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Insilico Docking Analysis of Capsaicin Alkaloids from Red chilli against Breast Cancer

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Autodock

A B S T R A C T

Breast cancer is the second leading cause of cancer death in women next to lung cancer. BRCA1 is a human tumor suppressor gene. Genetic variations/mutations in the BRCA1 gene leads to over expression of the BRCA1 protein which kicks off the uncontrolled cell duplication in humans. *Capsicum annum* (or) Chilli peppers are popular spices in many parts of the world. Their properties of aroma, flavor and pungency account for their extensive usage. Chilli pepper also contains many biological active compounds including capsaicinoids, which are pungent in nature.The chilli samples were found to possess seven identified compounds including Capsaicin, Dihydrocapsaicin, Nordihydrocapsaicin, Homocapsaicin and Homodihydrocapsaicin. In addition, capsicum possess biological activities of viz antioxidant, anticancer, antidiabetic etc.The potential ligand candidate was identified from Pubchem database.Lipinski rule was employed to check the ligand likeliness of the compound. The 3D crystal structure of the protein was retrieved from Protein Data Bank (PDB) and protein binding sites of the compounds were identified. Protein active sites were identified using CASTp server and these active residues are used to find better inhibitor. The present study analyzed the molecular docking studies on the target protein BRCA1 which is responsible for breast cancer with the compound capsaicin which is evolved from red chilli. The docking studies was done by "Autodock" software tool.

Introduction

Capsicum annum is one among the oldest cultivated plants in the world (Neelam Gurnani, *et al.,* (2016)). Capsicum are popular spices in many parts of the world. Their properties of color, aroma, flavor and pungency account for their extensive usage (Chanthai, *et al.,* (2014)).

Capsicum annum or chilli pepper an extensively found vegetable belonging to the family solanaceae (Govinarajan (1991) Pruthi (2003)), has earned a great nutritional value (Zachariah (2008), Kumar O.A (2009)) since chilli pepper is a promising source of vitamins and minerals (Kumar,

(2010), Pawar, (2011)). Chilli pepper also contains many biological active compounds, including capsaicinoids which are pungent in nature (Whiting, *et al.,* (2012)). Famous compounds that are enlisted as capsaicinoids are capsaicin, dihydrocapsaicin, homo-capsaicin, homo-dihydrocapsaicin, nordihydro-capsaicin. Major part (greater 90%) of chilli pepper capsaicinoids consists of two most potent compounds capsaicin and dihydrocapsaicin.

Various bioactivities of the capsaicin in particular, are found to be Antioxidant (Materska, Peruka I (2012)), Anticancer (Sancho, (2002)), Anti-inflammatory (Macho *et al.,* (2003)), Antimicrobial and many others (Ohnuki, (2001)). The molecular weight, chemical name and molecular formula of this capsaicin are 305.40g/mol, trans-8-methyl-N-vanilyl-6-nonenamide and C18H27NO3. The chemical structure of this lipophilic alkaloid is given in figure1 (Nelson E.K (1923)). Breast cancer in women is a major cancer health problem. It is widespread cancer among women both in developed and developing countries. BRCA1 is a classical tumor suppressor gene (Karthikeyan Muthusamy, *et al.,* (2011)). In the presence of a BRCA1 mutation, women have 70-80% life time risk of developing breast cancer (Joseph Gerad Rakesh *et al.,*). Tumor suppressor proteins helps in preventing the cells from growing and in the too fast cell division of the cells or in the uncontrolled manner. In the nucleus of a normal cells, BRCA1 protein interacts with some other protein for the breaks of DNA. These breaks are caused due to natural and medical radiation or any other environmental exposures, and they also occur at the time of genetic exchange of a chromosome in the preparation of the cell division. It plays a crucial role in maintaining the stability of the genetic information of a cell (Shilpi pal *et al.,* (2016)). Multiple functions of BRCA1 may contribute to its tumor suppressor activity, including roles in DNA repair, cell cycle control and transcriptional regulation.

BRCA1 has been mapped to chromosome 17q21. BRCA1 is linked to the hormone homeostasis in the breast cancer and ovaries. In addition epidemiological studies have demonstrated that prophylactic oophorectomy in women who carry BRCA1 mutations Prevents occurrence and reoccurrence of breast cancer by 75% (Karthikeyan Muthusamy, *et al.,* (2011)).

Materials and Methods

Uniprot

Uniprot is a comprehensive, high quality and free online database of protein sequence and functional information, mainly derived from genome sequencing projects. It contains a large amount of information about the biological function of proteins derived from the research literature ((https://www.ncbi.nlm.nih.gov/pubmed/25348405)). The primary sequence of BRCA1 has been retrieved and the accession number is P38398.

Protein Structure Preparation

The Protein Data Bank (PDB) is a crystallographic database for three dimensional structure data of large biological molecules such as proteins and nucleic acids. The 3D crystal structure of the targeted breast cancer protein BRCA1(ID:1T15) was retrieved from the Protein Data Bank(PDB) (www.rcsb.org/pdb) structural and active site studies of the protein were done by using Pymol molecular visualization software (Senthil Raja, *et al.,* (2011)).

Pubchem

It is a product of NCBI data base. Useful for collecting the information about the specified chemicals. It is an online archive containing the information of all the known chemicals their properties and their biological importance. The user can use these chemicals based on their function and download their structures for other analysis. The 2D structure of the capsicum compounds of capsaicin, dihydrocapsaicin, homocapsaicin, homodihydrocapsaicin and nordihydrocapsaicin are obtained from the Pubchem (Shilpi pal *et al.*, (2016)).

ACD Chemsketch

ACD/Chemsketch is the powerful chemical drawing and graphics package from ACD/Labs software. Which will draw molecular structures, reactions and calculate chemical properties very quickly and easily. The three dimensional structures of capsaicin, dihydrocapsaicin, homocapsaicin, homodihydrocapsaicin and nordihydro-capsaicin were drawn by chemsketch.

Open Babel

Open babel is a software is used to interconvert chemical file format. It is an open collaborative project allows to search, covert, analyze all store data from molecular modelling, chemistry, solid-state materials, biochemistry or related areas.

Lig and Structure Preparation

In this study for the ligand capsaicin, dihydrocapsaicin, homocapsaicin, homo-dihydrocapsaicin and nordihydrocapsaicin the 2D structure and chemical formula were obtained from Pubchem. The Pubchem ID of capsaicin (1548943), dihydrocapsaicin (107982), homocapsaicin (6442566), homodihydro-capsaicin (3084336) and nordihydro-capsaicin (168836) is as follows. The structure of capsaicin and dihydrocapsaicin was computed by drawing using chemsketch software (chemically intelligent drawing interface freeware). This was followed by ligand construction using chemsketch draw mode 3D structure optimization were compute and finally ligand as ”MOL” file format and then mol file was converted and save as “PDB” using open babel molecular editor software. The protein and ligand files which are prepared were then taken for docking.

Docking Methodology

Auto Dock is a suite of automated docking tools. The software is used for modeling flexible small molecules such as drug molecules and it’s binding to receptor proteins of known three dimensional structures. It uses Genetic Algorithms for the conformational search and is a suitable method for the docking studies.

The technique combines simulated annealing for conformation searching searching with a rapid grid based method of energy evaluation.

Auto Dock tools are used to prepare, run and analyze the docking simulations, In addition to modeling studies. After the grid generation, the processed ligand was docked with the protein to evaluate the interaction between each target protein and ligand.

Interaction were hydrophilic, Vaanderwaals and hydrophobic. The interaction strength varies from protein to protein based out its affinity procedure, the ligand. During the auto-docking procedure the ligand confirmation was retained, followed by the extra precision mode selection.

Visualization and analysing docking results

Pymol is an open source tool to visualize molecules available from (www.pymol.org). PyMol has excellent capabilities in creating high quality images from 3D structures; it has well developed functions for manipulating structures and some basic functions to analyze their chemical properties. The possibilities to write scripts and plugins as well as to incorporate pyMol in custom software are fast and superior to most other programs. Once the target ligand was docked against all protein of interest, the result were visualized for their interactions, binding energy, H-bond formation and few other parameters using the pyMol software.

Results and Discussion

Sequence Retrieval

The sequence of BRCA1 is retrieved from uniprot database and sequence accession number is P38398organism is *Homo sapiens.*

Structure Retrieval

The three dimensional structure (crystal structure) of BRCA1 is derived from PDB database and its PDB ID is 1T15. Three dimensional is visualized using RASMOL Pink color showing alpha helix, yellow color showing beta sheets and white color showing turns.

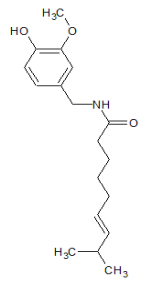
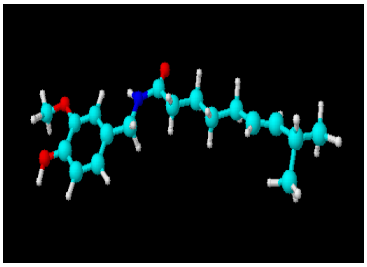
Preparation of Ligand

For further docking analysis of the compounds capsaicin, dihydrocapsaicin, homocapsaicin, homodihydrocapsaicin and nor dihydrocapsaicin from Red Chilli are taken. The two-dimensional structures of the ligand were generated using the ACD/Chem sketch tool. This software contains tools for 2D cleaning, 3D optimization and viewing. These data are saved as a molecular format file (MDL MOL format).

The molecular format converter tool (Open Babel) is used to convert this file into the PDB format and is used during docking analysis. The structure and molecular formula of capsaicin and dihydrocapsaicin compounds was shown in Table.1.

According to Lipinski's rule of a compound having not more than 5 hydrogen bond donors (OH an NH groups), not more more than 10 hydrogen bond acceptors (notably N and O), molecular weight under 500g/mol, partition coefficient log P of less than 5 was shown in Table.2.

Table.1 Compounds are extracted from Red Chilli

S.NO	COMPOUND	MOLECULAR FORMULA	2D STRUCTURE	3D STRUCTURE
1.	Capsaicin	C18 H27 NO3		

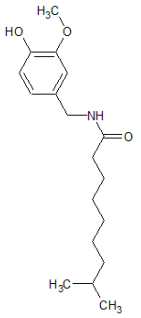
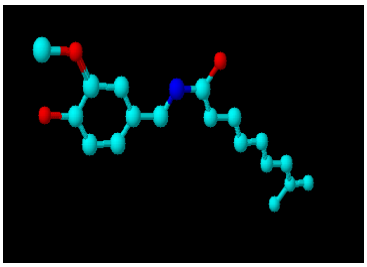
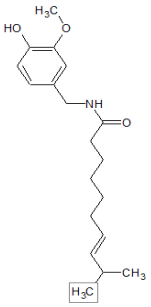
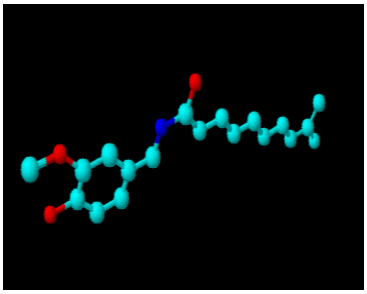
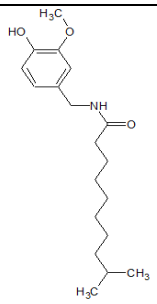
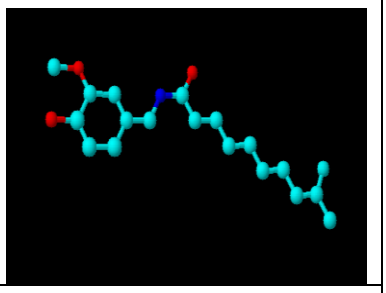
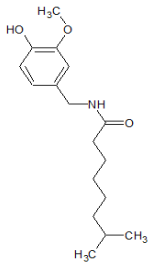
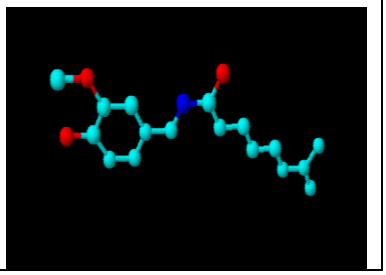
2.	Dihydrocapsaicin	C18 H29 NO3		
3.	Homocapsaicin	C19 H29 NO3		
4.	Homodihydrocapsaicin	C19 H31 N03		
5.	Nordihydrocapsaicin	C17 H27 NO3		

Table.2 Lipinski's rule of compounds

COMPOUNDS NAME	MOLECULAR WEIGHT	NO.OF HYDROGEN BOND DONOR	NO.OF HYDROGEN BOND ACCEPTOR
Capsaicin	305.418 g/mol	2	3
Dihydrocapsaicin	307.434 g/mol	2	3
Homocapsaicin	319.445 g/mol	2	3
Homodihydrocapsaicin	321.461 g/mol	2	3
Nordihydrocapsaicin	293.407 g/mol	2	3

Table.3 Docking interaction between BRCA1 and Capsaicin

BRCA1		CAPSAICIN	DISTANCE Å	BINDING SCORE (Kcal/mol)
RESIDUE	ATOM	ATOM		
ILE1680	O	H	2.7	-6.28
LEU1701	O	H	2.9	
PRO9	N	O	2.2	

Table.4 Docking interaction between BRCA1 and Dihydrocapsaicin

BRCA1		DIHYDROCAPSAICIN	DISTANCE Å	BINDING SCORE (Kcal/mol)
RESIDUE	ATOM	ATOM		
ILE1680	O	H	3.0	-5.16
ASN1678	N	O	3.2	

Table.5 Docking interaction between BRCA1 and Homocapsaicin

BRCA1		HOMOCAPSAICIN	DISTANCE Å	BINDING SCORE (Kcal/mol)
RESIDUE	ATOM	ATOM		
LYS 1759	N	O	2.8	-5.59
SER 1755	O	H	3.2	
TYR 1845	O	H	3.2	
TRP 1837	O	H	3.6	
ARG 1762	O	H	3.5	

Table.6 Docking interaction between BRCA1 and Homodihydrocapsaicin

BRCA1		HOMODIHYDROCAPSAICIN	DISTANCE Å	BINDING SCORE (Kcal/mol)
RESIDUE	ATOM	ATOM		
ARG 1758	O	H	3.2	-5.01
CYS 1847	O	H	3.1	

Table.7 Docking interaction between BRCA1 and Nordihydrocapsaicin

BRCA1		NORDIHYDROCAPSAICIN	DISTANCE Å	BINDING SCORE (Kcal/mol)
RESIDUE	ATOM	ATOM		
ILE1680	N	O	3.5	-5.93
GLU 1682	O	H	3.1	

Table.8 Overall docking results between BRCA1, Capsaicin, Dihydrocapsaicin, Homocapsaicin, Homodihydrocapsaicin and Nordihydrocapsaicin compounds

COMPOUNDS	KEY RESIDUE	DOCKING ENERGY (Kcal/mol)	NO.OF HYDROGEN BONDS
Capsaicin	ILE1680,LEU1701, PRO9	-6.28	2
Dihydrocapsaicin	ILE1680, ASN1678	-5.16	1
Homocapsaicin	LYS 1759, SER 1755, TYR 1845, TRP 1837, ARG 1762	-5.59	1
Homodihydrocapsaicin	ARG 1758, CYS 1847	-5.01	1
Nordihydrocapsaicin	ILE1680, GLU 1682	-5.93	1

Fig.1 The chemical structure of Capsaicin, Dihydrocapsaicin, Homodihydrocapsaicin, Nordihydrocapsaicin and Homacapsaicin

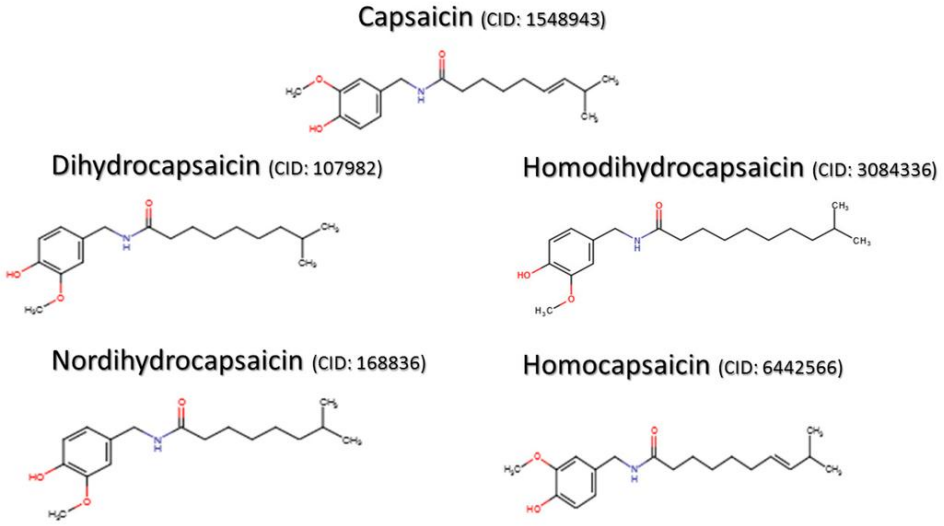


Fig.2 Crystal structure of the BRCA1 visualized using RASMOL

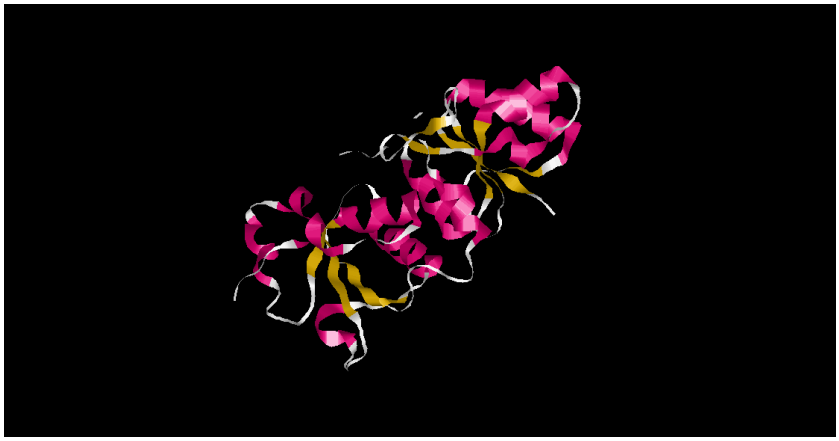
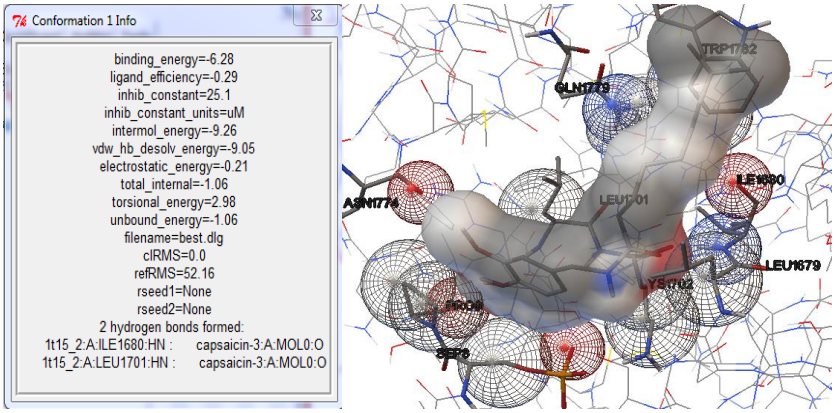
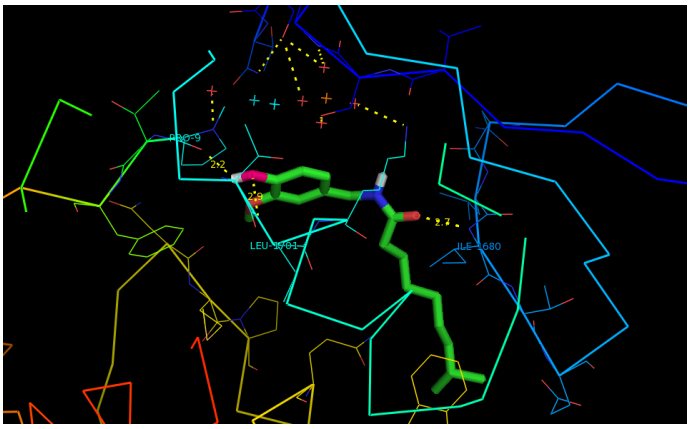


Fig.3 Docking of BRCA1 and capsaicin: (a) Binding energy (b)Interaction between BRCA1 and Capsaicin as visualized using Auto Dock (c)Hydrogen bond forms between BRCA1 and Capsaicin is visualized using PYMOL



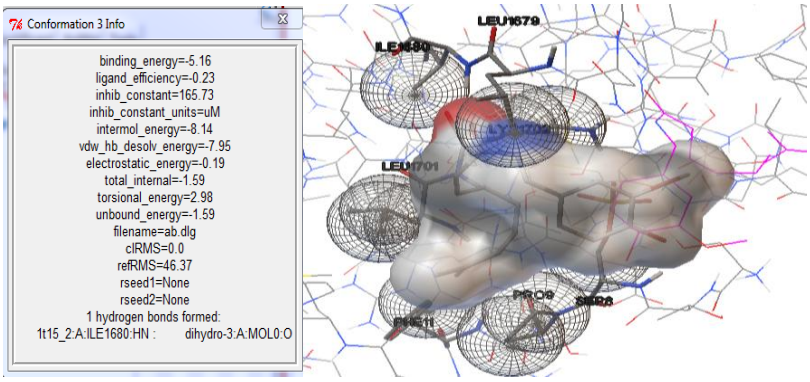
(a) (b)



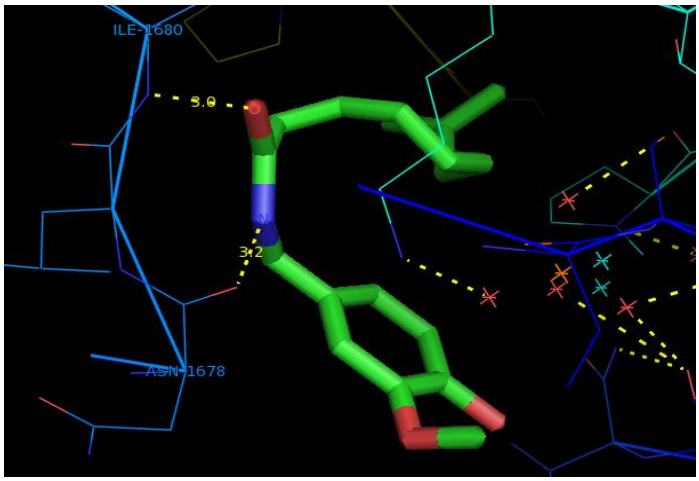
(c)

Molecular docking study of the capsaicin against BRCA1

Fig.4 Docking of BRCA1 and Dihydrocapsaicin (a) Binding energy (b)Interaction between BRCA1 and Dihydrocapsaicin is visualized using Auto Dock (c)Hydrogen bond forms between BRCA1 and Dihydrocapsaicin is visualized using PYMOL

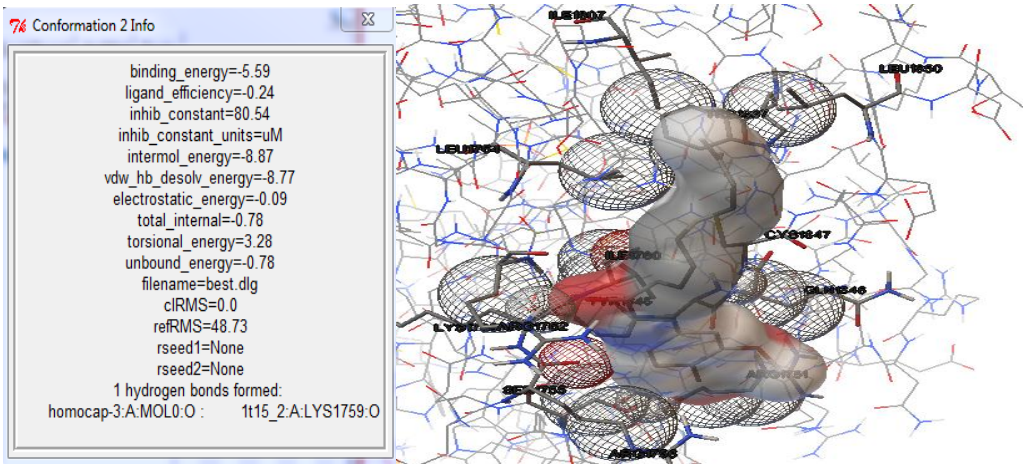


(a) (b)

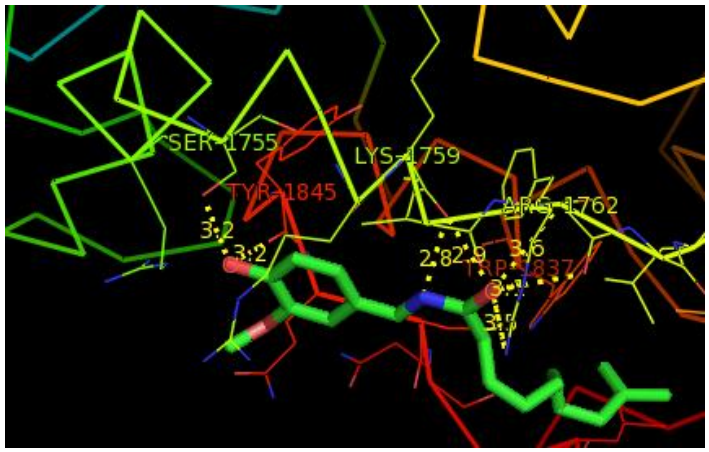


(c)

Fig.5 Docking of BRCA1 and Homocapsaicin (a) Binding energy (b) Interaction between BRCA1 and Homocapsaicin is visualized using Auto Dock (c) Hydrogen bond forms between BRCA1 and Homocapsaicin is visualized using PYMOL

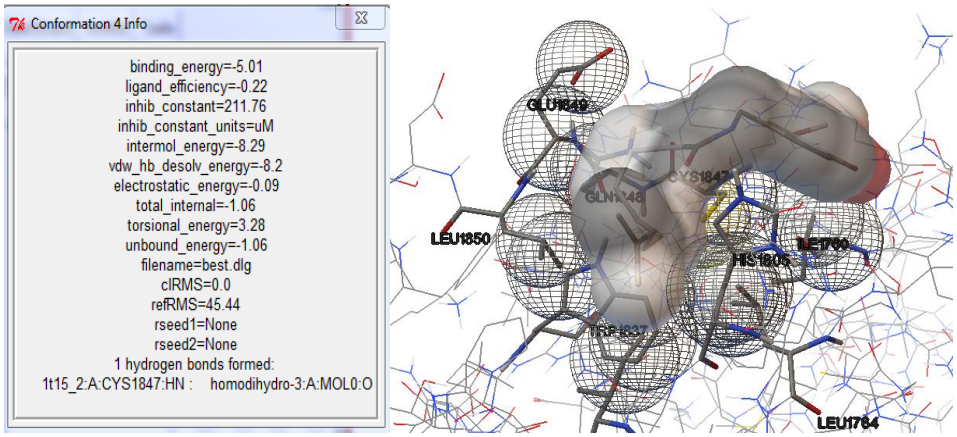


(a) (b)

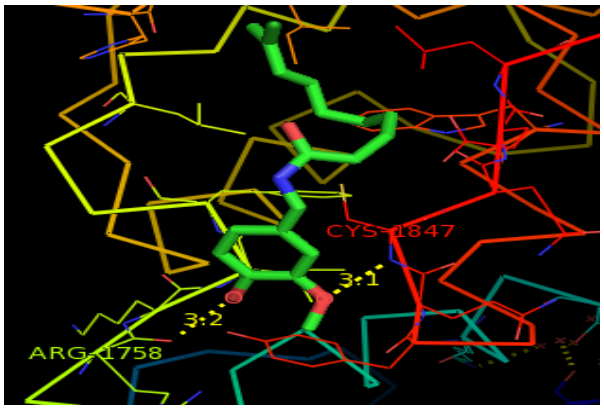


(c)

Fig.6 Docking of BRCA1 and Homodihydrocapsaicin (a) Binding energy (b) Interaction between BRCA1 and Homodihydrocapsaicin is visualized using Auto Dock (c) Hydrogen bond forms between BRCA1 and Homodihydrocapsaicin is visualized using PYMOL

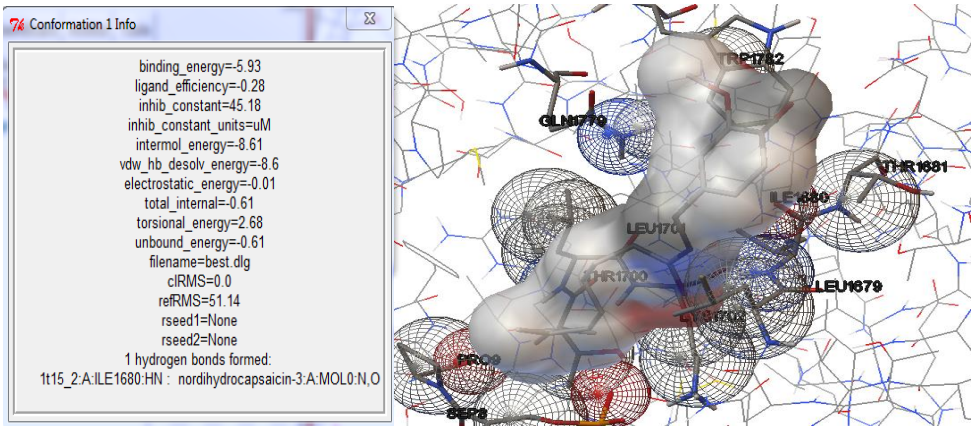


(a) (b)

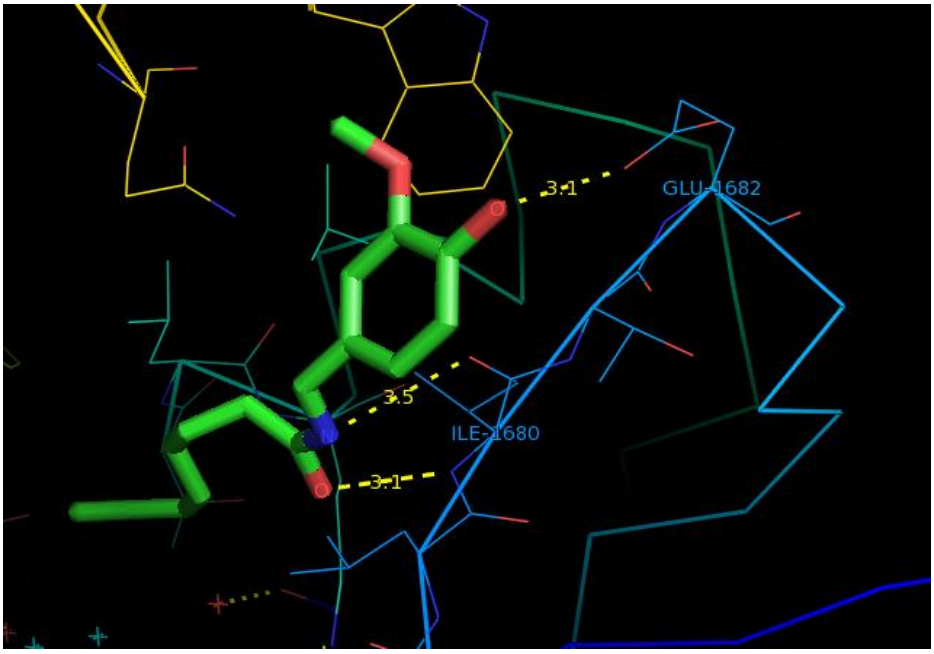


(c)

Fig.7 Docking of BRCA1 and Nordihydrocapsaicin (a) Binding energy (b) Interaction between BRCA1 and Nordihydrocapsaicin is visualized using Auto Dock (c) Hydrogen bond forms between BRCA1 and Nordihydrocapsaicin is visualized using PYMOL



(a) (b)



(c)

The alkaloid compound capsaicin are docked against BRCA1. The graphical user interface program "Auto Dock Tools" was used to prepare, run and analyze the docking simulations. Koll man united atom charges, salvation parameters and polar hydrogens were added into the receptor PDB file for the preparation of protein in docking simulation (Good sell, 1999; Jones, 1997; Rarey, 1996) requires precalculated grid maps, one for each atom type present in the flexible molecules being docked and its stores the potential energy arising from the interaction with rigid macromolecules. This grid must surround the region of interest in the rigid macromolecule. The grid box size was set at 126,126 and 126Å (x, y and z) to include all the amino acid residues that present rigid macromolecules. Auto grid 4.2 program, supplied with Auto Dock was used to produce grid maps. The spacing between grid points was 0.375 Å. The Lamarckian Genetic Algorithm (LGA) (Morris, 1998) was chosen search for the best conformers.

The best ligand-receptor structure from the docked structures was chosen based on the lowest energy and minimal solvent accessibility of the ligand. The alkaloid compound capsaicin and BRCA1 binding energy are shown in figure 3a -3b and the interactions visualization using the Pymol Visualizer.

The docking study between capsaicin compound from Red Chilli against BRCA1 in receptor and ligand complex. The docked structures were analyzed and the interactions were seen. Hydrogen bond interactions and binding distance between donors and acceptors were measured for the best conformers. From the binding energy values, the anticancer activity of a ligand to corresponding receptor was predicted.

Capsaicin compound are eco-friendly, safer and cheaper for the treatment of breast cancer. The present study is aimed to analyze the molecular docking studies on the target protein BRCA1 which is responsible for breast cancer with the compound capsaicin, dihydrocapsaicin, homocapsaicin, homodihydrocapsaicin and nordihydro-capsaicin which is evolved from red chilli.

Capsaicin are rich in alkaloid compounds of medicinal value. The Insilico docking studies was done by "Autodock" software tool. Capsaicin is having best binding score (-6.28 Kcal/mol) than the other four compounds. Hence it has been concluded capsaicin as a novel inhibitor for BRCA1 protein in breast cancer.

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