaries. There are three forms of ovarian cancer. The outer surface of the ovary is damaged and covered by tumor cells in epithelial tumors and other types of ovarian cancer are germ cell tumors, and stromal tumors [12].

Certain malignancies may only respond to certain cancer therapies, such as targeted therapies and immunotherapies when have certain biomarkers. There are estrogen receptors that could be essential for treating ovarian cancer. In regular ovarian epithelium, the expression of ERβ receptor is higher than that of ERα, however, the proportion is switched in ovarian cancer therapy of ovarian cancer using estrogen-blocking drugs [13]. PI3K/AKT signaling pathway is often downregulated in tumors, it has now been identified as a key target for the treatment of cancer and it is observed that 12% of mutation occurs with mutation in PIK3CA. The activity toward PI3K and mTOR inhibitors is predicted by the PIK3CA mutations [14]. The nuclear receptors class includes the progesterone receptor (PR), a part of which specifically controls the activation and target genes in relation to hormonal stimuli. Positive chemotherapeutic response is associated with progesterone receptor expression [15].

Cedrus deodara is a medicinal plant, and its derivatives exhibit a wide range of physiochemical properties. *Cedrus deodara* is mostly utilized in Ayurveda medicine since it is non-toxic and has a wide range of therapeutic uses. As was already noted, *Cedrus deodara* offers numerous medicinal benefits, including anti-inflammatory, anti-malarial, antibacterial, and anticancer qualities. As it has been demonstrated that this plant can alter a variety of biological pathways, its anticancer properties have attracted attention. The fact that *C. deodara* is used as a supplement and has good nutritional value demonstrates its pharmacological safety. Numerous studies have established its safety and advantages [15].

In this study, 30 *C. deodara* derivatives were selected based on their pharmacological properties. The docking result of the protein-ligand showed that the ligands oleanolic, 7beta-hydroxy

dehydroabietic acid and 15-hydroxyabieta7,13 diene-18oic acid showed the lowest binding affinity toward the target protein 1A28. For the protein 1X7E, ligands oleanolic, 7beta-hydroxy dehydroabietic acid, and *C. deodara* show the least binding affinity and for the protein 4FJY the ligands oleanolic, 7beta-hydroxy dehydroabietic acid and deodarin shows the lowest binding affinity as shown in the Table 2. The ligand oleanolic, 7beta-hydroxy dehydroabietic acid shows the lowest binding affinity in all 3 target proteins. *In vitro* and *in vivo* studies of anticancer and anti-tumor cells are conducted for this compound. OA (Okadaic acid) methyl ester is a secondary metabolite that shows cytotoxic effects on the Hela cells. Oleanolic acid has many other physiochemical activities like anti-diabetic activity, anti-microbial activity, anti-hypertensive effect, anti-inflammatory potential, and anti-parasitic activity [16]. As for the ligand 7beta-hydroxy dehydroabietic acid it has been documented that it has anticancer and anti-plasmodial properties. *In vitro and In vivo* studies of this ligand against lung cells have been investigated. Both the ligands show the best inhibitory action against all three target proteins this has the potential to be used as a multi-target drug [17].

Infugem is a drug used for the treatment of ovarian cancer. Gemcitabine hydrochloride is the drug name of Infugem. It is an FDA-approved drug. It is also used to treat breast cancer, non-small lung cancer, and pancreatic cancer [18]. Melphalan is also used to treat ovarian cancer. Alkeran is the brand name, and the drug name is Melphalan. This drug is used for the treatment of myeloma and ovarian epithelial cancer. This drug is orally administrated [19]. This drug is docked with the target proteins 1A28,1X7E and 4FJY and the lowest binding affinity was documented as shown in Table 1. Further, this ligand was subjected to visualization. The interaction was visualized using BIOVIA Discovery Studio. The analysis of the top three ligands showed that docking with 1A28 revealed that Leu715 and Arg766 are the most common amino acids. Leu387 and His524 are the common amino acids seen in the protein 1X7E. For 4FJY, showed that Phe694, Arg690, Trp201, and Asp788 are the common amino acids. ADMET analysis for all the phytochemicals has been performed it was observed ligand Taxifolin 3'-glucoside (PubChem ID: 14187089) does not fulfill the Lipinski Rule of 5. ADMETlab 2.0 pharmacological studies were performed. The Oleanolic acid and 7-beta-Hydroxydehydroabietic acid ligands showed the lowest binding affinity towards all three target proteins. By comparing the docking results of phytochemicals and FDA-approved drugs, it is seen that the plant phytochemicals have the best binding affinity, and all the phytochemicals fulfill the criteria of ADMET analysis. According to the result observed from docking, we can conclude that the ligands oleanolic acid and 7beta-hydroxydehydroabietic acid show inhibitory action against all three target proteins. Further *In vitro* study must be performed.

CONCLUSION

Cedrus deodara is a medicinal plant and derivatives of this plant have many physiochemical properties. By docking the phytochemical of this plant against the target protein of ovarian cancer like phosphoinositide 3-kinases (4FJY), estrogen receptor (1X7E), and progesterone receptor (1A28). The result showed that the ligand oleanolic acid (10494) and 7beta-hydroxy dehydroabietic acid (13370052) both show the lowest binding affinity for all three target proteins 1A28 (-15.8), 1X7E (-14.6), 4FJY (-16.3) and 1A28 (-11.9), 1X7E (-12.5), 4FJY (-13.1), respectively. On the other hand, 15-hydroxyabieta7, 13 diene-18-oic acid (643004) has a binding affinity for protein 1A28(-9.1). Deodarone (14657303) has a good binding affinity for protein 1X7E (-9.0) and deodarin (131852604) has the best binding affinity for 4FJY(-9.1) as mentioned in Table 2. The docking of the target protein with approved market drugs (Infugem and Melphalan). The lowest binding affinity of Infugem for 1A28(-6.3),1X7E (-7.8) and 4FJY (-4.4). For Melphalan the lowest binding was 1A28(-6.6), 1X7E (-5.8) and 4FJY (-10.5). By comparing the binding affinity of the drug and the derivatives against all the 3 target proteins, we can conclude that *C. deodara* shows the best inhibitory action towards the protein target of ovarian cancer, and *in vitro* studies can be performed for further study of this compound.

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Abbreviations

ER	Estrogen receptor.
PI3K	Phosphoinositide 3-kinases.
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha. mTOR Mammalian target of rapamycin.
ADMET	Absorption, distribution, metabolism, excretion, and toxicity.

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