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ANTICANCER POTENTIAL OF ISOLATED PHYTOCHEMICALS FROM *HOPEA ODORATA* AGAINST BREAST CANCER: *IN SILICO* MOLECULAR DOCKING APPROACH

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ABSTRACT

Breast cancer malignancy is prevailing among the women not only from the developing countries but also from the developed one at the rate of 18% of total population worldwide. One of the main causes of breast cancer is estrogen receptor alpha. Over expression of estrogen receptor is seen in number of cases of breast cancer. The aim of this study was to screen out the effective bioactive compounds from *Hopea odorata* namely Ampelopsin H, Balanocarpol, Betulinic acid, Betulonic acid, Caryophyllene oxide, Friedelin, which may be potential inhibitors of estrogen receptor alpha (ER-α) for searching a drug against the breast cancer. A wide range of docking score found during molecular docking by Schrodinger. Ampelopsin H, Balanocarpol, Betulinic acid, Betulonic acid, Caryophyllene oxide, Friedelin showed the docking score -6.244, -1.963, -4.499, -3.803, -7.236, -4.710 respectively. Among all the compounds Caryophyllene oxide showed best docking score towards estrogen receptor alpha. So, Caryophyllene oxide is the best compounds for selective inhibitors of estrogen receptor alpha, as it possessed best value in Molecular docking. Further *in vivo* investigation need to identify estrogen receptor alpha inhibitory activity of isolated compounds from *Hopea odorata*.

KEYWORDS: *Hopea odorata*, Estrogen receptor alpha, Breast cancer, Caryophyllene oxide, Ampelopsin H.

INTRODUCTION

Breast cancer is a family of illnesses where cells in the breast tissue develop and divide without everyday manipulate. As the maximum common most women in modern societies, breast cancer is a complicated and important disease. Even though approximately 87% of all cases survive for 5 years, nearly half of all women die from to breast cancer by one decade after diagnosis.[1-3] ER signaling is complicated. ER is known to associate with numerous cofactors that act at multiple levels, including transcription, translation and even post translation. The classical estrogen pathway is the direct binding of estrogen-responsive elements by using ligand-activated ER to alter gene expression. Estrogen may also act as a co-activator of other transcription elements to show on oncogenes in breast most cancers in the non-classical pathway.[4-6] Moreover, estrogen can stimulate fast, extranuclear (nongenomic) signaling occasions, along with the activation of the Src/Ras/Erk signaling pathway.

Molecular docking methodologies are of terrific importance in the making plans and layout of new drugs. These strategies goal to expect the experimental binding mode and affinity of a small molecule within the binding site of the receptor target of interest. A successful docking methodology must be able to correctly predict the native ligand pose the receptor binding site (i.e.to find the experimental ligand geometry within a certain tolerance limit) and the associated physical-chemical molecular interactions.[7]

Hopea odorata is a species of plant in the Dipterocarpaceae family. It is found in Bangladesh, Cambodia, India, Laos, Malaysia, Myanmar, Thailand and Vietnam.[8] It is a large tree reaching up to 45 m in height with the base of the trunk reaching a diameter of 4.5 m. It grows in forests, preferably near rivers, at altitudes between 0 and 600m. In places such as West Bengal and the Andaman Islands, it is often planted as a shade tree.[9] Valued for its wood, it is a threatened species in its natural habitat.[10] The dammar of this tree is stated to have medicinal assets utilized in treating sores and wounds.[11] Phytochemical studies reported that the heartwood of *H. Odorata* has certain types of phenolic compounds.[12] These polyphenols are said to be useful as antioxidants, anticarcinogens, scavengers of free radicals and therefore have implications for the prevention of pathologies such as cancer and cardiovascular disease.[13,14]

The aim of this study was to screen out the effective bioactive compounds from *Hopea odorata*, which may be potential inhibitors of estrogen receptor alpha (ER-α) in future and may act as a drug which may be effective in preventing the breast cancer.

MATERIALS AND METHODS

Protein Preparation

Three-dimensional crystal Structure of estrogen receptor alpha (PDB id: 3ERT) was downloaded in pdb format from the protein data bank.[15] After that, the structure was prepared and refined using the Protein Preparation Wizard of Schrödinger-Maestro v10.1. Charges and bond orders were assigned, hydrogens were added to the heavy atoms, selenomethionines were converted to methionines, and all waters were deleted. Using force field OPLS_2005, minimization was carried out setting maximum heavy atom RMSD (root-mean-square-deviation) to 0.30 Å.

Ligand Preparation

Compounds were retrieved from PubChem databases, i.e. Ampelopsin H (CID 161557), Balanocarpol (CID 478626), Betulinic acid (CID 64971), Betulonic acid (CID 9933683), Caryophyllene oxide (CID 14350) and Friedelin (CID 91472). The 3D structures for these were built by using Ligprep2.5 in Schrödinger Suite 2015 with an OPLS_2005 force field. Their ionization states were generated at pH7.0±2.0 using Epik2.2 in Schrödinger Suite. Up to 32 possible stereoisomers per ligand were retained.

Receptor grid generation

Receptor grids were calculated for prepared proteins such that various ligand poses bind within the predicted active site during docking. In Glide, grids were generated keeping the default parameters of van der Waals scaling factor 1.00 and charge cutoff 0.25 subjected to OPLS 2005 force field. A cubic box of specific dimensions centered around the centroid of the active site residues (Reference ligand active site) was generated for the receptor. The bounding box was set to 14 Å × 14 Å × 14 Å for docking experiments.

Glide Standard Precision (SP) ligand docking

SP flexible ligand docking was carried out in Glide of Schrödinger-Maestro v 10.1.[16, 17] within which penalties were applied to non-cis/trans amide bonds. Van der Waals scaling factor and partial charge cutoff were selected to be 0.80 and 0.15, respectively for ligand

atoms. Final scoring was performed on energy-minimized poses and displayed as Glide score. The best-docked pose with lowest Glide score value was recorded for each ligand.

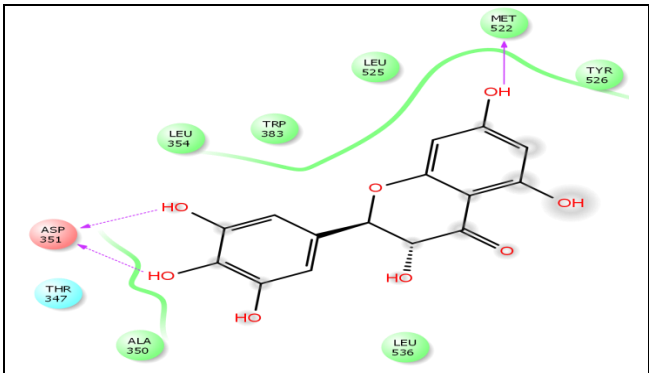
RESULTS

In silico Molecular Docking analysis

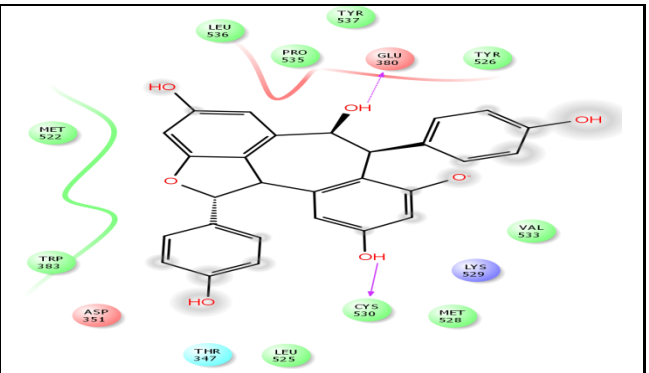
Advances in computational techniques have enabled virtual screening to have a positive impact on the discovery process. Virtual screening utilizes docking and scoring of each compound from a dataset and the technique used is based on predicting the binding modes and binding affinities of each compound in the dataset by means of docking to an X-ray crystallographic structure[18] Grid based docking study was used to analyze the binding modes of molecules with the amino acids present in the active pocket of the protein.[19] In order to study the interaction of the compounds Ampelopsin H, Balanocarpol, Betulinic acid, Betulonic acid, Caryophyllene oxide, Friedelin with estrogen receptor alpha (ER-α). We performed Glide docking analysis by Schrodinger suite v10.1, where among of these compounds Caryophyllene oxide shows highest docking score shown in Table 1. The negative and low value of free energy of binding demonstrates a strong favorable bond between 3ERT and Caryophyllene oxide in most favourable conformations. The results of docking analysis were described in Table 1 and the docking figure showed in Figure 1.

Table 1: Docking results of Ampelopsin H, Balanocarpol, Betulinic acid, Betulonic acid, Caryophyllene oxide, Friedelin with estrogen receptor alpha (PDB: 3ERT).

Compound Name	Docking Score	Glide emodel	Glide energy
Ampelopsin H	-6.244	-54.755	-39.103
Balanocarpol	-1.963	-45.124	-36.664
Betulinic acid	-4.499	-40.481	-33.961
Betulonic acid	-3.803	-38.306	-31.462
Caryophyllene oxide	-7.236	-28.811	-21.916
Friedelin	-4.710	-43.963	-34.177



A. Ampelopsin H



B. Balanocarpol

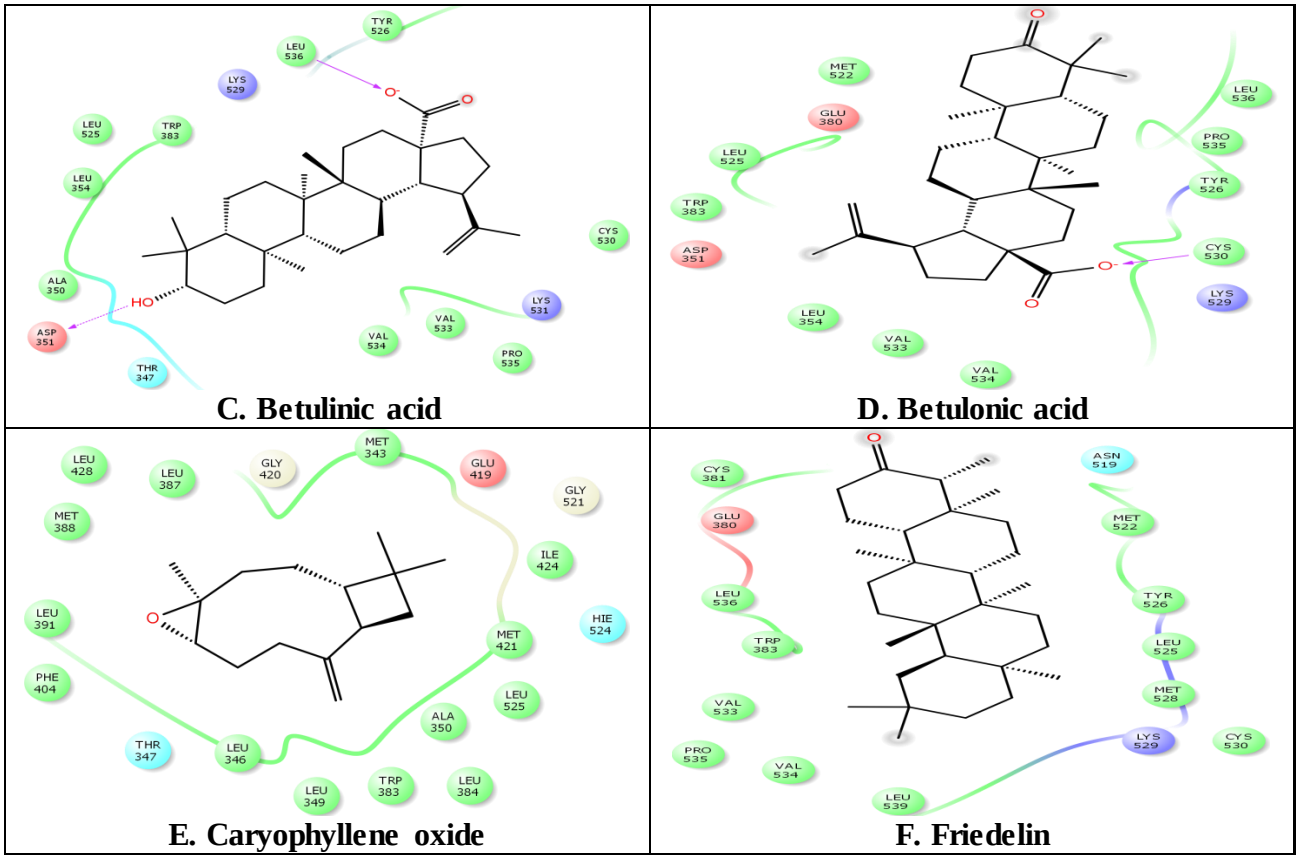


Figure 1: Docking results of A. Ampelopsin H, B. Balanocarpol, C. Betulinic acid, D. Betulonic acid, E. Caryophyllene oxide, F. Friedelin with estrogen receptor alpha (PDB: 3ERT).

DISCUSSION

Breast cancer is known as a death sentence and second major cause of death in world. Ratio of breast cancer in is one in nine in case of women.[20] Main cause of breast cancer is over expression of estrogen receptor alpha.[21] Therefore ER-α is used as a target for prevention of breast cancer. Tamoxifen is an antagonist of ER-α and commercially available as a drug to control the breast cancer.[22] It binds with Arg394 and blocks the function of estrogen receptor and inhibits the function of ER-α.[23]

Docking allows the scientist to virtually screen a database of compounds and predict the strongest binders based on various scoring functions. It explores ways in which two molecules, such as drugs and an enzyme Human estrogen receptor fit together and dock to each other well, like pieces of a three-dimensional jigsaw puzzle. The molecules binding to a receptor, inhibit its function and thus act as drug. In recent research, computer aided drug designing (CADD) helps the researcher to decrease the time and money for drug designing projects.[24] Molecular docking is very helpful in studying the interactions of ligand

molecules with the target protein before its *in vitro* synthesis. Docking is performed through computer programs like Maestro.

To screen out the effective bioactive compounds from *Hopea odorata* namely Ampelopsin H, Balanocarpol, Betulinic acid, Betulonic acid, Caryophyllene oxide, Friedelin, which may be potential inhibitors of estrogen receptor alpha (ER-α) for searching a drug against the breast cancer. We performed Glide docking analysis by Schrodinger suite v10.1. A wide range of docking score found during molecular docking. Ampelopsin H, Balanocarpol, Betulinic acid, Betulonic acid, Caryophyllene oxide, Friedelin showed the docking score -6.244, -1.963, -4.499, -3.803, -7.236, -4.710 respectively. Among of these compounds Caryophyllene oxide shows highest docking score shown in Table 1. The negative and low value of free energy of binding demonstrates a strong favorable bond between 3ERT and Caryophyllene oxide in most favourable conformations.

CONCLUSION

Among all the compounds Caryophyllene oxide showed best docking score towards estrogen receptor alpha. So, Caryophyllene oxide is the best compounds for selective inhibitors of estrogen receptor alpha, as it possessed best value in Molecular docking. Further *in vivo* investigation need to identify estrogen receptor alpha inhibitory activity of isolated compounds from *Hopea odorata*.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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