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MOLECULAR DOCKING STUDIES OF CANTHIN-6-ONE FROM *SIMAROUBA GLAUCA* AGAINST EGFR TYROSINE KINASE

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Keywords:

EGFR - tyrosine kinase, Binding energy, Docking studies, Canthin-6-one

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ABSTRACT: In recent years, *in silico* approaches have been predicting novel drug targets. The objective of this study was to analyze the inhibitory action of canthin-6-one alkaloid by computational docking studies. For this study, natural metabolite canthin-6-one isolated from *Simarouba glauca* was used as ligand for molecular interaction. The crystallographic structure of molecular target Epidermal Growth Factor Receptor (EGFR) tyrosine kinase was obtained from Protein Data Bank (PDB) database (PDB ID: 1M17). Gemcitabine, Cisplatin and Thiotepa were taken as the standard for comparative analysis. Computational docking analysis was performed by using online program PATCHDOCK. The canthin-6-one showed optimum binding affinity with a molecular target (EGFR - tyrosine kinase) with the binding energy of (-248.25) as compared to the standard drugs Gemcitabine (-188.48), Cisplatin (-45.26) and Thiotepa (-190.89). These results indicated that canthin-6-one could be one of the potential ligand to treat cancer. These potential drug candidates can further be validated in wet lab studies for its proper function.

INTRODUCTION: *Simarouba glauca* belongs to family Simaroubaceae, commonly known as "The Paradise Tree" or "King Oil Seed Tree" or "Laxmitaru Tree", is a versatile multipurpose evergreen tree having a height of 7-15 m with tap root system. It is a poly-gamo-dioecious tree and a potential source of biodiesel [1]. In India, it is mainly observed in Andhra Pradesh, Karnataka and Tamil Nadu etc. It can adapt a wide range of temperature, has the potentiality to produce 2000 - 2500 kg seed/ha/year [2] can grow well in marginal lands / wastelands with degraded soils [3] and therefore considered as a major forest tree [4].

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This plant is well known for its different types medicinal and pharmacological properties. The bark and leaf extract of *S. glauca* is well known for its different types of pharmacological properties such as haemostatic, antihelmentic, antiparasitic, antidysenteric, antipyretic and anticancerous [5]. The leaf, fruit, pulp and seed of *S. glauca* are known to possess medicinal properties such as analgesic, antimicrobial, antiviral, astringent, emmenagogue, stomachic, tonic and vermifuge [6].

J. F. Rivero-Cruz *et al.*, (2005) have demonstrated activity-guided fractionation of a chloroform-soluble extract of *Simarouba glauca* twigs collected from a plot in southern Florida afforded six canthin-6-one type alkaloid derivatives, canthin-6-one, 2- methoxycanthin- 6- one, 9-methoxycanthin-6-one, 2-hydroxycanthin-6-one, 4, 5- dimethoxycanthin- 6- one and 4, 5- dihydroxy-canthin-6-one [7].

Canthin-6-one was first isolated in 1952 by Haynes *et al.*, from Australian Pentaceras australis (Rutaceae) [8, 9]. Since then, more than forty members of this class of alkaloids have been reported from several plants primarily of the Rutaceae [9, 10] and Simaroubaceae [9, 7] families, but also from Malvaceae, [9] Amaranthaceae, [9] Caryophyllaceae, [9, 11] Zygophyllaceae, [12] and recently from fungi (Boletus curtisii Berk.) [13]. Several of these alkaloids have been bioassayed and show interesting pharmacological activities [9, 14, 15]. Canthin-6-one and some derivatives isolated from *Zanthoxylum chiloperone* var. *angustifolium* displayed interesting antifungal activities [16, 17].

Gemcitabine is a nucleoside analog used as chemotherapy. Gemcitabine is used in various carcinomas: non-small cell lung cancer, pancreatic cancer, bladder cancer and breast cancer [20]. Cisplatin is one of the most potent chemotherapy drugs widely used for cancer treatment [21]. N, N'N'-triethylenethiophosphoramide (Thio TEPA) is a cancer chemotherapeutic member of the alkylating agent group, now in use for over 50 years. It is a stable derivative of N, N', N''- triethylene-phosphoramide (TEPA). It is mostly used to treat breast cancer, ovarian cancer and bladder cancer [22].

Epidermal growth factor receptors (EGFRs) are a large family of receptor tyrosine kinases (TK) expressed in several types of cancer, including breast, lung, esophageal, and head and neck. EGFR and its family members are the major contributors of a complex signalling cascade that modulates growth, signalling, differentiation, adhesion, migration and survival of cancer cells. Due to their multidimensional role in the progression of cancer, EGFR and its family members have emerged as attractive candidates for anti-cancer therapy [18]. Specifically the aberrant activity of EGFR has shown to play a key role in the development and growth of tumour cells, where it is involved in numerous cellular responses including proliferation and apoptosis [19]. In this study, docking of target protein (EGFR tyrosine kinase) was carry out with compound canthin-6-one and to evaluate the compound docking and active site binding.

MATERIALS AND METHODS:

Preparation of Macromolecule: The three dimensional structure of epidermal growth factor receptor (EGFR) tyrosine kinase (PDB ID: 1M17) was downloaded from the RCSB protein Data Bank [23]. The hydrogen atoms were added to the target protein molecule after removing the water molecules for docking.

Selection and Preparation of Ligand Structure: Ligand, which interacts with protein's binding sites, is a small molecule. There are several possible mutual conformations in which binding may occur. These are commonly called binding modes [24]. The SDF file of canthin-6-one was obtained from PubChem database [25] and then converted to PDB file with the help of Open Babel [26] and the PDB file of standard drugs Gemcitabine, Cisplatin and Thiotepa was taken from DrugBank Database [33].

Analysis of Target Active Binding Sites: The enzyme epidermal growth factor receptor (EGFR) tyrosine kinase was retrieved from the RCSB Protein Data Bank with PDB ID: 1M17. Active sites of the enzyme were identified by CASTp [37] server. CASTp (Computed Atlas of Surface Topography of proteins) is used to verify the binding sites of a protein. It includes annotated functional information of specific residues on the protein structure [27].

Molecular Docking Analysis: A computational ligand-target docking approach was used to analyze structural complexes of the epidermal growth factor receptor (EGFR) tyrosine kinase with canthin-6-one and standard drugs in order to understand the structural basis of this protein target specificity. Finally, docking was carried out by online program PATCHDOCK [28, 34]. PATCHDOCK program serves to find different docking transformations which can yield good complementarity in its molecular shape based on molecular docking algorithm. The PDB format of both protein and alkaloid including standard drugs was sent to PATCHDOCK server for docking. The docked structure was further analyzed by using UCSF Chimera [36].

RESULT AND DISCUSSION: In this present study, the interactions between the epidermal growth factor receptor (EGFR) tyrosine kinase (target) with canthin-6-one and standard drugs (ligands) was studied to explore their binding

mode, docking study was performed using online program PATCHDOCK with UCSF Chimera. Epidermal growth factor receptor (EGFR) tyrosine kinase (PDB ID: 1M17) structure was derived from RCSB Protein Data Bank and used as a target for docking simulation. The details of canthin-6-one and standard drugs (Gemcitabine, Cisplatin and Thiotepa) are mentioned in **Table 1**. The 3D structure of protein and ligands was visualised by using Rasmol [35] as show in **Fig. 1** and **Fig. 2** respectively.

TABLE 1: PROPERTIES OF CANTHIN-6-ONE COMPOUND AND REFERENCE DRUGS

		Reference Drugs		
Name of the compound	**Canthin-6-one**	**Gemcitabine**	**Cisplatin**	**Thiotepa**
Alternative name	6H-Indolo(3,2,1-de)(1,5) naphthyridin-6-one	4-amino-1-[(2R,4R,5R)-3,3-difluoro-4-hydroxy-5-(hydroxymethyl)oxolan-2-yl]pyrimidin-2-one	Cis-Diaminedichloro-platinum	tris(aziridin-1-yl)-sulfanylidene-$l^{5}-phosphane
Molecular weight	220.231 g/mol	263.201 g/mol	298.03 g/mol	189.217 g/mol
Molecular formula	$C_{14}H_8N_2O$	$C_9H_{11}F_2N_3O_4$	$Cl_2H_4N_2Pt$	$C_6H_{12}N_3PS$
X LogP3	2.4	-1.5	.	0.5
Hydrogen Bond Donor Count	0	3	2	0
Hydrogen Bond Acceptor Count	2	6	2	4
Rotatable Bond Count	0	2	0	3
Exact Mass	220.064 g/mol	263.072 g/mol	296.94 g/mol	189.049 g/mol
Monoisotopic Mass	220.064 g/mol	263.072 g/mol	296.94 g/mol	189.049 g/mol
Heavy Atom Count	17	18	5	11

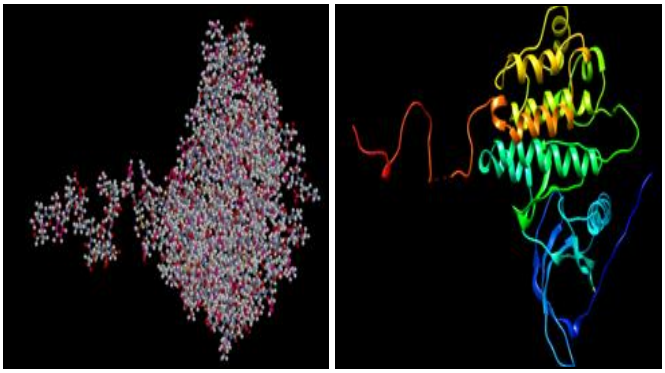
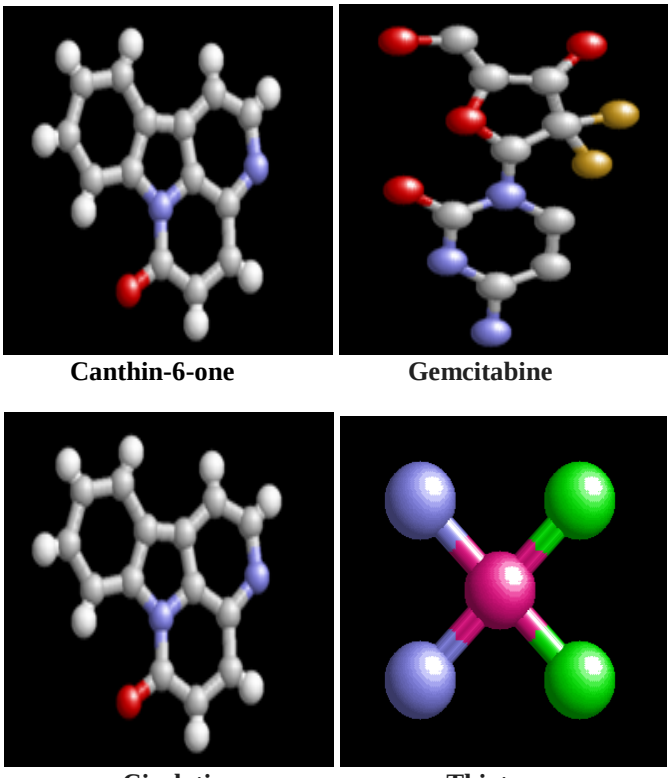


FIG. 1: RASMOL VIEW OF 3D STRUCTURE OF EGFR - TYROSINE KINASE

Binding Site of the Protein: The detection of ligand - binding sites is often the starting point for protein function identification and drug discovery. In our study, CASTp server predicted active site of our target protein - Epidermal growth factor receptor (EGFR) tyrosine kinase as shown in **Fig. 3**. The active sites of EGFR - tyrosine kinase protein comprises of amino acid residues are LEU694, GLY695, GLY697, ALA698, PHE699, VAL702, LYS704, ALA719, LYS721, GLU722, LEU723, LYS730, ALA731, LYS733, GLU734, ILE735, ASP737, GLU738, VAL741, MET742, CYS751, ARG752, LEU764, THR766, GLN767, LEU768, MET769, PRO770, GLY772, CYS773, ASP776, ARG812, ASP813, ARG817, LEU820, LYS828, THR830, ASP831, PHE832, GLY833, LEU834, ALA835, LYS836, ALA847, GLU848, GLY849, LYS851, VAL852.



Canthin-6-one **Gemcitabine**

Cisplatin **Thiotepa**

FIG. 2: RASMOL VIEW OF 3D STRUCTURE OF LIGANDS

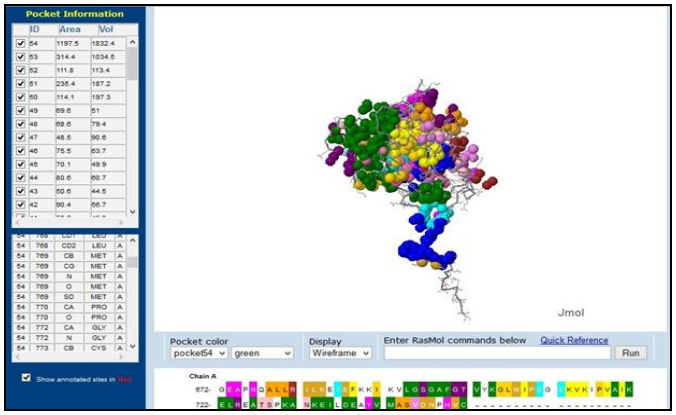


FIG. 3: ACTIVE SITES CAVITY OF EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) TYROSINE KINASE (1M17) FROM CASTP ONLINE SERVER

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 [29]. To study the binding mode of canthin-6-one in the binding site of epidermal growth factor receptor (EGFR) tyrosine kinase (target enzyme), docking studies was performed and energy values were calculated from the docked conformations of the protein-inhibitor complexes. The target protein - EGFR tyrosine kinase with canthin-6-one and standard drugs was docked using an automated molecular docking server PATCHDOCK in order to find out how the chemical compounds inhibit the target protein structure EGFR - tyrosine kinase based on the negative binding affinities values [38] as shown in **Fig. 4, 5, 6** and **7**.

Solution No	Score	Area	ACE	Transformation
161	1444	186.00	-22.74	1.84 0.43 1.37 14.57 -10.85 52.98
162	1432	239.70	-222.81	0.21 0.01 -2.12 28.19 4.25 56.08
163	1426	176.70	-43.31	2.70 1.26 0.65 15.71 -12.28 52.91
164	1418	246.10	-228.45	-0.08 -0.10 -0.67 22.92 3.36 56.50
165	1394	174.90	-36.74	-1.95 -0.88 -1.65 16.80 -7.99 60.33
166	1358	181.40	-32.29	1.73 1.12 1.38 15.20 -9.71 51.66
167	1338	247.80	-262.59	0.44 0.22 0.15 14.45 -1.68 53.64
168	1328	237.40	-235.10	-0.45 -0.25 2.96 27.02 -2.34 54.92
169	1290	247.10	-242.39	0.01 -0.06 0.87 21.92 -2.15 56.52
170	1240	242.70	-208.74	0.19 0.06 -2.88 30.62 2.36 55.59
171	1186	227.00	-226.47	-0.10 -0.21 -2.28 27.24 1.98 55.10
172	1164	245.20	-248.25	2.92 -0.03 -2.40 28.53 2.64 56.21
173	908	257.20	-177.51	0.87 -0.35 0.72 24.92 -1.50 57.20
174	824	213.30	-117.46	1.82 0.31 2.14 29.25 -3.40 50.86

FIG. 4: DOCKING SCORE OF CANTHIN-6-ONE WITH EGFR-TYROSINE KINASE IS (-248.25)

Solution No	Score	Area	ACE	Transformation
81	2134	294.60	-47.96	1.18 -0.73 -1.75 17.08 -1.87 61.06
82	2132	351.10	-155.12	-0.27 -0.12 1.53 22.78 -5.71 56.07
83	2118	250.00	-17.15	1.80 -0.55 2.01 19.33 -18.51 57.63
84	2100	363.40	-122.72	-2.52 1.26 -1.25 23.56 0.92 46.83
85	2090	235.80	-72.67	0.15 0.10 -1.02 13.42 4.76 52.39
86	2082	369.50	-116.79	-0.28 0.08 -1.21 23.70 7.85 54.68
87	2018	385.20	-117.29	0.54 -0.02 1.57 27.29 -7.06 55.07
88	1998	361.70	-154.28	-0.27 0.35 1.90 26.68 -6.17 52.96
89	1966	322.30	-138.57	-3.09 -1.02 1.22 22.54 -2.30 59.80
90	1946	260.80	6.35	-1.76 -0.66 -1.40 15.32 -5.43 59.12
91	1944	237.70	-3.91	-0.16 0.45 2.62 20.04 -8.42 49.80
92	1890	394.50	-158.06	0.36 0.35 2.16 29.47 -6.49 52.92
93	1870	371.90	-177.44	-0.13 1.17 1.74 24.49 -4.45 46.85
94	1852	238.70	14.85	1.62 0.95 1.49 15.20 -13.04 51.06
95	1804	364.60	-164.69	-0.02 -0.44 -2.07 26.15 5.54 57.47
96	1804	370.70	-159.01	0.66 1.06 0.78 23.59 -3.24 48.85
97	1800	377.50	-111.38	-0.59 -1.19 -1.32 27.81 2.95 60.81
98	1676	365.70	-183.28	-0.17 0.39 2.23 29.20 -6.37 52.87
99	1660	343.30	-188.48	0.27 0.02 -0.28 13.02 3.37 53.87
100	1646	365.00	-163.62	-0.30 -0.08 -0.14 19.00 3.40 55.96

FIG. 5: DOCKING SCORE OF GEMCITABINE WITH EGFR-TYROSINE KINASE IS (-188.48)

Solution No	Score	Area	ACE	Transformation
1	1622	185.00	-23.65	0.72 0.22 1.77 28.11 0.08 54.10
2	1592	179.00	-25.55	-1.50 0.62 -2.77 28.23 -0.78 53.69
3	1576	166.20	-38.60	-0.12 -0.08 0.46 20.12 -1.47 54.09
4	1556	169.90	-45.26	-0.45 -0.16 -2.97 19.89 -1.98 54.20
5	1540	166.50	-40.73	3.02 -0.47 -2.24 20.57 -1.88 54.10
6	1488	169.80	-29.70	1.47 -0.82 0.76 27.45 -0.77 54.48
7	1482	167.80	-29.84	-0.69 -0.04 -2.40 27.22 0.09 54.89
8	1394	147.90	-27.99	2.57 -0.60 2.63 27.11 -0.29 53.86
9	1348	153.10	-12.98	-1.63 -0.73 -0.87 26.91 0.79 53.79
10	1346	163.40	-39.93	-3.10 -0.33 0.87 26.65 -0.42 56.04
11	1316	150.70	-31.15	-3.06 -1.36 -0.87 27.02 0.01 55.48
12	1004	124.00	-27.47	-1.36 -0.23 1.96 26.08 0.96 55.11

FIG. 6: DOCKING SCORE OF CISPLATIN WITH EGFR-TYROSINE KINASE IS (-45.26)

Solution No	Score	Area	ACE	Transformation
121	1478	281.00	-160.61	0.25 0.36 0.29 21.62 -7.12 51.89
122	1474	298.30	-159.43	-0.67 -0.50 -2.83 23.68 3.85 59.89
123	1466	287.80	-179.54	0.54 0.69 1.12 25.20 -5.11 49.34
124	1460	291.90	-178.09	-2.97 -0.44 -0.91 28.74 4.73 58.22
125	1412	287.30	-176.14	3.13 -0.07 -1.97 32.40 0.76 56.21
126	1384	286.40	-166.53	0.20 -0.08 2.16 32.73 0.77 55.49
127	1296	289.00	-183.19	-0.05 -0.45 -1.38 20.00 1.35 57.91
128	1274	292.10	-124.66	-1.73 0.59 -2.50 33.69 2.07 56.15
129	1182	287.80	-190.89	2.44 0.20 2.62 25.20 -6.77 50.32
130	1178	281.60	-182.73	-2.94 -0.17 -2.40 30.92 -1.47 58.07
131	1046	283.10	-177.76	-3.14 -0.31 0.92 19.72 1.27 57.32
132	952	277.90	-170.82	-0.12 -0.20 1.15 30.22 -4.43 57.55

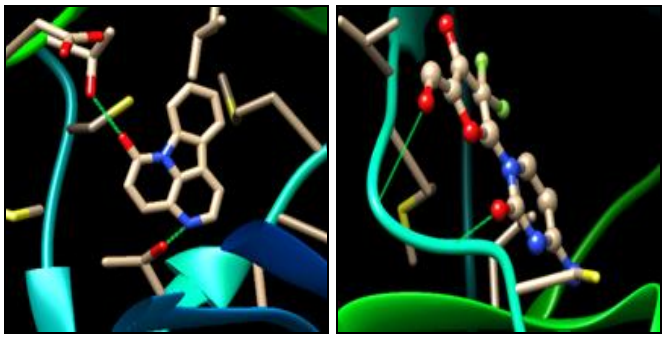
FIG. 7: DOCKING SCORE OF THIOTEPA WITH EGFR-TYROSINE KINASE IS (-190.89)

Docking studies yielded crucial information concerning the orientation of the inhibitors in the binding pocket of the target protein. The minimum binding energy indicated that the epidermal growth factor receptor (EGFR) tyrosine kinase (target enzyme) was successfully docked with canthin-6-one as showed in the **Table 2** and **Fig. 8**.

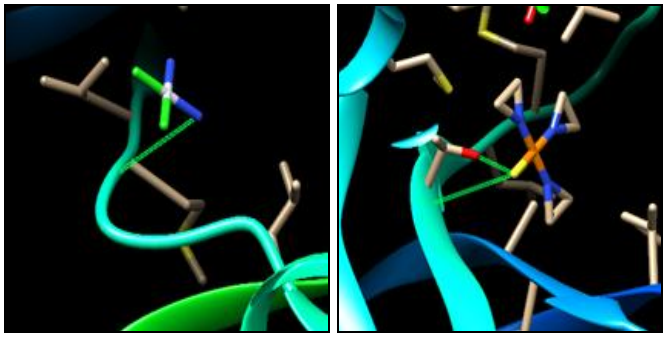
TABLE 2: DOCKING SCORE OF CANTHIN-6-ONE AND REFERENCE DRUGS WITH EGFR-TYROSINE KINASE

Name of Compounds		EGFR - Tyrosine Kinase (Target Protein)	Number of hydrogen bond
Canthin-6-one (Alkaloid)		(-248.25)	2
Reference Drugs	Gemcitabine	(-188.48)	2
	Cisplatin	(-45.26)	1
	Thiotepa	(-190.89)	2

The molecular docking results clearly show that the binding values of Canthin-6-one with EGFR tyrosine kinase are (-248.25). Whereas the binding value of the existing drugs Gemcitabine, Cisplatin and Thiotepa with EGFR tyrosine kinase is (-188.48), (-45.26) and (-190.89) respectively as in **Table 2**. Similar type of studies with Quercetin and Resveratrol compound was performed by Muthukala *et al.,* [30] and Manimaran *et al.,* [31] respectively. The protein-ligand interaction plays an important role in structural based designing [32]. Epidermal growth factor receptor (EGFR) tyrosine kinase protein residues Thr 766, Thr 830 was formed H-bond with canthin-6-one molecule. Canthin-6-one showed relatively good binding affinity (-248.25) as compared to Gemcitabine, Cisplatin and Thiotepa as standard which showed minimum binding energy of (-188.48), (-45.26) and (-190.89) respectively. Finally, Canthin-6-one with EGFR tyrosine kinase showed negatively high binding values when compared to the existing drugs, Gemcitabine, Cisplatin, Thiotepa. Thus, we can say that Canthin-6-one is a potential anticancer agent for EGFR tyrosine kinase protein structure which is clearly shown in **Fig. 8**.



Canthin-6-one **Gemcitabine**



Cisplatin Thiotepa

FIG. 8: HYDROGEN BONDING INTERACTIONS BETWEEN LIGANDS WITH EGFR-TYROSINE KINASE

In the present *in silico* investigation, we elucidated one finding that we used the alkaloid compound (Canthin-6-one) derived from plant (Simarouba glauca) and found that this bioactive compound acted as potential anticancer agent for the target protein, namely, EGFR tyrosine kinase. Analysis of ligand binding interaction with the Epidermal growth factor receptor (EGFR) tyrosine kinase protein can be useful for new preventive and therapeutic drug for cancer. Based on the molecular drugs docking and binding affinities of the target protein EGFR tyrosine kinase with the ligands, it was found that the alkaloid Canthin-6-one has high binding values than the existing drugs Gemcitabine, Cisplatin, Thiotepa. 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.

CONCLUSION: In this study, the molecular docking was applied to explore the binding mechanism and to correlate its docking score with the activity of Canthin-6-one compound. Docking studies of the Canthin-6-one with epidermal growth factor receptor (EGFR) tyrosine kinase showed that this ligand is good molecule which docks well with EGFR - tyrosine kinase target. The results are helpful for the design and development of novel drug having better inhibitory activity against various types of cancer. From this study, we conclude that Canthin-6-one is one of the best anticancer phytochemical agents. These potential drug candidates can further be validated in wet lab studies for its proper function.

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CONFLICT OF INTEREST: The authors report no conflict of interest.

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