Journal of Applied BioScience Research 1(2014) 20-23

Journal of Applied BioScience Research

In Silico molecular docking studies for the Human estrogen receptor (ESR-1) from the *Plumeria rubra* and *Entada purseatha*

Narasimharao Bhogireddy[1], Gayathri Muppalaneni[1], Pardhasaradhi Mathi[1], Venkateswara Rao Talluri[1], Venkata Raman Bokka[2*]

1 Department of Biotechnology, K L University, Green fields, Vaddeswaram, Guntur Dist-522 502, AndhraPradesh, India.
2 Department of Basic Sciences-Chemistry, Madanapalle institute of technology and science, Madanapalle, Chittoor Dist-517 325, AndhraPradesh, India.

ARTICLE INFO
Received in 28 August 2014 Received in revised form 7september 2014 Accepted 10 September 2014

Abstract

Estrogen Receptor 1 (ESR1) is a human estrogen receptor alpha coding gene. It is a ligand activated transcription factor and member of nuclear receptor family. 70% of cancer cells express estrogen receptors. Here, we have analyzed plant compounds as a part of potent inhibitors for breast cancer. Molecular docking studies were carried out using plant compounds against ESR1 protein with commercially available drugs as positive controls. Among many plant compounds five of them are showing best glide score against ESR1 protein target. These observations find application for the consideration of such compounds for further validation towards inhibiting the target.

Key words: Ligand, inhibitor, Estrogen receptor, ESR1, molecular docking (MD).

1.0 Introduction

Breast cancer is the most commonly diagnosed cancer in women and responsible for 27.8% of all new cancer cases among women. It is estimated that there are 57, 230 new breast cancer cases each year [18]. Though very rarely, also men can be suffering from breast cancer. In India, it is the second most common cancer in women. More frequently, it is hormone-dependent i.e. hormones stimulate the cancer cells to grow. This means that the growth of the cancer cells can be down regulated by the oppositely active hormones or so called anti hormones.

Corresponding author: VenkataRaman Bokka
Email: drbvraman@gmail.com

Now a day's hormone therapy is possible as an adjuvant treatment on breast cancer as well as with metastasis. Mainly, surgery, radio, chemo, and hormonal therapy form a common combination which has to be coordinated for each individual treatment. The natural female sex hormone estrogen, 17b-estradiol (E2), which plays a prominent role in mediating the maturation, proliferation, differentiation, apoptosis, inflammation, metabolism, homeostasis, and brain function and influences the growth and development of breast cancer [3, 15, 8]. The biological activity of E2 in hormone-sensitive tissues is actively regulated by the inter conversion by 17b-hydroxysteroid dehydrogenase between E2 and the less active hormone, estrone [14].

For the deficiency of E2, and its numerous involvement and particular importance, in healthy women may be associated with an increased risk of various diseases. On the contrary, the normal existence of E2 in women with hormone-positive breast cancer may worsen the disease. However, the hormone therapy means that synthetic estrogens and in particular, anti-estrogens are used to inhibit the physiological activities of E2, that would **Structure of estrogen receptor:** This is a ligand-inducible transcription factor that belongs to the nuclear receptor super family and acts as a dimeric species. In the early 1960s, Jensen and Jacobsen first demonstrated that a specific protein was responsible for the concentration of physiological levels of E2 in target tissues [4, 5, 9]. This protein is now known as the ER. ERα and ERβ represent two separate gene products. The hERα protein consists of 596 amino acids with a molecular weight of 66 kDa [6] and is located on chromosome 6 [11], while the hERβ sequence encodes a protein of 530 amino acid residues with a molecular weight of 59 kDa [17] and is positioned on chromosome 14 [16]. Like other nuclear receptors, the ER has a multi domain structure consisting of six functional regions, from the N-terminal A/B domain to the C-terminal F domain, which show various degrees of sequence conservation.

otherwise stimulate the growth and development of breast cancer, so as to control and treat the disease. There are a number of constraints that have deterred companies from investing in new anticancer drugs. Development of novel compounds to combat breast cancer is needed. Taking into consideration of protein in this current study of Estrogen receptor 1 (ESR1).

Advances in computational techniques have enabled virtual screening to have a positive impact on the drug discovery process. An advantage of this technique is that based on the predicted binding affinity data. The three dimensional structure of the protein-ligand composite could be served as a considerable source of understanding the way of protein interact with one another and perform biological functions [10]. Therefore, it is worthwhile to know the comprehensive structure of protein-ligand and its complexes at atomic level and is one of the significant subjects in biological sciences. Therefore activities can be quantified in a biochemical assay thereby reducing the time and expenditure in identifying new leads[13,12].

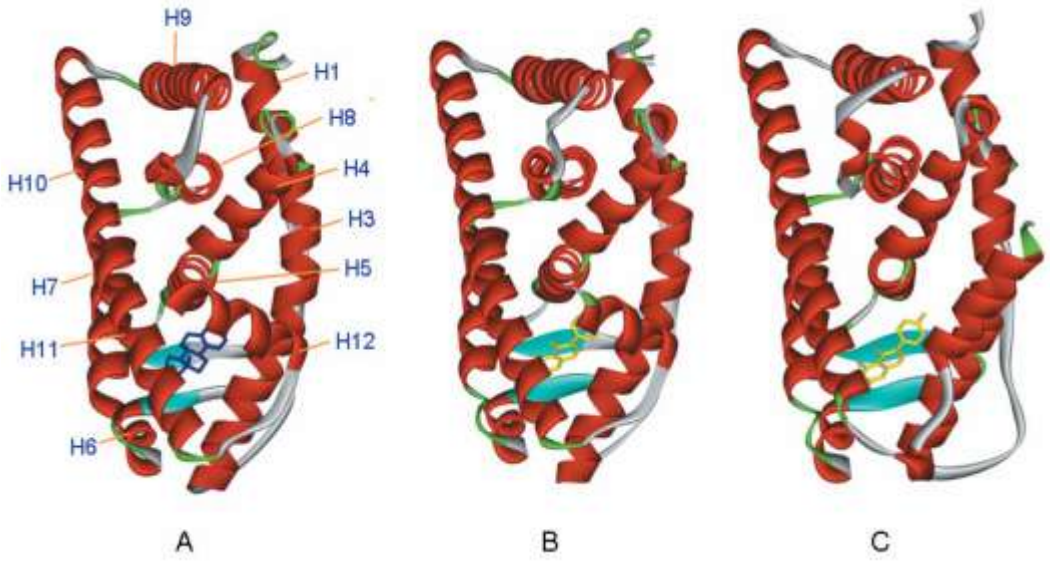

Fig.1 3D structure of the ERα (A, ligand E2; B, ligand genistein) and ERβ (C, ligand genistein) LBD monomer

2.0 Materials and methods

In this study, Protein is identified and downloaded from Protein Data Bank [2]. Preparation was done by using Schrodinger maestro 9.2. From GC-MS analysis, 40 plant compounds were selected from ethanolic extract of *Plumeria rubra* and *Entada purseatha* plants based on the studies reported in literature and prepared by using ligprep wizard in maestro 9.2.

2.1 Protein-ligand docking

It is a process for promising and consistent scoring scheme to evaluate the protein-ligand complex in which two molecules fit together in 3D space. It is a key tool in structural biology and computer-aided drug design [19]. The goal of ligand and protein docking is mainly to predict the predominant binding

mode(s) of a ligand with a protein of known three-dimensional structure. Schrodinger 9.3 is used for molecular docking analysis. Receptor docking is done by Glide [Grid-Based Ligand Docking with Energetics] in Schrodinger suite [7]. Glide is an integrated platform and a systematic approach for searching conformations, orientations and positions of ligand in the receptor site using a series of hierarchical filters which improves the binding affinities by lowering the penalties.

3.0 Results and Discussion

Molecular docking has become a vital part of contemporary drug research. Flexible ligand based high-throughput virtual screening (HTVS) mode of Glide is carried out and identified inhibitors against the pdb. Then, all these ligands are docked with the original protein. The process of docking using the Receptor Grid Generation protocol with centroid at the active site of the enzyme generated grid file represented the shape and properties of receptor on a grid for more accurate scoring of ligand pose. More than one crystal structures (1JNX, 1N5O, 1OQA, 1JM7, 1T2U, 1T2V, 1T29, 1Y98 and 1T15) are available for the ESR1 in Protein Data Bank. The selective ESR1 inhibitor's gained acceptance by many earlier works such as the molecular docking study of the designed ligands with human estrogen receptor (PDB ID: 1R5K) shows that all the designed ligands are showing better docking score than that of prototype Clomifene which predicts that the designed ligands have the better binding affinity with the estrogen receptor than Clomifene. This prediction leads us to believe that the designed ligands will possibly be suitable for treatment of endometriosis. [1]

Table 1: Docking results of Commercial available drugs against ESR1 Protein

	PDB ID	Resolution	Ligand Name	Glide Score
	1R5K	2.70	GW538:(2E)-3-{4-[(1E)-1,2-DIPHENYLBUT-1-ENYL]PHENYL}ACRYLIC ACID	-5.57

Table 2:Docking results of plant compounds against ESR1 protein

Ligand name	H-Bonding	Sitemap	G-Score	Interacting residues
Glycidol stearate	-0.70	-0.14	-9.35	Tyr 526
N-Acetyl-L tyrosinamide	-1.26	-0.64	-8.73	Met 388,Glu353,Leu 346
(2-Hydroxy-3-oxo-1,4,6-cycloheptatrienyl)-p-benzoquinone	-0.59	-0.54	-8.66	Leu 346
Hexadecanoic acid, 2-hydroxy-1-(hydroxymethyl)ethyl ester	-1.97	-0.47	-7.44	Leu 346
2Furancarboxaldehyde	-1.36	-0.40	-6.89	Arg 394,Leu 387

The Glycidol stearate had good interactions and good glide score with the protein compared to ligand GW538 (with PDB ID: 1R5K).It has a hydrogen bonding of -0.70 and Tyr526 had an interaction towards the ligand molecule. This study will be useful in designing novel ESR1- inhibitors based on docking

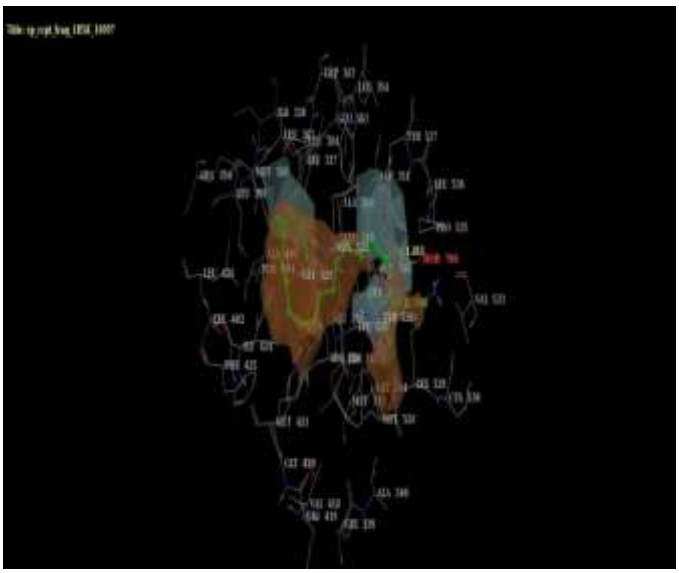

Fig 2: Docking result of the Glycidol sterate

4.0 Conclusion

In the present study, there is an increasing interest to inhibit the action of estrogen by binding to the estrogen receptor. Hence, the structure of ESR is screened using molecular docking techniques against for the natural compounds derived from the plants and commercially available drugs. Docking studies were performed in the Glide XP mode. The docking score, H-bond interactions were compared between the commercially available drugs and natural compounds derived from the plant. From the result, it has been concluded that a five compounds shows the best scoring function than the commercially available drug GW5638. These observations find application for concluded that these natural compounds derived from the plant could be a novel inhibitor for ESR1 protein.

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