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IN-SILICO MOLECULAR SCREENING OF NATURAL PLANT PRODUCTS FOR THE IDENTIFICATION OF NOVEL POTENTIAL CHEMOTHERAPEUTIC AGENTS AGAINST BREAST CANCER

K. S. N. M. Megana and Y. Suneetha *

Department of Zoology, Sri Venkateswara University, Tirupati - 517502, Andhra Pradesh, India.

Keywords:

Breast cancer, Anti-cancer, Natural compounds, HER2, Molecular docking, Bioinformatics tools

Correspondence to Author:
Dr. Y. Suneetha

Assistant Professor, Department of Zoology, Sri Venkateswara University, Tirupati - 517502, Andhra Pradesh, India.

E-mail: ysuneethareddy4@gmail.com

ABSTRACT: *In-silico* computational approaches help in ascertaining drug targets *via* bioinformatics tools. HER2 is the most valuable therapeutic target for breast cancer therapy. The overexpression of HER2 protein plays a very critical role in the progression of breast cancer. Plant-derived natural products have received increasing attention over the past 20-30 years for their potential as novel therapeutic agents. In the future, plant products may offer more effective medicines than synthetic drugs. The main aim of the current study helps to develop new anti-cancer drug candidates from natural and dietary compounds with the help of computational approaches. In this context, the plant-derived compounds resveratrol and its related analogs were taken and docked onto the protein active site (PDB ID:1M14) *via* structure-based virtual screening for the prediction of novel potential inhibitors, which may be used as anticancer drugs against breast cancer. Furthermore, Molinspiration server and Data warrior software tools were used to evaluate the ADMET profiling and physicochemical parameters of the screened compounds. The best compound was identified, showing good binding affinity value, have a positive bioactivity score as well as good pharmacokinetic properties. Among all the test candidates in the study, the compound [3-hydroxy-5-[(E)-2-(4-hydroxyphenyl)ethenyl]phenyl] hydrogen sulfate (CID: 25113755) was found to be the most potent lead molecule. So the compound (CID: 25113755) could be used as novel anti-breast cancer agent.

INTRODUCTION: HER2 is also called as neu oncogene. Human epidermal growth factor receptor (HER) is a family of receptors plays a significant role in the focalization of numerous cancers. The receptor family consists of HER-1; HER-2; HER-3; HER-4, respectively [1]. The over-expression of HER-2 oncogene has been revealed to play a significant role in the progression of certain types of breast cancer [2, 3, 4]. Breast cancer has become a fatal disease among women in developing countries [5].

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According to the American cancer, society estimated new breast cancer cases in the United States for the year 2018 is 266, 120. [6] Patients with breast cancer have various therapeutic interventions include surgery, radiation therapy, chemotherapy, and hormone therapy [7]. Many of the distinguished breast cancer risk factors are western lifestyle patterns and environmental factors, low physical activity, western diet, over fatness, *etc.* [8, 9]

Natural compounds play an important role in cancer treatment and prevention. Recent studies suggested that high dietary intakes of raw and leafy vegetables, whole grains, along with related lifestyle significantly decrease the risk and prevalence of breast cancer [10, 11]. It can be evaluated that 1/3 of cancer-related deaths in the US can be evaded through proper dietary

modification. So, natural compounds have continually been investigated for the discovery of new drugs in pharmaceutical development and these products shown to have a wide range of pharmacological activities in clinical studies [12, 13].

Currently, more than 40-50% of drugs have been designed from plant-derived products, among them; 75-80% of anticancer drugs were developed from natural ingredients [14]. Resveratrol (RES) (3, 5, 4′-trihydroxytrans-stilbene) is a naturally occurring polyphenol and a member of the stilbene family. It is highly found in red wine, peanuts, mulberries, cranberries, dark chocolates, cocoa solids, soy, and skin of grapes [15, 16, 17]. It possesses a wide range of biological properties such as anti-viral [18] antiaging, anti-oxidant [19] and chemoprotective advantage against breast cancer. Due to its anticancer activity, it can be recognized as chemopreventive agent [20]. It takes years to discover a drug and bring to real-world use.

So to reduce the expenditure and time we used *in-silico* methods for the identification of novel leads or hits. Today, a variety of tools and software's available for docking calculations. Among them, Auto Dock Vina is the most modern version which has been widely used for virtual screening [21]. Here, we report binding affinity values of resveratrol related compounds using a set of open source molecular docking approach.

This article certainly focuses on natural compounds for the discovery of novel drug candidates towards the treatment of breast cancer.

MATERIALS AND METHODS:

In-silico Docking Analysis:

Ligand Preparation and Selection of Molecular Targets: Eleven potential compounds, including resveratrol and its analogs, were identified from the PubMed literature, which showed inhibitory effects on breast cancer. The X-ray crystal structure of the natural compounds was downloaded in "Structure Data Format" from Pub Chen compound database (http://pubchem.ncbi.nlm.nih.gov/). The breast cancer protein, namely HER2 (ID: 1M14), was chosen for our study. The correct crystal structure of the cancer target has been obtained from the RCSB Protein Data Bank (http://www.rcsb.org/pdb/home/home.do).

Calculation of Molecular Properties and Bioactivity Score: "Rule of 5" properties are a set of molecular descriptors used by Lipinski in formulating his "Rule of 5." The rule is helpful in the drug designing process. Molecular mass, lipophilicity (Log P), hydrogen bond acceptors (HBA), Hydrogen bond donors (HBD), bioactivity score, which was calculated using the online chemo informatics tool Molinspiration (http://www.molinspiration.com/).

***In-silico* Toxicity Potential Assessment:** The ADME and toxicity profile of different properties of compounds in the early stage is a crucial step in the drug discovery process. Toxic parameters of all the ligands were screened using computational analysis using Bioinformatics software Osiris Data Warrior. (http://www.openmolecules.org/data warrior.html).Toxicity profile includes screening for mutagenic, carcinogenic, & skin irritant.

RESULTS AND DISCUSSION:

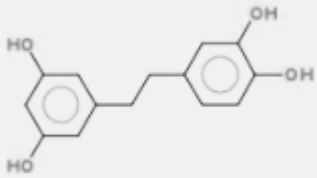
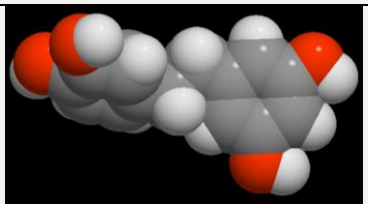
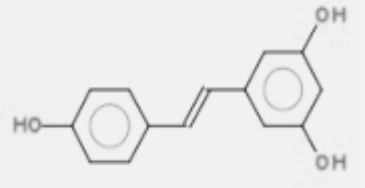
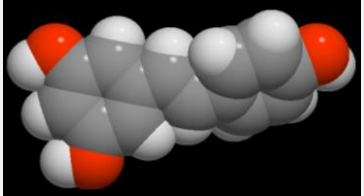
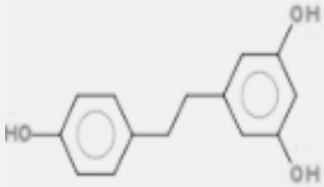
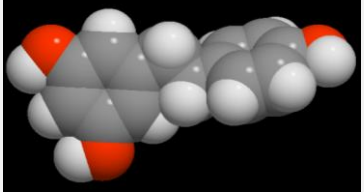
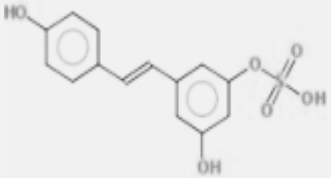
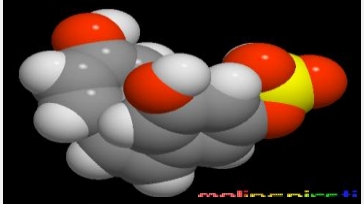
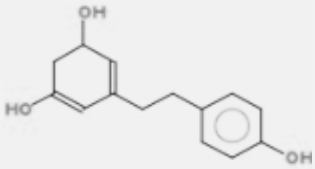
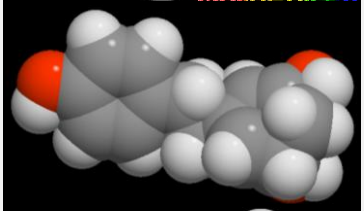
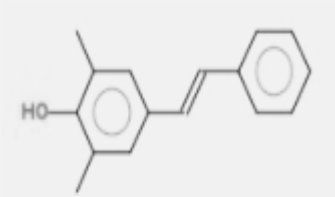
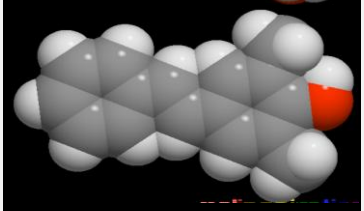
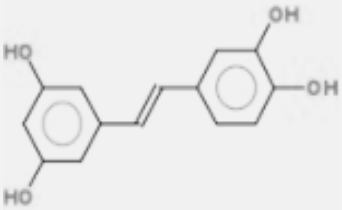
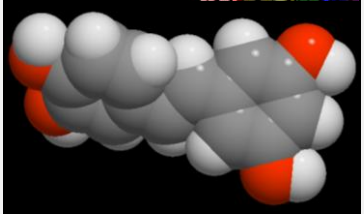
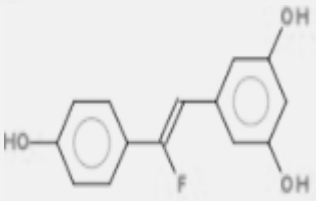
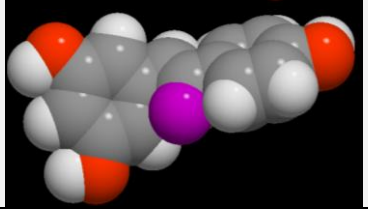
Structures of Selected Ligands: In this study structure of selected resveratrol and their related analogs, which are used as ligands are drawn with the help of Pub Chem. 2-Dimensional, as well as 3-Dimensional structures, were used for docking studies, as shown in **Table 1**.

Molecular Docking Studies on Resveratrol and their Related Compounds against a Target Protein Involved in Breast Cancer: Pub Chem database search showed eleven compounds that are related to natural compound resveratrol. To study the interaction and binding affinity of resveratrol and its analogs, all these compounds were docked with the receptor structure using Auto Dock Vina in Pyrx program by constructing the grid box with a dimension of 96×65×50 points around the region where the ligand was bound in the protein structure.

After the completion of the screening, the docked protein-ligand complexes were analyzed to examine the interactions. The pose having the highest binding affinity value, was selected for further analysis. The binding affinities of best-docked complexes namely, [3-hydroxy-5-[(E)-2-(4-hydroxyphenyl) ethenyl] phenyl]hydrogen sulphate (CID:25113755); 4-[2-(3, 5-dihydroxy phenyl) ethyl] benzene-1, 2-diol (CID:152444); 5-[(Z)-2 -

fluoro-2 -(4-hydroxyphenyl) ethenyl] benzene-1, 3-diol (CID:67144664); 5-[2-(4-Hydroxyphenyl) ethyl] benzene-1, 3-diol (CID:185914) showing high dock score -7.7, -7.4, -7.1, -7.0 Kcal/mol respectively. The virtual drug screening scores of top leads are tabulated in **Table 2**.

TABLE 1: 2D & 3D STRUCTURES OF SELECTED COMPOUNDS

Ligand ID	2-D Structure	3D Structure
152444		
1548910		
185914		
25113755		
5326961		
6365297		
667639		
67144664		

71816176

73659198

445154

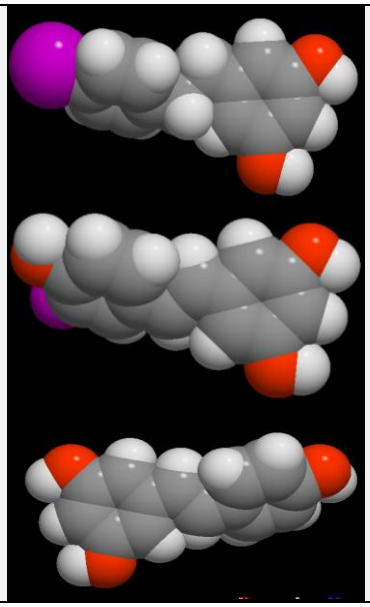


TABLE 2: AFFINITY SCORES OF BEST PROTEIN-LIGAND ASSOCIATION

ID	Docking score	Compound name
25113755	-7.7	[3-hydroxy-5-[(E)-2-(4-hydroxyphenyl)ethenyl]phenyl] hydrogen sulfate
152444	-7.4	4-[2-(3,5-dihydroxyphenyl)ethyl]benzene-1,2-diol
67144664	-7.1	5-[(Z)-2-fluoro-2-(4-hydroxyphenyl)ethenyl]benzene-1,3-diol
185914	-7.0	5-[2-(4-hydroxyphenyl)ethyl]benzene-1,3-diol
445154	-6.9	5-[(E)-2-(4-hydroxyphenyl)ethenyl]benzene-1,3-diol
73659198	-6.9	5-[(E)-2-(3-fluoro-4-hydroxyphenyl)ethenyl]benzene-1,3-diol

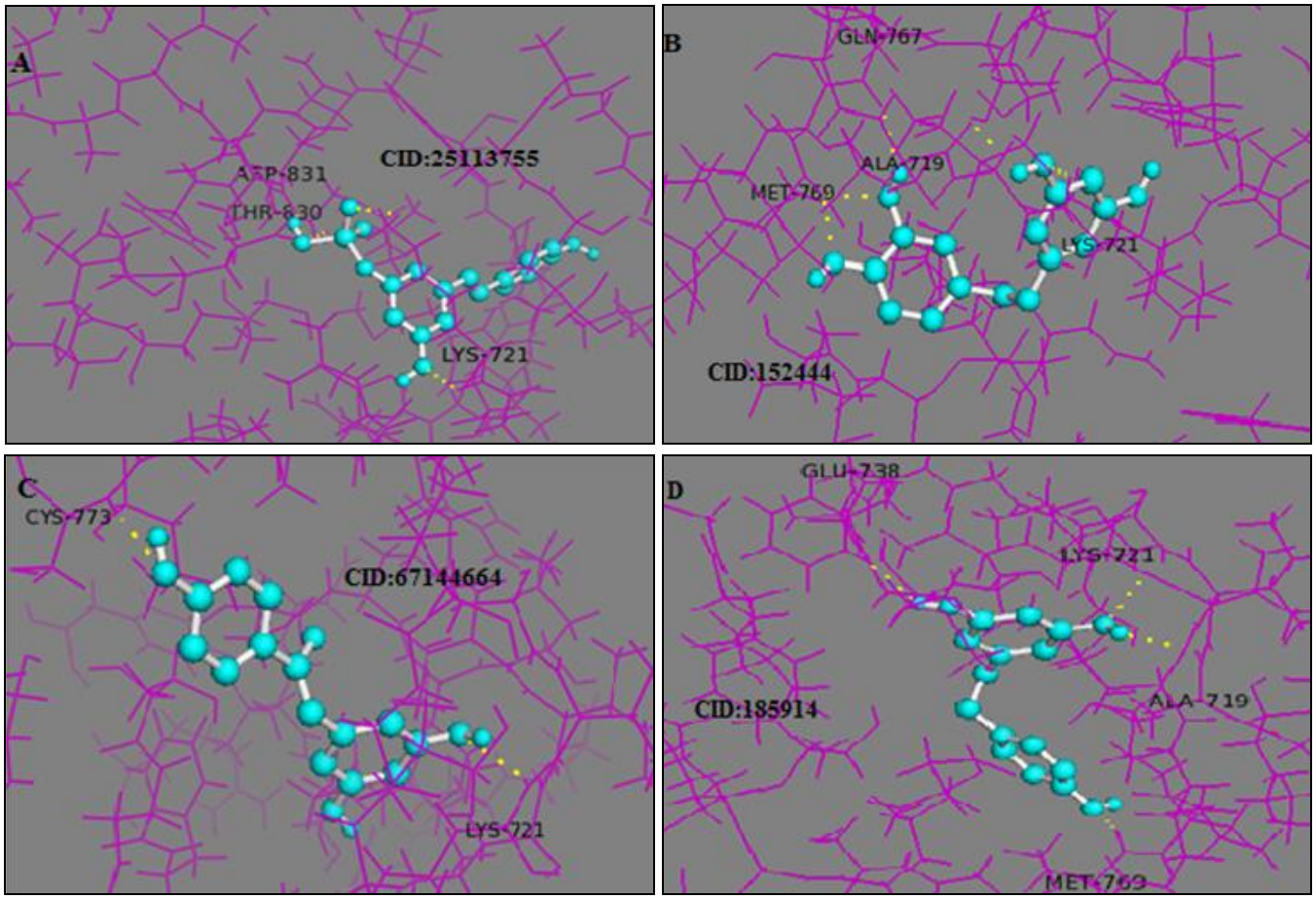


FIG. 1: THE INTERACTION OF LIGANDS WITH THE HER2 AND THEIR CORRESPONDING INTERACTING RESIDUES

Their respective interaction with the target protein and their corresponding interacting residues is shown in **Fig. 1(A-D)**.

Assessment of Bioactivity Score & Lipinski Properties: Eleven ligands were chosen for the investigation of bioactivity score and Lipinski properties. The SMILES format of each selected natural compound was uploaded into Molinspiration web services [22]. The equivalent molecular properties and bioactivity scores were retrieved. All the compounds showed no violations of all the five rules. The molecular weight of compounds less than 500, partition coefficient less than 5, Number of rotatable bonds less than 10, *etc*. The Log P value of top leads was found below five. Results of Lipinski properties of best virtual hits are depicted in **Table 3**. By analyzing the results of Molinspiration, it was known that the compounds have obeyed 'Rule of five' and satisfy all bioactivity parameters, such as follows: GPCR ligand, Ion channel modulator, nuclear receptor ligand, protease inhibitor, an enzyme inhibitor, and kinase inhibitor [23].

All these parameters were predicted by its score. The highest activity has the highest probability to be active. The score lies between -0.50 to +0.50 then the compounds can consider for oral drugs. The compound [3-hydroxy-5-[(E)-2-(4-hydroxy-phenyl) ethenyl] phenyl] hydrogen sulfate (CID: 25113755) satisfies the Lipinski properties and bioactivity score, are shown in **Table 4**.

TABLE 3: PHYSICOCHEMICAL PROPERTIES OF THE TOP LIGANDS

Compound ID	Chemical Formula	M log P	TPSA	HBA	HBD	No. of rotatable bonds	No. of violations	Volume
25113755	$C_{14}H_{12}O_6S$	0.58	104.06	6	3	4	0	247.34
152444	$C_{14}H_{14}O_4$	1.92	80.91	4	4	3	0	221.13
67144664	$C_{14}H_{11}FO_3$	2.77	60.68	3	3	2	0	211.85
185914	$C_{14}H^{14}O_3$	2.41	60.68	3	3	3	0	213.11
445154	$C_{14}H_{12}O_3$	2.99	60.68	3	3	2	0	206.92

TABLE 4: CALCULATION OF BIOACTIVITY SCORE OF BEST COMPOUND

Ligand ID	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
25113755	0.33	0.03	-0.06	0.20	0.39	0.65

Toxicity Prediction Analysis: Based on the results from the Data warrior, the mutagenicity and carcinogenicity screening tests revealed the four ligands are non-mutagens and non-carcinogens. The following results represent that those compounds which were passed all toxicity parameters can be developed as future chemo preventive agents for the treatment of cancer. *In-silico* toxicity profiles of all the parameters are illustrated in **Table 5**.

TABLE 5: TOXICITY PARAMETERS OF BEST COMPOUNDS

Chemical formula	$C_{14}H_{12}O_6S$	$C_{14}H_{14}O_4$	$C_{14}H_{11}FO_3$	$C_{14}H_{14}O_3$
Log S	-2.188	-2.07	-2.979	-2.366
Mutagenicity	None	None	None	None
carcinogenicity	None	None	None	None
irritant	None	None	None	None

CONCLUSION: The work based on *in-silico* studies showed that CID: 25113755 possess the good anticancer activity and better binding affinity value against the selected target protein HER2. And also this compound shows low molecular weight, it has no bad effect in toxicity profile and satisfied the Lipinski as well as bioactivity parameters. This new inhibitor can be recommended as a potential therapeutic drug candidate for the treatment of breast cancer. In future research work, the ADME & Toxicity profiles of these promising anticancer compounds can be tested in the wet lab, and *in-vivo* studies and research can proceed to clinical trials.

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