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Insilico - Docking analysis of crude ethanolic extract of *Borreria hispida* (L.) K. Schum against Breast cancer targets

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KEYWORDS

Borreria hispida, GCMS analysis, docking and breast cancer

A B S T R A C T

Cancer is a neoplasmic deadly disease that involves unregulated cell division and tissue invasiveness. Existing lines of cancer treatment include surgery, radiation, and chemotherapy. These modern lines of treatment produce serious side effects. Recent studies established that herbs and herbal medicine are free from serious side effects. The aim of the present study is to evaluate the ethanolic plant extract subjected to GC-MS analysis and docking. In the present investigation, The GC-MS analysis revealed the presence of thirty two compounds. These compounds were subjected to pre ADMET analysis for identifying potent breast cancer leads. Breast cancer targets were downloaded from RCSB PDB for docking studies. Seven lead compounds were selected for docking studies based on preadmet insilico analysis. Using Discovery studio 4.0 the following compounds bicyclo[3.1.1]heptane,2,6,6-trimethyl, cyclohexane,1-methyl-4-(1-methylethenyl)-trans, 7-thiabicyclo [4.1.0]heptane,2-methyl-, cyclo-2,5- hexa-diene-1,4-dione, 2-methyl -5- (4-morpholinyl)-, squalene, 2-methyl-3-(3-methyl-but-2-enyl)-2-(4-methyl-pent-3-enyl)-oxetane, supraene, benzene, 2-[(tert-butyldimethylsilyl)oxy]-1-isopropyl-4-methyl, beta-amyrin, alpha-amyrin, olean-12-ene, 3- methoxy)-, urs-12-ene and 9,19-cycloergost-24(28)-en-3-ol,14-dimethyl-, (3.beta.,4.alpha.,5.alpha)- were docked with breast cancer targets. The phytochemicals present in the ethanolic extract of *Borreria hispida* showed anticancer activity against breast cancer.

Introduction

In breast cancer, breast cells lose their normal control and start to proliferate at higher rate as compared to normal cells. Breast cancer is the most familiar form of cancer which affects the women's around the world and the second major form of cancer which is a cause of death next to the lung cancer. Rate of breast cancer is high in developed countries as compared to the developing countries (1). Number of molecular factors are determined which are used in diagnosis and remedy of breast cancer. Estrogen receptor alpha(ER-α) is most commonly used molecular marker for

breast cancer. ER-α is the member of nuclear receptor family which controls number of physiological processes. Estrogen is the ligand of ER which activates the estrogen receptor. Overexpression of ER-α is seen in breast cancer (2). Ratio of ER positive breast cancers is sixty percent (3).

Medicinal plants and their extracts are used as a source of medicine. 25% of total medicines are taken from the plants in well developed countries while in developing countries rate is much higher (4). Phytochemicals are molecules present in plants and control the number of diseases. Aim of this study was to screen out the effective bioactive compounds which may be potential inhibitors of ER-α in future and may act as a drug which may be effective in preventing the breast cancer.

Current study was totally based on the screening of phytochemicals from the plant *Borreria hispida* to find out the potent biomolecules having strong bonding actions as compared to tamoxifen.

Materials and Methods

Insilico docking studies-selection of lead and target molecule

Phytochemicals were identified by interpreting mass spectrum of GC-MS analysis of ethanolic extract of *B. hispida* using the database of National Institute Standard and Technology (NIST) which is having more than 62000 patterns.

The mass spectrum of the unknown component was compared with the spectrum of the known components stored in the NIST library. The name, molecular weight and structure of the component of the test materials were ascertained from the NIST library and used as lead compounds.

Pharmaco-kinetic, Pharmaco-dynamic profiling and *Insilico* docking studies, of the plant *B. hispida* was carried out by the steps described by Sneha (2014). Pub-MED, Medline database reference was used to retrieve information on breast cancer genes. Docking studies were carried out in Discovery studio.

Results and Discussion

SDF file format of the following genes were downloaded and saved for docking studies. From the receptor and script option water molecules and ligand molecules were selected and deleted. From the menu: Tools - select Define and Edit binding site and click receptor cavities to predict the number of poses or active sites. The results are presented in Fig a, b, c

The 2D structural files of the phytochemicals were retrieved in the form of SDF file format from PubChem ID, Nist –Cas Registry Number and Chem spider ID and were saved in desk top (Table 14a and 14b). These files were converted in to 2d mol file using smile converter (online tool Url - https://cactus.nci.nih.gov/translate/) and were further subjected to Pharmaco-kinetic and Pharmaco-dynamic analysis. The eleven compounds (highlighted with background colour) were finally selected for docking study. The compounds which includes (1) 7-Thiabicyclo [4.1.0] heptane,2-methyl, (2) 9,19-cycloergost -24 (28) –en -3-ol, (3) 14-dimethyl (3.beta.,4.alpha.,5.alpha) - (4) Alpha-amyrin, (5) 2-Methyl-3-(3-methyl-but-2-enyl)-2-(4-methyl-pent-3-enyl)-oxetane, (6) Beta-Amyrin, (7) Benzene,2-(tert-butyl dimethy sily)oxy]-1-isopropyl--methyl, (8) Cyclohexane,1-methyl-4-(1-methylethenyl)-trans, (9) Olean-12-ene, (3-Methoxy)-, (10) Squalene/Supraene and (11) Urs-12- ene were docked in Discovery Studio.

Table.1 Best docking score of ethanolic extract of *B. hispida* with ER Alpha and compared with Tamaxifen citrate

S.No	Cancer Target	Lead molecule Pub chem. ID	Pose No	lig. score1	lig.score 2	PLP1	PLP2	Jain	PMF	Dock score
Ref.	**Tamaxifen citrate**	**5035**	**1**	1.52	3.59	42.74	42.49	1.07	35.74	89.0686
1	4jc3-ER ALPHA	96082	1	0.97	2.37	31.15	30.89	1.72	52.66	17.429
		62790856	1	0.3	2.43	29.06	28.63	-0.34	28.09	12.706
		96082	2	-3.69	-7.81	-20.23	13.53	0.6	51.24	297.344
		62790856	2	-3.42	-5.99	-41.74	-5.9	-3.39	20.12	120.835
		550119	2	-4.33	-7.93	-16.97	6.59	-3.52	29.54	102.913

Fig. a Breast cancer proteins - BCAR 3, BRCA 1, BRCA 2 and IGF-IR

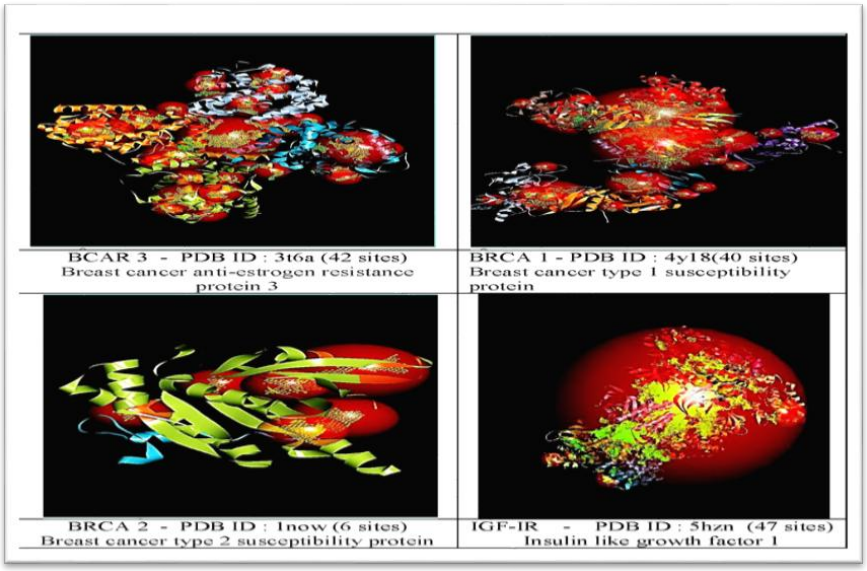


Fig. b Breast cancer proteins - Her2, MMP9, Pten and TP53

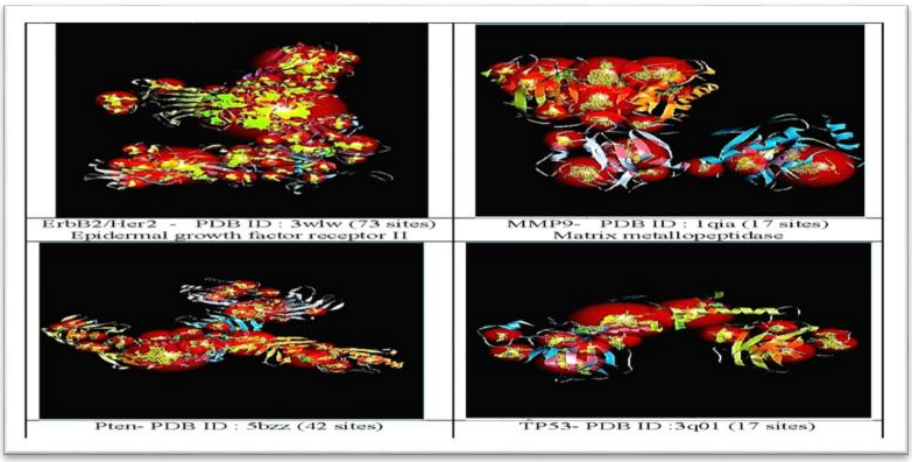


Fig. c Breast cancer protein – ER-alpha

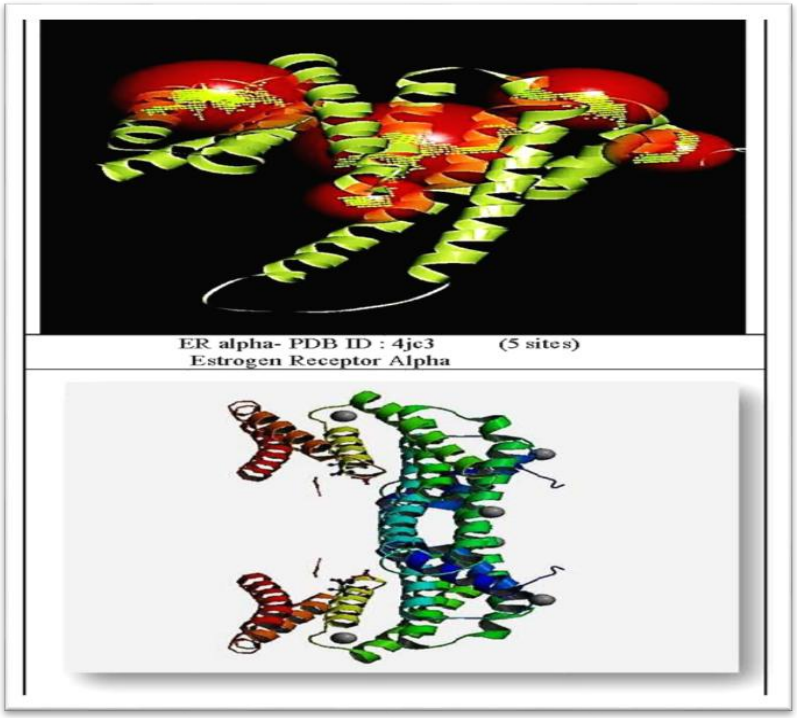


Fig.4 Docking of 7-Thiabicyclo [4.1.0] heptane, 2-methyl-with ER-Alpha, B- 2D diagram

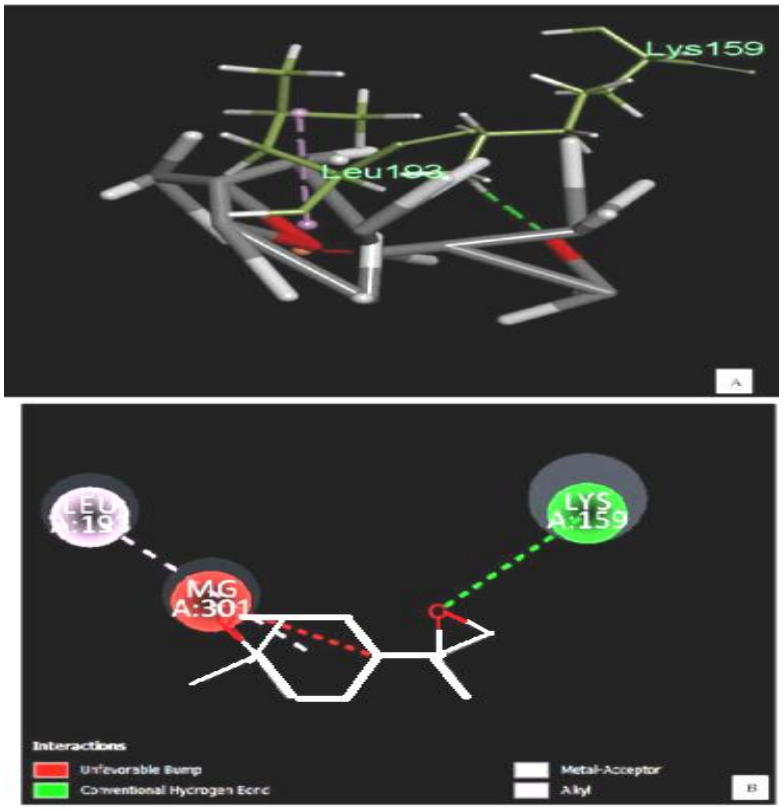


Fig.5 Docking of Benzene, 4-methyl-1 [(tert-Butyl dimethyl silyl) oxy with ER-Alpha, B - 2D diagram

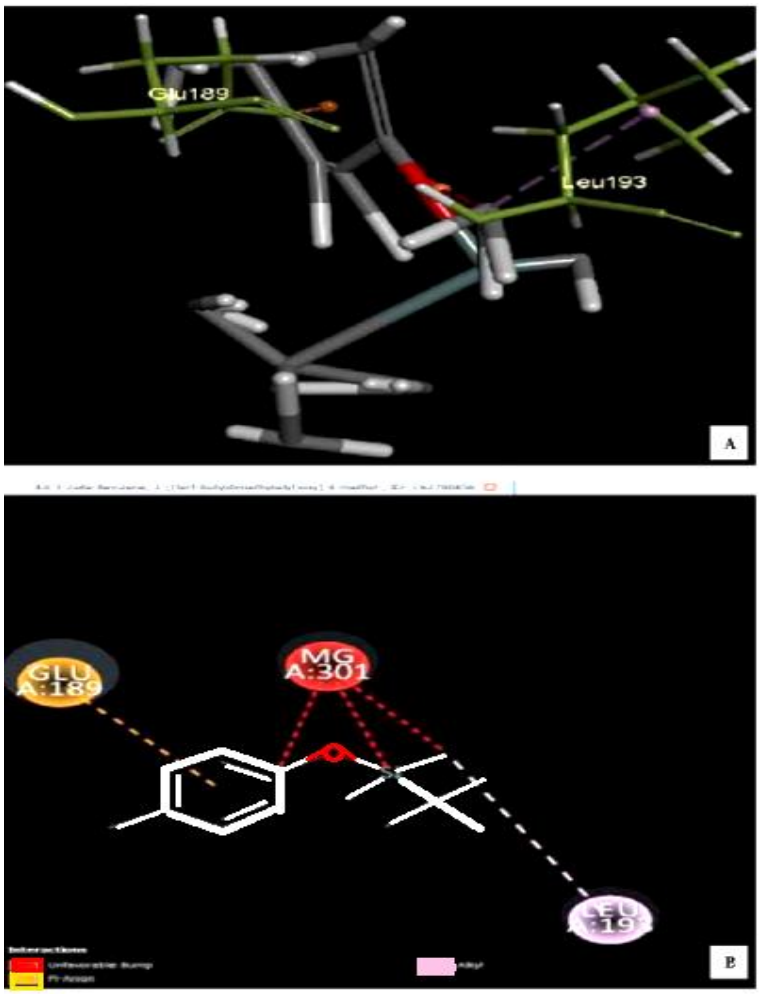
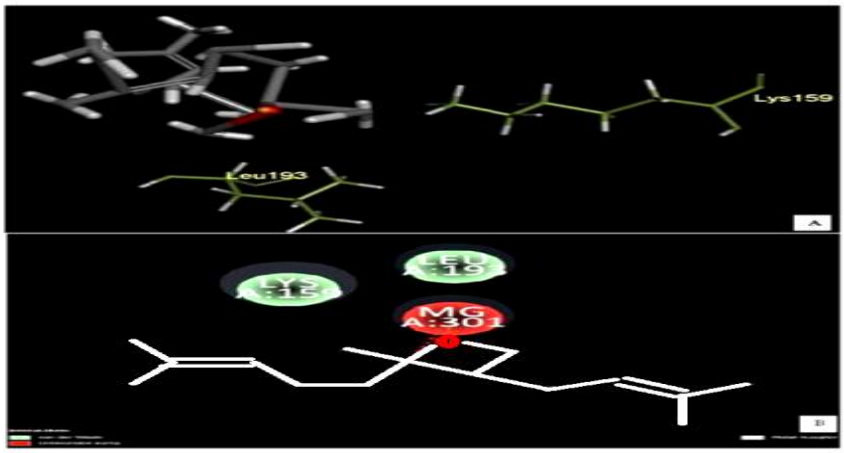


Fig.6 Docking of 2-Methyl-3-(3-methyl-but-2- enyl)- 2-(4-methyl-pent-3-enyl)-oxetane with ER-Alpha and it's 2D diagram



All the eleven lead molecular files of were opened in Discovery studio 4.0 (docking software) and clubbed together as a single file and cleared the geometry. First 4jc3 was opened; water molecules and Ligand molecules were deleted and the force field was applied. Dock the anti-cancer target 4jc3 against 11 selected lead molecules. The three molecules; 7-Thiabicyclo [4.1.0] heptane, 2-methyl, and Benzene, 2-[(tert-butyldimethyl silyl) oxy]-1-isopropyl-4-methyl and 2-Methyl-3-(3-methyl-but-2-enyl)-2-(4-methyl-pent-3-enyl)-oxetane only showed the result. From the docking result pose number, lig.score1, lig.score2, PLP 1, PLP2, Jain, PMF and Dock score were selected and compared.

Among the 32 identified phytochemicals only three compounds produced docking score. Among the 3 lead compound (Fig 4,5 and 6) 7-Thia bicyclo [4.1.0] heptane, 2-methyl was chosen the best with the dock score of 297.344 and three times greater than the value when compared with the drug used for breast cancer Tamaxifen citrate which shows 89.0686 dock score. Hence *insilico* docking studies of ethanolic extract of *B. hispida* showed the anticancer activity against ER alpha. Further the dosage and preclinical study would add a complete knowledge to the herbal world.

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