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Evaluation of Potential EGFR Inhibitors for Non-small Cell Lung Cancer: A Structure-based Virtual Screening and Molecular Dynamics Study

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Non-small cell lung cancer is a leading cause of cancer deaths globally. EGFR is one of the attractive drug targets for non small cell lung cancer. It was first identified receptor tyrosine kinase receptor. It plays a critical role in the variety of biological activity apoptosis, cell cycle progression,

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differentiation, development, and transcription. Somatic mutation occurs in human EGFR. After that the normal function of EGFR was over expressed can leads to develop lung cancer. In this study we have identified three potential compounds using structure based virtual screening. Then thus compounds were evaluated ADME properties, all the compounds are under acceptable range with predicted ADME properties, then thus protein-ligand complex stability were carried out using Gromacs. The stability of the protein-ligand complex is stable throughout entire simulation, especially MET 769 is significant for stability of the complex. Furthermore, invitro cytotoxicity assay were performed for the best one compounds against non small cell lung cancer cell line.

Keywords: EGFR; virtual screening; molecular dynamics simulation; In vitro cytotoxicity.

1. INTRODUCTION

Lung cancer is one of the most prevalent and cause topmost cancer related demise around the world. In 2015 221,200 (105, 590 Female, 115,610 Male) new cases are diagnosed with lung cancer and 158,040 (71,660 Female, 86,380 Male) cases dies from it. Totally 1.8 million people were affected with lung cancer in globally [1]. Roles played by growth factor receptors have been identified to play an important role as they function in many cellular processes like cell proliferation, differentiation and survival. Epidermal growth factor is mainly transmembrane glycoprotein located on the short arm of chromosome 7 that encode a protein of 1186 amino acids mainly expressed on the surface of normal cells [2]. The receptor has a molecular weight of 170 KDa encoded by C-erbB-1 proto-oncogene and originates from cells present on skin, liver and gastrointestinal tract. Based on the structure and function, the growth factor receptor is divided into four types - HER1/EGFR/C-erbB-1, HER2/C-erbB-2, HER3/C-erbB-3, and HER4/C-erbB-4. The epidermal growth factor 1 and C-erbB-2 proteins have shown 82% homology with their tyrosine kinase domain [3,4]. The epidermal growth factor receptor, possessing angiogenic properties or activity, binds with number of endogenous ligands like epidermal growth factor, transforming growth factor-α, amphiregulin, heparin, binding EGF, β-cellulin. They two main ligands, EGF and TGF, mainly bind with EGFR for its normal functionality. The two ligands when bind with EGFR undergo dimerization and auto phosphorylation to initiate cell proliferation, differentiation, migration and survival in normal cell [5]. EGFR mainly consists of three regions - extracellular EGF binding domain, short trans membrane region with a single hydrophobic anchor sequence and intracellular domain with tyrosine kinase activity. The binding of EGF with EGFR induces conformational catalytic changes within the receptor and increases the intrinsic tyrosine kinase activity resulting in auto phosphorylation [6]. Domain IV is the focus of ligand binding research, however the extracellular amino terminal end can split into domains I, II, III, and IV. At the SH2 region of EGFR, the phosphorylated tyrosine kinase of EGFR interacts either directly or indirectly with Grb2, PLC, GAMA 1, GAP, and Syp phosphorylated NCK. These connections facilitate the activation of MAPK and elevated levels of RAS, JUN, and fos oncogene production [7]. Hepatitis B and Epstein-Barr virus expression are subsequently caused by MAPK activation, which modifies the activity of the EGFR tyrosine kinase. Mutations that cause overexpression of EGFR can result in a wide range of cancers, including bladder, head and neck, kidney, ovarian, 16–36% breast, and 40% glioblastoma. 65-75% of non-small-cell lung carcinomas and colorectal cancers [8]. To reduce expenditure, time consumption and reduce the number of candidates and experimental animals associated with novel drug discovery and development, computer aided molecular designing were used. virtual screening is a fast, accurate and inexpensive powerful tool to identify the potential leads with desired properties for various drug targets [9]. In this current research scenario, we performed structure based virtual screening to recognize the effective hit molecules from Zinc database. The identified hit compounds were further taken into theoretical ADME calculation by using Gromacs, molecular dynamic simulation and invitro cytotoxicity assay.

2. MATERIALS AND METHODS

2.1 Structure Based Virtual Screening

Structure based virtual screening is one of the rapid, accurate, efficient computational approach utilizing in early stages of drug designing and development project for identification of efficient novel molecules from huge chemical database with desired biological properties. In this study

we performed different docking strategy for filtering hit compounds by utilizing Glide version 5.5. Before docking, the preparation of therapeutics target and ligand is crucial step of docking to eradicate the steric hindrances of docking. The therapeutic X-ray crystal structure of 3D coordinates information of human lung cancer protein EGFR (PDB ID: 1M17) with complex Erlotinib, was retrieved from the protein data bank. Then the target structure was further imported into protein preparation wizard panel for refinement, eliminate HOH atom, co-crystallized molecule erlotinib and assigning bond orders, treating metals, treating disulfides. building missing heavy atoms and formal charges, adjusting bond orders, hydrogen atom was added and target protein structure energy was minimized until the average RMSD reached 0.30Å by using OPLS3 force field [10]. Then the refined protein structure was further imported into receptor grid generation panel for grid generation, in this step binding pocket information play on pivotal role in structure-based drug designing. The found drug molecule erlotinib in the crystal structure of EGFR and we collected the binding pocket residues from research articles. The residues mainly responsible for protein-ligand interaction of EGFR. So, the grid package was generated same position of the erlotinib by selecting the centroid of the selected residues and we set the grid box at (20Å×20Å×20Å) by applying receptor grid generation panel rooted with Schrodinger suite. then the grid constructed file were input file for molecular docking studies. The 5, 40, 745 were downloaded from zinc database in the SDF format, all ligands were prepared using LigPrep. In this ligand preparation step we put forth following criteria (i) the OPLS3 force field were used for ligand energy minimization (ii) we generate all possible ionization and tautomers/stereoisomers states at pH ¼ 7.0±2.0 (iii) the *desalt* -option were generated (iv) one low energy conformer were generated per ligand, then the prepared ligands subsequently taken into structure based virtual screening process using Glide. The refined protein and ligand structure were used as input file for further glide filtration against EGFR Ligand and Receptor docking incorporated into maestro. In this Glide filters steps it possesses three different ligand screening routes, namely HTVS (high throughput virtual screening), SP (standard precision) and XP (extra precision) modes. The OPLS3 force field parameters were applied while performing docking calculations. Then the molecules with the best Glide score and Glide energy, hydrogen bond interaction, hydrophobic interaction were visually inspected by using Glide XP visualizer panel. The overall virtual screening workflow were represented in Fig. 1.

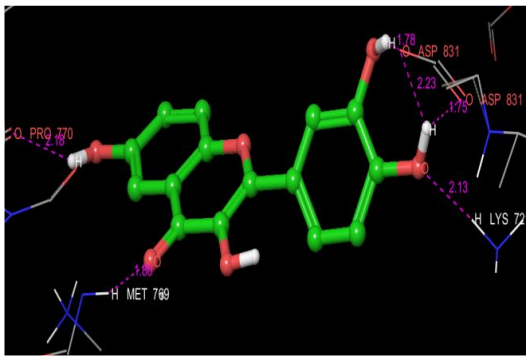
2.2 ADME Properties Prediction

ADME properties evaluation play on important role in drug discovery project. Now days failure rate of drug candidate increases in clinical stage due to undesired pharmacokinetics properties. Because the determination of experimental ADME is time consuming, expensive process. Most of the pharmaceutical companies spend more amount to increase the success rate of drug candidate. So pharmaceutical company and research group mostly believed computational approach for ADME calculation. Qikprop [11] is most popular, inexpensive, time saving method were employed for evaluation of Drug like properties. All the ligands were neutralized before being used QikProp. The neutralization is very significant step as without neutralization activity of the ligand no properties will be predicted in the normal mode. Here we predicted following physically significant descriptors and pharmaceutically relevant properties. These are partition coefficient (QPlogP octanol/water), The water solubility (QP log S), H-bond donor, H-bond acceptor, QPPCaco2, Blood/brain barrier, LogIC_{50} value for blockage of K+ channels (QPlogHERG), Percentage of human oral absorption are mentioned.

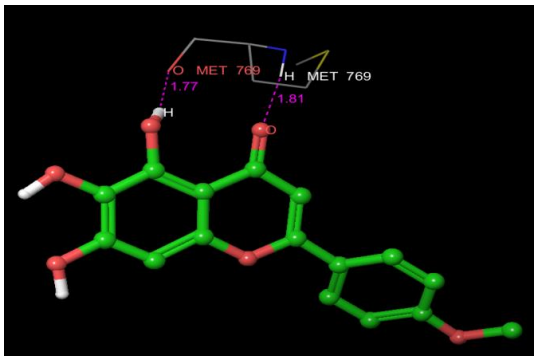
2.3 Molecular Dynamics Simulation

In order to examine whether the designed inhibitor remains bound in the presence of explicit solvent from a dynamic point of view, the molecular dynamic simulation was performed with GROMACS 96-53a6 force fields [12] with the periodic boundary conditions (PBC) by using GROMACS 4.0 package for Linux. The topology files and charges for the ligand atoms were generated by the Dundee PRODRG2.5 Server (beta) [13]. Before starting the simulations, all the models were solvated with the explicit simple point charge (SPC) water in a cubic box. The models were covered with a water shell of 1.0 nm from the surface of the protein. The system was neutralized with six chlorine ions to replace the six SPC water molecules. Subsequently, the energy minimization was performed for the system concerned by using the steepest descent until touching a tolerance of 100kJ/mol. And then, the 20 ns MD simulations were carried out

3, 6, 3', 4'-Tetrahydroxyflavone



Velutin



scutellarein 4'-methyl ether

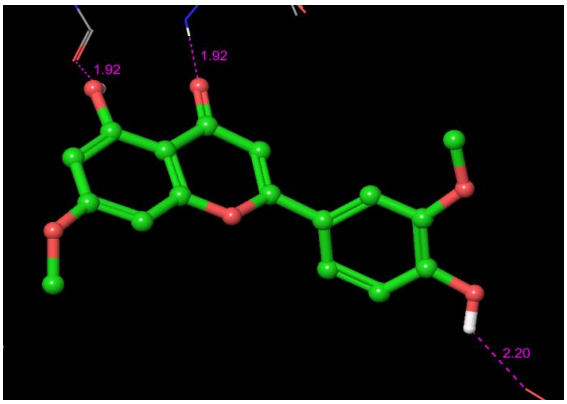


Fig. 1. Structure of the three lead molecules. The ZINC database ID of the lead molecules are as follows: ZINC00008662- 3, 6, 3', 4'-Tetrahydroxyflavone, ZINC14813963-Scutellarein 4'-methyl ether, ZINC05732373-Velutin

with a time step of 1 fs; the corresponding coordinates were stored every 100 fs. The PME algorithm was used to calculate the electrostatic interactions. All simulations were run under the periodic boundary condition with NVT ensemble by using Berensen's coupling algorithm for keeping the temperature at 310 K and pressure at 1atm. All bonds were constrained by using the LINCS algorithm. The GROMACS 4.0 package was utilized to analyze the result.

3. RESULTS AND DISCUSSION

3.1 Scrutinization of Inhibitors from Zinc Database

Structure based virtual screening is a rapid method for the identification of effective novel inhibitors against a therapeutic target. In the present study, we have performed virtual screening of lead-like compounds from the ZINC database to identify desired potential inhibitors against EGFR. The lead-like subset of the ZINC database contains 5, 00, 000 compounds. Initially, we screened 10,000 ligands obtained from HTVS mode then the ligands were allowed to interact with binding site of target protein EGFR, A total of 10,000 compounds were obtained from the output of HTVS then the compounds were subsequently subjected to SP docking [14], On the basis of the SP docking score, were used for XP docking. The Glide XP docking helped in eliminating the false positives and the scoring function was much more stringent than the HTVS and SP docking. Finally, four ligands were obtained from Glide XP mode, three potential drug-like molecules significantly satisfy the pharmacokinetic factors that are defined for human use and qualify as potential drug-like molecules. Finally, we identified four compounds with the maximum glide scores (ZINC6525297, ZINC39317, ZINC14643909, ZIC4096947), as enlisted in Table 1. The 2D structure of the ligands were depicted in Fig. 2.

they are: Gossypetin (ZINC6525297), 5,3',4'-Trihydroxyflavone (ZINC39317),2-(3,4-Dihydroxy -phenyl)-5,6-dihydroxy-7-methoxy-chroman-4-one; (ZINC14643909), Trans-3,3',4',5,5',7-Hexa-hydroxyflavanone (ZINC40969 47). The interacting residues for these lead molecules are shown in Table 1 and their structures are shown in Fig. 1.

3.2 Binding Mode of 3, 6, 3', 4'-Tetrahydroxyflavone

Six hydrogen bond interactions between the highest hit compound 3,6,3',4'-Tetrahydroxyflavone and the binding pocket area of EGFR were found when we examined the binding mechanism of this compound within the EGFR active site. First, a bond length of 1.80Å was formed between the backbone hydrogen atom of MET 769 and the backbone oxygen atom of 3,6,3',4'-Tetrahydroxyflavone. The second is that the backbone oxygen atom of the PRO 770 interacted closely with the hydrogen atom of the 3,6,3',4'-Tetrahydroxyflavone. has a 2.18Å binding gap. The third is that the hydrogen atom of LYS721 had a significant interaction with the oxygen atom of the hit compound 3,6,3',4'-Tetrahydroxyflavone at a bond distance of 2.13Å [15]. furthermore the hydrogen atom of the hit compounds 3,6,3',4'-Tetrahydroxyflavone were nicely bonded with oxygen atom of the negative charged residue of ASP 831 with bond distance (1.75 Å, 2.23Å, 1.78Å), Likewise, series of key amino acids located in the ATP allostearic site such as CYS 773, LEU 820, VAL 702, LEU 768, PHE 771, ALA 719 accounts for hydrophobic interactions . We recorded glide score and glide energy as -8.837 Kcal/mol and -58.013 Kcal/mol respectively. Structure of the three lead molecules, he binding pose of the three lead molecules with EGFR were reported in Figs. (1,2).

3.3 Binding Mode of Velutin

The binding conformation of velutin within the active site of the EGFR has been analyzed. The glide score and glide energy values for velutin were -8.55Kcal/mol and -54.86 kcal/mol, respectively. Upon the examination of docking features between velutin and EGFR it was found only three hydrogen bond interactions. First one is hydrogen atom of the Velutin was well interacted with the side chain oxygen atom of the negative charged residue of GLU 738 with bond length (2.20Å). Second one is backbone oxygen atom of the hydrophobic residue of MET 769 were tightly interacted with oxygen atom of the velutin with bond distance (1.92Å), furthermore the hydrogen atoms of the velutin were nicely bonded with backbone oxygen atom of the hit 3 with, bond distance (1.92Å). Furthermore, LEU 768, ALA 719, ILE 765, ILE 720, VAL 702, MET 742 a number of hydrophobic interactions was bound between velutin in to EGFR [16,17].

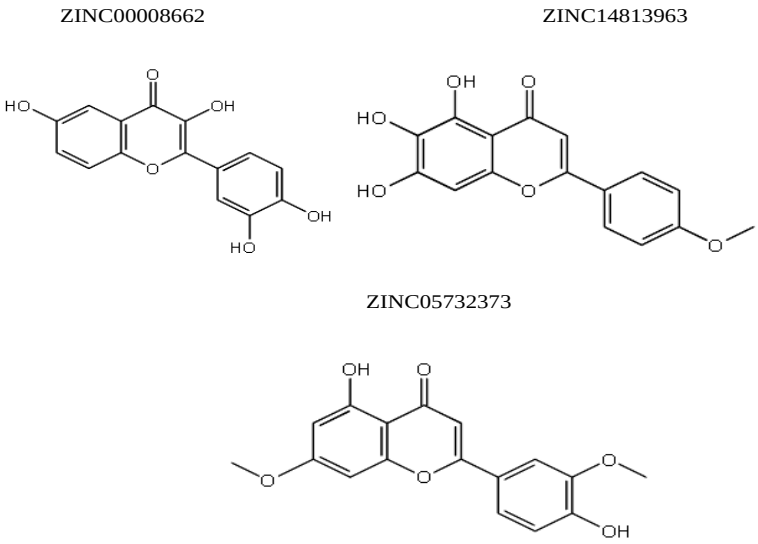


Fig. 2. Structure of the three lead molecules. ZINC00008662- 3, 6, 3', 4'-Tetrahydroxyflavone, ZINC14813963- Scutellarein 4'-methyl ether, ZINC05732373-Velutin

Table 1. Glide extra-precision (XP) results for three lead molecules and Co-crystal molecule Erlotinib, by use of Schrodinger 9.5.

S. No	Compound ID	Glide Score	Glide Energy	Interacting Residues	Distance (Å)	Hydrogen bond donor	Hydrogen bond Acceptor
1	ZINC00008662	-8.83	-58.01	MET 769	1.80	A:MET 769: (H)H	Ligand: (O)
				PRO 770	2.18	Ligand: (H)	A:PRO 770: (O)
				LYS 721	2.13	A:LYS721: (H)HZ3	Ligand: (O)
				ASP 831 (3)	1.75	Ligand: (H)	A:ASP831: (O)OD1
					2.23	Ligand: (H)	A:ASP831: (O)OD2
					1.78	Ligand: (H)	A:ASP831: (O)OD2
2	ZINC14813963	-8.70	-48.00	MET 769	1.77	Ligand: (H)	A:MET 769: (O)O
				MET 769	1.81	A:MET 769: (H)H	Ligand: (O)
3	Zinc05732373	-8.55	-54.86	MET 769	1.92	Ligand: (H)	A:MET 769: (O)O
				MET 769	1.92	A:MET 769: (H)H	Ligand: (O)
				GLU 738	2.20	Ligand: (H)	A:GLU 738: (O)OE2
4	Erlotinib (Co-crystal)	-8.57	-75.01	CYS 773	1.96	A:CYS 773: (H)H	Ligand: (O)
				Met 769	2.23	A:MET 769: (H)H	Ligand: (N)

3.4 Binding Mode of Scutellarein 4'-Methyl Ether

The binding conformation of scutellarein 4'-methyl ether within the active site of the EGFR has been analyzed. The glide score and glide energy values for scutellarein 4'-methyl ether were -8.70Kcal/mol and -48.00kcal/mol were reported in Table 1, respectively. Upon the examination of docking features between scutellarein 4'-methyl ether and EGFR it was found only two hydrogen bond interactions. First one is backbone hydrogen atom of the MET 769 was well interacted with oxygen atom of the scutellarein 4'-methyl ether with bond length (1.81Å). finally hydrogen atom of the scutellarein 4'-methyl ether were tightly interacted with backbone oxygen atom of the scutellarein 4'-methyl ether with bond distance (1.77Å), Furthermore, VAL 702, ALA719, LEU 820, MET 742, LEU 764, PRO 770, a number of hydrophobic interaction were bound between scutellarein 4'-methyl ether in to EGFR [18,19].

3.5 ADME Properties Prediction

The *insilico* ADME calculation of three newly recognized hits were assessed by employing QikProp. The above three hit molecules having effective oral absorption and membrane penetration capabilities based on Lipinski's rule of five. The hit compounds molecular weight lower than 500kDa, less than 5 H-bond donors, less than 10 hydrogen bond acceptors and the lipophilicity of logP below 5. All the predicted role of five properties are adequate ranges act as potential drug behavior. Then the hit molecules were further taken into calculation of ADMET by use of QikProp in Table 2. For the three lead molecules, the aqueous solubility (QPlogS) critical for estimation of absorption and distribution of drug within the body range between -4.024 to -2.792 respectively. Cellular permeability (QPPCaco2) responsible for drug metabolism and its access to the biological membrane is within the acceptable range 49 to 578 [20].

Overall, the percentage of human oral absorption for the compounds ranged from 60% to 90%. The predicted IC50 value for the blockage of HERG K+ channels (QPlogHERG) are in the acceptable range of below -5. The predicted value of binding to human serum albumin (QPksha) fit well in the acceptable range ~ -0.370 to ~0.160. The predicted Brain/Blood barriers are under acceptable range ~ -1.881to -0.890. All the pharmacokinetics parameters are fit well with the acceptable range defined for use of human.

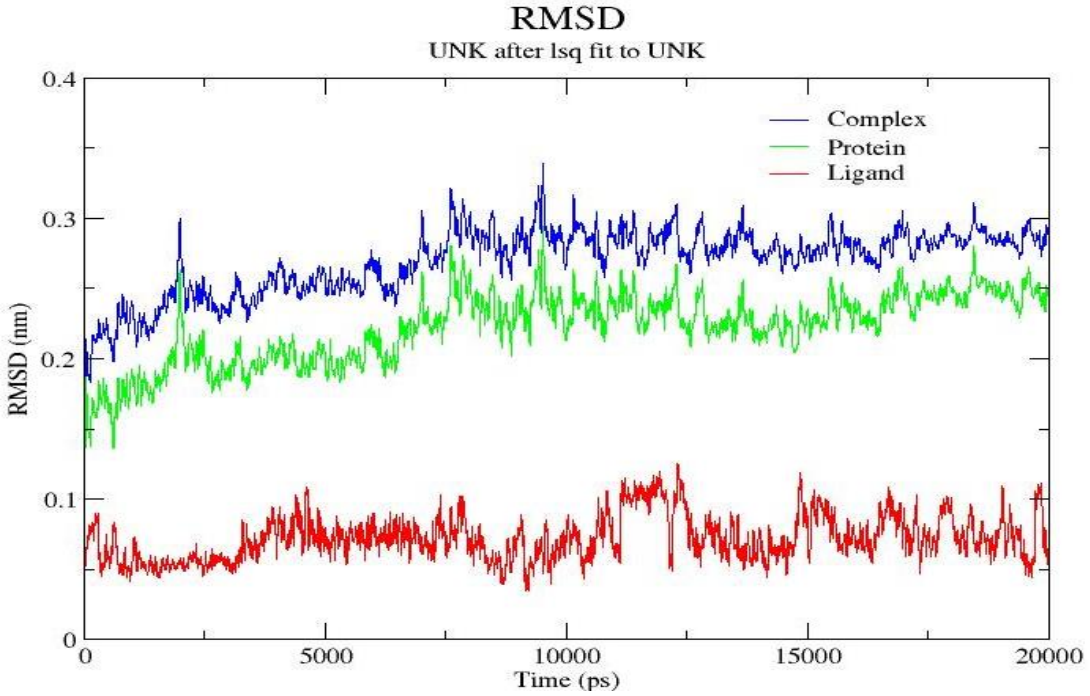


Fig. 3. RMSD of small molecule in active site residues during the simulation in EGFR protein (blue), protein (green), and ligand (red)

Table 2. ADME properties of the three lead molecules as verified by using Qikprop (Schrodinger 9.5)

Ligand ID	QPlogS	Logp Caco2	Percent human oral absorption	HERG LogIC $_{50}$	QPlogKhsa	LogBB	MW	HBD	HBA	QPlog (o/w)
ZINC00008662	-2.792	49	60	-5.073	-0.370	-1.881	286.240	4	5.5	0.499
ZINC14813963	-3.572	167	78	-5.058	-0.004	-1.383	300.267	2.000	4.500	1.871
Zinc05732373	-4.024	578	90	-5.172	0.160	-0.890	314.294	1.000	4.500	2.715

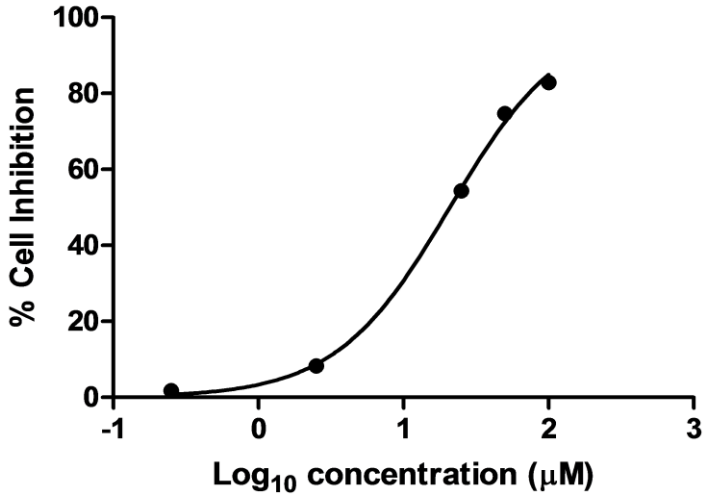


Fig. 4. Nonlinear regression graph showing the IC50 value of the 3, 6, 3', 4'-Tetrahydroxyflavone

3.6 Molecular Dynamic Simulation

Under certain circumstances, it becomes impeccably evident there is need for simulate and evaluate the docked complexes by various quantum biology-based approaches. In this study, Gromacs is engaged to find the stability of EGFR-ligand complex under dynamic settings. The complex is well studied to reveal the stability of the complex which is determined by ligand RMSD trajectories of ligand, protein and complex were depicted in Fig. 3. The protein ligand attained equilibrium after 20 ns; it suggests that computed trajectories were stable. Fig. 3 & 4 shows the binding pose of the protein and ligand complex with an interval of 5ns up to 20ns beginning from 0ns. Initially we identified 8 hydrogen bond interactions, when we raised the simulations up to 5ns, we happened to observe only three hydrogen bond interactions. Subsequently one hydrogen bond interaction we were able to identify both in 10 and 15ns. Similar bonding of hydrogen was carried up to 20ns. MET 769 of EGFR is the residue which was found to be very consistent in forming hydrogen bond with the ligand [21]. With the interpretations of molecular dynamics studies, it is vivid that MET 769 is very crucial for stability of the protein - ligand complex.

4. CONCLUSION

In this present study we have identified three potential lead molecules using Glide docking. The best one compound 3, 6, 3', 4'-Tetrahydroxyflavone was further employed as molecular dynamics simulation. Above mentioned compound is more stable in active site of the protein during molecular dynamics simulation. Especially that the residue MET 769 is significant for stability of the protein-ligand complex then the hit molecules were further filtered by Lipinski rule of five, ADME properties. The compound is satisfied under acceptable range with predicted with ADME properties. Furthermore, the compound was taken into invitro cytotoxicity assay. Finally, the new lead compounds obtained can be targeted for further experimentation leading to clinical trials.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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