Research Article

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POTENTIAL COMPOUND DERIVED FROM *CATHARANTHUS ROSEUS* TO INHIBIT NON SMALL CELL LUNG CANCER (NSCLC)

Senthilraja P*, Kayitare John[1], Manivel G[1], Manikandaprabhu S[1], Anand Krishnamurthy[2]
[1]Bioinformatics, Department of Zoology, Annamalai University, Chidambaram, Tamil Nadu, India
[2]Biovia Senior Scientist, Life Science, Modeling and Simulations, India

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***Corresponding author**
Dr. P. Senthilraja, M.Sc., M.Phil., Ph.D., Assistant professor in Bioinfomatics, Department of Zoology, Annamalai University, Annamalainagar-608 002, Chidambarm, Tamil Nadu, India E-mail: lionbioinfo@gmail.com

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ABSTRACT

The aim of this study was to carry out GC-MS analysis of Catharanthus roseus plant leaves extract to inhibit the non-small cell lung cancer. *Catharanthus roseus* plant leaves were extracted with methanol and five compounds were identified from GC-MS analysis. Epidermal growth factor receptor (EGFR), is a receptor tyrosine kinase (RTK) which is frequently over-expressed and malignant proliferation of non-small cell lung cancer (NSCLC). The 3D crystal structure of the non-small cell lung cancer responsible protein (ID: 2ITO) were retrieved from the protein data bank (PDB). Discovery studio is a well-known suite of software for molecular docking. It is developed and distributed by Accelrys. The protein ligand docking was performed in flexible docking by Discover Studio. From the GC-MS analysis two compounds 4-piperidineacetic,1-acetyl-5-ethyl-2-[3-[2-hydroxyethyl]-1H-indol-2-yl]-a-methyl-methyl ester and 2H-Pyran,tetrahydro-2-[12-penta decynyloxy], exhibited potential effect against human epidermal growth factor receptor (EGFR) responsible for the non-small cell lung cancer.

Keywords: GC-MS analysis, *Catharanthus roseus,* Non-Small Cell Lung Cancer (NSCLC), Discover Studio.

INTRODUCTION

Cancer is an abnormal growth and proliferation of cells. It is a frightful disease because the patient suffers pain, disfigurement and loss of many physiological processes. Cancer may be uncontrollable and incurable, and may occur at any time at any age in any part of the body. It is caused by a complex; poorly understood interplay of genetic and environmental factors[1]. Cancer is the second leading cause of death economically developed countries and the third in emergent nations[2]. Lung cancer is a second leading cause of death in worldwide accounting for 1.59 million deaths in 2012. It's a cause of morbidity and mortality among men and women[3]. That's followed by two types of lung cancer. Small cell lung cancer (SCLC) and Non-small cell lung cancer (NSCLC); non-small cell lung cancer is much more common and accounts for 75-85% causes of all lung cancers. Mutations in the EGFR kinase are a cause of non-small cell lung cancer[4]. Epidermal growth factor receptor (EGFR), is a receptor tyrosine kinase which is frequently over-expressed in non-small cell lung cancer. This receptor plays an important role in tumors cell survival and activated phosphorylated EGFR results in the phosphorylation of downstream proteins that cause cell proliferation, invasion, metastasis and inhibition of apoptosis. Expression appears to be dependent on histological subtypes, most frequently expressed in squamous cell carcinoma but also frequently expressed in adenocarcinomas and large cell carcinoma[5]. EGFR including more than 75-85 % of non-small cell lung cancers, it was one of the first molecules to be selected for the development of targeted therapies[6-8]. The receptor belongs to the ErbB/HER family of ligand-activated RTKs, which includes four structurally similar members EGFR/HER1, ErbB2/HER2, ErbB3 / HER3 and ErbB4/HER4, has been clinically validated as a leading approach to selectively target cancer cells[9]. Mutant receptor has been reported in many cell types such as gliomas, non-small cell lung cancer, prostate, breast, ovary and stomach cancer[10-12]. Currently two small molecule kinase inhibitors, ZD1839 (Iressa) and OSI774 (Tarceva), are in clinical use for the treatment of lung cancer. There are more than ten EGFR inhibitors currently being tested in clinical trials. Among them there are several covalent inhibitors such as HKI-357, HKI-272, EKB569[13], BIBW2992[14] and PF2998044[15] which target a unique cysteine 797 residue located at the lip of the EGFR ATP binding site[16]. The development of specific antagonists targeting the EGFR has proved to be a promising therapeutic concept. There are two classes of EGFR antagonists which have been used in clinic: anti-EGFR monoclonal antibodies and small-molecule EGFR tyrosine kinase inhibitor (TKIs). During the past two decades, a lot of compounds with different skeletons were reported as EGFR TKIs, such as 4-anilinoquinoline-3-arbonitriles[17-19], 1H-pyrazolo [3, 4-d] pyrimidines[19], pyrrolotriazines[20], 4-amino-6-arylaminopyrimidines[21] and thienopyrimidine[22-24]. The 4-(phenylmethyl) amino and 4-(3 bromophenyl) amino were evaluated for their inhibitory activities against EGFR tyrosine kinases that led to some interesting findings on structure activity relationships of these compounds[25]. Considering EGFR is a rational target for antitumor strategies, one of the most important methods to inhibit EGFR is to block tyrosine kinase at ATP-binding site in cytoplasmic domain by small-molecule inhibitors. The representative frame of inhibitor is 4-anilinoquinazolines, such as gefitinib (ZD-

1839; Iressa) and lapatinib (GW2016; Tykerb) approved in the U.S[26] 4-anilinoquinazoline and 4-anilinoquinoline scaffolds bearing a 2, 2, 6, 6-tetramethylpiperidine-N-oxyl (TEMPO) have been synthesized and evaluated for their ability to inhibit EGFR tyrosine kinase and A431 cell lines[27], pyrrolopyrimidine AEE788[28] and the irreversible inhibitor HKI-272[29], among them 4-anilinoquinazoline is the most successful skeleton to modify to be an effective anticancer drug. Medicinal plants play a vital role for the development of new drugs, its natural origin and lesser side effects. It is getting popularized in developing and developed countries. The bioactive extract should be standardized on the basis of active compound. The bioactive extract should undergo safety studies. Combined therapies have the synergistic, potentiative, agonistic/antagonistic pharmacological agents within themselves that work together in a dynamic way to produce therapeutic efficacy with minimum side effects Almost, 70 % modern medicines in India are derived from natural products[30]. *Catharanthus roseus* is a medicinal plant with a prolific secondary metabolism characterized by the production of more than 130 different terpenoid indole alkaloids (TIAs), which are believed to protect the plant against herbivorism, and include the anticancer vinblastine and vincristine, the antihypertensive ajmalicine and the sedative serpentine[31,32]. The great pharmacological importance of the TIAs associated with the low abundance of the anticancer drugs in the plant (around 0.0005 % DW)[33]. *In-silico* screening is one of the most convenient methods to evaluate millions of molecules and obtain novel compounds. In the last few years, *In-Silico* Virtual Screening (VS) studies were performed by using the docking approach[34,35]. In this work for *C. roseus* leaves methanolic extract was identified by GC-MS analysis. The structure of the compound was retrieved from Pubchem. The retrieved compounds are performed to *in silico* docking study (Protein- Ligand interaction) by Discover Studio Version 4.0 (Accelry's Software Inc. USA). The higher docking energy values are good binding energy and hence more efficient in blocking the activity of the particular protein[36].

MATERIAL AND METHODS

Collection of Plant Samples

The leaves of *Catharanthus rosues* samples were collected from Karunguzhi (village), Cuddalore district, Tamil Nadu, India. This plant was collected in the morning session (during 8am- 10am) and packed polyethylene bag. The sample were transported to the Laboratory in Annamalai University and kept at room temperature for this processing; the Herbarium accession number 272, identified in Department of Botany, Annamalai University, Chidambaram, India

Preparation of Sample

The leaves of plant sample were washed with tap water and dried under room temperature for 10 days. Approximately about 100 g of leaves were ground using a heavy duty grinder for 15 sec. The dry samples were homogenized in grinder for 3 min to mesh size. The air dried leaves of *C. rosues* were pulverized into powdered form.

Extraction of Leaves

The powder leaves of *C. rosues* (100 g) were extracted with methanol (500 ml) with 48 hours at temperature between 60-65^{0}C by using soxhlet extractor. The solvent was evaporated by evaporator to obtained viscous semi solid masses. The semi dry methanol crude extract 30 g was suspended in water. The crude extract was filtered separately through whatman No: 4, filter paper to obtain dust free plant crude extract. This extract were concentrated and dried by using rotary evaporator under the vacuum.

GC-MS Analysis

The GC-MS analysis of organic methanol extracts isolated from leaves *C. rosues* were carried out. Helium was used as the carrier gas at a flow rate of 1 ml/min. The temperature was programmed at a flow rate of 1ml/min. The temperature was programmed at 80^{0}C for 5 min then increased up to 300^{0}C at the rate of 15^{0}C/min. The temperature of injector and E1 detector (70ev) was 280^{0}C and 300^{0}C, respectively 2 µl of plant extract was injected with GC-MS manually.

Preparation of protein structure

The structural information of the macromolecules determined by x-ray crystallographic and NMR methods are available in the PDB. The 3D structure Epidermal Growth Factor Receptor (PDB I.D: 2ITO) was downloaded from the Protein Data Bank (PDB) (http://www.rcsb.org/pdb/). The water molecules were removed from protein file 2ITO before docking. Energy minimization was done by applying for CHARMM (Chemistry at HARvard Macromolecular Mechanics) force fields, It's a program for macromolecular dynamics; it can be used for energy minimization, normal modes and crystal optimizations and also incorporates free energy methods for chemical and conformational free energy calculations.

Preparation of Ligand structures

The identified Chemical compounds namely 4-piperidineacetic,1-acetyl-5-ethyl-2- [3-[2-hydroxyethyl]-1H-indol-2-yl]-a-methyl, methyl ester and 2H-Pyran,tetrahydro-2-[12-pentadecynyloxy] was derived from *Catharanthus roseus* plant leaves and these compound structure were retrieved from Pubchem online server. Both of these compounds were under investigation of Chem Sketch (Chemically intelligent drawing interface free ware developed by Advance Chemistry Development, Inc., (http://www.acdlabs.com) chem sketch was used to construct the structure of the ligands. The ligand molecules were generated and the three dimensional optimizations were done and then saved as MOL file (a file format for holding information about the

atoms, bonds, connectivity and coordinates of a molecule).

Docking analysis

The docking analysis was performed by Discover Studio Version 4.0 (Accelry's Software Inc. USA) for the EGFR non-small cell lung cancer protein interaction with GC-MS of *Catharanthus rosues* leaves extract compounds. Fitting points were added to hydrogen bonding groups on the protein. The interaction between the binding pockets of target EGFR protein and investigation compound was to find out the accurate binding model for the active site of protein. The mechanism of ligand placement was based on binding site position. The protein ligand docking energy values performance of the 5 compounds was based on the Scoring functions which is implemented in docking program to make various assumptions and simplifications to fit best complexes, which includes terms of hydrogen bonds employed by Discovery Studio to rank the docked bases and to assess the binding site and the number of rotatable bonds present.

RESULTS

The methanol extract of *Catharanthus roseus* plant leaves (Figure 1) was analyzed by GC-MS and these compounds was identified from the sample using Helium at 280^0C-300^0C. Based on the results of GC-MS analysis Retention Time (RT) peaks (Figure 2) five compounds was identified from extract of *C. roseus* leaves extract. These five compounds are namely (RT = 14.97) Corynan-17-ol, 18, 19-didehydro-10-methoxy-, acetate [ester], (RT = 16.22) 4-piperidineacetic,1-acetyl-5-ethyl-2-[3-[2-hydroxyethyl]-1H-indol-2-yl]-a-methyl-, methyl ester, (RT = 17.47) 2H-Pyran, tetrahydro-2- [12-pentadecynyloxy], (RT=17.8) 2H-Pyran-2-one, tetrahydro-6-nonyl-, and (RT = 19.15) Cholestan-3-ol,2-methylene. Compounds 2D structure and its properties were shown in Table 1. The Epidermal Growth Factor Receptor (EGFR) responsible for non-small cell lung cancer (NSCLC) protein structure (Figure 3) was retrieved from PDB. The extracted two compounds were docked with EGFR protein. From these two compounds which exhibit higher lib dock score values were noted. The Compound (A) 4-piperidineacetic, 1-acetyl-5-ethyl-2-[3-[2-hydroxyethyl]-1H-indol-2-yl]-a methyl ethyl ester (Figure 4) interacts with EGFR protein, it formed 4 hydrogen interactions between the target and Libdock score value was 112.10 (Figure 5). The compound (B) 2H-Pyran, tetrahydro-2- [12-pentadecynyloxy] (Figure 6) interacts with EGFR formed one hydrogen bonding and Libdock score value was 106.2 (Figure 7). From above findings the compound A exhibit highest Libdock score.

Figure 1: *Catharanthus roseus* plant and *C. roseus* plant leaves

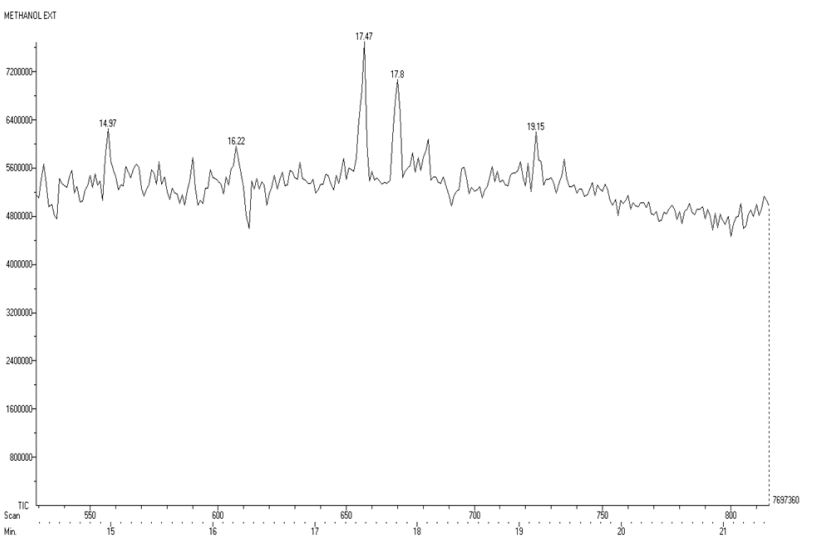
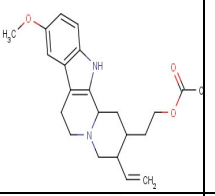
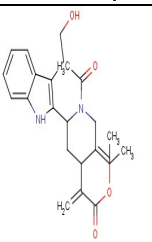
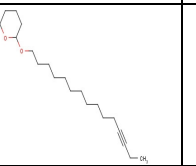
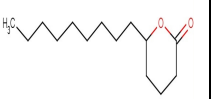
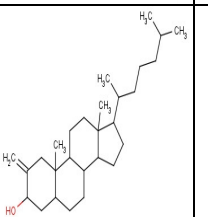


Figure 2: GC-MS of *Catharanthus roseus* leaves

Table 1: Properties of chemical compounds

Compound Name	Compound ID	Molecular Formula	Molecular Weight [g/mol]	Compound Structure	Hydrogen Donor and Acceptor
Corynan-17-ol, 18, 19-didehydro-10-methoxy-, acetate (ester)	550058	$C_{22}H_{28}N_2O_3$	368.46932		1,4
4-piperidineacetic, 1-acetyl-5-ethyl-2-[3-[2hydroxyethyl] -1H-indol-2-yl]-a-methyl-methyl ester.	5379474	$C_{23}H_{28}N_2O_4$	396.47942		2,4
2H-Pyran, tetrahydro-2- [12-pentadecynyloxy]	41961	$C_{20}H_{36}O_2$	308.49864		0,2
2H-Pyran-2-one, tetrahydro-6-nonyl-	520296	$C_{14}H_{26}O2$	226.35504		0,2
Cholestan-3-ol, 2-methylene, (3a, 5a).	3240	$C_{27}H_{48}O$	388.66942		1,1

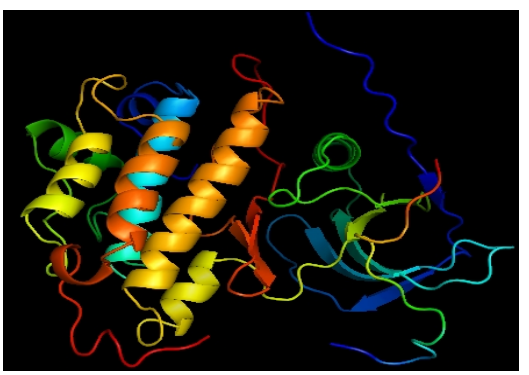


Figure 3: Crystal structure of EGFR protein

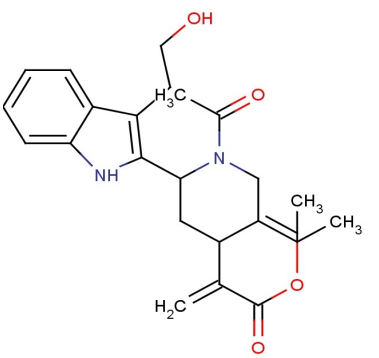


Figure 4: Structure of 4-piperidineacetic, 1-acetyl-5-ethyl-2-[3-[2-hydroxyethyl]-1H-indol-2-yl]-a-methyl-, methyl ester

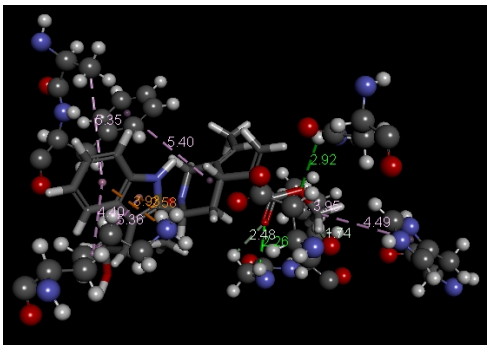


Figure 5: 3D Interaction between EGFR complex to 4-piperidineacetic, 1-acetyl-5-ethyl-2-[3-[2hydroxyethyl] -1H-indol-2-yl]-a-methyl-methyl ester

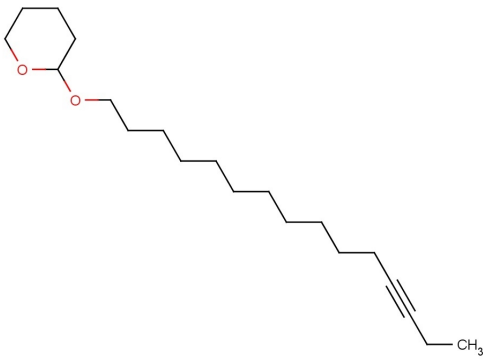


Figure 6: Structure of 2H-Pyran, tetrahydro-2- [12-pentadecynyloxy]-

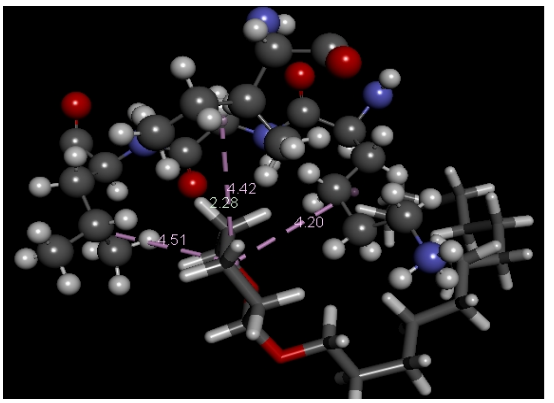


Figure 7: 3D Interaction between EGFR complex to 2H-Pyran, tetrahydro-2- [12-pentadecynyloxy]

DISCUSSION

Natural source are increasingly used in identification of new medicinal agents which are important for many clinical purposes. Molecular docking is important methods in computerized drug designing for targeted disease. Herbalism has a long tradition of use of outside of conventional medicine. It is becoming now more as main stream due to improvements in analysis and quality control along with advances in clinical research. *Catharanthus roseus* commonly called Madagascar periwinkle is herbaceous plant which exhibits the anti-cancer activity. This plant produces a diverse array of secondary metabolites that are pharmaceutically important and used as chemotherapeutic agents in the treatment of several types of cancers. This study was structure-based drug design for Non-Small Cell lung cancer. *In Silico* technique strongly supports and helps to identify the novel and more potent inhibitors through the mechanism of Ligand-Receptor interaction. Many drugs are available for clinically non-small cell lung cancer (NSCLC). Here we used GC-MS analysis of extraction of *Catharanthus roseus* plant leaves for inhibiting NSCLC responsible protein. The new investigation of 4-piperidineacetic, 1-acetyl-5-ethyl-2-[3-[2-hydroxyethyl]-1H-indol-2-yl]-a-methyl-methyl ester compound was higher with stronger binding affinity and hydrogen bond interactions. There are 4 hydrogen bond interactions results with corresponding amino residues for LYS-745, ASN-842, ASP-855, GLY-857 and libdock score value was 112.106. The present *In-silico* docking study proves the *Catharanthus roseus plant* leaves extract compounds as higher libdock score value to inhibit the epidermal growth factor receptor (EGFR) responsible for non-small cell lung cancer. Our previous research has already proved that marine source phytochemicals are used as drug for blocking BRCA1 Breast cancer protein[37,38]. Always natural source are eco-friendly and less side effects. Our present study suggest that *Catharanthus roseus* plant leaves extract compounds are potential drug for inhibiting non-small cell lung cancer.

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