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Molecular Docking Analysis of *Berberis aristata* Phytocompounds as Potential Growth Factor Receptor Blockers in Cancer Therapy

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Abstract

Middle-aged and older women are susceptible to breast cancer (BC), a potentially fatal condition. When breast cancer is diagnosed, the median age is 62. Breast cancer diagnoses in women under 45 are comparatively uncommon, whereas the bulk of breast cancer diagnoses occur in women 62 and older. Growth factor receptors are interesting therapeutic targets because of their critical role in the pathophysiology of cancer. Vascular endothelial growth factor receptors (VEGFR-2) and human epidermal growth factor receptors (HER-2) have a role in the development and spread of cancer. To determine their HER-2 binding affinity, 39 phytocompounds from Berberis aristata were chosen. PyRx, a virtual screening tool, was used for molecular docking. Databases including PubChem, Indian medicinal plants, phytochemistry, and therapeutics were used to obtain the molecular structures of the compounds and the targeted proteins. Protein Data Bank sum generation and BIOVIA Discovery Studio tools were used to validate the protein structures. Additionally, ADMET was used to assess the ligands' pharmacokinetic characteristics.

Keywords: Breast cancer (BA), Human epidermal growth factor receptors (HER-2), ADMET analysis, Molecular docking, *Berberis aristata* (BA)

INTRODUCTION

The objective of this project is to assess the HER-2 receptor, a crucial target in the treatment of breast cancer, and the binding affinity of 39 phytocompounds from BA. The study explores potential lead compounds through molecular docking with PyRx. Protein structures are verified using BIOVIA Discovery studio, and pharmacokinetic characteristics of ligands are evaluated using ADMET analysis. With almost 2 million new cases recorded in 2020, breast cancer (BC) was the most common cancer diagnosed in women globally. Because of changes in risk factor trends, improvements in detection techniques, and improvements in cancer registration, its incidence and fatality rates have increased during the past three decades [1]. The development and treatment of breast cancer are significantly influenced by the extracellular domain of the human epidermal growth factor receptor 2 (HER2) [2]. About 15–20% of breast tumors overexpress the transmembrane receptor tyrosine kinase HER2, which causes aggressive tumor development and a poor prognosis [3]. Treatment options for BC include hormone therapy, targeted therapy, radiotherapy, chemotherapy, surgery, and immunotherapy. However, side effects, recurrence, and treatment resistance are drawbacks. Treatment for triple-negative BC is difficult since it lacks precise targets [4]. Through PI3K/Akt and MAPK signaling, the HER2 protein promotes unchecked cell proliferation, which is a major factor in aggressive BC [5]. HER2-targeting monoclonal

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antibodies and tyrosine kinase inhibitors improve survival, but resistance persists, and new therapeutic strategies are needed [6]. Before the advent of HER2-targeted therapies, HER2-enriched cancers had the poorest prognosis among all subtypes and exhibited faster growth than luminal tumors. Notably, many ER-positive/HER2-positive tumors belong to the luminal B category, indicating that the HER2-enriched subtype is distinct from clinically HER2-positive breast cancer.

The traditional Ayurvedic medicinal plant BA has several therapeutic applications. It works well against bleeding, fever, inflammation, diarrhea, and bacteria. Additionally, studies reveal that its methanol extract can combat a variety of cancer cell types, including those found in the breast, colon, and cervical regions [7]. Among the important phytochemicals found in BA are beta-hydrastine, tetrahydropalmatine, oxyberberine, and (+/–Karachine) [8]. By visually screening hundreds of compounds, molecular docking is an essential approach in drug discovery that simulates and predicts how drug molecules interact with target proteins, increasing process efficiency and lowering costs. By locating important binding sites and amino acid interactions, this method aids in the comprehension of pharmacological processes. When used in conjunction with protein purification and pharmacological screening [9], it confirms predictions and permits in-depth structural analysis. The following search terms were used: berberine, BA, analytical techniques of BA, anticancer activity of BA, anticancer potential of berberine, and anticancer cell lines against berberine [10].

METHODS

Ligand Retrieval

A total of 39 secondary metabolites of BA and its derivatives, derived from the phytochemical components of the plant, were selected for investigation using the IMPPAT database (https://cb.imsc.res.in/imppat/) [11]. The two-dimensional (2D) structures, canonical SMILES, and PubChem CID representations of these compounds were retrieved in SDF format from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) [12].

Protein Retrieval

The three-dimensional structure of the extracellular region of the growth factor receptor 2 (HER2) was obtained in PDB format from the Protein Data Bank (PDB) of the Research Collaboratory for Structural Bioinformatics (https://www.rcsb.org/). This protein was resolved using X-ray diffraction at a resolution of 3.2Å. The SWISS-MODEL platform (https://swissmodel.expasy.org/) [13] was utilized to model the missing residues of the protein structure. HER2 plays a crucial role in cancer research, particularly in breast and stomach cancers. A targeted treatment called trastuzumab (Herceptin) is intended to prevent HER2 overexpression, which is linked to aggressive tumor growth.

Protein Purification

The structure of 1S78 has been instrumental in the development of HER2-targeted therapies. Given that the free energy of water molecules aligns with its crystallographic structure, the 1S78 protein was purified by removing all water molecules to prevent any potential impact on docking outcomes. Additionally, extraneous chains were eliminated, retaining only the A-chain. To enhance the quality of the purified protein, polar hydrogen atoms were added, while prebound heteroatoms and complex ligands were removed from the structure (Figure 1). Protein purification was conducted using BIOVIA Discovery Studio [14]. Furthermore, secondary structure prediction and Ramachandran plot analysis of the purified structures were performed using the PDBSumGenerate website (https://www.ebi.ac.uk/thornton-srv/databases/pdbsum/Generate.html).

Pharmacological Investigations

The pharmacological properties of the ligands were evaluated using Swiss ADME (http://www.swissadme.ch) [15]. Physiochemical characteristics, including molecular size, flexibility, saturation, and lipophilicity, were analyzed. Ligand selection was based on Lipinski's Rule of Five to identify the most suitable candidates. Additionally, ADMETLAB 2.0 (https://admetmesh.scbdd.com) was employed to assess the toxicity profiles of the ligands [16].

Molecular Docking

The plant-derived phytocompounds were imported into PyRx as ligands, while the purified 1S78 protein was uploaded as the macromolecule. OpenBabel was utilized to convert the ligands from SDF to PDB format [17]. For the active site, grid center coordinates were set at X = 69.1278, Y = 71.720, and Z = 207.4772, with dimensions (in angstroms) of X = 99.1093, Y = 76.9993, and Z = 69.6867 (1S78). After individually docking each ligand against the protein 1S78 using the PyRx web server, energy minimization was performed. Based on binding affinity with the target protein, the top-performing compounds – Oxyberberine, Tetrahydropalmatine, Beta-Hydrastine, and (+/–)-Karachine – were selected for further analysis. To obtain the highest binding scores in PyRx, the ligands underwent nine different combinational modifications. The binding affinity corresponding to zero root mean square deviation (RMSD) values was assessed as the optimal docking conformation, as these exhibited the lowest binding scores among all conformations. For each target protein, the top five conformations with the lowest binding affinity were selected to determine the optimal binding complex. Once the docked ligand structures were extracted as PDB files, DS BIOVIA Discovery Studio was used to visualize their interactions.

Visualization

The structure visualization tool BIOVIA discovery studio software was used to display the results (docked structures) from PyRx. Using BIOVIA Discovery Studio Visualizer, the best-binding conformations were obtained in PDB format. The conformations with the highest binding scores were downloaded in PDB format, and their 2D and 3D models were generated using the Dassault Systèmes BIOVIA Discovery Studio Visualizer.

RESULTS

Selection of Phytocompounds

BA is widely recognized for its significant inhibitory effect in the pathophysiology of various immunological disorders and cancers. As shown in Figure 1, (1S78) BA compounds and their derivatives were selected from the IMPPAT database to identify a potential treatment candidate. The two-dimensional structures of the top four ligands, exhibiting the highest binding affinities with the protein 1S78, were retrieved from PubChem based on docking results. These structures were visualized using BIOVIA, as detailed in Table 1.

Analysis of Protein Structures: The Ramachandran Plot

The Ramachandran plot illustrates the energetically favorable regions where amino acid torsions align within a single protein structure. For the purified 1S78 protein, the Ramachandran plot was generated using PROCHECK (Figure 2), while PROSITE was employed to analyze its secondary structure (Figure 3). The red regions on the plot indicate sterically permissible zones that contribute to a stable peptide structure. In silico studies require that amino acids be located within these sterically favorable regions at least 88% of the time. In the allowed regions of the Ramachandran plot, 90% of the amino acid residues (555 residues) are present, while only 0.5% (1 residue) falls within the disallowed region. The remaining 10% are distributed across sub-regions. Based on an analysis of 118 structures with a resolution of at least 2.0 Å and an R-factor not exceeding 20.0, a high-quality model should have over 90% of residues in the most favored regions. These residues include three-terminal residues, 44 glycine residues, and 34 proline residues.

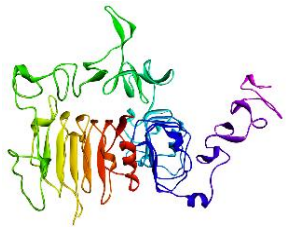

Figure 1. Purified protein HER2 (PDB ID: 1S78).

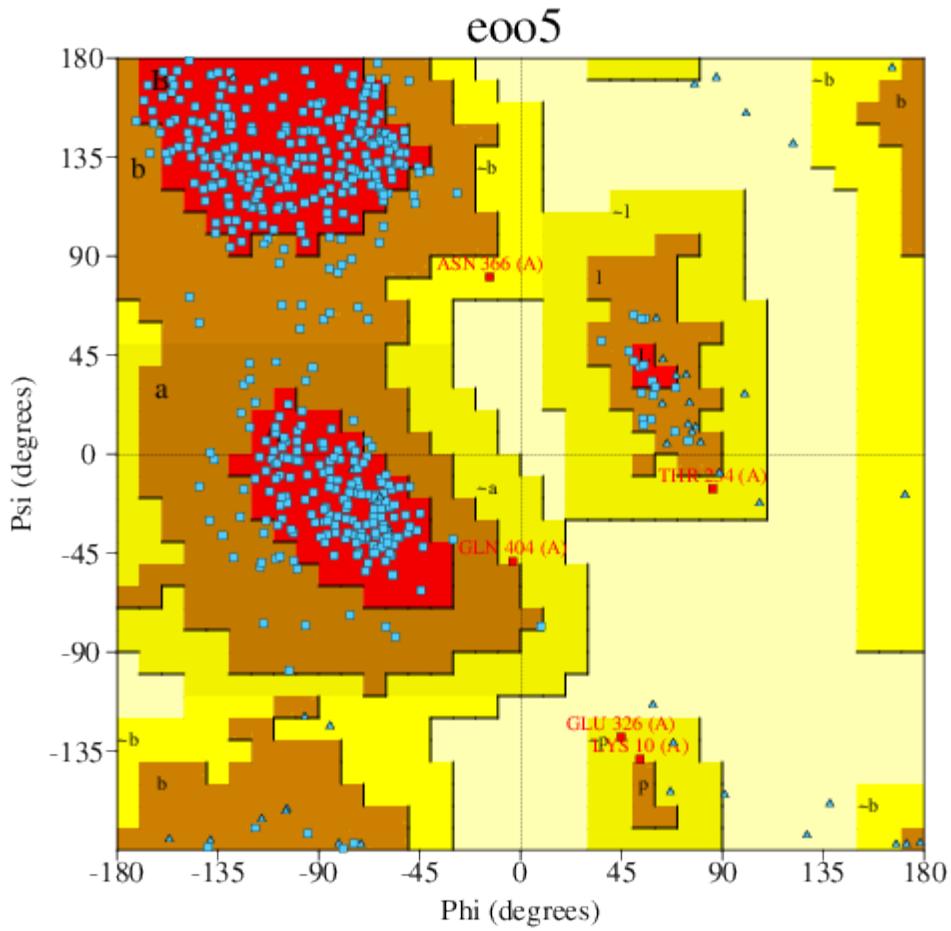

Figure 2. Ramachandran plot of 1S78 protein using PDBsum.

Covalent Forces in the Main Chain

The main-chain bond angles measure 0.42, while the main-chain bond lengths are 0.61. These values are compared with the ideal bond lengths and angles established from small-molecule data by Engh & Huber (1991). Consequently, structures modified with various constraints may exhibit significant deviations from standard values.

Swiss ADME Analysis

ADMET and Drug Likelihood10. The bioavailability score is a key factor in drug similarity analysis, used to evaluate the potential effectiveness of oral drug candidates. This scoring system is based on the structural properties of small molecules. The Lipinski Rule of Five is applied to filter small molecules and determine their drug-like characteristics. Additionally, the PAINS score helps assess the medicinal chemistry properties of therapeutic compounds by highlighting substructures that consistently produce strong responses, regardless of the protein target. For physicochemical evaluation, ligands are screened based on specific criteria: Lipophilicity (xLogP: –0.7 to +5.0), Size (Molecular weight: 150–500 g/mol), Polarity (Topological Surface Area: 20–130 Å²), Saturation (sp^3 hybridization: not less than 0.25) and Flexibility (Rotatable bonds: fewer than 9) All five physicochemical screening criteria were satisfied by the top four ligands (Table 2). The Lipinski Rule of 5 serves as the most reliable guideline for pharmacologically evaluating potential drug compounds. According to this rule, a drug should have a molecular weight between 150 and 500 Daltons, a lipophilicity value below 4.15, fewer than 5 hydrogen bond donors, fewer than 10 hydrogen bond acceptors, and a molar refractivity ranging from 40 to 130 Å². After undergoing evaluation based on the Lipinski criteria, the top four ligands met all the required standards with no deviations (Table 3).

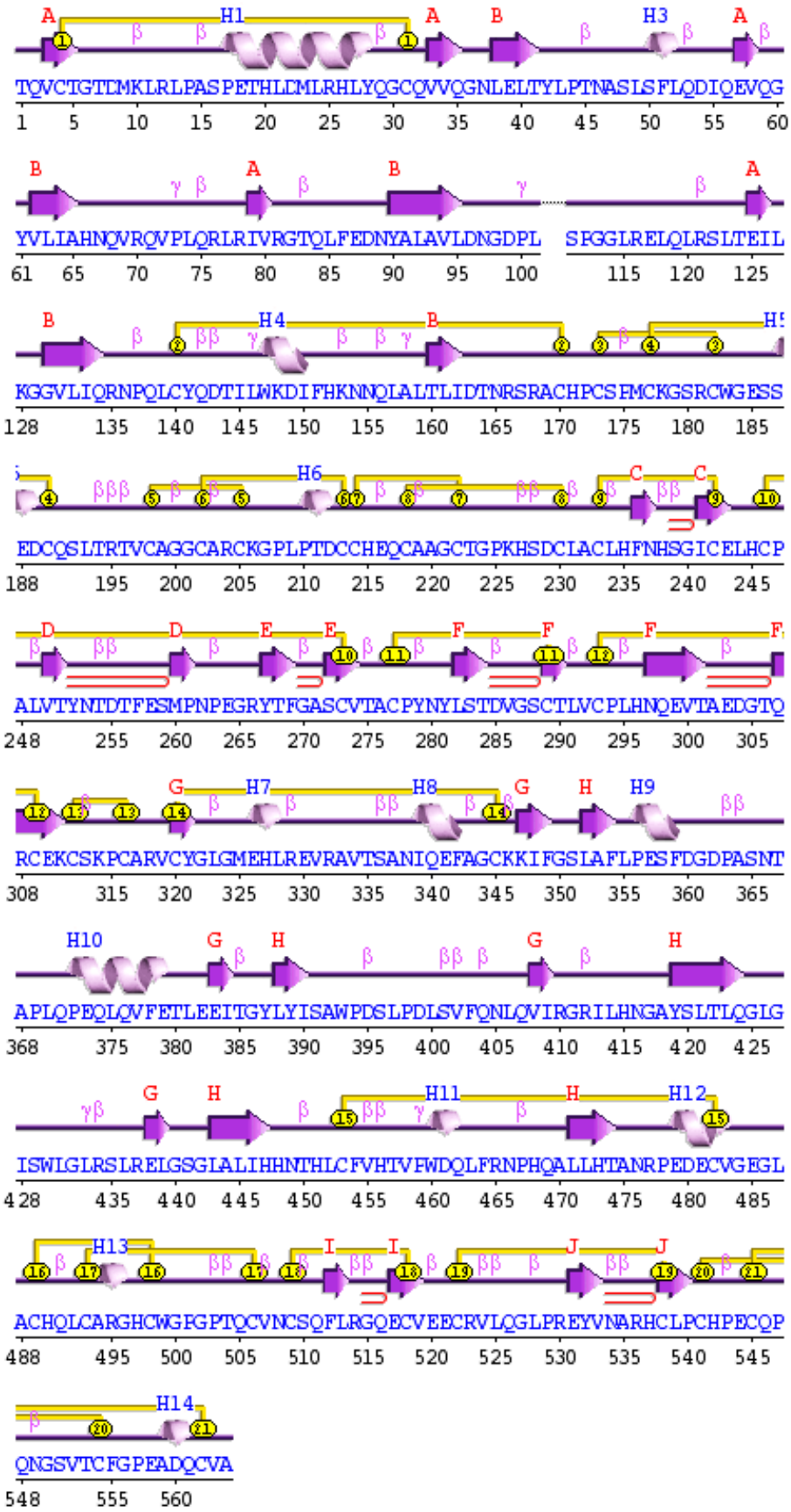

Figure 3. Secondary structure of protein 1S78.

ADME Analysis

The ADME analysis evaluates the drug's solubility, glycoprotein permeability, human gastrointestinal absorption, and ability to penetrate the blood–brain barrier (Table 4). The drug's potential to cross the blood–brain barrier (BBB) is a key factor in determining its suitability for treatment. This information is crucial for drug development. High gastrointestinal (GI) absorption is important to enhance the drug's effectiveness. For optimal medicinal activity, oral medications should ideally exhibit both high gastrointestinal absorption and solubility.

Toxicity Prediction

The key factors in toxicity prediction include several important parameters, such as skin sensitivity, carcinogenicity, respiratory toxicity, AMES toxicity, rat oral acute toxicity, FDAMDD, hERG blockers, H-HT, and DILI (Table 5).

Molecular Docking Analysis

It is revealed that the ligands oxyberberine, beta-hydrastine, tetrahydropalmatine, and (+/–)-karachine had the strongest binding affinity for the target protein peroxiredoxin Asp f3 (Table 6).

Visualization

The locked complex was visualized in BIOVIA, as the ligand beta-hydrastine exhibited the lowest binding energy with the target protein. The 3D and 2D interaction diagrams (Figures 4a and 4b) clearly show that the ligand interacts with amino groups in the protein's A chain, including residues Ala 232, Ala 271, Val 3, Glu 57, Phe 269, and Cys 230.

Table 1. PubChem ID and canonical smiles of top 4 ligands.

PubChem ID	Metabolites	Canonical Smiles
11066	Oxyberberine	COc1c(OC)ccc2c1c(=O)n1c(-c3cc4OCOc4cc3CC1)c2
197835	Beta-hydrastine	CN1CCC2=CC3=C(C=C2[C@@H]1[C@@H]4C5=C(C(=C(C=C5)OC)OC)C(=O)O4)OCO3
5417	Tetrahydropalmatine	COC1=C(C2=C(CC3C4=CC(=C(C=C4CCN3C2)OC)OC)C=C1)OC
630739	(+/–)-Karachine	CC12CC3C4=C(C1C5(N3CCC6=CC7=C(C=C65)OCO7)CC(=O)C2)C=CC(=C4OC)OC

Table 2. Physiochemical properties of ligands.

Ligands	Molecular Weight	Fraction Csp3	Rotatable Bonds	TSPA	Lipophilicity
Oxyberberine	351.35	0.25	2	58.92	96.8
Beta-hydrastine	383.39	0.38	3	66.46	103.38
Tetrahydropalmatine	355.43	0.43	4	40.16	103.99
(+/–)-Karachine	433.5	0.5	2	57.23	121.51

Table 3. Information about the Lipinski rule's characteristics gathered from Swiss absorption, distribution, metabolism, and excretion.

Ligands	Molecular Weight	MLogP	Hydrogen Donors	Hydrogen Acceptors	Molar Refractivity
Oxyberberine	351.35	2.38	0	5	96.8
Beta-hydrastine	383.39	2	0	7	103.38
Tetrahydropalmatine	355.43	2.2	0	5	103.99
(+/–)-Karachine	433.5	2.77	0	6	121.51

Table 4. Swiss absorption distribution metabolism excretion data on absorption, distribution, and metabolism.

Ligands	Blood-Brain Barrier	GI	PGP	Solubility (LOGSw-SILICOS

	Penetration	Absorption	Substrate	IT)
Oxyberberine	Yes	High	Yes	–5.82
Beta-hydrastine	Yes	High	No	–5.13
Tetrahydropalmatine	Yes	High	Yes	–5.87
(+/–)-Karachine	Yes	High	No	–6.71

Source: GI: Gastrointestinal, PGP: P-glycoprotein.

Table 5. Toxicity categorization.

Ligands	hERG	H-HT	DILI	Ames	ROA	Carcinogenicity	Respiratory
Oxyberberine	0.104	0.11	0.67	0.855	0.037	0.953	0.874
Beta-hydrastine	0.535	0.198	0.441	0.256	0.626	0.652	0.883
Tetrahydropalmatine	0.253	0.118	0.603	0.149	0.514	0.062	0.945
(+/–)-Karachine	0.208	0.389	0.056	0.222	0.248	0.715	0.927

Source: hERG: Human ether-a-go-go related gene, DILI: Drug-induced liver injury, ROA: Rat oral acute, H-HT: Human hepatotoxicity.

Table 6. Ligands' affinity for binding to the HER2 protein.

Ligands	Binding Affinity
Oxyberberine	–7.7
Beta-hydrastine	–8.2
Tetrahydropalmatine	–12
(+/–)-Karachine	–7.7

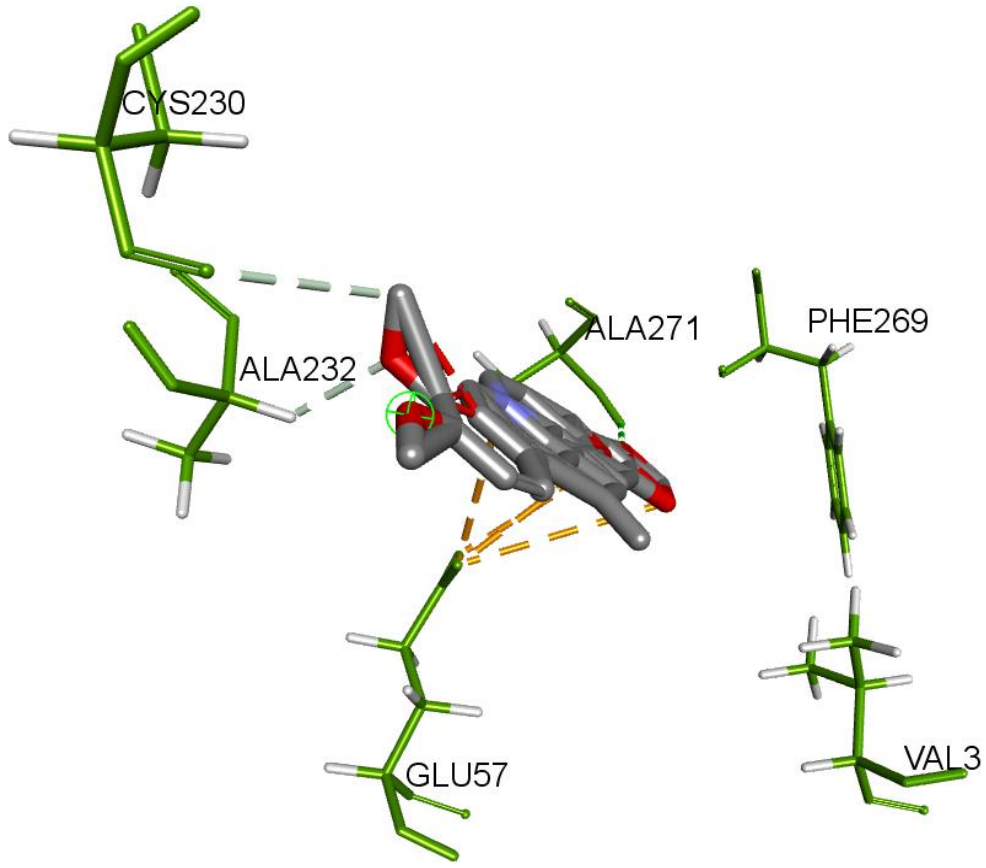

Figure 4. (a) 3D structure of visualization of molecular interactions of 1S78 with Tetrahydropalmatine ligand.

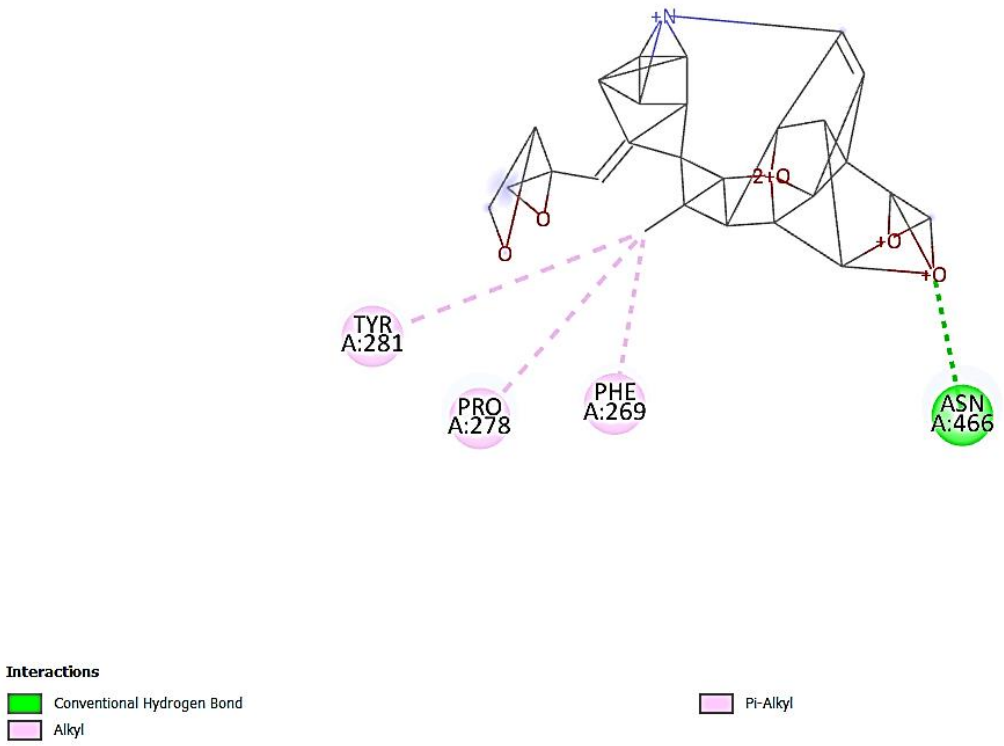

Figure 4. (b) 2D structure Visualization of molecular interactions 1S78 with Tetrahydropalmatine ligand.

DISCUSSIONS

Chronic illnesses, such as cancer, metabolic disorders, and cardiovascular diseases require long-term treatment. However, prolonged use of chemical therapies can lead to significant adverse effects [18]. BA is a natural treatment known for its safety and effectiveness in managing various pathological conditions, making it a promising option for long-term disease management [19]. Its roots are thick, woody, cylindrical, and heavily branched, featuring a knotty texture with scaly, longitudinal wrinkles [20]. They have a yellowish-brown color and are cut into varying lengths, reaching up to 45 mm in diameter. The plant produces two to five seeds, ranging in color from yellow to pink, each weighing approximately 25 mg [20]. The investigation of antitumor efficacy of BA using Ehrlich ascites carcinoma-bearing mice under controlled conditions. BA has been recognized for its significant anticancer properties in Ayurveda and traditional ethnobotanical practices in Northern India [21]. To obtain meaningful translational insights for potential human studies, the anticancer effects were specifically evaluated in advanced stages (10 days post-tumor injection). Among the two extracts tested, the alcoholic extract demonstrated greater effectiveness than the aqueous extract, strongly indicating that the observed effect is influenced by the type and concentration of phytochemicals present. A preliminary phytochemical analysis identified flavonoids and alkaloids as the primary constituents of BA. It has been reported that flavonoids are largely insoluble in water, whereas alkaloids are more soluble in organic solvents, such as ethanol [22]. Since alkaloids are generally known for their cytotoxic properties [23], their presence may explain the potent cytotoxic effect observed in the ethanol extract. In vitro studies using Ehrlich ascites carcinoma cells demonstrated that all treatments increased the proportion of dead cells (stained with trypan blue), indicating their cytotoxic effects. This was further confirmed by the extracts' performance in the brine shrimp lethality assay, which is known to correlate well with cytotoxic activity and anticancer properties [24, 25]. A similar mechanism may be involved when the extract is injected into the tumor growing in the mice's peritoneal cavity, leading to reduced tumor weight gain and improved survival. Berberine, an isoquinoline alkaloid found in plants of the *Berberidaceae* family, particularly *Berberis aristata*, has been reported to exhibit anticancer properties

in both in vitro and in vivo study models [26]. Based on previous research on berberine's antitumor effects, the authors suggest that berberine may not be the sole contributor to the antineoplastic effects of *Berberis aristata* extracts in Ehrlich ascites carcinoma-bearing mice.

CONCLUSIONS

To evaluate the effects of various phytochemicals on the HER2 protein, we employed computational methods using PyRx. Molecular docking was performed systematically through a virtual screening tool. This study utilized a drug repurposing strategy – also known as drug repositioning, refiling, or retasking – to identify new therapeutic applications for existing or investigational drugs. With further medical research, this emerging approach is expected to undergo significant advancements. The incidence of breast cancer has been rising, primarily affecting middle-aged women. While several vaccines are being developed to detect this disease, medicinal plants also play a crucial role in the development of new drugs, making them just as important as immunizations.

Acknowledgment

I sincerely appreciate Deekshitha M. for her valuable guidance and advice. I would also like to express my gratitude to BioNome for its assistance in scientific research services and for providing computational facilities.

Dispute of Interest

There is no conflict of interest, according to the authors.

List of Abbreviations

ADMET	Absorption, Distribution, Metabolism, and Toxicity
GI	Gastrointestinal Absorption
BA	Berberis aristata
BC	Breast cancer
NMR	Nuclear Magnetic Resonance
PDB	Protein Data Bank
RCSB	Research Collaboratory for Structural Bioinformatics
SDF	Structure data format
PGP	P-glycoprotein
SMILES	Simplifies Molecular Input Line Entry system
TPSA	Topological Polar surface

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