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Assessing the Specificity of Paclitaxel towards the Marker Proteins of Breast Cancer Using *In silico* Molecular Docking Study

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Authors' contributions

The manuscript is a team effort of all the authors. Author VSK identified the drug molecule, carried out preliminary works concerning to this research including literature review, studied the physical characters of the chosen drug and written a manuscript. Author TVAK performed the molecular docking study with drug candidate "Paclitaxel" and carried out revision of the manuscript. The corresponding author VP supervised the whole of the research and given the constructive suggestions to execute the research work in correct direction and revised the manuscript several times. All the authors have examined and accepted the final version of the manuscript.

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ABSTRACT

Breast cancer is highly prevalent next to lung cancer. Breast cancer occurs as a result of mutation in the genes like proto-oncogenes as well as tumor suppressor genes in a single clone of cells in the ductal and glandular regions of the breast. The drugs used to prevent breast cancer are Raloxifene hydrochloride and Tamoxifen citrate. The drugs used to treat breast cancer are Abemaciclib, Paclitaxel, Everolimus, Imatinib, Alpelisib, Anastrozole. Although several drug molecules had been developed, their specificity towards the potential breast cancer specific marker proteins such as activated threonine kinase 2/Protein kinase B (AKT2), cell division protein kinase 6 (CDK6), estrogen receptor (ER), human epidermal growth factor receptor type 2 (HER2), and poly ADP ribose polymerase1 (PARP1) need to be studied *in silico*. The present study was

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undertaken 1) to assess the specificity of paclitaxel towards the breast cancer specific marker proteins using molecular docking analysis and 2) to identify various physico-chemical properties of drug molecules including absorption, distribution, metabolism and excretion (ADME). The interaction between paclitaxel and the target proteins of breast cancer was analyzed using the Schrodinger Maestro Ver.2018.4. The results of the present study reveal that paclitaxel shows good binding interactions with the target proteins in the following order, ER > PARP1 > AKT2 >CDK6 > HER2. Among the five proteins, ER and PARP1 showed good binding interactions as compared to AKT2, CDK6 and HER2 proteins. The ADME properties of paclitaxel were predicted using QikProp module of Schrodinger Maestro version 2018.4. The present study warrant further studies which helps in the development of potent anticancer drug to treat breast cancer.

Keywords: Cancer; breast cancer; paclitaxel; AKT2; CDK6; ER; HER2; PARP1; ADME; Schrodinger; QikProp.

1. INTRODUCTION

Cancer refers to a disease state involving uncontrolled proliferation of body cells and is also known as neoplasm. The International Agency for Research on Cancer (IARC), a unit of World Health Organization (WHO) reported that 28 types of cancer are found in 184 countries and the cancer burden is alarmingly increasing. In 2025 the incidence of cancer would be 19.3 million. The breast, lung, and colorectal cancers are the top three cancers contribute to more than 43% of all cancers. The annual raise of cancer incidence is about 1-2% [1]. Increase in cancer prevalence is a socio-economic burden to human life [2]. The breast Cancer is a leading type of cancer next to lung cancer. The breast cancer (also known as malignant breast neoplasm) is a type of cancer of breast tissue, and also a primary cause of global cancer fatality (14%) [3]. 5-10 % of the breast cancer is associated with known gene mutations of BRCA1 and BRCA2 inherent from parents. In addition, the aged women are more prone to breast cancer [4,5].

The drugs approved for the prevention of breast cancer are Raloxifene hydrochloride and Tamoxifen citrate. The drugs in use for the treatment of breast cancer are Abemaciclib, Paclitaxel, Everolimus, Imatinib mesylate, Alpelisib, Anastrozole, Doxorubicin hydrochloride [6]. Although several drugs and formulations are used to treat breast cancer, they cause side effects and show evidence of non-specific binding with the proteins of cancer microenvironment. Hence, it is appropriate to develop an ideal drug to treat breast cancer. The drugs targeting specific genes or proteins related to breast cancer can alter the signaling pathways responsible for cancer cell proliferation, invasion and angiogenesis [7].

Paclitaxel is a naturally occurring tricyclic diterpenoid with a molecular formula of $C_{47}H_{51}NO_{14}$ (Fig. 1), isolated from the bark and needles of *Taxus breifolia*. Paclitaxel is a successful anticancer drug due to its exclusive anticancer mechanism [8]. In the present study, *in silico* molecular docking of paclitaxel on certain marker proteins of breast cancer such as Protein kinase B (AKT2), Cell division protein kinase 6 (CDK6), Estrogen Receptor (ER), Human epidermal growth factor receptor type 2 (HER2), and poly ADP ribose polymerase 1 (PARP1) was carried out using Schrodinger Maestro version 2018.4. In addition to these, the drug likeness, absorption, distribution, metabolism, and excretion (ADME) properties were also assessed based on Lipinski's rule of five by employing "QikProp" module of Maestro version.

2. MATERIALS AND METHODS

2.1 Ligand Preparation

The ligand "paclitaxel" (Fig. 1) was imported from the PubChem data bank [9], saved in .sdf format for computational calculations and placed into Maestro workspace. The ligand was prepared using LigPrep module of Schrodinger suite (Maestro version 11.8) [10]. The 2D structure of the ligand was converted into 3D with its likely tautomers and ionization states at pH 7.0 ± 2.0. The ligand was further generated and geometrically minimized by means of optimized potential liquid simulations (OPLS-2005) force field using "LigPrep" module for further docking analysis [11,12].

2.2 Protein Preparation

The chosen proteins namely, AKT2 (PDB code: 3D0E) [13], CDK6 (PDB code: 4AUA) [14], ER (PDB code: 3ERT) [15], HER-2 (PDB code:

3PP0) [16], and PARP1 (PDB code: 2RCW) [17] were identified and imported from the protein data bank (PDB) (http://www.rcsb.org/pdb/-home/home.do). The features of the protein structure from the protein data bank is not appropriate to carry out molecular docking study since they contain heavy atoms with or without co-crystallized ligand, water molecules, metal ions and co-factors. The resolution of the target proteins are, 2.00 Å (AKT2), 2.31 Å (CDK6), 1.90 Å (ER), 2.25 Å (HER2) and 2.80 Å (PARP1) and were considered as good for further analysis. The 3D structure of the protein was prepared using protein preparation wizard module of Schrodinger suite Maestro version 11.8 and preprocess, regenerate states, optimization and minimization (OPLS-2005) were performed [18].

2.3 Preparation of Grid

The grid was prepared using receptor-grid generation tool of Schrodinger Maestro version 11.8, where the binding/active site of the target protein co-crystallized with ligand molecule. Later the co-crystallized ligand will be expelled and occupied by a new ligand with same binding orientation [18].

2.4 Docking

Molecular docking study was performed using GLIDE program of Schrodinger Maestro (version 11.8) to examine the binding orientation of the ligand and selected target proteins (PDB ID) of breast cancer. The 3D structure of the protein was obtained from the protein data bank. The target proteins and its corresponding codes are as follows: AKT2 - 3D0E; CDK6 - 4AUA; ER - 3ERT; HER-2 - 3PP0 and PARP1 - 2RCW. The active site of the proteins also known as Grid was targeted and created. The active site includes the ligand and its interacting amino acids. The docking was carried out using the minimized ligand with Grid generated proteins. The extra precision (XP) was applied throughout the docking study for all proteins and the best docked pose was documented for each protein with the lowest glide/docking score [19,20].

2.5 ADME Prediction

The theoretical ADME properties of the ligand from the data set were predicted using the QikProp tool of Schrodinger Maestro (version 11.8). An about ten physically significant descriptors and pharmacological parameters of the ligands were analyzed. The water solubility of the ligand/compounds is playing a significant role in absorption, distribution, metabolism, excretion and the bioavailability [21,22]. The bioavailability of a molecule will be predicted using the Lipinski's rule of five, which is a familiar filter of choice. The Lipinski's rules follow the five parameters which includes: a) compound should not have a molar mass greater than 500 Daltons; b) no more than 5 hydrogen bonds; c) not more than 10 hydrogen bond acceptors and an octonal/water partition coefficient "log P" should not be greater than 5 [23]. The Lipinski's rule and pharmacokinetic parameters such as absorption, distribution, metabolism and excretion (ADME), were predicted using QikProp tool of Schrodinger Maestro (version 11.8) [24] (Schrodinger QikProp, 2018).

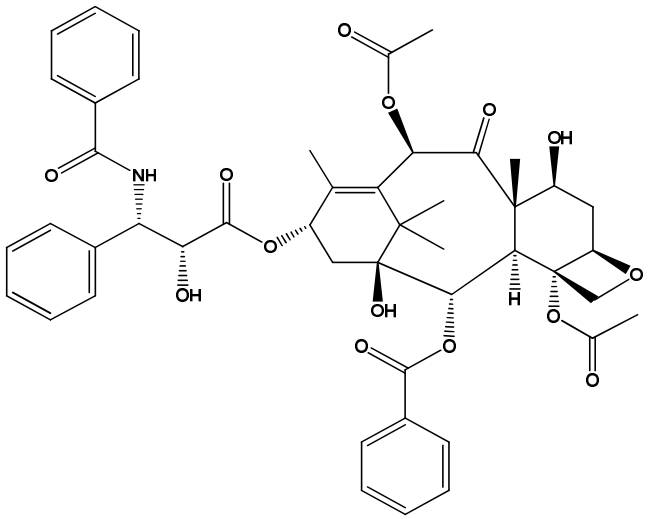

Fig. 1. The structure of paclitaxel

3. RESULTS AND DISCUSSION

Molecular docking studies involve computational tools which help in designing a drug molecule to target a protein [25]. Docking analysis provides details on the affinity, binding orientation and the biological activity of a drug molecule to their target proteins [26]. AKT2, also known as serine threonine kinase or protein kinase B is a key protein of PI3K/AKT signaling. The primary functions of AKT is to control the characteristics of cancer namely, tumor growth, survival and metastasis [27]. However, abnormal expression of Akt causes breast cancer in female. The mechanism of action of AKT2 is initiated by growth factor binding to transmembrane receptors, which inturn activates phosphoinositide-3-kinase (PI3K). PI3K then catalyses the conversion of phosphatidylinositol-4,5-bisphosphate to phosphatidylinositol-3,4,5-trisphosphate, a second messenger which is essential for the recruitment of Akt to the plasma membrane. Akt can be phosphorylated and activated by phosphatidylinositol-3, 4, 5-trisphosphate-dependent kinase (PDK1). Akt activation has impact on cancer cell cycling, growth and survival [28].

CDK6 is a cyclin-dependent kinase that helps in the development of cells at the early G1 phase of cell cycle by forming complexes with D-type cyclins such as D1, D2 and D3 [29]. The CDK6-cyclin D complex is involved in the G1 to S cell cycle progression and negatively regulates cell differentiation. CDK6 regulate the activity of tumor suppressor protein retinoblastoma (Rb). An increase in the expression of CDK6 is well connected with various cancers whereas very low levels were found in non-cancerous cells. CDK6-null mice were found to be normal suggesting an oncogenic role for CDK6 [30]. CDK6 represents a promising target for anti-cancer therapy] [31].

Estrogen production from androgens is mediated by aromatase. ER-α mediated extranuclear signaling enhances aromatase enzymatic activity which is implicated in the tumor progression. ER-α play vital role in the development of breast cancer. The administration of hormones that block ER functions or the induction of local and systemic estrogen production is used as a strategy to treat ER-α positive breast cancer. The extra nuclear actions of ER are emerging as an important target for tumorigenic and metastatic control. Hence, the targeting of extra-nuclear actions of ER can control the development and metastasis of ER-α positive breast cancer [32].

HER2 is a protein of the epidermal growth factor (EGF) family and the members of EGF are, HER1 (erbB1), HER2 (erbB2), HER3 (erbB3), and HER4 (erbB4). EGF is a 185 kDa transmembrane protein located in the long arm of chromosome 17. Human epidermal growth factor receptor 2 (HER2) is up-regulated during breast cancer to an extent of around 20 to 30 percent and could be correlated with severity, higher re-occurring rate and augmented death during breast cancer [33]. PARP1 acts as an important catalyst in DNA repair and involved in the pathway of tumorigenesis. The expression of PARP1 was increased significantly in cancers of breast, uterus, lung, ovary, skin and non-Hodgkin's lymphoma. Loss of PARP1 activity following treatment with PARP inhibitors can lead to enhanced cancer cell death. Hence, PARP1 inhibitors are used for the treatment of numerous malignancies concerned with dysfunctional DNA repair mechanisms and triple-negative breast cancer (TNBC) [34].

Paclitaxel promotes the arrangement of tubulin into microtubules and prevent the separation of microtubules which hinders cell cycle progress as well as mitosis and slow down the proliferation of cancer cells [30]. US-Food and Drug Administration (FDA) approved paclitaxel for the management of advanced ovarian cancer [35] and then it was extensively used in the treatment of breast cancer, colorectal cancer, and squamous cell carcinoma of urinary bladder. Moreover, it is also used for the management of diseases such as head and neck cancers, small-cell and non-small-cell lung cancers (NSCLCs), and AIDS [36]. Apart from cancer, paclitaxel is also used in the treatment of coronary heart disease, inflammation, axon regeneration as well as degenerative brain diseases, renal and hepatic fibrosis [37]. Paclitaxel-bound liposomes were studied *In vitro* and *In vivo* and demonstrated to be effective in the treatment of pancreatic cancer [38]. Paclitaxel treatment resulted in apoptosis of cancer cells both *In vitro* and *In vivo* conditions [35]. The combination of paclitaxel and palbociclib therapy to patients with Rb^+ advanced breast cancer has been reported to be safe without evidence of toxicity in phase I trial [39]. However, paclitaxel also showed cardiotoxic effects [40] and exert dermatological problems to patients with gynecological organ malignancy [41].

3.1 Molecular Docking Results

The molecular docking study was performed with the target proteins such as AKT2, CDK6, ER, HER2 and PARP1 against the prepared ligand "paclitaxel" using "ligand docking" module of Schrodinger Maestro (version 11.8). After successful docking, the parameters such as docking score, Glide evdw (Van Der Waals energy), ecoul (Coulomb energy), Glide energy and the interacting residues (Hydrogen bond/ π- π bond) against the target proteins were obtained. The degree of interaction between the target proteins and paclitaxel was evaluated. The results demonstrated that paclitaxel exhibited good docking score and interacted well with the crucial amino acid residues of the each target protein (Tab.1). The predicted docking scores of the study were negative. More negative docking score is an indicator of greater binding affinity/interaction with the target protein/receptor [42].

The predicted docking score of AKT2 against paclitaxel was calculated as -6.35 and a hydrogen bond interaction was also observed with the amino acid residues such as THR162, LYS191 as well as H20680. In addition to these, a pi-pi interaction was also noticed with the amino acid PHE443 of AKT2. The docking score of CDK6 with paclitaxel was -5.86 and a hydrogen bond interaction was seen with the amino acid residues namely, ILE19, LYS29, ASP102 and LYS111. The docking score of ER protein was found to be -10.63 and a hydrogen bond interaction was noticed with residues such as H2031, CYS530 and VAL534. The docking score of HER2 protein with paclitaxel was -3.55 and a hydrogen bond interaction was observed with amino acid residues such as H20129 and ARG811. Interestingly, paclitaxel showed a good docking score of -10.11 with PARP1 and have a hydrogen bond interaction with amino acids residues such as GLU102, MET229, LYS242, ASN245 and GLU327 respectively, and it also showed a pi-pi interaction with the amino acids namely, TYR228,TYR235 and TYR246 (Table 1).

Based on the docking score, paclitaxel exhibited excellent binding interactions with the active site of all the selected proteins of our interest. The 2D and 3D interactions of paclitaxel with the respective target proteins (A to E) are given in Figs. 2 and 3 respectively. The hydrogen bonding as well as pi-pi interactions of paclitaxel with the target proteins namely, AKT2 (Fig. 2A), CDK6 (Fig. 2B), ER (Fig. 2C), HER2 (Fig. 3D) and PARP1 (Fig. 3E) were shown clearly. The predicted Glide evdw (Van Der Waals energy), ecoul (Coulomb energy) and Glide energy of the target proteins such as AKT2 (-61.84, -9.23 & -71.07), CDK6 (-50.06, -13.55 & -63.60), ER (-35.87, -9.79 & -45.67), HER2 (-39.11, -7.32 & -46.43) and PARP1 (-60.51, -13.67 & -74.20) respectively are given in Table 1. The results of the present study depicted that the paclitaxel showed good interactions with all the chosen proteins. Based on the docking score, the order of target protein binding with paclitaxel was, ER (-10.63) > PARP1 (-10.11) > AKT2 (-6.35) > CDK6 (5.86) > HER2 (-3.55). Among these, ER and PARP1 showed greater binding with paclitaxel as compared to other target proteins such as AKT2, CDK6 and HER2.

Table 1. The docking score, glide evdw (van der waals energy), ecoul (coulomb energy), interacting residues and the type of interaction of paclitaxel with breast cancer marker proteins. The docking scores calculated using glide program of Schrodinger Maestro (version 2018.1). Where, HB denotes hydrogen bonding; Pi-Pi denotes π-π bond

Name of the drug	Target protein	Docking score	Glide evdw	Glide ecoul	Glide energy	Interacting residues (HB/Pi-Pi)
Paclitaxel	AKT2	-6.35	-61.84	-9.23	-71.07	THR162, LYS191 and H20680/PHE443
	CDK6	-5.86	-50.06	-13.55	-63.60	ILE19, LYS29, ASP102 and LYS111
	ER	-10.63	-35.87	-9.79	-45.67	H2031, CYS530 and VAL534
	HER2	-3.55	-39.11	-7.32	-46.43	H20129 and ARG811
	PARP1	-10.11	-60.51	-13.67	-74.20	GLU102, MET229, LYS242, ASN245 and GLU327/TYR228,TYR235 and TYR246

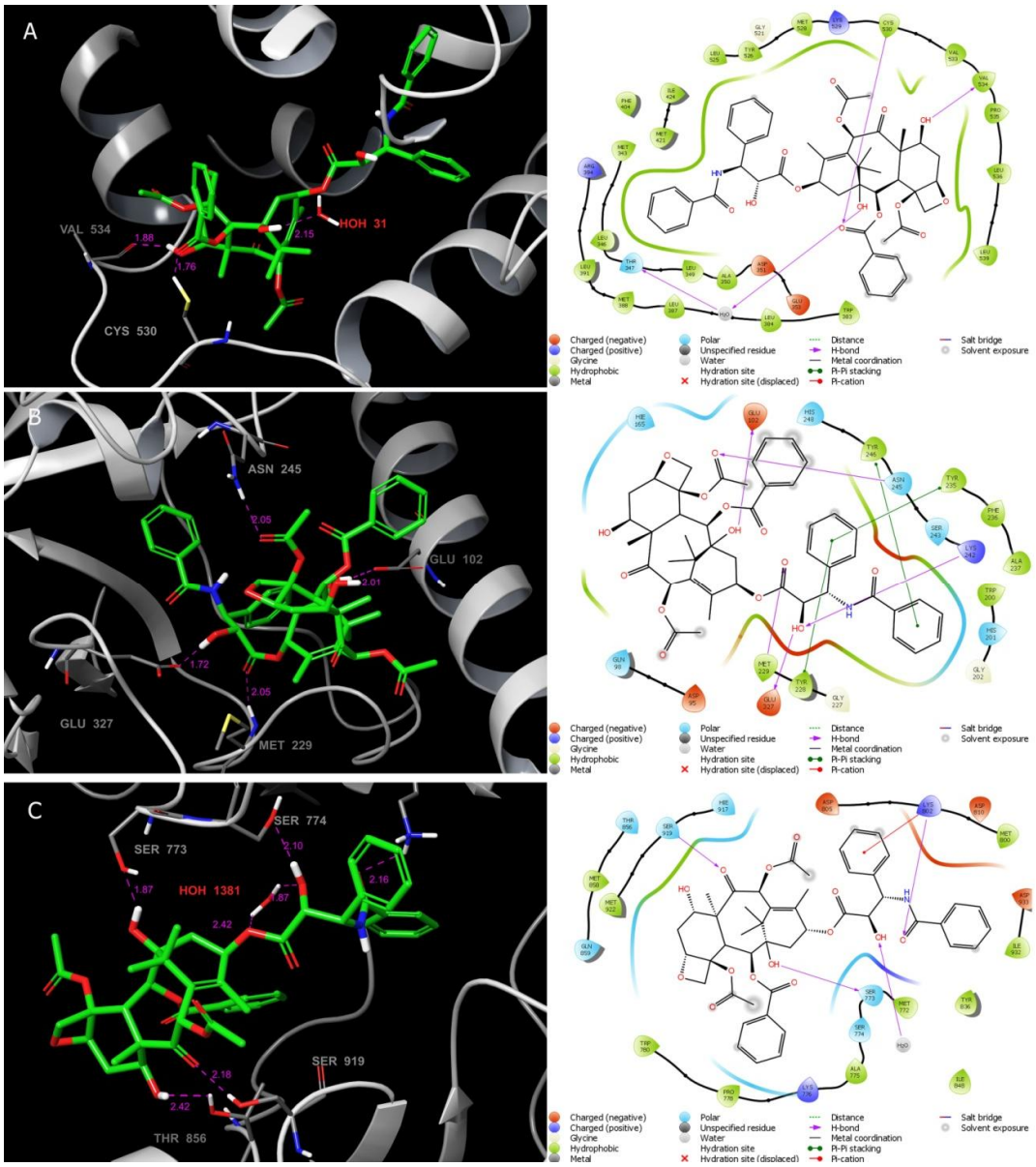

Fig. 2. Binding orientations of paclitaxel with the crystal structure of AKT2 (A); CDK6 (B); ER (C) and its hydrogen-bond interactions with amino acids

3.2 ADME Results

The computational biology approaches have gained considerable attention by the pharmaceutical researchers involved in drug discovery process since they are high-throughput method and cost effective [43] Among these, the Lipinski's rule of five or rule of thumb is also a tool, which was used in the present study to evaluate the drug likeness as well as certain pharmacological or biological activity of a new ligand/chemical entity. The rule portrays the molecular properties and ADME characters of a drug in human body. In addition to these, Lipkinski's rule is playing an active role in lead structure design, step-wise increase in the activity and selectivity of a compound to ensure drug-like physicochemical properties. The Lipinski's rule includes, (i) no more than 5 hydrogen bond donors, (ii) no more than 10 hydrogen bond acceptors, (iii) a molecular mass less than 500 daltons and (iv) octanol-water partition coefficient (QPlogP) not greater than 5 [23].

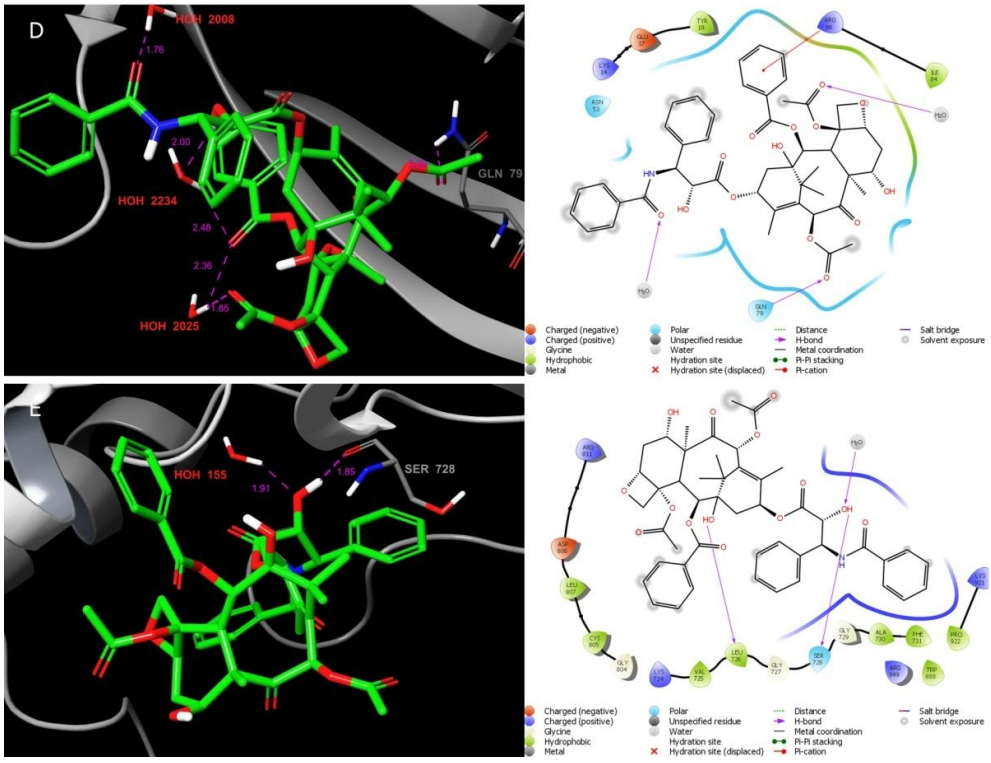

Fig. 3. Binding orientations of paclitaxel with the crystal structure of HER2 (D); PARP1 (E) and its hydrogen-bond interactions with amino acids

The ADME properties of the prepared ligand "paclitaxel" were assessed using QikProp module of Schrodinger (Maestro version 11.8). Around ten physically relevant and pharmacologically significant parameters of paclitaxel were determined. The program also predicted various parameters of Lipinski's rule of five namely, molecular weight (MW), hydrogen bond donor (HBD), hydrogen bond acceptor (HBA) and octanol/water partition coefficient (QPlogP (O/W). Moreover, the noteworthy pharmacokinetic parameters such as aqueous solubility (QPlogS), IC_{50} value for blockage of HERG K^+ channels (QPlogHERG), blood/brain partition coefficient (QPlogBB), predicted human oral absorption (PHOA), and QPPCaco-gut-blood barrier/cell permeability in nm/s were also identified.

From the results of Lipinski's rule, it was observed that the parameters such as HBD-3 (<5), HBA-17.65 (>10) and QPlog (o/w)-4.52 (<5) comply with the rules but other properties such as MW-853.92 (≤500) as well as rule of five -2 (0) was didn't met the criteria (Table 2). The predicted values for the pharmacokinetic properties are QPlogS: -4.96 (-6.5 to 0.5), QpHERG: -6.2 (<-5), QPlogBB: -1.98 (-3 to 1.2), PHOA: 67 (>80high & <25poor) and QPPCaco: 160 (>500high, <25poor) (Table 3). The result of ADME properties showed a slight violation in Lipinski's rule and good deed in pharmacokinetic properties. Thus, the drug paclitaxel is a good drug candidate for the development of targeted drug delivery system to treat breast cancer.

Table 2. The scores of paclitaxel predicted by a QikProp module of Schrodinger based on the Lipinski's rule. Where, MW denotes molecular weight, HB-Hydrogen bond and QPLogP (O/W) octanol/water partition co-efficient

Name of the Drug	Factors of Lipinski's rule of 5				
	MW (<500)	HB-Donor (<5)	HB-Acceptor (<10)	QPlogP (O/W) (<5)	Rule of 5 (0)
Paclitaxel	853.92	3	17.65	4.52	2

Table 3. Predicted ADME values of paclitaxel using a QikProp module of Schrodinger. Where, QPlogS denotes aqueous solubility, QpHERG-predicted IC_{50} value for blockage of HERG K^+ channels, QPlogBB-Brain/blood partition coefficient, PHOA- Predicted human oral absorption and QPPCaco-gut-blood barrier/cell permeability in nm/s

Name of the Drug	Pharmacokinetic properties				
	QPlogS (-6.5 to 0.5)	QpHERG (<-5)	QPlogBB (-3 to 1.2)	PHOA (>80 high, < 25 poor)	QPPCaco (>500 high, <25 poor)
Paclitaxel	-4.96	-6.2	-1.98	67	160

4. CONCLUSION

The results obtained confirm that paclitaxel has good binding interaction with target proteins such as AKT2, CDK6, ER, HER2, and PARP1 through hydrogen bond, polar and pi-pi bonds. Interestingly, the predicted Lipinski's and ADME scores for paclitaxel were within the acceptable range with a slight violation. Further, paclitaxel interacted well with the target proteins of breast cancer with low energy to inhibit the cell signaling pathways effectively. Paclitaxel shows good binding interactions with the target proteins in the following order, ER > PARP1 > AKT2 >CDK6 > HER2. Interestingly, ER and PARP1 showed better binding affinities towards paclitaxel as compared to other target proteins such as AKT2, CDK6 and HER2 proteins. The present study pave way for further studies which rationalize anticancer therapy based on the expression of breast cancer proteins.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Agha BM, Ahmadi F, Mohammadi E, Hagizadeh E, Varvarani A. Physical, emotional and social dimension of quality of life among breast cancer women under chemotherapy. Iranian Journal of Nursing Research. 2007;1(3):55-65.
2. Maliheh P, Maryam H, Abbas A, Peyman J, Mohammad S, Tahereh D, et al. Does a rehabilitation program improve quality of life in breast cancer patients?. Payesh. 2010;9(1):61-68.
3. Roses DF. Breast cancer. 2nd ed. Elsevier Inc: Philadelphia, PA; 2005.
4. Rebecca LS, Kimberly DM, Ahmedin J. Cancer statistics. CA: A Cancer Journal for Clinicians. ACS Journals. 2020;7(1):7-30. DOI: 10.3322/caac.21590
5. Anonymous. American cancer society: Cancer facts & figures 2020, Atlanta; 2020. Available:https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2020.html Accessed 23 August 2020.
6. Anonymous. About cancer: Cancer treatment, National Cancer Institute. cancer.gov; 2020. Available:https://www.cancer.gov/about-cancer/treatment Accessed 23 August 2020.
7. Anonymous. Understanding targeted therapy: How cancer is treated, cancer.net editorial board, ASCO.org. 2020. Available:https://www.cancer.net/navigatin

g-cancer-care/videos/treatments-tests-and procedures/what-are-targeted-therapies-cancer-treatment
Accessed 25 August 2020.

8. Wani MC, Taylor HL, Wall ME, Coggon P, Mcphail AT. Plant antitumor agents. VI. The isolation and structure of taxol, a novel antileukemic and antitumor agent from *Taxus brevifolia*. J Am Chem Soc. 1985; 88:2325-2327.
DOI: 10.1021/ja00738a045
9. Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, et al. PubChem update: Improved access to chemical data. Nucleic Acids Research. 2019;47(1):1102-1109.
DOI: 10.1093/nar/gky1033
10. Anonymous. Schrödinger release. Maestro, Schrödinger, LLC. New York, NY, 2018;4.
11. Anonymous. Schrödinger release. LigPrep, Schrödinger, LLC. New York, NY. 2018-4.
12. Ajay-Kumar TV, Athavan AAS, Loganathan C, Saravanan K, Kabilan S, Parthasarathy V. Design, 3D QSAR modeling and docking of TGF-β type I inhibitors to target cancer. Comput Biol Chem. 2018;76:232-244.
DOI: 10.1016/j.compbiolchem.2018.07.011
13. Heerding DA, Rhodes N, Leber JD, et al. Identification of 4-(2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-7-{[(3S)-3-piperidinylmethyl]oxy}-1H-imidazo[4,5-c]pyridin-4-yl)-2-methyl-3-butyn-2-ol (GSK690693), a novel inhibitor of AKT kinase. J Med Chem. 2008;51(18):5663-5679.
DOI: 10.1021/jm8004527
14. Cho YS, Angove H, Brain C, et al. Fragment-based discovery of 7-Azabenzimidazoles as potent, highly selective, and orally active CDK4/6 inhibitors. ACS Med Chem Lett. 2012; 3(6):445-449.
DOI:10.1021/ml200241a
15. Shiau AK, Barstad D, Loria PM, et al. The structural basis of estrogen receptor/ coactivator recognition and the antagonism of this interaction by tamoxifen. Cell. 1998;95(7):927-937.
DOI: 10.1016/S0092-8674(00)81717-1
16. Aertgeerts K, Skene R, Yano J, et al. Structural analysis of the mechanism of inhibition and allosteric activation of the kinase domain of HER2 protein. J Biol Chem. 2011;286(21):18756-18765.
DOI: 10.1074/jbc.M110.206193
17. Park CH. PARP complexed with A620223. In Press; 2008.
DOI: 10.2210/pdb2RCW/pdb
18. Anonymous. Schrodinger release 2018-4: Protein Preparation Wizard; Epik, Schrödinger, LLC, New York. NY. Impact, Schrödinger, LLC, New York, NY, 2018; Prime, Schrödinger, LLC, New York, NY, 2018.
19. Anonymous. Schrodinger Release. Glide, Schrödinger, LLC, New York, NY. 2018;4.
20. Friesner RA, Murphy RB, Repasky MP, Frye LL, Greenwood JR, Halgren T, et al. Extra precision glide: Docking and scoring incorporating a model of hdrophobic enclosure for protein-ligand complexes. J. Med. Chem. 2006;49:6177-6196.
DOI: 10.1021/jm051256o
21. Ajay Kumar TV, Kabilan S, Parthasarathy V. Discovery of inhibitors of TGF-β Type I receptor using QSAR, pharmacophore modelling and toxicity assessment techniques/study to target Cancer. Der Pharma Chemica. 2016;8(22):17-21.
22. Tahlan S, Kumar S, Ramasamy K, et al. *In-silico* molecular design of heterocyclic benzimidazole scaffolds as prospective anticancer agents. BMC Chemistry. 2019; 13(1):90.
DOI: 10.1186/s13065-019-0608-5
23. Anonymous. Schrödinger Release. QikProp, Schrödinger, LLC, New York. NY. 2018;4.
24. Lipinski CA. Lead and drug-like compounds: the rule-of-five revolution. Drug Discovery Today: Technologies. 2004;1(4):337-341.
DOI: 10.1016/j.ddtec.2004.11.007
25. Pagadala NS, Syed K, Tuszynski J. Software for molecular docking: A review. Biophys Rev. 2017;9(2):91-102.
26. Kitchen DB, Decornez H, Furr JR, Bajorath J. Docking and scoring in virtual screening for drug discovery: Methods and applications. Nature Reviews Drug Discovery. 2004;3 (11):935–49.
DOI: 10.1038/nrd1549
27. Hinz N, Jucker M. Distinct functions of AKT isoforms in breast cancer: A comprehensive review. Cell Commun Signal. 2019;17(1):154.
DOI: 10.1186/s12964-019-0450-3
28. Chau NM, Ashcroft M. Akt2: A role in breast cancer metastasis. Breast Cancer Res. 2004;6(1):55-57.
DOI: 10.1186/bcr739

29. Sofie N, Karoline K, Veronika S. The role of CDK6 in cancer. International Journal of Cancer. 2020:1-8.
DOI: 10.1002/ijc.33054
30. Weaver BA. How Taxol/paclitaxel kills cancer cells. Mol Biol Cell. 2014;25:2677–81.
DOI: 10.1091/mbc.E14-04-0916
31. Tadesse S, Yu M, Kumarasiri M, Le BT, Wang S. Targeting CDK6 in cancer: State of the art and new insights. Cell cycle. 2015;14(20):3220-3230.
DOI: 10.1080/15384101.2015.1084445
32. Cortez V, Mann M, Brann DW, Vadlamudi RK. Extranuclear signaling by estrogen: role in breast cancer progression and metastasis. Minerva Ginecol. 2010; 62(6):573-583.
33. Mitri Z, Constantine T, Regan OR. The HER2 Receptor in Breast cancer: Pathophysiology, clinical use, and new advances in therapy. Chemother Res Pract. 2012;2012:743193.
DOI: 10.1155/2012/743193
34. Ossovskaya V, Koo IC, Kaldjian EP, Alvares C, Sherman BM. Upregulation of poly (ADP-Ribose) Polymerase-1 (PARP1) in triple-negative breast cancer and other primary human tumor types. Genes Cancer. 2010;1(8):812-821.
DOI: 10.1177/1947601910383418
35. Mori T, Kinoshita Y, Watanabe A, Yamaguchi T, et al. Retention of paclitaxel in cancer cells for 1 week *in vivo* and *in vitro*. Cancer Chemother. 2006;58(5):665-672
36. Chen K, Shi W. Autophagy regulates resistance of non-small cell lung cancer cells to paclitaxel. Tumor Biol. 2016;37: 10539-44.
DOI: 10.1007/s13277-016-4929-x
37. Zhang DS, Yang RH, Wang SX, Dong Z. Paclitaxel: New uses for an old drug. Drug Des Dev Ther. 2014;8:279-84.
DOI: 10.2147/DDDT.S56801
38. Okomoto Y, Taguchi K, Sakuragi M, et al. Preparation, charecterization, and *In vitro*/*In vivo* evaluation of paclitaxel bound albumin-encapsulated liposomes for the treatment of pancreatic cancer. ACS omega. 2019;4(5):8693-8700.
39. Clark AS, McAndrew NP, Troxel A, Feldman M et al. Combination paclitaxel and palbociclib: Results of a phase I trial in advanced breast cancer. Clin Cancer Res. 2019;25(7):2072-2079.
40. Osma M, Elkady M. A prospective study to evaluate the effect of paclitaxel on cardiac ejection fraction. Breast Care (Basel). 2017;12(4):255-259.
41. Su M, Chen G, Lin J, et al. Paclitaxel-related dermatological problems: Not only alopecia occurs. Taiwanese Journal of Obstetrics and Gynecology. 2019;58(6): 877-879.
42. Bassyouni F, El Hefnawi M, El-Rashed A, Rehim MA. Molecular modeling and biological activities of new potent antimicrobial, antiinflammatory and anti-nociceptive of 5-nitro indoline-2-one derivatives. Drug Des. 2017;6(2):1-6.
43. Sharma D, Kumar S, Narasimhan B, Ramasamy K, Lim SM, Shah SAA, et al. 4-(4-Bromophenyl)-thiazol-2-amine derivatives: Synthesis, biological activity and molecular docking study with ADME profile. BMC Chem. 2019;13(60): 1-16.
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