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MOLECULAR DOCKING ANALYSIS OF COMPARISON BETWEEN INDOLE ALKALOID COMPOUNDS FROM *CATHARANTHUS ROSEUS* WITH THE TARGETS FOR BREAST CANCER

S. Aishwariya [1], M. Viji [1], C. Ireen [1], P. Vijayalakshmi [3], S. Indu [3] and M. Rajalakshmi [1, 2, * 3]

DBT-BIF Centre [1], Department of Zoology [2], Holy Cross College (Autonomous), Tiruchirappalli - 620002, Tamil Nadu, India.
Department of Biotechnology & Bioinformatics [3], DBT-BIF Centre, Kolkata - 700064, West Bengal, India.

Keywords:

Breast cancer, Vinblastine, Vincristine, ADMET, Molecular Docking

Correspondence to Author:
Dr. M. Rajalakshmi

Assistant Professor in Biotechnology, Department of Zoology,
Holy Cross College (Autonomous), Tiruchirappalli - 620002, Tamil Nadu, India.

E-mail: rajalakshmi@hcctrichy.ac.in

ABSTRACT: Endocrine-disrupting chemicals are environmental pollutants that have been associated with a wide range of diseases, including breast cancer, the most prevalent cancer in women worldwide, according to the WHO. Among the different cancers affecting the female population, breast cancer has the highest incidence and mortality rate. The incidence of breast cancer is 100 times higher in women than in men. The incidence of breast cancer is alarmingly high, so the need for a novel approach with fewer side effects is currently needed to improve the quality of life of the patients. *Catharanthus roseus* is a plant species belonging to the *Apocynaceae* family that is used worldwide in phytotherapy. The indolic alkaloids (vincristine and vinblastine) isolated from *C. roseus* are approved and used in clinical trials. The interest of the study lies in the comparison of indole alkaloids (vincristine and vinblastine) against breast cancer targets through *in-silico* studies. The work of the study lies upon downloading target and ligand. The targets that are associated with breast cancer were downloaded from PDB. The ligands (vincristine and vinblastine) were downloaded from PubChem. To compare and calculate ADMET properties and drug-likeliness for vincristine, vinblastine, and the reference drug (paclitaxel), Molecular interaction of cancer targets with vincristine and vinblastine. Based on the results, vinblastine has a greater and better number of binding affinities towards breast cancer proteins. From the analysis, it says that vinblastine has a better potential to treat breast cancer.

INTRODUCTION: Cancer is one of the deadliest diseases, which includes abnormal cell growth. The spread may occur directly, *via* the bloodstream, or via the lymphatic system [1]. Numerous organs can be affected by cancer, and each type of cancer has specific traits.

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Among the different cancers affecting the female population, breast cancer has the highest incidence and mortality rate. The incidence of breast cancer is 100 times higher in women than in men. According to previous studies, this type of cancer caused 5,70,000 deaths in 2015 [2].

Throughout the world, 25% of women are diagnosed with this type of cancer. 30% of new cancer cases among women were reported as breast cancer in America in 2017 [3]. In 2004, according to the global cancer burden, the death rate was 8.8 million, and the estimation can increase with an increase in population. The death rate is expected

to increase by 10-fold in the year 2030, and the incidence may increase to 26.4 million [4]. Oncogene and anti-oncogene mutations and abnormal amplification play important roles in the development and spread of tumours. Two well-known anti-oncogenes for the risk of breast cancer are BRCA1 and BRCA2. The BRCA genes are found on chromosomes 13q12 and 17q21, respectively. Dysregulation of the cell cycle checkpoint, abnormal centrosome duplication, and genetic instability are due to a deficiency of BRAC 1 [5]. High-grade invasive ductal carcinomas with a luminal phenotype are more prevalent in breast cancers linked to BRCA2 [6].

Overexpression of human epidermal growth factor receptor 2 (HER2), an oncogene located on 17q21, was observed in 20% of primary breast cancer [7]. Overexpression of EGFR is found in more than 30% of cases of inflammatory breast cancer (IBC), a very aggressive subtype of breast cancer [8]. Ageing is one of the important risk factors. The study reported that in America, the age of the women associated with breast cancer is 40-60. Reproductive factors such as early menarche, late menopause, late age at first pregnancy, and low parity can increase the breast cancer risk [9].

Screening, chemoprevention, biological prevention, and immunotherapy are some measures that facilitate the treatment of breast cancer. Though a number of treatments are available, the incidence of breast cancer is alarmingly high, so the need for a novel approach with fewer side effects is currently needed to improve the quality of life of the patients.

According to previous studies phytotherapy can also treat cancer. Based on the study, one such plant is *Catharanthus roseus,* a perennial tropical plantbelonging to the *Apocynaceae* family. The plant is widely distributed in areas like America, Africa, Australia, the southern part of Europe, the Pacific Ocean islands, and India. The plant is used as remedies against diseases like diabetes, diuretics, and cough [10]. The plant contains more than 180 various indole alkaloids used in worldwide traditional medicine. Alkaloids have been shown to have numerous therapeutic uses that are extremely beneficial to people. Alkaloids have been shown to have anti-inflammatory [11–12], antiviral [13], antimicrobial/bacterial [14], and an impact on neurodegenerative disorders and central nervous system (CNS) disease [15]. Alkaloids are highly valued for their anticancer properties in addition to these [16]. The alkaloids pericalline, perivine, leurosivine, perividine, and vindoline show antiviral activity against vaccinia and polio type III viruses. The plant extract of C. *roseus* has anti-virus activity against dengue type II virus [17], anti-bacterial activity towards *Salmonella typhi*, and *Shigella boydii* [18], and it also exhibited predominant antifungal activity against *Rigidoporus microporus, Ganoderma philippii*, and *Phellinus noxius* [19].

The two main vinca alkaloids used for cancer therapy against leukaemia, Hodgkin's disease and solid tumours are vincristine and vinblastine [20]. The indole alkaloid vincristine is approved to treat acute leukaemia, neuroblastoma, Wilm's tumour, and refractory autoimmune thrombocytopenia. Another compound isolated from *c.roseus* is a microtubule destabilizer (vinblastine). According to previous studies, vinblastine, when combined with mitomycin and Taxol, is used as the first line of treatment in advanced ovarian and breast cancer, non-small cell lung cancer (NSCLC) [21], and Kaposi's sarcoma [22].

Vinblastine is commonly used to treat breast cancer, ovarian cancer, malignant lymphoma, Hodgkin's disease, and choriocarcinoma [23]. The current work is designed to analyse the pharmacokinetic properties and *in silico* analysis of indole alkaloids (vincristine and vinblastine) with breast cancer targets to determine which compounds have higher efficacy.

METHODOLOGY:

Target Preparation: The targets were downloaded from the PDB database in PDB format. The targets used are BAK (PDB ID: 2YV6), BAX (PDB ID: 2K7W), BCL-2 (PDB ID: 1G5M), BCL-XL (PDB ID:1G5J), Caspase-3 (PDB ID: 1GFW), Caspase-6 (PDB ID :2WDP), Caspase-8(PDB ID: 5JQE), Caspase-9 (PDB ID: 1NW9), P52(PDB ID :1A3Q), P65 (PDB ID:1NFI), P100 (3DO7), CAT (PDB ID:1QQW), SOD (PDB ID: 1SPD), GPX2 (PDB ID:2HE3), CDK-4 (PDB ID: 3G33), CDK-6 (PDB ID: 1G3N), Cyclid-D1 (PDB ID:2W99), Cyclidin-D3 (PDB ID:3G33), CDK-6 (PDB ID :1G3N), P21 (PDB ID :1AXC), P27 (PDB

ID:1JSU), EGFR (1M17) and HER 2 (3PP0). Thus, targets were prepared by removing any heteroatoms, water molecules chains, and other associated ligand groups using Discovery Studio Biovia visualiser client.

Ligand Preparation: Before starting a virtual screening, all the chemical structures for a certain pharmacological target must be gathered. Many compound databases have been created recently that store a variety of chemical and biological data in addition to the structure of the compound molecules. One such database is PubChem. By using the canonical smiles, the 2D structure of the ligands (active compounds and reference drugs) was generated using ACD/labs Chemsketch. Paclitaxel is used as a reference drug in this study.

Pharmacokinetics Properties: The pharmacokinetic properties like Lipinski rule of five and ADMET were obtained through pkCSM online server.

Molecular Docking: PyRx version 0.8 is used to prepare all protein and ligand files for docking and to generate docking parameter input files. All PDB files for proteins and ligands were converted into PDBQT format using PyRx. The ligands were inserted using an open babel. The Universal Force Field (UFF) served as the energy reduction parameter, and the optimization algorithm used conjugate gradient descent.

As a result, the stronger binding capacity is demonstrated by the lower binding energy score, and the results were downloaded in PDB and CSV file formats. The visualization process is done by the Biovia 2021 R2 client software package, which analyzes the H-bond interaction and other intermolecular interactions between the target and the receptors.

RESULTS AND DISCUSSION: Due to the high incidence of breast cancer worldwide, it is a cause for concern on a global scale. The increasing upsurge in breast cancer cases highlights the need for multi-level disease care. Effective management should begin at the outset with strict cancer screening programmes or a cancer registry, followed by efficient diagnostic and therapeutic approaches. Breast cancer is extremely variable in terms of morphology and at the molecular level, necessitating several therapy modalities depending on the molecular subtype. Clinical prognoses for breast cancer patients vary depending on their subtype. The enhanced molecular testing that will aid in early detection and improved survival is highlighted by the heterogeneity of breast cancer. Even though there are various treatment are available for breast cancer, they are cost effective and each of them have their own side effect. As a result of the search to reduce the risk of those treatment and to manage breast cancer, the Food and Drug Administration (FDA) has approved over 60% of antineoplastic medications that come from natural sources (e.g., vincristine, topotecan, or paclitaxel). These medications can be used as lead compounds with minor modifications or in their monomeric form [24].

Phytotherapy is a booming filed that comprisesa number of phytocompound that are used against various kinds of disease. One such plant is *Catharanthus roseus* which is an herbal plant widely used in traditional medicine. Various compounds were isolated from this plant, the two most important compound are vinblastine and vincristine. Vinblastine is used to treat several cancers, including Kaposi's sarcoma, neuroblastoma, Hodgkin's and non-Hodgkins's lymphomas, mycosis fungoides, and testicular cancer. Vinblastine is considered to suppress mitosis at metaphase through its interaction with tubulin, which accounts for the majority of its anticancer effect. Vinblastine causes the microtubule to crystallise and causes mitotic arrest or cell death when it attaches to the mitotic spindle's microtubular proteins [25].

On other hand vincristine, it is sold under numerous brand names, many of which have various formulations, such as Vincasar and Marqibo (liposomal injection). Acute leukemia, malignant lymphoma, Hodgkin's disease, acute erythremia, and acute panmyelosis are among the conditions for which vincristine is prescribed. Because of its distinctive clinical toxicity (neuropathy) and absence of considerable bone-marrow suppression (at acceptable doses), vincristine sulphate is frequently used as a component of polychemotherapy [26]. The structures for reference drug, and indole alkaloid compounds is obtained through chemsketch **Fig. 1.**

Structure of Ligands and Reference Drug:

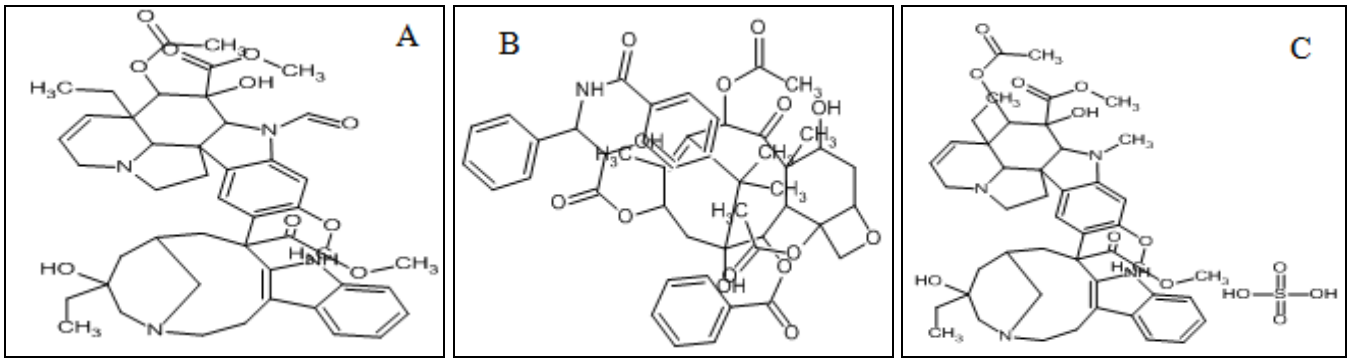


FIG. 1: 2D STRUCTURE OF (A) PACLITAXEL (B) VINCRISTINE (C) VINBLASTINE WERE DRAWN THROUGH ACD/LABSCHEMSKETCH

Lipinski Rule of Five and Pharmacokinetics Properties: The active compounds and reference drug were subjected to checking whether they follow the "Lipinski Rule of Five" through the pkCSM tool **Table 1**. Lipinski himself stated that his "Rule of Five" is not applicable to natural products. Both (vinblastine and vincristine) were naturally obtained; the molecular weight and hydrogen donor-acceptor of these compounds do not come under the Lipinski rule of 5. But it follows the log p-value, rotatable bond, and hydrogen bond donor. The reference drug, paclitaxel, is a synthetic drug that follows the rule. The absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties of the ligands were obtained through the pkCSM tools **Table 2**. The indole alkaloid compounds vincristine and vinblastine exhibited good absorption values. In distribution properties, VDss is used to analyze the distribution of drugs in tissue rather than plasma. The values of the compounds are >0.45, whereas vincristine and vinblastine have (1.654 and 1.582) values, respectively, indicating a small amount of the compound distributed in tissue. BBB and CNS parameters are quite important to know whether a drug has the ability to cross the brain or not. The compounds have values less or equal to -1 and -3 in the BBB and CNS, respectively, which are poorly distributed in the brain and could not penetrate the CNS. In metabolism, the two main isomers (CYP2D6 and CYP3A4) of CYP450 play a crucial role in drug metabolism. The compounds act as substrates and inhibitors for CYP3A4, but they don't act as substrates or inhibitors for CYP2D6. In excretion, the value of total clearance is low, indicating the high bioavailability of the compound, and the compounds are not substrates for renal OCT2. In terms of toxicity properties, the compounds are not inhibitors of hERG, which does not cause QT prolongation, and they don't possess hepatotoxicity, which could not lead to liver injury.

TABLE 1: LIPINSKI RULE OF 5 FOR THE LIGANDS PACLITAXEL, VINCRISTINE AND VINBLASTINE

Ligand	Mol. weight	Log P	#Rotatable bonds	# Acceptors	#Donors	Surface area
Paclitaxel	853.9	3.7357	10	14	4	357.885
Vincristine	824.972	3.5175	8	12	3	349.301
Vinblastine	909.068	3.3381	7	14	5	372.777

TABLE 2: ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION AND TOXICITY PROPERTIES OF PACLITAXEL, VINCRISTINE AND VINBLASTINE

Properties	Paclitaxel	Vincristine	Vinblastine
Absorption Parameters			
Water solubility	-3.158	-3.016	-3.042
Caco2 permeability	0.623	0.545	0.565
Intestinal absorption	100	79.88	78.106
P-Glycoprotein substrate	Yes	Yes	Yes
Distribution parameters			
VDss	1.458	1.654	1.582
Fraction unbound	0	0.318	0.308

BBB	-1.731	-1.239	-1.078
CNS	-3.95	-3.28	-3.107
Metabolism parameters			
CYP2D6 substrate	No	No	No
CYP3A4 substrate	Yes	Yes	Yes
CYP2D6 inhibitor	No		
CYP3A4 inhibitor	Yes	Yes	Yes
Excretion parameters			
Total clearance	0.36	0.53	0.41
Renal OCT2 Substrate	No	No	No
Toxicity parameters			
hERG inhibitor I	No	No	No
hERG inhibitor II	No	Yes	Yes
Oral rat acute toxicity	2.776	2.5	2.495
Hepatotoxicity	Yes	No	No

Moleucular Interactions: In order to anticipate the level of activity or binding affinity of the interaction between the receptor and the ligand, a computer technique called molecular docking first determines the preferred location of a molecule (the ligand) in relation to a second molecule (the receptor) when the two molecules join to form a stable complex. The interactions were run for three ligands (paclitaxel, vincristine, and vinblastine) against twenty-three targets associated with breast cancer. The molecular docking was run through Pyrx software and visualised through Bio *via* the 2021 visualizer client. According to Bhatnagar, the indole alkaloid compound vinblastine has better binding affinity with α/β-tubulin than vincristine [27].

Even though previous studies say that vinblastine and its derivative, vindesine, are often more effective than vincristine and vinepidine in reducing cell proliferation in culture, the purpose of the paper is to compare which indole alkaloid compound has the highest efficacy against the breast cancer protein through computational analysis. The interactions through docking between targets and ligands were shown below **Fig. 2–16**, and the binding affinity and polar interactions between the targets and reference drug were listed below **Table 3.** In the apoptotic marker, the compound vinblastine shows better binding affinity towards BCL-XL (-7.4), and it shows double H-bond interaction (Arg-104, Asn-140). When vinblastine docks with cell cycle proteins, it shows high binding affinity for CDK4 (-7.5) and a single H-bond interaction (Gln-193). For other proteins like NFKβ, oxidative stress, and the breast cancer gene, the compound vinblastine shows a good number of binding affinities towards P100 (-7.7), CAT (-8.5), and HER-2 (-7.5). While vincristine shows binding affinity as (-7.2, -8.9, and -7.1), When comparing the H-bond interactions, vinblastine shows a single H-bond interaction (Gln-157) for P100; for oxidative stress proteins, it shows two H-bond interactions (Asn-338, Arg-382) towards CAT; and finally, for HER-2, it shows four H-bond interactions (Ile-886, Arg-756, Phe-731, Gly-732). Vincristine shows a single H-bond interaction with CDK-4 (Arg-168) for p100 and BCL-Xl, it does not show any H-bond interaction; for the oxidative stress protein CAT, it shows four H-bond interactions (Asn-338, Glu-420, Gln-415, Asn385); and for HER2, it shows a single H-bond interaction (Ala-698).

Thus, as a result of the comparison between vinblastine and vincristine, the compound vinblastine has better potential to treat breast cancer. In order to anticipate the level of activity or binding affinity of the interaction between the receptor and the ligand, a computer technique called molecular docking first determines the preferred location of a molecule (the ligand) in relation to a second molecule (the receptor) when the two molecules join to form a stable complex. The interactions were run for three ligands (paclitaxel, vincristine and vinblastine) against twenty-three targets -associated with breast cancer. The molecular docking was run through Pyrx software and visualized through Bio *via* 2021 visualizer client type. According to Bhatnagar, the indole alkaloid compound vinblastine has better binding affinity with α/β-tubulin than vincristine [27]. Even though previous studies says that Vinblastine and its derivative, vindesine, were often more effective than vincristine and vinepidine in

reducing cell proliferation in culture. The work of the paper is to compare which indole alkaloid compound has highest efficacy towards the breast cancer protein through computational analysis. The interactions through docking between targets and ligands were shown below **Fig. 2** to **Fig. 16** and the binding affinity and polar interactions between for the targets and reference drug were listed below **Table 3**. In apoptotic marker the compound vinblastine shows better binding affinity towards BCL-XL (-7.4), and it shows double H- bond interaction (Arg-104, Asn-140). When vinblastine docked with cell cycle proteins it shows high binding affinity for CDK4 (-7.5) and shows single H-bond interaction (Gln-193). For other proteins like NFKβ, Oxidative stress and Breast cancer gene the compound vinblastine shows good number of binding affinities towards P100(-7.7), CAT (-8.5), and HER-2(-7.5). While vincristine shows binding affinity as (-7.2, -8.9, and –7.1). When comparing the H-bond interaction, vinblastine shows single H-bond interaction (Gln-157) for P100, for oxidative stress protein it shows two H- bond interaction (Asn-338, Arg-382) towards CAT and finally for HER-2it shows four H- bond interaction (Ile-886, Arg-756, Phe-731, Gly-732). Vincristine shows single H-bond interaction towards CDK-4 ((Arg-168) for p100 and BCL-Xl it does shown any H-bond interaction, for oxidative stress protein- CAT it shows four H-bond interaction (Asn-338, Glu-420, Gln-415, Asn385) and for HER2 it shows single H-bond interaction (Ala-698). Thus, as a result of comparison between vinblastine and vincristine the compound vinblastine has better potential to treat breast cancer.

Molecular Interaction of Brest Cancer Targets with Paclitaxel:

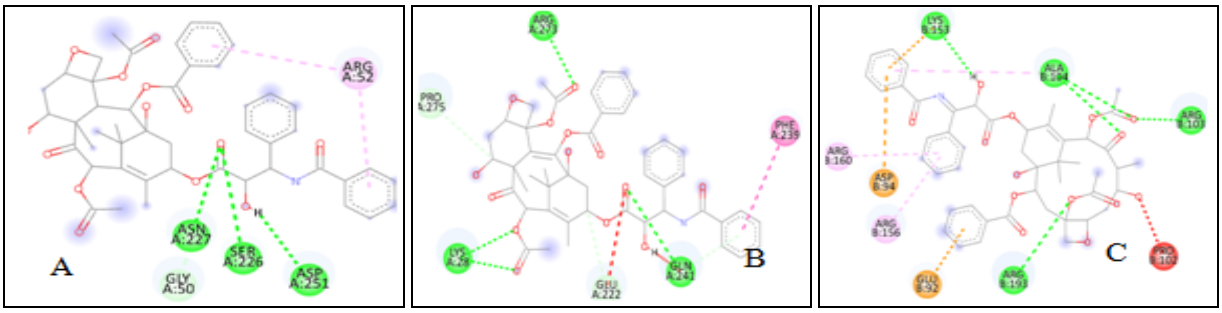


FIG. 2: MOLECULAR INTERACTIONS OF (A) P52, (B) P65, (C) P100 NFKB PROTEINS ARE DOCKED WITH PACLITAXEL

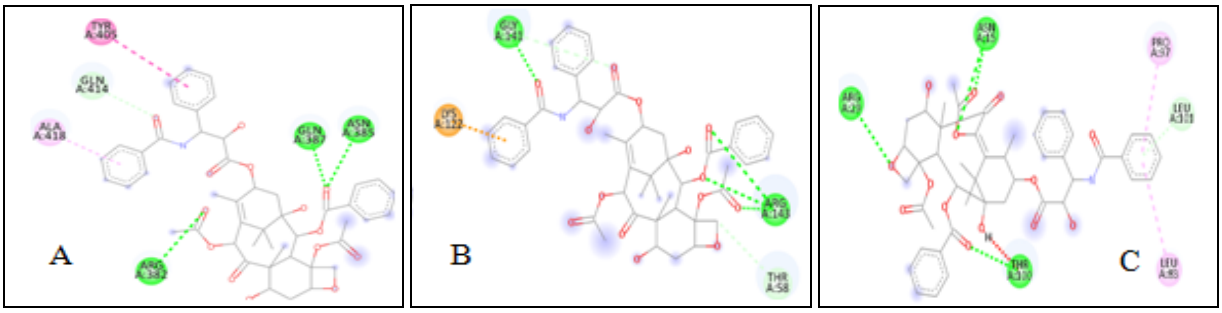
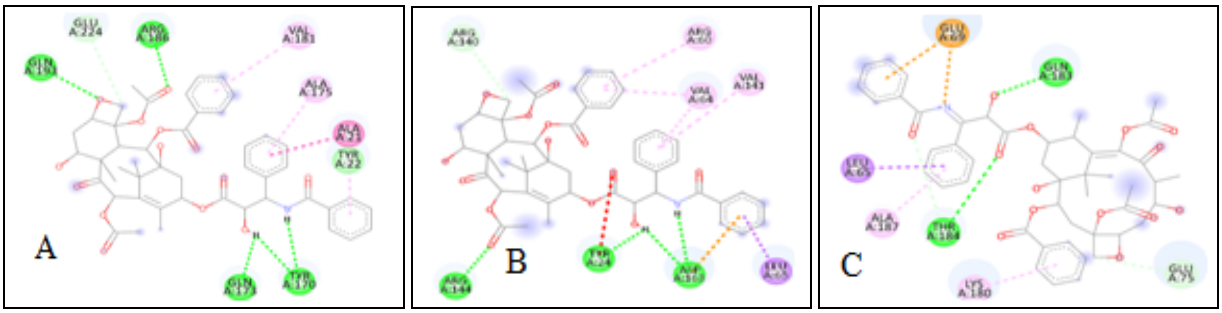


FIG. 3: MOLECULAR INTERACTIONS OF (A) CAT, (B) SOD, (C) GPX2 OXIDATIVE STRESS, PROTEINS ARE DOCKED WITH PACLITAXEL



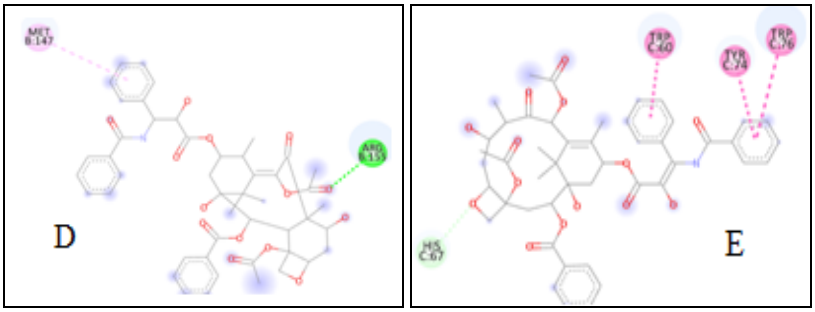


FIG. 4: MOLECULAR INTERACTIONS OF (A) CDK-4, (B) CDK-6, (C) CYCLIN D1, (D) P21, (E) P27 CELL CYCLE PROTEINS ARE DOCKED WITH PACLITAXEL

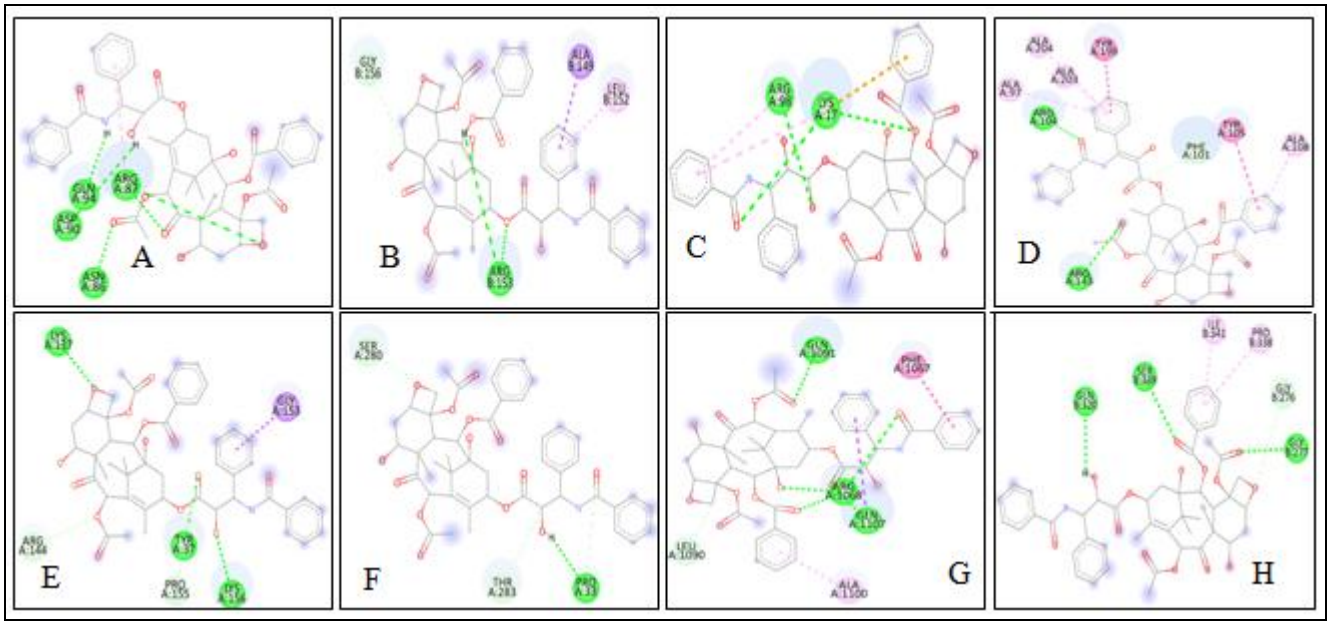


FIG. 5: MOLECULAR INTERACTIONS OF (A) BCL-XL, (B) BCL-2, (C) BAX, (D) BAK, (E) CASPASE -3, (F) CASPASE-9, (G) CASPASE-6, (H) CASPASE-8, APOPTOTIC PROTEINS DOCKED WITH PACLITAXEL

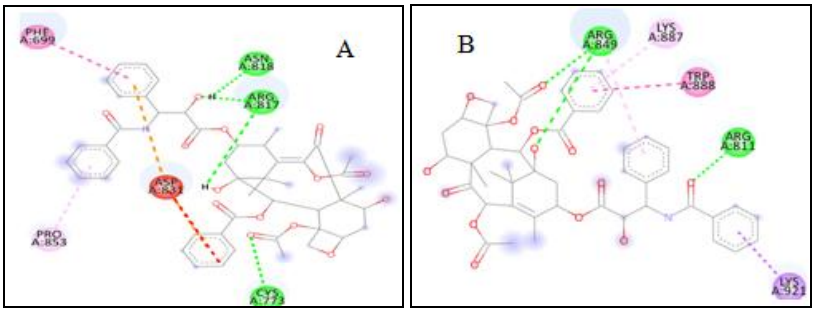


FIG. 6: MOLECULAR INTERACTIONS OF (A) EGFR, (B) HER 2 ARE DOCKED WITH PACLITAXEL

Molecular Interaction of Brest Cancer Targets with Vincristine:

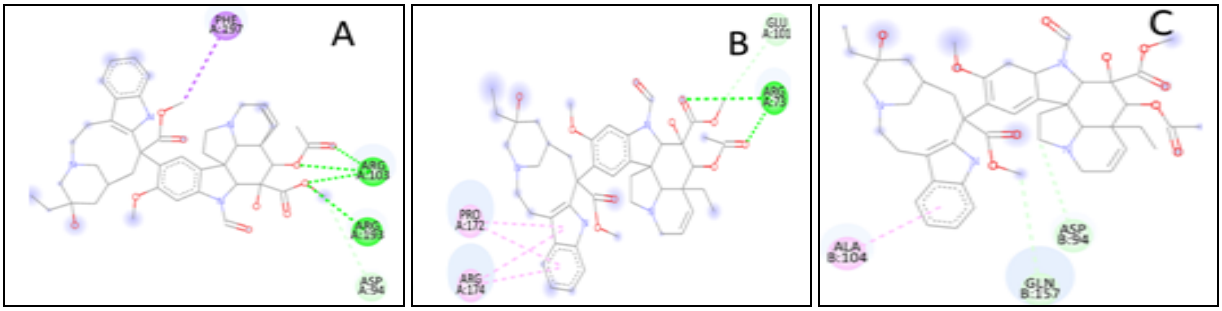


FIG. 7: MOLECULAR INTERACTIONS OF (A) P52, (B) P65, (C) P100 NFKB PROTEINS ARE DOCKED WITH VINCRISTINE

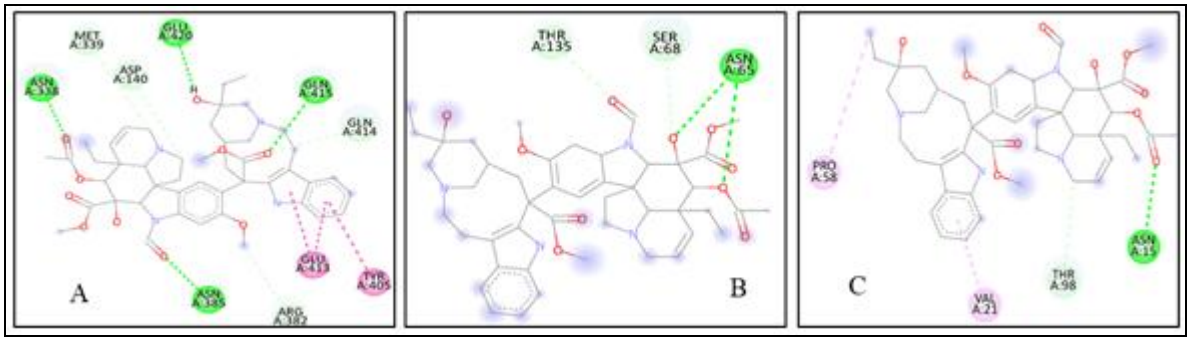


FIG. 8: MOLECULAR INTERACTIONS OF (A) CAT, (B) SOD, (C) GPX2 OXIDATIVE STRESS, PROTEINS ARE DOCKED WITH VINCRISTINE

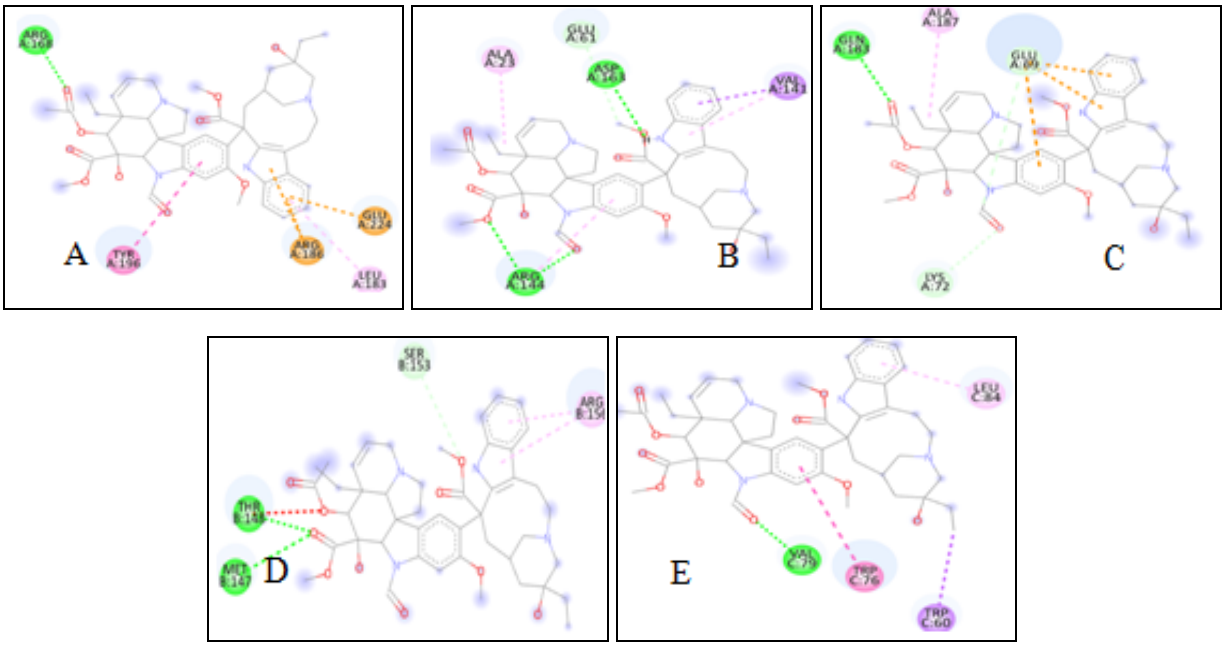


FIG. 9: MOLECULAR INTERACTIONS OF (A) CDK-4, (B) CDK-6, (C) CYCLIN D1, (D) P21, (E) P27 CELL CYCLE PROTEINS ARE DOCKED WITH VINCRISTINE

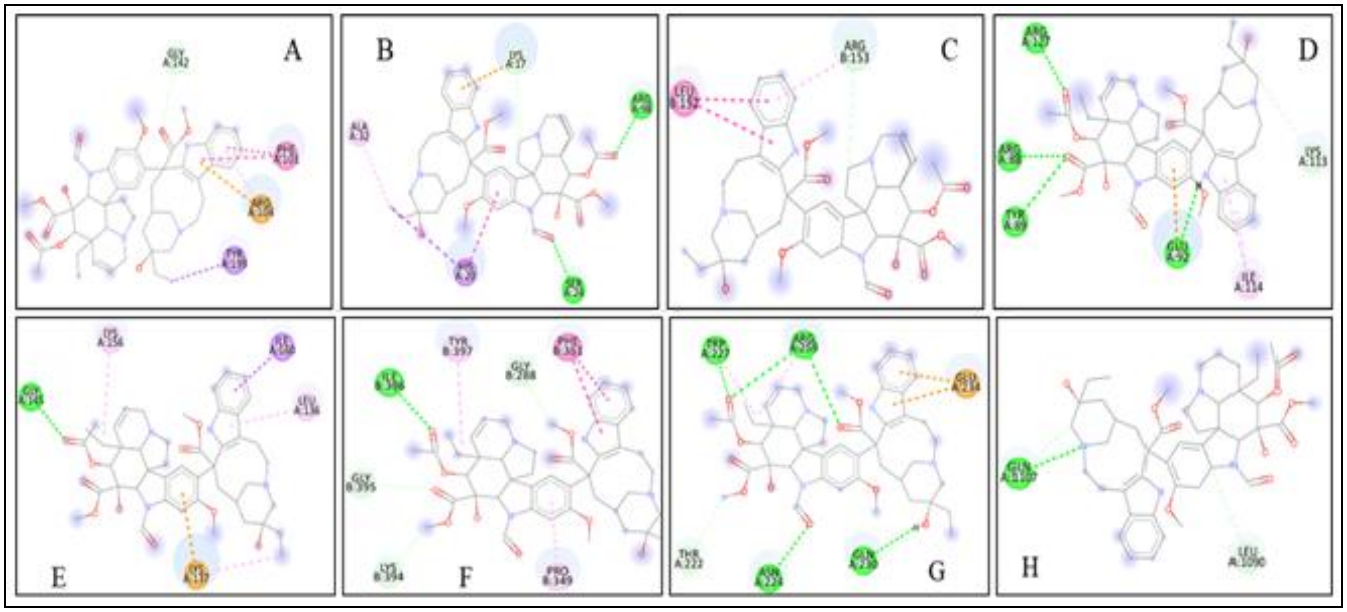


FIG. 10: MOLECULAR INTERACTIONS OF (A) BCL-XL, (B) BCL-2, (C) BAX, (D) BAK, (E) CASPASE -3, (F) CASPASE-9, (G) CASPASE-6, (H) CASPASE-8, APOPTOTIC PROTEINS DOCKED WITH-VINCRISTINE

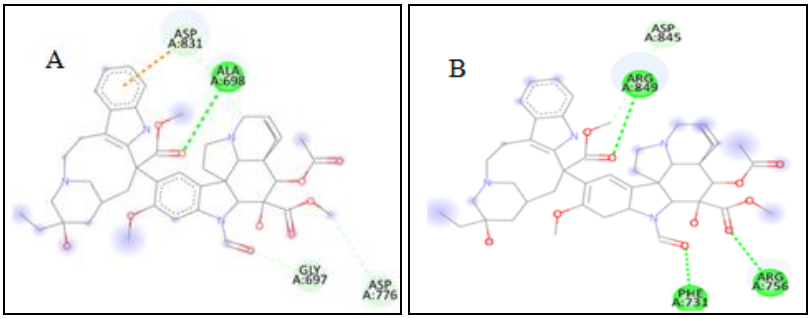


FIG. 11: MOLECULAR INTERACTIONS OF (A) HER 2 (B) EGFR ARE DOCKED WITH VINCRISTINE

Molecular Interaction of Brest Cancer Targets with Vinblastine:

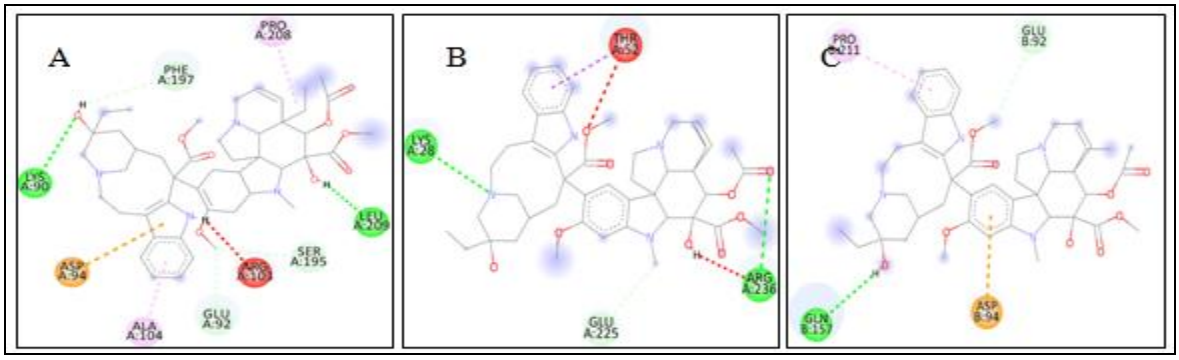


FIG. 12: MOLECULAR INTERACTION OF (A) P52, (B) P65, (C) P100 NFKB PROTEINS ARE DOCKED WITH VINBLASTINE

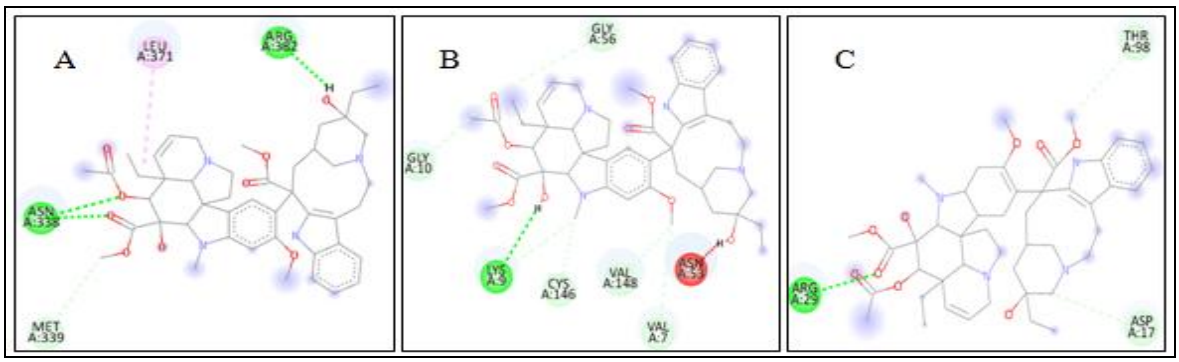


FIG. 13: MOLECULAR INTERACTION OF (A) CAT, (B) SOD, (C) GPX2 OXIDATIVE STRESS PROTEINS ARE DOCKED WITH VINBLASTINE

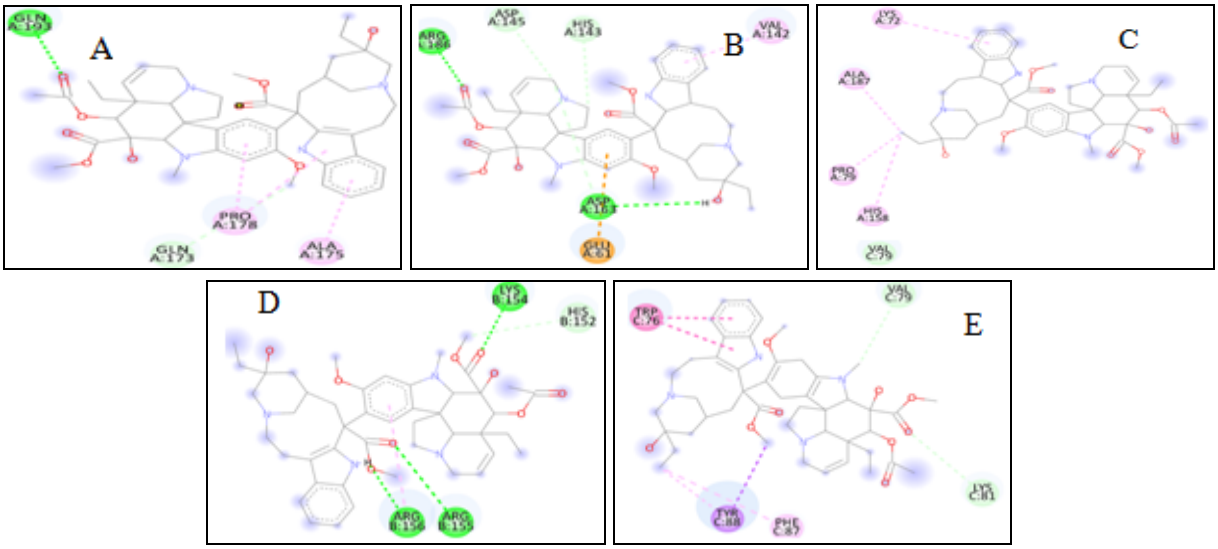


FIG. 14: MOLECULAR INTERACTIONS OF (A) CDK-4, (B)CDK-6, (C) CYCLIN D1, (D) P21, (E) P27 CELL CYCLE PROTEINS ARE DOCKED WITH VINBLASTINE

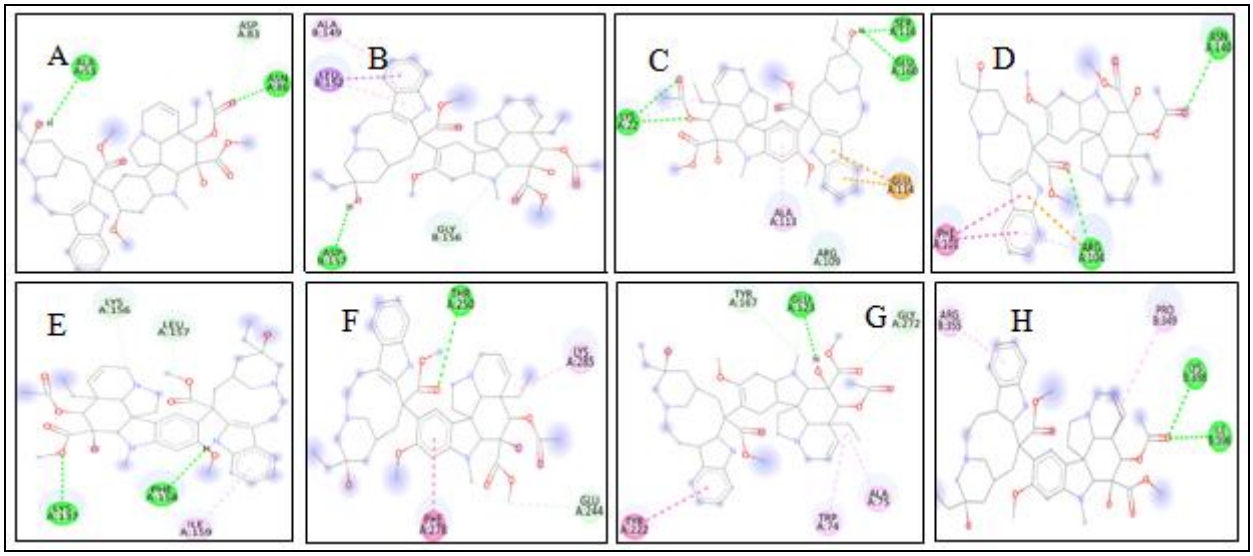


FIG. 15: MOLECULAR INTERACTIONS OF (A) BCL-XL, (B) BCL-2, (C) BAX, (D) BAK, (E) CASPASE -3, (F) CASPASE-9, (G) CASPASE-6, (H) CASPASE-8, APOPTOTIC PROTEINS DOCKED WITH VINBLASTINE

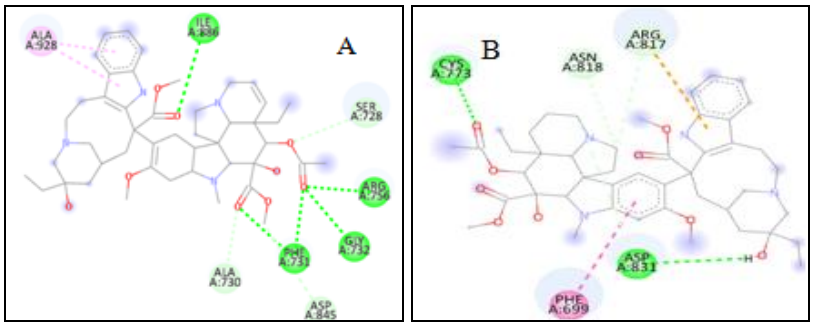


FIG. 16: MOLECULAR INTERACTIONS OF (A) HER 2 (B) EGFR ARE DOCKED WITH VINBLASTINE

TABLE 3: BINDING AFIINITIES AND H-BOND INTERACTION FOR TARGETS AND REFERENCE DRUG

Marker type	Markers	Binding affinity			Hydrogen bond interaction		
		Vinblastine	Vincristine	Paclitaxel	Vinblastine	Vincristine	Paclitaxel
Apoptotic Markers	BAK	-6.9	-7.4	-7.1	Ala-53, Asn-86	Arg-127, Arg-88, Tyr-89, Glu-92	Arg-87, Asn-86, Asp-90, Gln-94
	BAX	-5.9	-5.4	-4.4	Asp-157	-	Arg-153
	Bcl-2	-7.4	-6.9	-7.5	Lys-22, Ser-116, Glu-160	Arg-98, Ser- 24	Arg-98, Lys-17
	Bcl-XL	-7.4	-7.0	-7.9	Arg-104, Asn-140	-	Arg-104, Arg-143
	Caspase-3	-6.7	-6.8	-6.8	Lys-137, Phe-158	Gly-145	Lys- 137, Lys-156, Tyr- 37
	Caspase-6	-6.4	-6.6	-6.8	Thr-250	Trp-227, Arg-259, Asn-224, Gln-230	Pro-33
	Caspase-8	-7.6	-7.7	-9.6	Glu-123	Gly-1107	Arg-1068, Gln-1107, Gln-191
	Caspase-9	-6.8	-6.8	-7.7	Lys-398, Ile-396	Ile-396	Gln-320, Gly-277, Ser- 339
	CDK-4	-7.5	-7.0	-9.4	Gln-193	Arg-168	Gln-193, Arg-186, Gly-173, Thy-170
	CDK-6	-7.1	-8.3	-7.4	Arg-186, Asp-163	Asp-163, Arg-144	Arg-144, Thr-24, Asp-163
Cell cycle	Cyclin-D1	-7.1	-7.2	-7.8	-	Gln-183	Thr-184, Gln-

							183
	P21	-5.5	-6.3	-4.6	Lys-154, Arg-156, Arg-155	Thr-148, Met-147	Arg-155
	P27	-6.2	-7.0	-7.5	-	Val-79	-
	P52	-7.3	-7.1	-7.0	Lys-90, Leu-209	Arg-103, Arg-193	Asn-227, Ser-226, Asp-251
NFkB	P65	-7.7	-7.2	-7.2	Lys-28, Arg-236	Arg-73	Arg-273, Gln-243, Lys-28
	P100	-7.7	-7.2	-9.1	Gln-157	-	Lys-153, Ala-104, Arg:193, Arg-103
	CAT	-8.5	-8.9	-7.3	Asn-338, Arg-382	Asn-338, Glu-420, Gln-415, Asn-385	Gln-387, Asn-385, Arg-382
Oxidative stress	SOD	-6.6	-6.6	-5.9	Lys-9	Asn-65	Gly-141, Arg:143
	GPX2	-7.0	-6.5	-7.6	Arg-29	Asn-15	Arg-29, Thy-100, Asn-15
Breast cancer markers	HER 2	-7.5	-7.1	-8.8	Cys-773, Asp-831	Ala-698	Arg-849, Arg 811
	EGFR	-7.5	-7.0	-8.2	Ile-86, Arg-756, Phe-731, Gly-732	Arg: 849, Phe-731, Arg- 756	Asn-818, Arg-817, Cys-773

CONCLUSION: On the basis of comparison between the compound's vinblastine has greater and good number of binding affinities towards breast cancer proteins. So, from the analysis it says that vinblastine has a better potential to treat against breast cancer. Subsequent exploitation of the compound through experimental studies in the future will provide insights into developing vinblastine into effective drug moieties.

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REFERENCES:

1. Dollinger M, Rosenbaum EH and Cable G: Understanding Cancer in Everyone's guide to cancer therapy. Universal Press Syndicate Company 1991; 1–9.
2. Stewart BW & Wild CP: World cancer report. WHO Press 2014; Google Scholar [Ref list]
3. Siegel RL, Miller KD & Jemal A: Cancer statistics, CA: A Cancer Journal for Clinicians 2017; 67(1): 7–30.
4. Donepudi MS, Kondapalli K, Amos SJ & Venkanteshan P: Breast cancer statistics and markers. Journal of Cancer Research and Therapeutics 2014; 10(3): 506–511.
5. Deng CX: BRCA1: Cell cycle checkpoint, genetic instability, DNA damage response and cancer evolution. Nucleic Acids Research 2006; 34(5): 1416–1426.
6. Elizalde PV, Cordo Russo RI, Chervo MF & Schillaci R: ErbB-2 nuclear function in breast cancer growth, metastasis and resistance to therapy. Endocrine-Related Cancer 2016; 23(12): 243–257.
7. Pires DE, Blundell TL & Ascher DB pkCSM: Predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. Journal of Medicinal Chemistry 2015; 58(9): 4066–4072.
8. Zhang D, LaFortune TA, Krishnamurthy S, Esteva FJ, Cristofanilli M, Liu P, Lucci A, Singh B, Hung MC, Hortobagy GN & Ueno NT: Epidermal growth factor receptor tyrosine kinase inhibitor reverses mesenchymal to epithelial phenotype and inhibits metastasis in inflammatory breast cancer. Clinical Cancer Research 2009; 15(21): 6639–6648.
9. Dall GV & Britt KL: Estrogen effects on the mammary gland in early and late life and breast cancer risk. Frontiers in Oncology 2017; 7: 110.
10. Nammi S, Boini MK, Lodagala SD & Behara RBS: The juice of fresh leaves of *Catharanthus roseus* Linn. reduces blood glucose in normal and alloxan diabetic rabbits. BMC Complementary and Alternative Medicine 2003; 3: 1–4.
11. Li S, Liu X, Chen X & Bi L: Research progress on anti-inflammatory effects and mechanisms of alkaloids from Chinese medical herbs. Evidence-Based Complementary and Alternative Medicine 2020.
12. Bai R, Yao C, Zhong Z, Ge J, Bai Z, Ye X & Xie Y: Discovery of natural anti-inflammatory alkaloids: Potential leads for the drug discovery for the treatment of inflammation. European Journal of Medicinal Chemistry 2021; 213: 113165.
13. Jafaar H. J, Isbilen O, Volkan E & Sariyar G: Alkaloid profiling and antimicrobial activities of Papaver glaucum and *P. decaisnei*. BMC Research Notes 2021; 14: 1-7.
14. Lin SX, Curtis MA & Sperry J: Pyridine alkaloids with activity in the central nervous system. Bioorganic & Medicinal Chemistry 2020; 28(24): 115820.
15. Majnooni MB, Fakhri S, Bahrami G, Naseri M, Farzaei MH & Echeverría J: Alkaloids as potential phytochemicals against SARS-CoV-2: approaches to the associated pivotal mechanisms. Evidence-based Complementary and Alternative Medicine 2021.

16. Yun D, Yoon SY, Park SJ & Park YJ: The anticancer effect of natural plant alkaloid isoquinolines. International Journal of Molecular Sciences 2021; 22(4): 1653.
17. Noor ZAW & Nazlina I: Efficacy of *Catharanthus roseus* extract against dengue virus type 2 infection in vitro. Indian Journal of Public Health Research and Development 2020; 11: 1320–1325.
18. Raza ML, Nasir M, Abbas T & Naqvi BS: Antibacterial activity of different extracts from the *Catharanthus roseus*. Clinical and Experimental Medical Journal 2009; 3(1): 81–85.
19. Zahari R, Halimoon N, Ahmad MF & Ling S. K: Antifungal compound isolated from *Catharanthus roseus* L. (Pink) for biological control of root rot rubber diseases. International Journal of Analytical Chemistry 2018; 8150610.
20. Moreno-Valenzuela O. A, Minero-Garcıa Y, Chan, W, Mayer-Geraldo E, Carbajal E & Loyola-Vargas VM: Increase in the indole alkaloid production and its excretion into the culture medium by calcium antagonists in *Catharanthus roseus* hairy roots. Biotechnology Letters 2003; 25(16): 1345–1349.
21. Takashima S, Kiyoto S, Takahashi M, Hara F, Aogi K, Ohsumi S, Mukai R & Fujita Y: Clinical experience with nanoparticle albumin-bound paclitaxel, a novel taxane anticancer agent, and management of adverse events in females with breast cancer. Oncology Letters 2015; 9(4): 1822–1826
22. Coderch C, Morreale A & Gago F: Tubulin-based structure- affinity relationships for antimitotic vinca alkaloids. Anti-Cancer Agents in Medicinal Chemistry 2012; 12(3): 219–225.
23. Jordan MA, Himes RH & Wilson L: Comparison of the effects of vinblastine, vincristine, vindesine, and vinepidine on microtubule dynamics and cell proliferation in vitro. Cancer Research 1985; 45(6): 2741–2747
24. Newman DJ & Cragg GM: Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. Journal of Natural Products 2020; 83(3): 770-803.
25. Jordan M & Kamath K: How do microtubule-targeted drugs work? An overview. Current Cancer Drug Targets 2007; 7(8): 730-742.
26. Graf WD, Chance PF, Lensch MW, En LJ, Lipe HP & Bird TD: Severe vincristine neuropathy in Charcot–Marie–Tooth disease type 1A. Cancer 1996; 77(7): 1356–1362.
27. Bhatnagar S, Srivastava R & Saxena R: Mode of action of vinca alkaloids against cancer using Insilco analysis technique. International Journal of Science and Research Archive 2022; 7(2): 181-188.

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