Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env.Pharmacol. Life Sci., Vol11 [4] March 2022 : 58-66

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

ORIGINAL ARTICLE **OPEN ACCESS**

In Silico Analysis of Lupeol Against for Breast Cancer

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ABSTRACT

Breast cancer is the most frequent cancer in women, and it has a high fatality rate around the world. The estrogen and progesterone receptors are predominantly expressed in breast cancer cells [MCF7 cells]. The receptor human 3-alpha hydroxysteroid dehydrogenase type 3 was studied in silico in association with NADP+, 5-alpha-androstane-3, 17-dione, and [3 beta, 5 alpha]-3 hydroxyandrostan-17-one, as well as the ligand Lupeol. With a binding affinity of -7.1, it is the most powerful. LYS2903, LEU2902, VAL2899, UNK1, VAL2867, ALA2868, and THR2864 were the interacting residues. It is also supported by literature reports as well as numerous plots. The conformations of chemicals and critical amino acid residues at the docking pocket of MCF7 cells protein were revealed using molecular docking. As a result, Lupeol may be an appealing medicine in the fight against the MCF7 cells.

Keywords: *Breast Cancer, High mortality, MCF7 cells, Molecular Docking, Lupeol*

Received 22.02.2022 Revised 13.03.2022 Accepted 21.03.2022

INTRODUCTION

Cancer is currently one of the major causes of death from diseases around the world, and without additional improvements and screening in producing new treatments to treat this sickness, it is expected to remain the leading cause of death from diseases in the coming years [1, 2]. Apart from lung cancer, breast cancer is fastest-growing cancer in women, and it kills more women than all other types of cancer combined. Breast cancer affects one in every 37 women or 3% of the population. More developments in the screening of medications for the treatment of breast cancer, as well as increased awareness of the signs and symptoms, are essential strategies to reduce the risk associated with the condition [3, 4]. Some of the signs and symptoms of breast cancer include the presence of fluid through the nipple, changes in the thickness of the breast skin, the formation of lumps, and enlargement [5, 6]. As the disease progresses, there may be swollen lymph nodes, pain, especially in the bone, and a decrease in breathing rate [7]. In the drug development process, drugs that modify the genes/proteins that regulate cancer cell survival, metastasis, apoptosis, and invasion are extremely important as prospective treatment targets [8]. Even though novel medicines have greatly lowered mortality in metastatic BC, anticancer drug resistance can lead to treatment failure [9].

A drug discovery process begins when there is a clinical disease for which there is no effective treatment. The potential drug molecule must have access to an ideal target, and the binding drug–target complex must elicit a biological reaction [10]. Docking is a computer technique that can predict drug-target complexes as well as the shape of the ligand when it binds to a protein target. The affinity of an association and the conditions for creating a complex are determined by the binding free energy of target–drug interactions [11]. Small molecules are promising novel medications that have a low molecular weight and can easily permeate cells [12]. In addition, molecular docking can be utilized to forecast how medicine will work.

MATERIAL AND METHODS

Protein Preparation

The macromolecule used in our docking investigation was found in the Protein Data Bank [PDB]. Crystal structure of human 3-alpha hydroxysteroid dehydrogenase type 3 in association with NADP+, 5-alpha-androstane-3, 17-dione, and [3 betas, 5 alpha]-3 hydroxyandrostan-17-one with PDB ID:4XO6 was chosen as the macromolecule for our research. With a resolution of 1.20AO [14], it is one among the X-Ray diffracted crystal structure compounds. The discovery studio program [Figure1] was used to eliminate all water molecules as well as tiny molecules [NAP, AOX, 5SD, SO4, GOL, and EDO]. After that, it's saved in the PDBQT format [13].

Ligand Preparation

Lupeol, a small molecule with a PubChem CID of 3D 259846 [Figure 2], was the 3D structure of the small molecule we chose. For docking compatibility, it was converted from SDF to PDB using the Open Babel program. The energy was reduced to a minimum and then saved in PDBQT format [14].

Active Site Prediction

The official location of the protein or more frequently than not, a stash at the protein's surface, comprises build-ups capable of substrate specificity that operate as proton benefactors or accepts regularly. Computational and written reports have set the official place apart.

Molecular Docking

The software Autodock Vina was used to accomplish molecular docking. The grid was built with a size of 72X64X25 and centered with the sizes of 15.9353, -1.5377, and 2.998 and co-crystallized after the protein and ligand were opened. The protein and ligand for docking were then chosen and run. The data were analyzed with the help of the discovery studio program. PNG records were used to obtain yields using receptors, molecule surfaces, and their linkages. The interactions of the docking molecules were also plotted in different ways and saved as JPEG files.

RESULTS AND DISCUSSION

Developing a potent breast cancer drug that targets progesterone receptors will be a breakthrough in the treatment of breast cancer. Although both estrogen and progesterone receptors interact with breast cancer cells, most breast cancer drugs are developed to target estrogen receptors only. About 80% of breast cancer cells are estrogen receptor-positive, with 65 percent also being progesterone receptor-positive, while 13% of total breast cancer cells are estrogen receptor-positive but progesterone receptor-negative, and 2% are estrogen receptor-negative but progesterone receptor-positive [15]. There is considerable evidence that the progesterone receptor is involved in the progression of breast cancer and that it could be employed to improve the efficacy of endocrine treatment [16]. Drug discovery is a labor-intensive and time-consuming process. A new medicine takes an average of 10–15 years to create. Because of its low cost and risk-free properties, drug repositioning, or the use of old treatments for new conditions, is an effective technique [17]. Several research has used systematic methodologies to reposition known drugs/molecules, using in silico and experimental methods.

Lupeol was docked with human 3-alpha hydroxysteroid dehydrogenase type 3 in complex with NADP+, 5-alpha-androstane-3, 17-dione [3 betas, 5 alpha]-3 hydroxyandrostan-17-one [3 betas, 5 alpha]-3 hydroxyandrostan-17-one with a PDB ID:4XO6. The protein and the ligand were synthesized beforehand, and the ligand's energy was minimized [928.20]. Literature reports were used to identify the active locations. There were also various confirmations identified. The amino acid with the largest negative binding energy was chosen, and an interaction study was conducted using Discovery Studio to determine the distance. With 14 interactions, the maximum binding affinity was -7.1.

LYS2903, LEU2902, VAL2899, UNK1, VAL2867, ALA2868, and THR2864 were the most critical amino acid residues that interact with the receptor. [Table 1] shows the distances between H-bonds and the H-bond interacting residues. The root means square deviation will be 0 in those conformations. [Table 2] shows the binding affinity of those compounds with the macromolecule in various conformations, as well as the Root Mean Square Deviation [RMSD] values of the interacting molecules [Protein and Ligand]. [Figures 3, 4, 5, 6, 7, 8, and 9] show the interactions of protein and ligand [Lupeol]. It can also be shown in many charts, such as the Ramachandran plot [Figure 10], the Hydrophobicity plot [Figure 11], and several contact plots, such as the CAlpha plot [Figure 12], the CBeta plot [Figure 13], Figures 14–16 show the side chain plot, H bond plot, and residue plot. As a result, Lupeol was a successful treatment for breast cancer.

Table 1. The molecular docking studies of compounds with human 3-alpha hydroxysteroid dehydrogenase type 3 in complex with NADP+, 5-alpha-androstane-3, 17-dione [3 beta, 5 alpha]-3 hydroxyandrostan-17-one

S. No	Compound name	Docking score	H-Bond Interaction	Distance
1.	Lupeol	-7.1	LYS2903	4.23
				4.27
				5.16
			LEU2902	4.76
				4.89
			VAL2899	4.19
				4.66
			UNK1	4.24
				4.55
			VAL2867	4.01
				4.86
				4.95
			ALA2868	3.81
			THR2864	2.80

Table 2 shows the various binding affinity and root mean square deviation [RMSD] Upper and Lower Bound values of Lupeol

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
protein_A_Lupeol_uff_E=928.20	-7.1	0	0
	-6.9	6.463	4.359
	-6.9	1.905	1.543
	-6.8	27.31	28.849
	-6.8	28.028	23.734
	-6.6	7.972	2.771
	-6.6	7.076	3.668
	-6.4	28.716	24.355
	-6.3	28.168	22.8

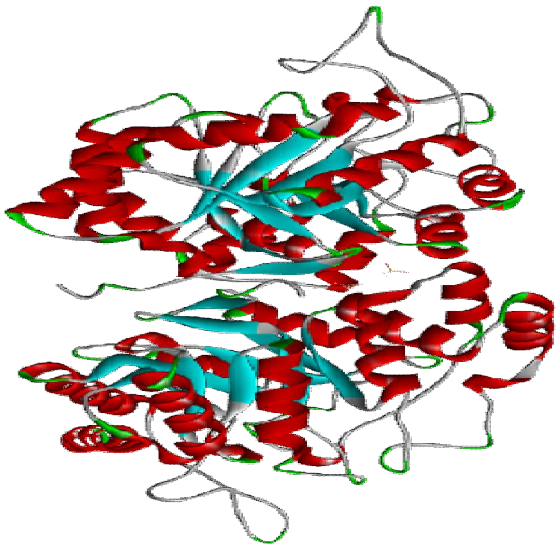


Figure 1 shows the 3d structure of human Brest cancer protein*.

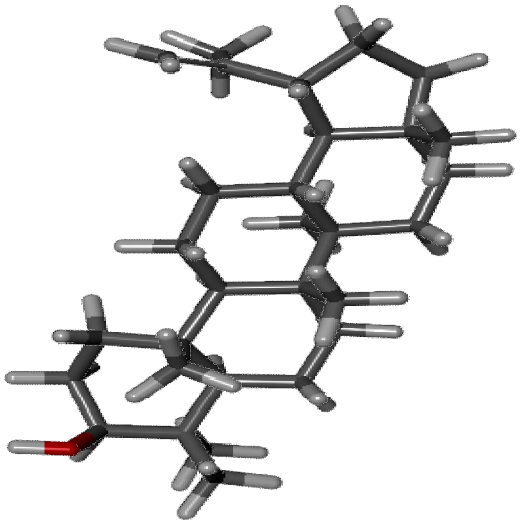


Figure 2 shows the 3d structure of ligand*

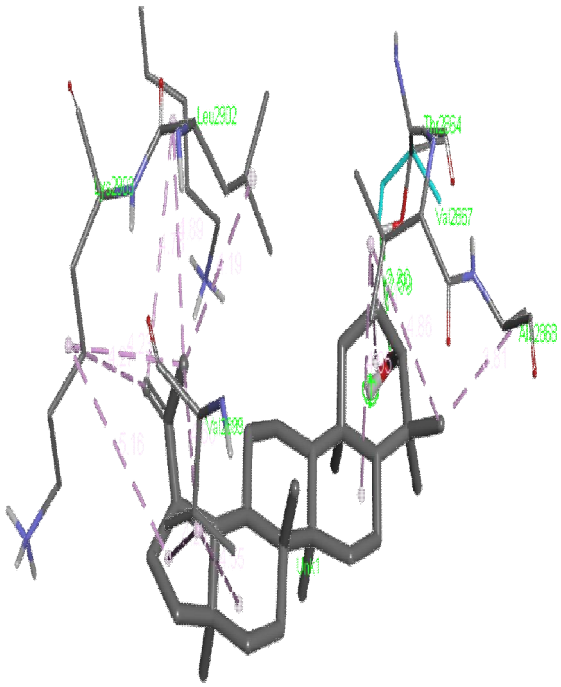


Figure 3 shows the interaction of ligand and protein

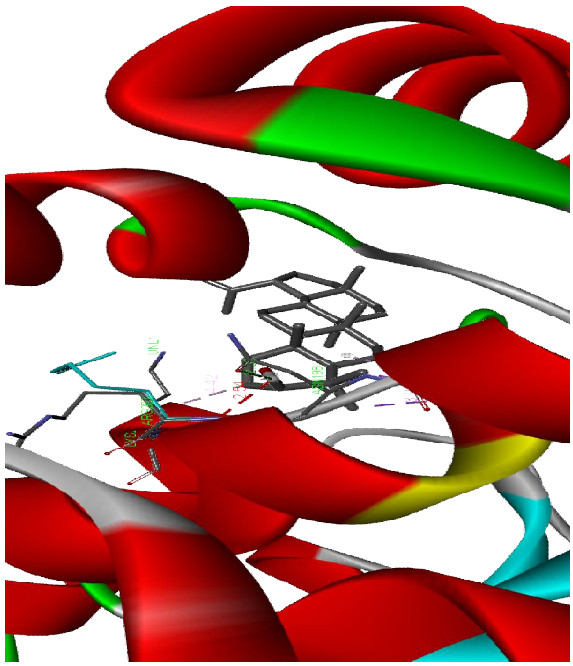
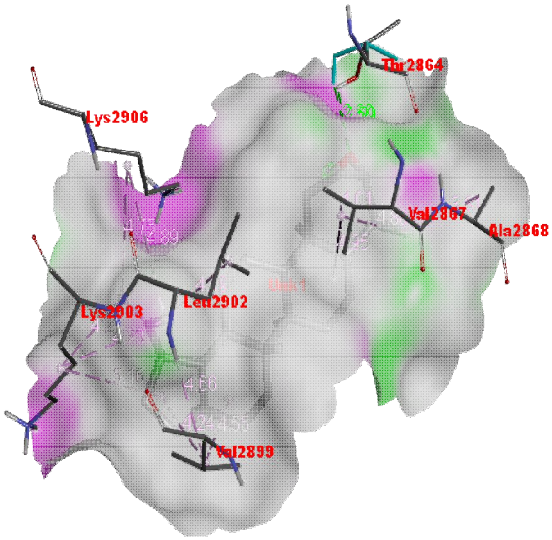


Figure 4 shows the interaction of ligand and protein with their receptors

***Protein**: 3-alpha hydroxysteroid dehydrogenase type 3 in complex with NADP+, 5-alpha-androstan-3, 17-dione [3 beta, 5 alpha]-3 hydroxyandrostan-17-one
***Ligand**: Lupeol

5.



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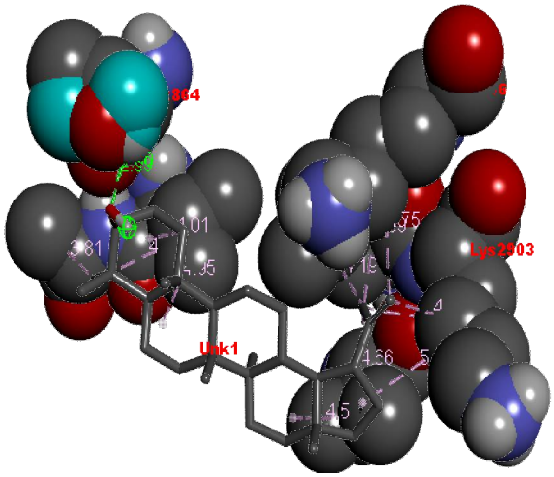
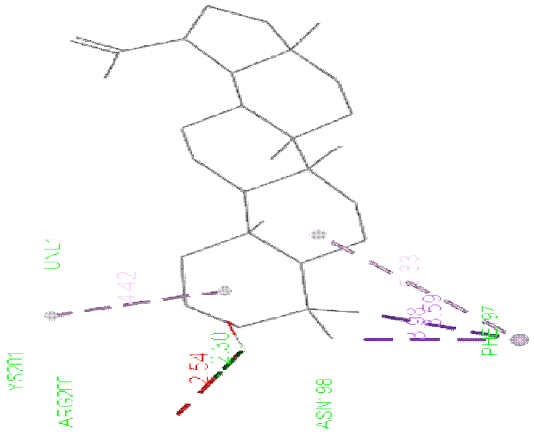


Figure 5,6 shows the interaction of Lupeol and human 3-alpha hydroxysteroid dehydrogenase type 3 in complex with NADP+, 5-alpha-androstane-3, 17-dione, and [3 beta, 5 alpha]-3 hydroxyandrostan-17-one

7.



8.

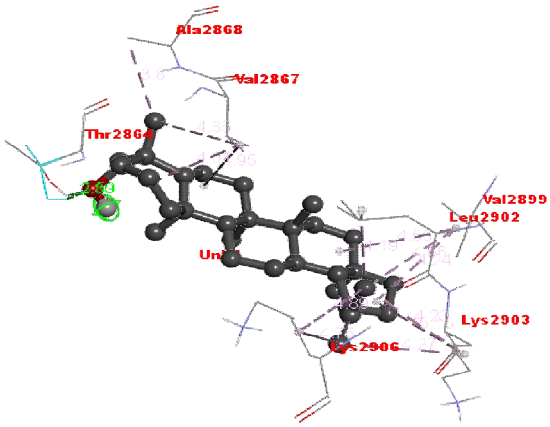


Figure 7,8 shows the interaction of Lupeol and human 3-alpha hydroxysteroid dehydrogenase type 3 in complex with NADP+, 5-alpha-androstane-3, 17-dione, and [3 beta, 5 alpha]-3 hydroxyandrostan-17-one

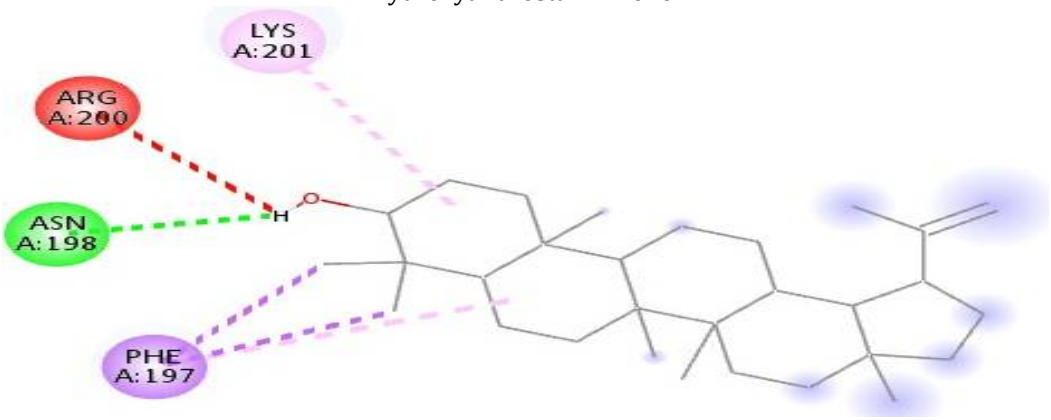


Figure 9 shows the 2d diagram of the interaction of Lupeol with human 3-alpha hydroxysteroid dehydrogenase type 3 in complex with NADP+, 5-alpha-androstane-3, 17-dione [3 beta, 5 alpha]-3 hydroxyandrostan-17-one

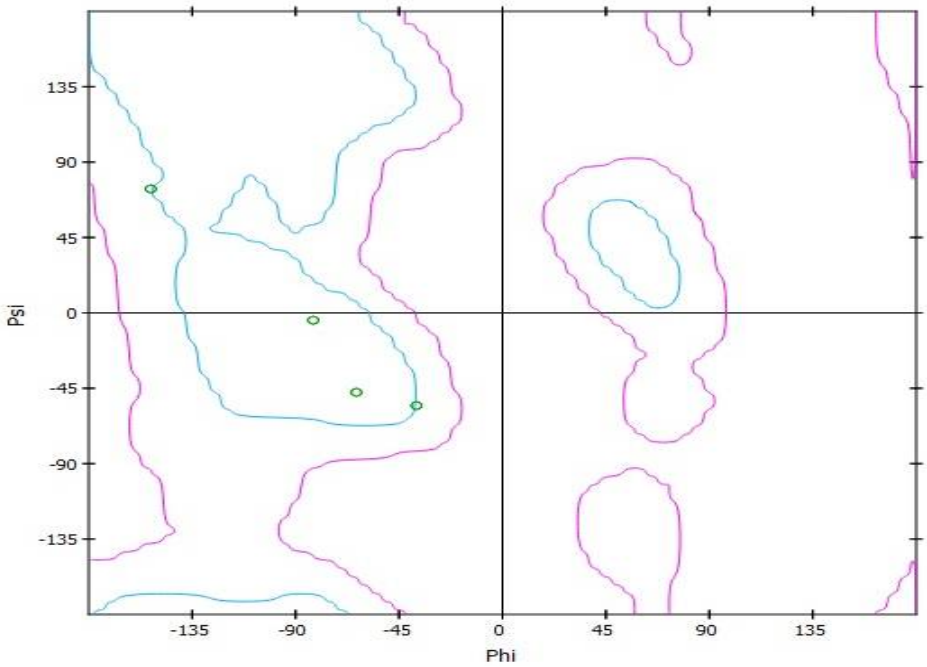


Figure 10 shows the interaction of Lupeol and human 3-alpha hydroxysteroid dehydrogenase type 3 in complex with NADP+, 5-alpha-androstan-3, 17-dione and [3 beta, 5 alpha]-3 hydroxyandrostan-17-one in **Ramachandran Plot**

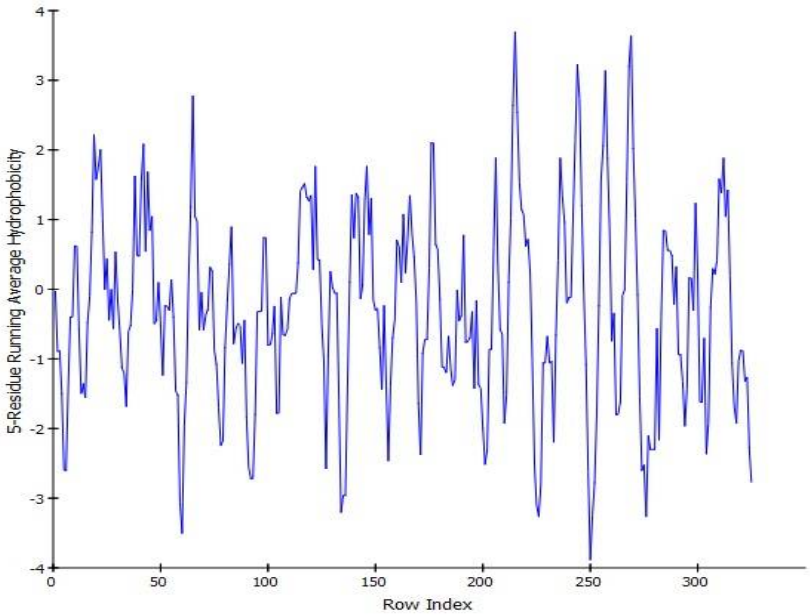


Figure 11 shows the interaction of Lupeol with human 3-alpha hydroxysteroid dehydrogenase type 3 in complex with NADP+, 5-alpha-androstan-3, 17-dione and [3 beta, 5 alpha]-3 hydroxyandrostan-17-one in **Hydrophobicity Plot**

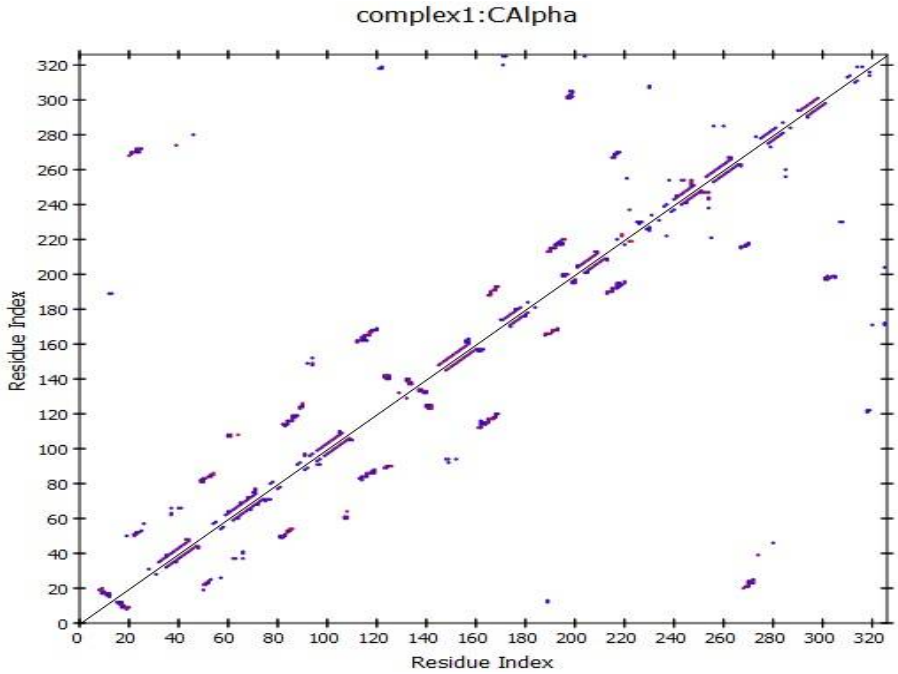


Figure 12 shows the interaction of Lupeol with human 3-alpha hydroxysteroid dehydrogenase type 3 in complex with NADP+, 5-alpha-androstan-3, 17-dione [3 beta, 5 alpha]-3 hydroxyandrostan-17-one in **C-alpha Plot**

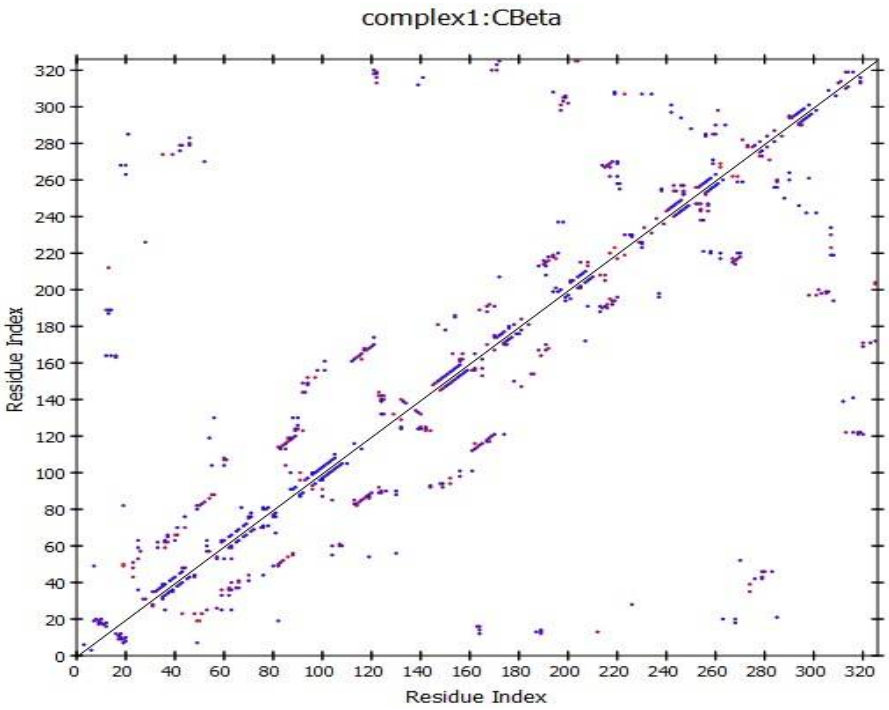


Figure 13 shows the interaction of Lupeol with human 3-alpha hydroxysteroid dehydrogenase type 3 in complex with NADP+, 5-alpha-androstan-3, 17-dione and [3 beta, 5 alpha]-3 hydroxyandrostan-17-one in **C-Beta Plot**

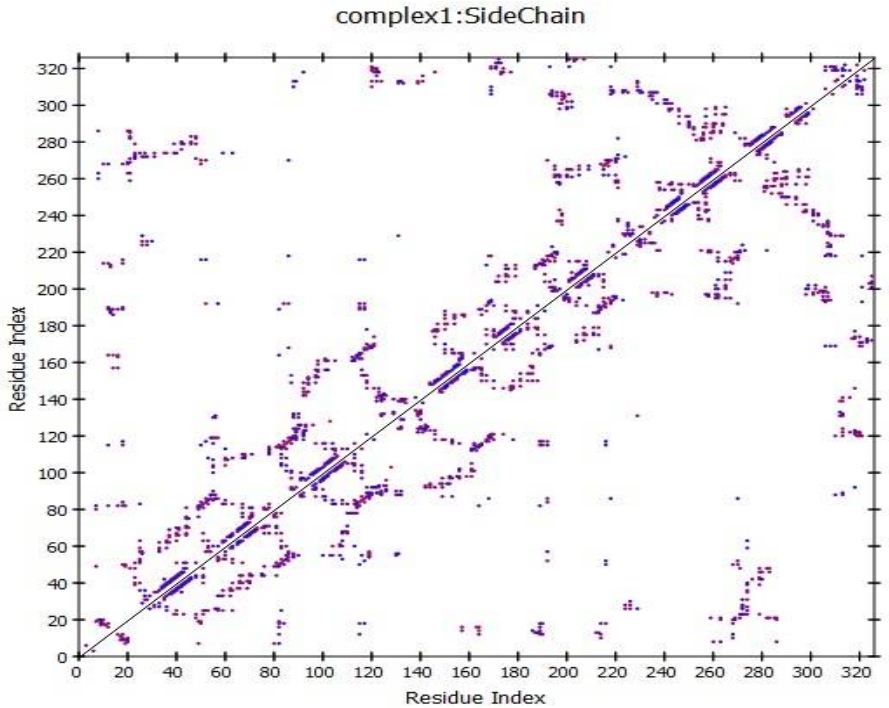


Figure 14 shows the interaction of Lupeol with human 3-alpha hydroxysteroid dehydrogenase type 3 in complex with NADP+, 5-alpha-androstan-3, 17-dione [3 beta, 5 alpha]-3 hydroxyandrostan-17-one in **Sidechain Plot**

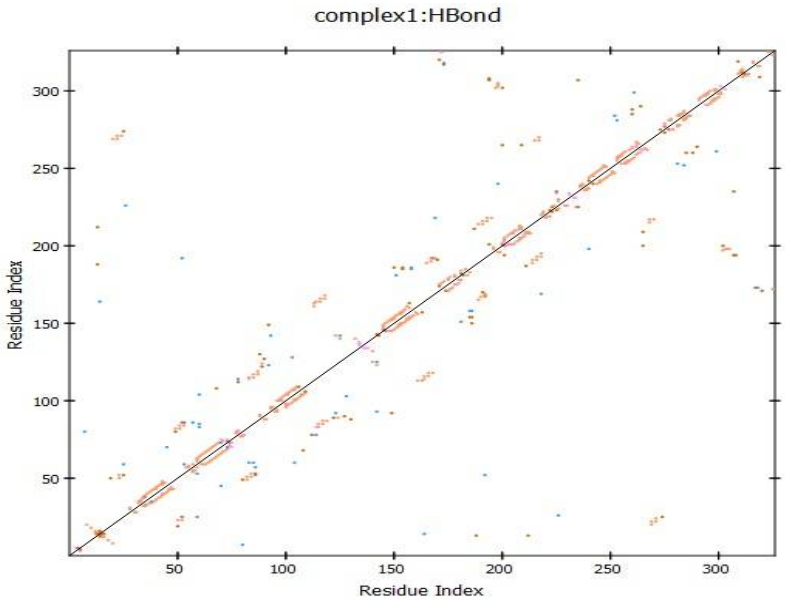


Figure 15 shows the interaction of Lupeol with human 3-alpha hydroxysteroid dehydrogenase type 3 in complex with NADP+, 5-alpha-androstan-3, 17-dione [3 beta, 5 alpha]-3 hydroxyandrostan-17-one in **H-bond Plot**

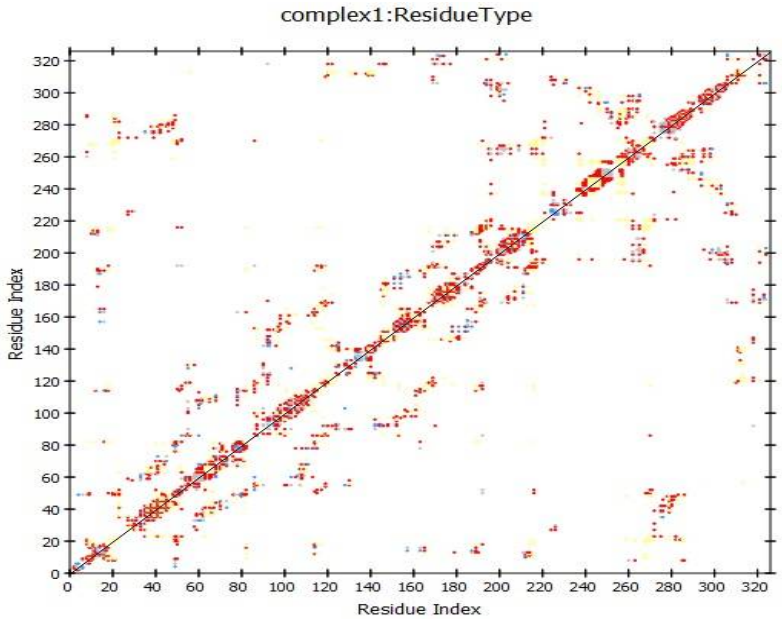


Figure 16 shows the interaction of Lupeol with human 3-alpha hydroxysteroid dehydrogenase type 3 in complex with NADP+, 5-alpha-androstan-3, 17-dione [3 beta, 5 alpha]-3 hydroxyandrostan-17-one in **Residue Plot**

CONCLUSION

Computational medicinal chemistry studies are being used to screen bioactive compounds with the optimal multi-target interactions for MCF7 cells. The molecules MCF7 cell protein and Lupeol were used to perform molecular docking in this work.

-7.1 was the highest binding affinity. LYS2903, LEU2902, VAL2899, UNK1, VAL2867, ALA2868, and THR2864 were identified to interact in the active sites. The ligand was firmly attached to the receptor protein. It's also supported by literature reviews and a variety of plots. As a result, we anticipate that the screened and developed compounds will be used as MCF7 cell lead candidates.

ACKNOWLEDGEMENT

For Docking Studies, the authors gratefully acknowledge the Department of Botany, Srimad Andavan Arts and Science College [Autonomous], Tiruchirapalli-620005, Tamil Nadu, India.

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CITATION OF THIS ARTICLE

T Baskaran, D Kandavel, V Aravindha, M Koperuncholan. *In Silico* Analysis of Lupeol Against for Breast Cancer. Bull. Env. Pharmacol. Life Sci., Vol11 [4] March 2022 :58-66.