ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Quantum chemical and Molecular docking studies of Naringin: A potent anti-cancer drug

Azar Zochedh A S[1], Asath Bahadur S[2], Thandavarayan Kathiresan[1*]
1, Department of Biotechnology, Kalasalingam Academy of Research and Education, Krishnankoil - 626126, Tamil Nadu, India
2Department of Physics, Kalasalingam Academy of Research and Education, Krishnankoil - 626126, Tamil Nadu, India
[*]- Correspondence to:
Thandavarayan Kathiresan
Department of Biotechnology Kalasalingam University Anand Nagar, Krishnankoil-626 126
Tamil Nadu, India.
Email: t.kathiresan@klu.ac.in
Phone: +91-4563-289042
Fax: +91- 4563-289322

Abstract
Breast cancer is one of the most frequent female cancer. The currently available therapeutics are induces cancer cell death and also developing side effects in healthy cells. To overcome the chemotherapeutic challenges, plant-based phytochemicals and nutraceuticals are consist efficient anticancer activity. Naringin is one of the plant derived flavonoids, naturally present in citrus fruits with anticancer activity. In this present study, we analyze the frontier molecular orbital (HOMO-LUMO) for chemical potential and stability of molecules and also the molecular docking studies of naringin to find the binding efficiency of ligand and breast cancer marker proteins. The 3D structure of proteins is retrieved from the RCSB protein data bank and the tool autodock vina helps in molecular docking studies. Among the seven target proteins, PR have efficient binding energy (-9.3 Kcal/mol), which confirms the potential to target breast cancer.
Keywords: Breast cancer, Naringin, HOMO-LUMO, Molecular docking

1. INTRODUCTION

Breast cancer is possibly well-known women cancer in the world. Breast cancer is difficult to recognize at early stages because of many biomolecular elements are involved in the process [1]. Malignant breast cancer is caused due to genetic changes, defective cell divisions [2] and hormonal imbalance [3]. The breast malignant growth is primarily diagnosed in between 20 to 60 years old [4]. The customary strategies for restoring breast cancer were dreary, tedious, and asset-burning-through. In the time of headway, various therapuetics are utilized to cure breast malignancy [5]. ICMR consensus, for the management of breast cancer, documented 1,44,000 new instances of breast cancer was accounted in India consistently. India was recorded third in cancer mortality with a proportion of 68.4% demise each year and almost 30% of the populace survives after 5 years of malignant growth diagnosis [6]. Currently, the target-based breast cancer drugs for available based on their cell surface receptor, angiogenesis blockade, histone deacetylase inhibitors, and other inhibitors survival pathway [7]. Breast cancer chemotherapy is set apart by focusing on the function of receptors like ERα (estrogen receptor alpha), PR (progesterone receptor), EGFR (epidermal development factor receptor), etc. Estrogen receptors (ER) play a fundamental part in the initiation and progression of breast cancer. Studies say that estrogen, explicitly17 β-estradiol has been accounted to upregulate the expression and function of c-Myc and cyclin D1 which prompts the advancement of the cell cycle from G1 stage to S stage in the epithelial cells of mammary organs. Hostile to estrogen therapy is a promising therapy of ER-positive breast malignancy [8]. The overexpression of PR is normally seen in breast cancer and this is directly identified with the over-articulation of ER as PR is the end product from estrogenic stimulation in target tissues which showed a functioning ER pathway. The over-expression of PR alongside ER gives a better prognosis to PR positive breast malignant growth and there are better odds of response to hormonal therapy [9]. Treatment with ER and PR antagonists can bring upon better treatment choices and prognoses. EGFR has been accounted for to assume a significant role in triple-negative breast cancer (TNBC) [10]. Since TNBC is phenotypically characterized as ER-negative, PR negative, and HER-2 negative, the treatment alternatives are very narrow [11]. Consequently, the utilization of EGFR halfway antagonists can show promising treatment strategies. The affirmed promoted helpful medications utilized for breast cancer are Tamoxifen, Trastuzumab, Paclitaxel, Capecitabine,

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Cyclophosphamide, Gemcitabine, Docetaxel, etc. which have enhanced side effects. The other medicinal options for the therapy of breast cancer are phytochemicals and their subsidiaries which have been demonstrated to show powerful anticancer activity [12]. As past examinations recommended that chemokine ligand 18 (CCL18) is a chemokine derived from tumor-related macrophages (TAMs) to prompt BC metastasis. Therefore, CCL18 is viewed as a potential drug target [13]. The BCL-2 family is a group of proteins that induced apoptosis through the alteration of the inner mitochondrial membrane and that have a central job in cell death regulation. Thus, BCL-2 has a considered drug targets and designed a 3D pharmacophore model to inhibitor of the antiapoptotic BCL-2 protein [14, 15]. Oncogenic proteins like tyrosine kinase, cell cycle regulators, and transcriptional factors are implicated in metastatic pathways in malignancy. The above proteins are interacting with HSP90 therefore, the Hsp90 inhibitors have been proposed as novel malignancy treatment [16].

In the current chemotherapy of breast cancer, there is a need for produced new drugs to overcomes the side effects and also identify the novel modulator which is acts as a therapeutic agent for breast cancer. So, plant phytochemicals are a novel new candidate for developing against cancer [17]. Naringin is one of the natural flavonoids present in grapes and citrus fruits. The molecular formula and molecular weight of naringin are C27H32O14 and 580.4g/Mol respectively. Its chemical formula of naringin is 4',5,7,-trihydroxyflavonone-7-rhamnoglucoside. Naturally, it possesses a distinct bitter taste of grapefruit juice and has strong antioxidant properties [18]. Many literature surveys have revealed that naringin is an intense compound as anticancer, anti-inflammatory, anti-ulcer, anti-osteoporotic, and antioxidant properties. Promising anticancer treatments from natural products can show anticancer action through enacting the apoptotic pathway [19, 20, 21].

Becke's three-parameter hybrid exchange functional and the Lee-Yang-Parr functional (B3LYP) helps to optimize computational quantum chemical investigation of a drug in the ground state [22, 23, 24]. By using *GAUSSIAN 09W* software and analyze the quantum chemical with DFT/B3LYP with 6-311++G(d,p) levels [25]. The three-dimensional images of HOMO and LUMO can be generated and visualized by Gauss View 5.0 [26].

In silico study gives likelihood for the drugs to be tried for in vitro and in vivo studies and bioinformatics studies can predict the protein and drug interactions. Accordingly, levelheaded medication planning along with structure-based displaying and quick screening of drugs offers the potential for distinguishing and building up the best lead particle against breast cancer[27]. The current study is concerned about the docking of flavanoid naringin and its application as an anticancer specialist to show up at a successful drug-like particle focusing on PR, HER, BCL2, EGFR, ERα, CCL18, and HSP90 responsible for Breast Cancer.

2. MATERIALS AND METHODOLOGY

2.1Preparation of the 3-dimensional structure of protein and ligands

The X-ray Crystallographic construction of PR, HER, BCL2, EGFR, ERα, CCL18, and HSP90 were retrieved from RCSB Protein Data Bank (PDB) (https://www.rcsb.org/),(PDB ID: 4OAR, 2IOK, 4AQ3, 2J6M, 6WOK, 4MHE, and 2VCJ) was utilized as a potential anticancer drug target. The SDF file of naringin (PubChem ID: 442428) was retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/).

2.2Frontier molecular orbital (HOMO-LUMO) analysis

Computational quantum chemical investigation of naringin in the ground state was fully optimized by using Becke's three-parameter hybrid exchange functional and the Lee-Yang-Parr functional (B3LYP). Quantum chemical calculations were studied with DFT/B3LYP with 6-311++G(d,p) levels using *GAUSSIAN 09W* software package. Three-dimensional images of HOMO and LUMO were generated and visualized Gauss View 5.0. The molecular structure of naringin was optimized by DFT/B3LYP with a 6-311++G(d,p) basis set and displayed with an atomic numbering scheme. The highest occupied molecular orbital (HOMO) and lowest unoccupied molecules orbital (LUMO) are called as frontier molecular orbital (FMOs). HOMO-LUMO analysis plays a vital role during molecular interactions. Further, the energy difference between the molecular orbital delivers an important perspective about the chemical reactivates and optoelectronic properties of the molecule under analysis.

2.3 Molecular docking

The molecular docking process was performed using autodock vina program plug-in PyRx 0.8 (https://sourceforge.net/projects/pyrx/). The 7 breast cancer proteins are docked with naringin. Then the active site was analyzed by BIOVIA Discovery Studio Visualizer 2020 (https://discover.3ds.com/discovery-studio-visualizer-download). In PyRx targeted protein was loaded on vina wizard in .pdb format and ligand molecule was imported in .sdf format and was converted to .pdbqt format. Then grid box was chosen for the region to be docked. Finally, AutoDock Vina was executed and results were noted. Different binding sites and ligand conformations were tested and the best was chosen dependent on internal energy.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

2.4Making protein-ligand complex

The protein-ligand complex was built by using PyMol 2.4 (https://pymol.org/2/). Ligand molecule and processed targeted proteins from docking workspace in .pdbqt format were imported. Then the protein-ligand complex was built and the complex file was saved in .pdb format.

2.5 Studying protein-ligand interaction

The BIOVIA discovery studio client 2020 was a well-known Visualizer of the protein-ligand complex. The protein-ligand complex file was loaded on the graphical window in .pdb format and then charges were added. The complex molecule showed the 2D and 3D interaction of amino acids between protein and ligand.

3 RESULT AND DISCUSSION

3.1 Analysis of Frontier molecular orbital (HOMO-LUMO)

Figure 1: Optimized molecular structure of naringin

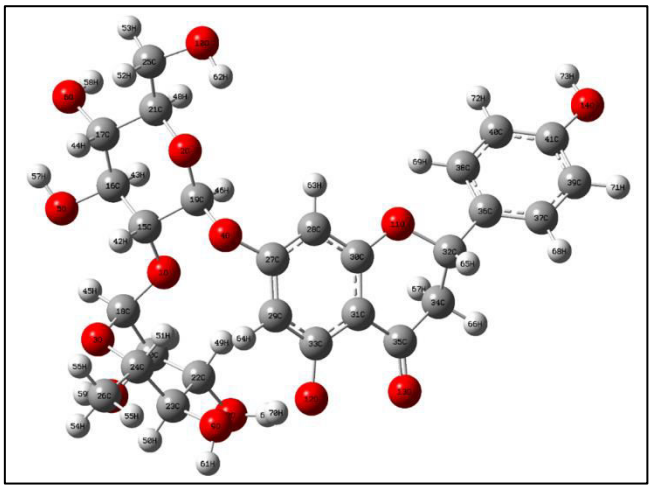
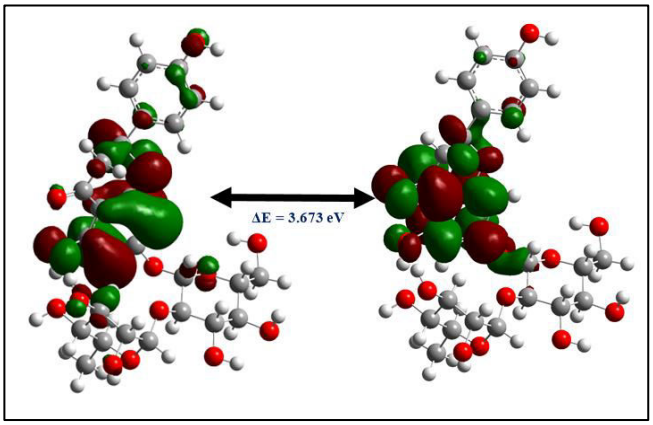


Figure 2: Molecular orbital energy diagram



FMO energy gap was been used to demonstrate the bioactivity from the intramolecular charge transfer of molecules. The frontier electron density is used to predict the most reactive state in π-electron systems, and it has been used to describe a wide variety of reactions in the integrated system. The ability to donate an electron is HOMO and the ability to accept an electron is LUMO. The molecular orbital energy diagram of the title molecule is given in Figure 2. From this Figure, the green and red colors represent the positive and negative phases which

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

indicates the charge transfer within the molecule. The FMO energy gap value $\Delta(E_{LUMO} - E_{HOMO})$ is 3.673 eV that reflects the high chemical stability of the molecule. Furthermore, HOMO-LUMO energies were used to calculate the quantum chemical descriptors such as electron affinity, electronegativity, chemical hardness, chemical potential, and global electrophilicity index. The quantum chemical descriptors were calculated by following Koopman's theorem.

Ionization potential (I)=$-E_{HOMO}$

Electron affinity (A) =$-E_{LUMO}$

Electronegativity (χ) = $\{(I+A)/2\}$ (1)

Chemical hardness (η) = $\{(I-A)/2\}$ (2)

Chemical Potential (μ) = $-(\chi)$ (3)

Global electrophilicity index (ω) = $(\mu^2/2\eta)$ (4)

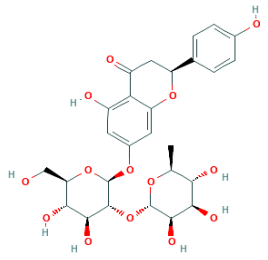
Table 1: Calculated energy values and quantum chemical descriptors details

Quantum chemical descriptors	Calculated values	
	(a.u)	eV
E_{LUMO}	-0.174	-4.735
E_{HOMO}	-0.309	-8.408
$\Delta(E_{LUMO} - E_{HOMO})$	0.135	3.673
Electron Affinity (A)	0.174	4.735
Ionization Potential (I)	0.309	8.408
Chemical Hardness (η)	0.068	1.850
Electronegativity (χ)	0.242	6.585
Chemical Potential (μ)	-0.242	-6.585
Global electrophilicity index (ω)	4.309	117.252

The calculated FMO energy values and quantum chemical descriptors details are listed in Table 1 and these parameters are associated with the chemical reactivity of the molecule. These descriptors are related to the electronic structure of the compound and the mechanism involved in the formation of a covalent bond between the nucleophile and the electrophile. This FMO energy gap suggested reflects the high chemical stability and it is responding to the biological activity of the molecule [28]. The chemical potential of the molecule is negative which means the molecule is stable and it is one of the important properties of the bioactive molecule.

3.2 Docking scores of naringin with targeted proteins

Table 2:Docking scores of naringin with targeted proteins

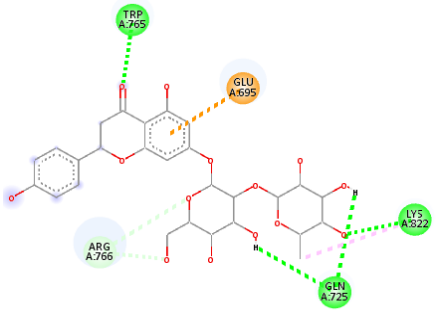
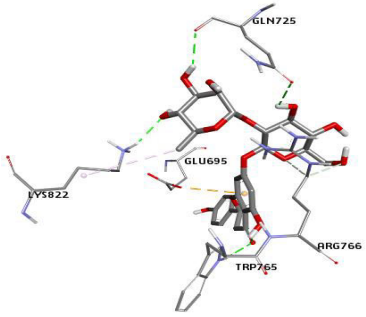
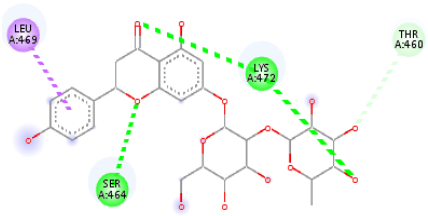
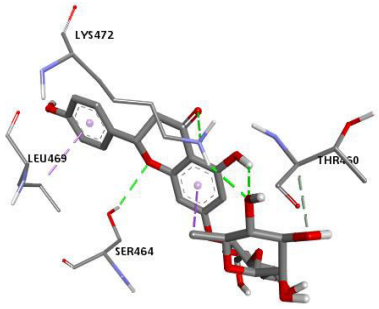
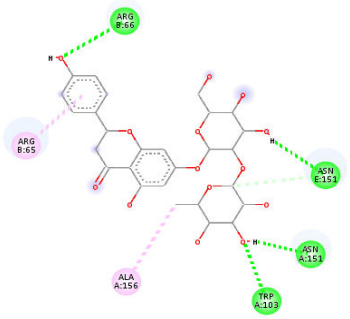
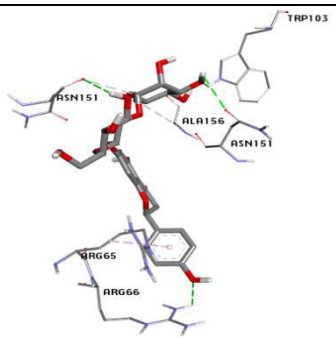
Drug/ Ligand	Structure of Naringin	Binding affinity (kcal/mol)						
		PR	HER	BCL2	EGFR	ERα	CCL18	HSP90
Naringin		-9.3	-9.1	-9	-8.3	-7.7	-7.7	-7

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

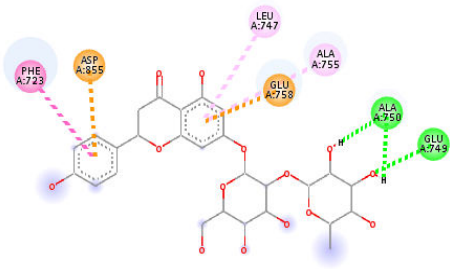
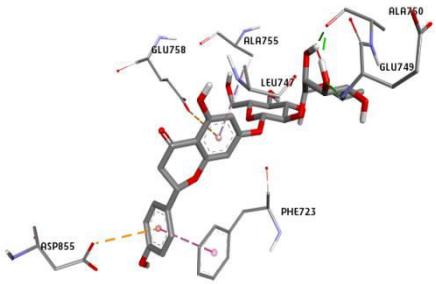
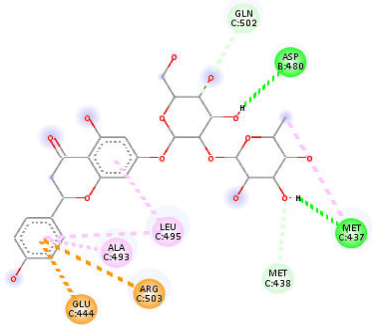
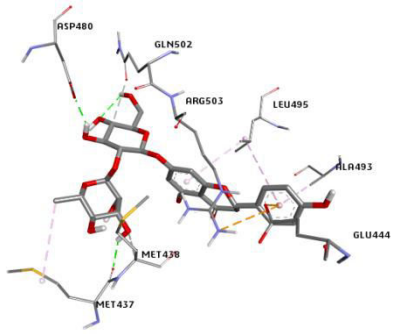
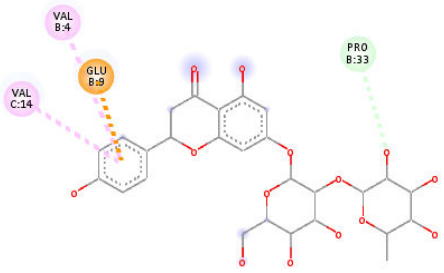
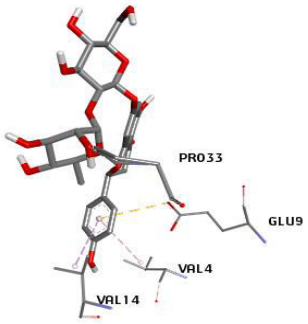
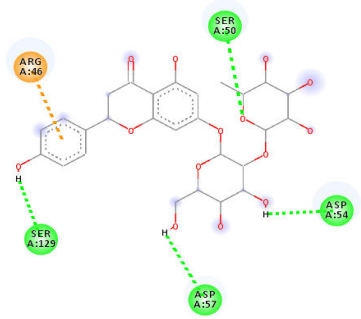
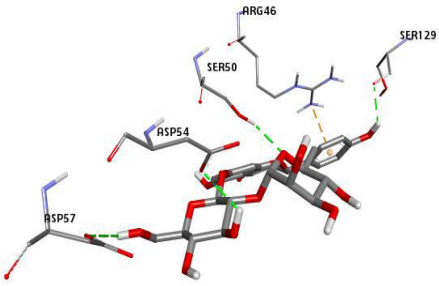
The Naringin was docked into the binding pocket of 8 proteins, and based on the docking score, PR (-9.3 Kcal/mol), HER (-9.1 Kcal/mol), BCL2 (-9 Kcal/mol), EGFR-8.3 Kcal/mol), ERα (-7.7 Kcal/mol), CCL18 (-7.7 Kcal/mol) and HSP90 (-7 Kcal/mol) were selected as a potent lead. In these eight evaluations, naringin shows the best docking confirmation with the binding affinity of −9.3 kcal/mol towards PR (progesterone receptor). Naringin was found to be tightly fit into the binding pocket and have efficient interaction at the active sites of the targeted protein.

3.3 Binding interaction of naringin with targeted proteins

Table 3: 2D and 3D interaction of naringin with targeted proteins

Target Protein	PDB ID	2D Interaction	3D Interaction
PR	4OAR		
HER	2IOK		
BCL2	4AQ3		

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

EGFR	2J6M		
ERα	6WOK		
CCL18	4MHE		
HSP90	2VCJ		

Naringin with PR formed four(4) Conventional H-Bond interaction with Trp765, Gln725 (2), and Lys822 at bond distances of 2.36268 Å, 2.37516 Å, 2.33323 Å, and2.33477 Å and two (2) Carbon H-Bond withArg766 (2) at distances 3.3894 Å and 3.23803 Årespectively. Also Naringin with PR formed one (1) hydrophobic interaction (Alkyl) with amino acid residue Lys822 at bond distance of 5.09988 Å. Other interactions includePi-Anion interaction (electrostatic) with Glu695 at bond distance of 3.74461Å. Naringin with HER formed three (3) Conventional H-Bond interaction withSer464 andLys472 (2), at distances 2.69857Å, 2.24842Åand 2.25837Å and one (1) Carbon H-Bond withThr460 at bond distance 3.75186Å. Also,Naringin with HER also formed one (1) hydrophobic interaction (Pi-Sigma) with Leu469 at bond distance 3.90821Å.Similarly, Naringin with BCL2formed four (4) Conventional H-Bond interaction with Trp103, Asn151 (2) and Arg66 at2.54358Å, 2.93838Å, 2.9086Å and 2.94965Å and one (1) Carbon H-Bond with Asn151 at 3.36967Å bond distances. In addition, Naringin with BCL2

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

formed two (2) hydrophobic such as Pi-Alkyl and Alkyl interactions with amino acid residues of Arg65 and Ala156at4.61244Å and4.0201 Å distances. Naringin with EGFR formed three (3) Conventional H-Bond interaction with Glu749,Ala750 (2) at distances2.05787Å, 1.77614Å and 1.80151Å respectively. Also, Naringin with EGFR formed three (3) hydrophobic interactions (Pi-Pi, Pi-Alkyland Pi-Alkyl) with Phe723,Leu747 and Ala755 at bond distances 4.93388Å, 5.09149Å and 5.11916Å. Other interactions formed by Naringin with EGFR include electrostatic type (Pi-anion interactions) with Glu758 and Asp855 at distances of 4.87053 and 4.05614 Å respectively. Naringin with ERα formed two (2) Conventional H-Bond interaction with Met437 and Asp480 (2.29024 Å and 2.00511 Å) and two Carbon H-Bond with Met438 and Gln502 at 3.59348 Å and 3.47536 Å respectively. Furthermore, Naringin with ERα formed four (4) hydrophobic interactions (Alkyl, Pi-Alkyl, Pi-Alkyl and Pi-Alkyl) with Met437, Ala493 and Leu495 (2) at 5.06295Å, 3.60401Å, 5.46536Å and 4.85918Å bond distances. In addition, Naringin with ERα formed two (2) electrostatic interactions (Pi-Cation and Pi-Anion) with Arg503 and Glu444 at distances 4.74773Å and 3.75046Å respectively. Naringin with CCL18 formed one (1) Carbon H-Bond with Pro33 at bond distance 3.44568 Å and two (2) hydrophobic interactions (Pi-Alkyl and Pi-Alkyl) with Val4 and Val14 at 5.25682 Å and 4.92703 Å respectively. Also, Naringin with CCL18 formed one (1) electrostatic interaction (Pi-Anion) with Glu9 at bond distance 4.29033 Å.Naringin withHSP90 formed four (4) Conventional H-Bond interaction with Ser50, Ser129, Asp57 and Asp54 at bond distances 2.26757Å, 2.19652Å, 2.75166Å, 2.40754Å respectively and one (1) electrostatic interaction (Pi-Cation) with Arg46 at bond distance 3.52576 Å. Manyof the molecular docking studies have stated that the number of hydrogen bonds and bond distances are the essential factors influencing the binding affinity of a ligand-receptor interaction [29]. This reason gives a structural insight as to why naringin was able to bind tightly with the active pocket of the target proteins.

4. CONCLUSION

In this study, the molecular docking was applied to explore the binding mechanism and to correlate its docking score with the activity of Naringin. Among all seven targeted proteinsnaringin shows higher Dock score with PR at binding affinity -9.3kcal/mol. The results of our present study can be useful for the design and development of drugs having better inhibitory activity against breast cancer protein. This potential drug naringin can further be validated in-vitro and in-vivo studies for its proper function against breast cancer.

REFERENCE

REFERENCE

1. Kelsey, J. L., Gammon, M. D., & John, E. M. 1993. Reproductive factors and breast cancer. Epidemiologic reviews, 15(1): 36-47.
2. Key, T. J., Verkasalo, P. K., & Banks, E. 2001. Epidemiology of breast cancer. The lancet oncology, 2(3), 133-140.
3. Easton, D. F., Ford, D., & Bishop, D. T. 1995. Breast and ovarian cancer incidence in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. American journal of human genetics, 56(1), 265 –271.
4. Pike, M. C., & Ross, R. K. 2000. Progestins and menopause: epidemiological studies of risks of endometrial and breast cancer. Steroids, 65(10-11): 659-664.
5. Müller, A., Homey, B., Soto, H., Ge, N., Catron, D., Buchanan, M. E., & Barrera, J. L. 2001. Involvement of chemokine receptors in breast cancer metastasis. nature, 410(6824), 50-56.
6. Mallath, M.K., Taylor, D.G., Badwe, R. A., Rath, G.K., Shanta, V., Pramesh, C.S., Digumarti, R., Sebastian, P., Borthakur, B.B., Kalwar, A., Kapoor, S., Kumar, S., Gill, J.L., Kuriakose, M.A., Malhotra, H., Sharma, S.C., Shukla, S., Viswanath, L., Chacko, R.T., Pautu, JL, Reddy, KS, Sharma, KS, Purushotham, AD & Sullivan, R. 2014. The growing burden of cancer in India: epidemiology and social context. The Lancet Oncology, 15(6): 205-212.
7. Harini, L., Karthikeyan, B., Srivastava, S., Suresh, S. B., Ross, C., Gnanakumar, G., &Kathiresan, T. 2017. Polyethylenimine-modified curcumin-loaded mesoporus silica nanoparticle (MCM-41) induces cell death in MCF-7 cell line. IET nanobiotechnology, 11(1), 57-61.
8. Wang, Z. Y. & Yin, L. 2015. Estrogen receptor alpha-36 (ER-α36): a new player in human breast cancer. Molecular and cellular endocrinology 418(3): 193–206.
9. Kiani, J., Khan, A., Khawar, H., Shuaib, F. & Pervez, S. 2006. Estrogen Receptor α-Negative and Progesterone Receptor-Positive Breast Cancer: Lab Error or Real Entity? Pathology oncology research 12: 223–227.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

10. Costa, R. et al. 2016. Targeting Epidermal Growth Factor Receptor in Triple Negative Breast Cancer: New Discoveries and Practical Insights for Drug Development. Cancer treatment reviews 53: 111–119.
11. Palma, G. et al. 2015. Triple negative breast cancer: looking for the missing link between biology and treatments. Oncotarget. 6(29): 26560–26574.

12. Nagini, S. 2017. Breast Cancer: Current Molecular Therapeutic Targets and New Players. Anticancer Agents Med Chem. 17(2): 152–163.

13. Chen, J.; Yao, Y.; Gong, C.; Yu, F.; Su, S.; Chen, J.; Liu, B.; Deng, H.; Wang, F.; Lin, L.; et al. 2011. CCL18 from Tumor-Associated Macrophages Promotes Breast Cancer Metastasis via PITPNM3. Cancer Cell, 19(4): 541–555.

14. Harini, L., Srivastava, S., Gnanakumar, G. P., Karthikeyan, B., Ross, C., Krishnakumar, V., &Kathiresan, T. 2019. An ingenious non-spherical mesoporous silica nanoparticle cargo with curcumin induces mitochondria-mediated apoptosis in breast cancer (MCF-7) cells. Oncotarget, 10(11), 1193.

15. Ziedan, N.I.; Hamdy, R.; Cavaliere, A.; Kourti, M.; Prencipe, F.; Brancale, A.; Jones, A.T.; Westwell, A.D. 2017. Virtual screening, SAR, and discovery of 5-(indole-3-yl)-2-[(2-nitrophenyl)amino] [1,3,4]-oxadiazole as a novel Bcl-2 inhibitor. Chem. Biol. Drug Des., 90(1): 147–155.

16. Koca, I.; Özgür, A.; Er, M.; Gümüs¸, M.; Cos¸kun, K.A.; Tutar, Y.2016. Design and synthesis of pyrimidinyl acyl thioureas as novel Hsp90 inhibitors in invasive ductal breast cancer and its bone metastasis. Eur. J.Med.Chem, 122: 280–290.

17. T. Mohan Viswanathan, Rajan Pradeepa, Ravi Lavanya, PalaniyappanAbinaya, Krishnan Sundar,ThandavarayanKathiresan. 2021. In Silico And Molecular Docking Prediction Studies Elucidate Anti Breast Cancer Activity Of Lycopene And Gallic Acid. J Cardiovasc. Dis. Res. 12(5): 503-509

18. Häussinger D, Sies H. 2013. Hepatic encephalopathy Clinical aspects and pathogenetic concepts. Arch. Biochem. Biophys. 536: 97–100.

19. Zhu H, Gao J, Wang L, Qian K, Cai L. 2018. In vitro study on reversal of ovarian cancer cell resistance to ciplastin by naringin via the nuclear factor-kB signaling pathway. Exp Ther Med; 15(3): 2643-2648.

20. El-Desoky AH, Abdel-Rahman RF, Ahmed OK, El-Beltagi HS, Hattori M. 2018. Anti-inflamatory and antioxidant activities of naringin isolated from Carissa carandas L.: in vitro and in vivo evidence. Phytomedicine; 15(42): 126-134.

21. Sun X, Fengbo L, Xinglong MA, Jianxiong MA, Zhao B, Zhang Y , Yanjun L, Jianwei LV , Meng X. 2015. The effects of combined treatment with naringin and treadmill exercise on osteoporosis in ovariectomized rats. Sci Rep.; 5: 13009.

22. . R.G. Parr, W. Yang. 1980. Density-Functional Theory of Atoms and Molecules, Oxford University Press. 3(2): 5-15.

23. W. Koch, M.C. Holthausen. 2000. A Chemist's Guide to Density Functional Theory, Wiley-VCH, Weinheim.

24. C.J. Cramer. 2003. Essentials of Computational Chemistry, Wiley, USA. 43(5): 1720-1723.

25. M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, Robb, M.A., Cheeseman, J.R., Scalmani, G., Barone, V., Mennucci, B., Petersson, G.A., Nakatsuji, H., Caricato, M., Li, X., Hratchian, H.P., Izmaylov, A.F., Bloino, J., Zheng, G., Sonnenberg, J.L., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Vreven, T., Montgomery Jr., J.A., Peralta, J.E., Ogliaro, F., Bearpark, M., Heyd, J.J., Brothers, E., Kudin, K.N., Staroverov, V.N., Kobayashi, R., Normand, J., Raghavachari, K., Rendell, A., Burant, J.C., Iyengar, S.S., Tomasi, J., Cossi, M., Rega, N., Millam, J.M., Klene, M., Knox, J.E., Cross, J.B., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R.E., Yazyev, O., Austin, A.J., Cammi, R., Pomelli, C., Ochterski, J.W., Martin, R.L., Morokuma, K., Zakrzewski, V.G., Voth,

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

G.A., Salvador, P., Dannenberg, J.J., Dapprich, S., Daniels, A.D., Farkas, O., Foresman, J.B., Ortiz, J.V., Cioslowski, J. and Fox, D.J.: 2010. Gaussian 09, Revision B.01. Gaussian Inc., Wallingford.

26. R. Dennington, T. Keith, J. Millam. 2009. Gauss View Version 5.0.8 Semichem Inc., Shawnee Mission KS.

27. Fuks, F., Burgers, W. A., Brehm, A., Hughes-Davies, L., & Kouzarides, T. 2000. DNA methyltransferase Dnmt1 associates with histone deacetylase activity. Nature genetics. 24(1):88-91

28. S. Christopher Jeyaseelan, R. Premkumar , K. Kaviyarasu, A. 2019. Milton Franklin Benial, Spectroscopic, quantum chemical, molecular docking and in vitro anticancer activity studies on 5-Methoxyindole-3-carboxaldehyde, Journal of Molecular Structure 1197: 134-146.

29. Fuks, F., Burgers, W. A., Brehm, A., Hughes-Davies, L., & Kouzarides, T. 2000. DNA methyltransferase Dnmt1 associates with histone deacetylase activity. Nature genetics, 24(1), 88-91.