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In silico inhibition study of phytocompounds derived from *Bryophyllum pinnatum*, *Cassia sieberiana*, *Cassia tora* and *Tamarindus indica* against breast cancer proteins

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Abstract

Breast cancer is a type of cancer that originates in the cells of the breast tissues. *B. pinnatum, C. sieberiana, C. tora and T. indica* are the four medicinal plants whose phytochemicals were used for this In silico study. In this study, eight different ligands were evaluated for their interactions with the human epidermal growth factor 2 (HER2) protein (PDB ID: 3pp0). The ligands, including Apigenin, Bryophyllin A, Catechin, Emodin, Islandicin, Quercetin, Sitosterol, and Taxifolin, were assessed based on binding scores and hydrogen bond interactions. Among these ligands, Apigenin exhibited the highest binding score (- 6.5 kcal/mol), indicating its strong binding affinity to the HER2 protein. Bryophyllin A also displayed a significant binding score (- 6.3 kcal/mol) and formed a hydrogen bond with Met 901. Catechin, while having a slightly lower binding score (- 5.9 kcal/mol), engaged in hydrogen bonds with Ser 728, Arg 849, and Asn 850. Emodin, Quercetin, and Taxifolin demonstrated moderate binding scores (- 6.2, - 6.4, and - 6.0 kcal/mol, respectively) and formed hydrogen bonds with Asp 863 and Met 801. Islandicin formed a hydrogen bond with Gly 787 and Leu 786, with a binding score of - 6.1 kcal/mol. Sitosterol exhibited the lowest binding score (- 5.3 kcal/mol) but still established a hydrogen bond with Asp 863 and Met 801. Overall, Apigenin and Bryophyllin A emerged as the most promising ligands due to their strong binding affinities and specific hydrogen bond interactions with HER2. However, experimental validation is essential to confirm these findings and explore their potential as inhibitors or modulators of HER2. Furthermore, all ligands were successfully docked to the active sites of the HER2 protein, indicating their potential relevance in targeting HER2-related pathways. Importantly, the ligands exhibited favorable pharmacokinetic properties with no violations, except for Sitosterol, which showed minor violations in Lipinski, Ghose, Egan, and Muegge's rules.

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Introduction

Breast cancer is a type of cancer that originates in the cells of the breast tissues. It primarily affects women but can also occur in men. It is characterized by the uncontrolled growth of abnormal cells in the breast tissue, forming a lump or mass called a tumor (Dashti *et al.*, 2020). Breast cancer can spread to other parts of the body through the lymphatic system or bloodstream, leading to metastasis (Iqbal and Iqbal, 2014; Pegram and Jackisch, 2023). Early detection and advancements in treatment have significantly improved the prognosis and survival rates for those diagnosed with breast cancer (Pegram and Jackisch, 2023). The exact causes of breast cancer are not fully understood, but several risk factors have been identified. These include genetics (family history of breast cancer or carrying certain mutations like BRCA1 and BRCA2), hormonal factors (early onset of menstruation, late menopause, hormone replacement therapy), age (risk increases with age), certain inherited gene mutations, exposure to ionizing radiation, obesity, alcohol consumption, and more (Sun *et al.*, 2017). While these factors can increase the risk, not everyone with these risk factors will develop breast cancer. Breast cancer can have wide-ranging effects on individuals physically, emotionally, and socially. Physically, it can lead to symptoms such as a lump in the breast, changes in breast size or shape, skin changes, and nipple discharge (Kim, 2021; Sun *et al.*, 2017). Emotionally, the diagnosis can cause anxiety, fear, depression, and uncertainty. Socially, it may impact relationships and daily life. The effects of treatment, including surgery, chemotherapy, radiation, and hormone therapy, can also cause physical and emotional challenges. Treatment for breast cancer depends on the stage and type of cancer, as well as individual factors (Iqbal and Iqbal, 2014; Pegram and Jackisch, 2023). Common treatments include surgery (lumpectomy or mastectomy), radiation therapy, chemotherapy, targeted therapy, hormone therapy, and immunotherapy (Burguin and Diorio, 2021; Moo *et al.*, 2019). Treatment plans may involve a combination of these approaches (Pegram and Jackisch, 2023). The goal is to remove or destroy the cancer cells, prevent recurrence, and improve overall quality of life (Moo *et al.*, 2019). Researchers have identified specific molecular and genetic targets that play a role in the development and growth of breast cancer. Targeted therapies focus on these specific molecules, receptors, and genetic mutations to inhibit cancer growth (Burguin and Diorio, 2021). Some targeted therapies are designed to block hormone receptors (such as estrogen or progesterone receptors), while others target overexpressed proteins like HER2. HER2, or human epidermal growth factor receptor 2, is a protein that plays a role in regulating cell growth and division. In some breast cancers, there is an overexpression or amplification of the HER2 gene, leading to an increased production of the HER2 protein (Hussain *et al.*, 2020; Iqbal and Iqbal, 2014). HER2-positive breast cancer is an important target in breast cancer treatment because the overexpression of HER2 is associated with more aggressive tumor growth and a poorer prognosis (Iqbal and Iqbal, 2014). Targeting HER2 can help slow down the progression of the cancer and improve treatment outcomes. In molecular docking studies, the HER2 (human epidermal growth factor receptor 2) protein is commonly used as a target protein, especially when investigating the binding of potential drug compounds or ligands (Iqbal and Iqbal, 2014; Pegram and Jackisch, 2023; Sohrab, 2022). HER2 is a protein that plays a role in regulating cell growth and division (Iqbal and Iqbal, 2014). In some breast cancers, there is an overexpression or amplification of the HER2 gene, leading to an increased production of the HER2 protein (Iqbal and Iqbal, 2014). HER2-positive breast cancer is an important target in breast cancer treatment because the overexpression of HER2 is associated with more aggressive tumor growth and a poorer prognosis. Targeting HER2 can help slow down the progression of the cancer and improve treatment outcomes. In molecular docking studies, the HER2 (human epidermal growth factor receptor 2) protein is commonly used as a target protein, especially when investigating the binding of potential drug compounds or ligands (Sohrab, 2022). These therapies aim to be more effective and cause fewer side effects compared to traditional chemotherapy. Local Nigerian floras, also known as plants or plant species, have been studied for their potential roles in traditional medicine and complementary treatments, including the treatment

of breast cancer. Some of these plants are believed to contain bioactive compounds with medicinal properties that could contribute to breast cancer treatment. However, it is important to note that while traditional remedies and plant-based compounds may show promise, they often need rigorous scientific validation before being recommended as standard treatments. Nigerian plant species that have been investigated for their potential roles in breast cancer treatment include; Annona muricata (Soursop or Graviola), Carica papaya (Papaya), Curcuma longa (Turmeric), Allium sativum (Garlic) and Azadirachta indica (Neem) (Ohiagu *et al.*, 2021). It's important to emphasize that while these plants show potential, further research is needed to better understand their mechanisms of action, optimal dosages, and potential interactions with conventional breast cancer treatments. Scientific validation through preclinical and clinical studies is crucial before any plant-based remedies can be recommended for breast cancer treatment. Other Nigerian medicinal plants with great pharmacological and ethnobotanical properties include; Bryophyllum pinnatum (BP), Cassia sieberiana (CS), Cassia (CT) Tora and Tamarindus Indica (TI) (Archer *et al.*, 2019; Meena and Niranjan, 2010; Pawar *et al.*, 2011; Sarwa *et al.*, 2014; Sookying and Duangjai, n.d.) (Fig. 1). These plants demonstrated plausible properties such as phytochemical, ethnobotanical, pharmacological and biological properties (Archer *et al.*, 2019; Faboro *et al.*, 2016; Khan and Odokpe, 2020; Meena and Niranjan, 2010; Ms and Ali, 2018; Salami *et al.*, 2013; Sarwa *et al.*, 2014; Sookying and Duangjai, n.d.). This study utilizes the potentials of BP, CB, CT and TI in the inhibition study of one of the breast cancer target proteins, HER2 through Insilco studies.

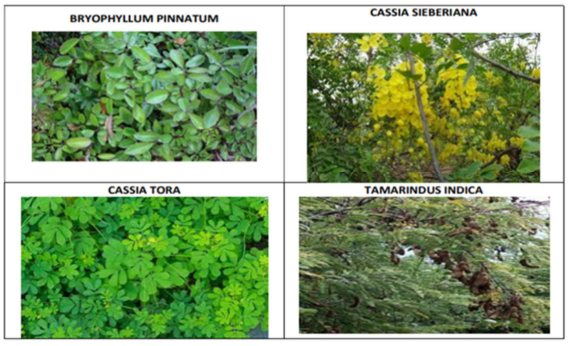

Fig. 1. Selected medicinal plants

Materials and methods

Ligand preparation

Hundreds of phytochemicals obtained from BP, CB, CT and TI plants were reported from literatures and were used in the study. The ligand preparation procedure followed a similar procedure reported from our previously reported literature (Muhammad *et al.*, 2023). Three-dimensional structures of the identified plants' phytochemicals were retrieved from the PubChem database (www.pubchem.ncbi.nlm.nih.gov) in SDF format, Minimized and converted to PDBQT with Pyrex-Open Babel software.

Protein target preparation

The protein preparation procedure also followed a similar procedure reported from our previously reported literature (Muhammad *et al.*, 2022). The PDB structure of human epidermal growth factor protein 2 (HER2) was retrieved from the Protein Data Bank (https://www.rcsb.org) (PDB ID: 3PP0). All hetero atoms were removed from the protein molecule using UCF Chimera (Version 1. 12).

Molecular docking

Structural-based virtual screening was employed to find the potential inhibitors of HER2 (3pp0) protein (Herrera-calderon *et al.*, 2020). The docking and scoring functions were validated before the docking was carried out. Phytochemicals that interacted with the 3pp0 catalytic site residues were selected for further studies.

Procedure for post docking analysis

Post molecular docking analysis was carried out by re-docking the suitable models of the ligands that binded to the active site of the 3pp0 protein using UCF Chimera (Version 1. 12) to obtain the protein-ligands complex and subsequently the suitable models, which are the compounds that interacted with the 3pp0 key catalytic residues were considered for post docking studies using Discovery Studio (Version 2.0) to study the protein – ligands interactions (Muhammad *et al.*, 2022).

ADMET analysis

The procedure used here is directly adopted from our previously reported literature (Muhammad *et al.*, 2023) SwissADME (www.swissadme.ch) and ADMETSAR (http://lmmd.ecust.edu.cn/admetsar2/) servers were utilizing to study the metabolic and toxicological properties of the phytocompounds. The canonical smiles of the phytocompounds were utilized to estimate the corresponding values of the ADMET (absorption, distribution, metabolism, excretion and toxicity) (Muhammad *et al.*, 2023).

Results and Discussion

Molecular docking analysis

The chemical structures of the selected ligands are shown in Fig. 2. These ligands are derived from medicinal plants selected for the study. These ligands indeed demonstrate plausible binding affinities to the HER2 protein (Table 1, Fig. 3).

The molecular docking is technically a physical interaction between a ligand and a protein target. In this study, the selected ligands were successfully and efficiently bonded to the active site of the HER2 to form a protein – ligands' complex as shown in Fig. 3. The following amino acid residues Leu726, Val734, Ala751, Lys753, Thr798, Gly804, Arg849, Leu852, Thr862, and Asp863 were found in common interaction as compared to the standard compound Lapatinib (Sohrab, 2022).

The results of the molecular docking typically comprise of the binding scores, root mean square deviations (RMSD) and the protein – ligands interactions. Binding scores and the protein – ligands interactions are presented in Table 1. The extent of the interactions that shows the specific bonding between the ligands and the HER2 amino acid residue is also presented in Fig. 4.

Root mean square deviation (rmsd) analysis

Root Mean Square Deviation (RMSD) is a measure of the structural similarity or deviation between two molecular structures, typically a reference (in this case, the original ligand conformation in the crystal structure 3pp0) and the docked ligand conformations.

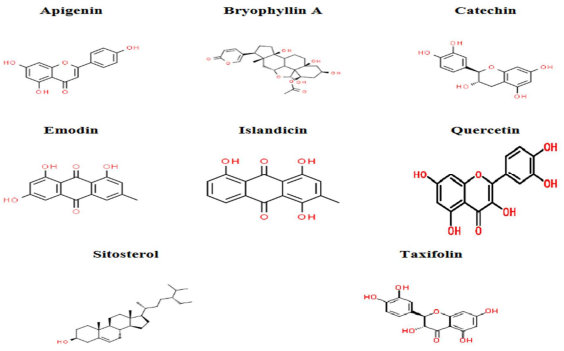

Fig. 2. Chemical structures of the selected ligands

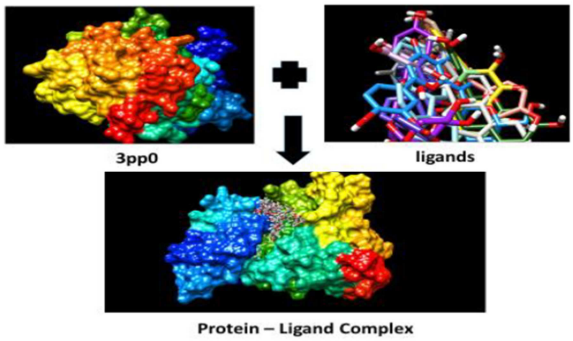

Fig. 3. Protein – Ligands' Complex

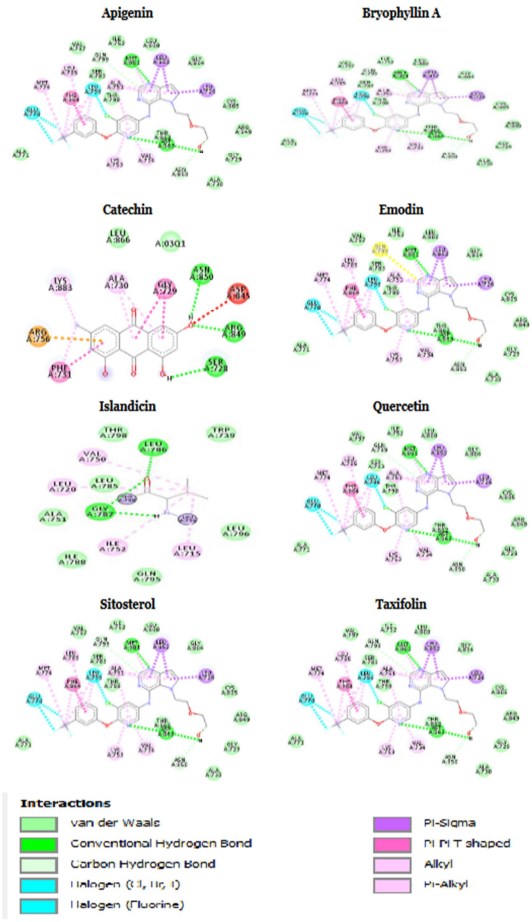

Fig. 4. Depiction of HER2 (3PP0) -ligands' interactions complexes

Table 1. Binding scores and 3PP0 residues' interactions with the ligands

Compound name	PubChem CID	Binding score (kcal/mol)	Hydrogen bond interaction	Other interactions
Apigenin	10151	-6.5	Asp 863, Met 801	Ala 751, Glu 770, Met 774, Phe 864, Thr 852, Thr 798, Val 734, Lys 753, Asn 850, Leu 726, Leu 796, Leu 852, Gln 799
Bryophyllin A	222284	-6.3	Asp 863, Met 901	Glu 770, Met 774, Phe 864, Thr 852, Val 734, Lys 753, Asn 850, Leu 726, Leu 726, Leu , Leu 796, Leu 852, Gln 799
Catechin	3220	-5.9	Ser 728, Arg 849, Asn 850	Ala 730, Arg 756, Asp 845, Gly 729, Lys 798, Phe 731
Emodin	439533	-6.2	Asp 863, Met 801	Glu 770, Lys 753, Asn 850, Leu 726, Leu 785, Gln 799
Islandicin	5280343	-6.1	Gly 787, Leu 786	Leu 715, Leu 726, Leu 796, Ile 752, Thr 798, Val 750
Quercetin	5280794	-6.4	Asp 863, Met 801	Glu 770, Met 774, Phe 864, Thr 798, Thr 862, Val 734, Lys 753, Asn 850, Leu 785, Leu 726, Leu 795, Leu 852, Gln 799,
Sitosterol	5280863	-5.3	Asp 863, Met 801	Ala 751, Glu 770, Met 714, Phe 864, Thr 862, Val 734, Lys 753, Asn 850, Leu 785, Leu 726, Leu 796, Leu 852, Gln 799
Taxifolin	9064	-6.0	Asp 863, Met 801	Ala 751, Glu 770, Met 774, Phe 864, Val 734, Lys 753, Asn 850, Leu 852, Leu 726, Gln 799

Table 2 presents the RMSD values of the ligands. Lower RMSD values indicate a closer structural match between the predicted and reference structures, suggesting a more accurate docking result. Here, we have eight ligands: Apigenin, Bryophyllin A, Catechin, Emodin, Islandicin, Quercetin, Sitosterol, and Taxifolin, and we are comparing their docked conformations against the reference structure of 3pp0. The RMSD values represent the deviation of the ligand's structure after docking from the original crystallographic structure of 3pp0. RMSD values within the lower and upper boundaries indicate that the docked ligand conformations are within an acceptable range of structural similarity to the reference structure (3pp0). Emodin and Islandicin have the lowest upper boundary RMSD values (1.668 and 1.838 Å, respectively), suggesting that their docked conformations closely resemble the reference structure. Quercetin has a low lower boundary RMSD (3.209 Å) and an even lower upper boundary RMSD (1.528 Å), indicating a very close match to the reference structure. Bryophyllin A, Catechin, and Taxifolin also have relatively low RMSD values within the specified boundaries, indicating good docking results. Apigenin and Sitosterol have slightly higher RMSD values, but they still fall within the acceptable range. Overall, these RMSD values suggest that the molecular docking simulations for these ligands against 3pp0 have resulted in conformations that closely resemble the crystallographic structure, with Emodin, Islandicin, and Quercetin showing particularly promising results in terms of structural similarity. However, further validation and analysis, such as considering binding energy and specific interactions, are necessary to draw more definitive conclusions about the binding affinities and biological relevance of these ligand-protein complexes.

Table 2. RMSD analysis data

Compound name	RMSD (Å) (Upper boundary)	RMSD (Å) (Lower boundary)
Apigenin	5.091	2.553
Bryophyllin A	4.822	3.304
Catechin	5.804	3.468
Emodin	6.828	1.668
Islandicin	6.841	1.838
Quercetin	3.209	1.528
Sitosterol	5.874	4.293
Taxifolin	5.472	3.220

Drug-likeness properties and ADMET screening

The drug-likeness properties entails the intrinsic properties demonstrated by the ligands after molecular docking and ADMET screening. This property entails the relationship between a chemical structure, composition, size and bonding chemistry between a ligand and the HER2 protein. The pharmacokinetics of BP, CS, CT and TI have been successfully carried out and the results were presented across Table 3-4.

Table 3. Structural properties of ligands

Ligand	Molecular formulae	MW (g/mol)	Heavy atoms	Aromatic	Rotatable bonds	H-Bond acceptors	H-Bond donors
Apigenin	$C_{15}H_{10}O_5$	270.24	20	16	1	5	3
Bryophyllin A	$C_{26}H_{32}O_8$	472.53	34	6	2	8	2
Catechin	$C_{15}H_{14}O_6$	290.27	21	12	1	6	5
Emodin	$C_{15}H_{10}O_4$	254.24	19	12	0	4	2
Islandicin	$C_{15}H_{10}O_4$	254.24	19	12	0	4	2
Quercetin	$C_{15}H_{10}O_7$	302.24	22	16	1	7	5
Sitosterol	$C_{29}H_{50}O$	414.71	30	0	6	1	1
Taxifolin	$C_{15}H_{12}O_7$	304.25	22	12	1	7	5

Table 4. Rules violations

Compound	Lipinski #violations	Ghose #violations	Veber #violations	Egan #violations	Muegge #violations
Apigenin	0	0	0	0	0
Bryophyllin A	0	0	0	0	0
Catechin	0	0	0	0	0
Emodin	0	0	0	0	0
Islandicin	0	0	0	0	0
Quercetin	0	0	0	0	0
Sitosterol	1	3	0	1	2
Taxifolin	0	0	0	0	0

Table 5. ADME properties

Ligand	GI absorption	BBB permeant	Pgp substrate	Bioavailability score	Lead-likeness #violations	Ali solubility	Synthetic accessibility
Apigenin	High	No	No	0.17	0	Moderately soluble	2.96
Bryophyllin A	High	No	Yes	0.55	1	Soluble	7.33
Catechin	High	No	Yes	0.55	0	Soluble	3.5
Emodin	High	Yes	No	0.55	1	Moderately soluble	2.47
Islandicin	High	Yes	No	0.55	1	Moderately soluble	2.47
Quercetin	High	No	No	0.55	0	Soluble	3.23
Sitosterol	Low	No	No	0.55	2	Poorly soluble	6.3
Taxifolin	High	No	No	0.55	0	Soluble	3.51

Structural properties such as number of heavy atoms, rotatable bonds, hydrogen donors and acceptors were all predicted. Parameters such as molecular weights, heavy atoms, number of aromatic rings, rotatable bonds, hydrogen bond donors and hydrogen bond acceptors are tools used in filtering the most effective drug- like compounds and the data are presented in Table 3. The presence of heavy atoms in drug molecules can have various effects on drug discovery, including influencing drug-target interactions, pharmacokinetics, and physicochemical properties. Key effects of heavy atoms in drug discovery include; increased molecular weight, hydrophobic interactions, electronic effects, metabolism and clearance, radiolabeling and imaging. Molecular weights of compounds that are supposed to be drug-like are characterized by having small molecular weights. Large molecular weights compounds are characterized by having molecular weights above 500 g/mol. Table 3 presents different molecular weights prediction scores of compounds under study. A total of zero compound have molecular weight less than 500 g/mol. This shows remarkable drug like properties of all the ligands. All ligands have hydrogen bond donor below 5 while 4 ligands have hydrogen bond acceptors above 5. Aromatic rings play a crucial role in drug discovery due to their unique chemical properties and interactions with biological targets. Aromatic rings also enhance binding interactions, target specificity, lipophilicity and metabolic stability. Predicted number of aromatic rings in each compound are presented in Table 3. Results show that most compounds show satisfactory amount of aromatic rings. The number of rotatable bonds in a drug molecule is an important factor in drug discovery and design. Number of rotatable bonds between 1 and 2 are reported from literature as excellent filters for drug-like compound evaluation

(Ogidigo *et al.*, 2018). Results show that most ligands possess number of rotatable bonds within acceptable range with the exception of Sitosterol, which has a rotatable bond of 6 as revealed in Table 3.

Drug-likeness and Rule of Five also play an important role in determining compound drug-likeness. The number of rotatable bonds is considered in the rule of five, a guideline used to assess drug-likeness. The rule of five suggests that drug molecules should have no more than five rotatable bonds to ensure optimal oral absorption and bioavailability. Table 4 presents different types of filters used in drug discovery. Some of these filters include Lipinki, Ghose, Veber, Egan and Muegge. These filters are one of the tools used in pharmacokinetics. The Lipinski's Rule of Five, also known as the Rule of Five, is a widely used guideline in drug discovery to assess the drug-likeness and oral bioavailability of organic compounds. The Ghose Rule, also known as the Ghose Filter, is a rule developed to assess the drug-likeness of organic compounds in drug discovery. It is based on a set of physicochemical properties that are important for oral bioavailability. Other rules include Veber, Egan and Muegge and the corresponding data are presented in Table 4. All the ligands show no violations except for Sitosterol which shows few violations corresponding to Lipinski, Ghose, Egan and Muegge, respectively as shown in Table 4. Similar study was also reported from literature (Ogidigo *et al.*, 2018).

Table 5 presents the parameters recorded for the absorption, distribution, metabolism and excretion (ADME) properties of the ligands. Ali solubility refers to the solubility parameter that characterizes the solubility properties of a substance based on its dispersion forces, polar forces, and hydrogen bonding forces. In drug discovery, the solubility of a compound is a critical factor as it directly affects its bioavailability, formulation development, and overall efficacy. Results show that 4 ligands are soluble, 3 moderate, 1poorly soluble and 0 insoluble (Table 5). This shows that the general solubility of most of these compounds are remarkable. The blood-brain barrier (BBB) is a highly selective barrier that separates the blood circulation from the brain and central nervous system (CNS). It plays a crucial role in protecting the brain from harmful substances but also poses a challenge in drug discovery and development. Results show that 6 ligands show excellent BBB properties while only 2 ligands violate BBB predictions (Table 5).

Lead-likeness is a concept in drug discovery that refers to the set of properties and characteristics that are commonly associated with successful drug leads. These properties are used as guidelines to assess the suitability of compounds for further development as potential drug candidates. Results show that 5 ligands demonstrate remarkable lead-likeness property, while only 1 ligand shows good lead-likeness property (Table 5). Gastrointestinal (GI) absorption is a critical factor in drug discovery as it determines the extent to which a drug is absorbed from the gastrointestinal tract into the bloodstream. The efficiency of GI absorption can significantly impact the bioavailability and therapeutic efficacy of a drug. Results show that all the ligands show high GI absorption characteristics while 1 show low GI absorption characteristics (Table 5). GI absorption directly affects the bioavailability of a drug, which is the fraction of the administered dose that reaches systemic circulation. Efficient GI absorption ensures a higher bioavailability, leading to a greater concentration of the drug available for distribution to target tissues. Poor GI absorption can result in low bioavailability and may necessitate higher doses or alternative administration routes to achieve therapeutic levels. P-glycoprotein (P-gp) is a membrane transporter protein that plays a crucial role in drug absorption, distribution, and elimination. It is involved in the efflux of a wide range of drugs and can impact their pharmacokinetics and therapeutic efficacy. Results show that 6 ligands show remarkable P-gp properties. Results show that all ligands demonstrate bioavailability values <1, which is translated as excellent range for bioavailability property (Table 5). Synthetic accessibility is a concept in drug discovery that relates to the ease and efficiency of synthesizing a chemical compound. It plays a crucial role in determining the practicality and feasibility of developing a drug candidate. Results show that values obtained in this study are within the acceptable range (1-10) (Table 5).

Table 6. Toxicological properties

Compounds	Carcinogenicity	Acute oral toxicity	Plasma protein binding	Water solubility
Apigenin	NA	III	1.08	-2.78
Bryophyllin A	NA	I	1.07	-4.309
Catechin	NA	IV	1.01	-3.10
Emodin	NA	III	1.08	-3.02
Islandicin	NA	III	1.07	-3.20
Quercetin	NA	II	1.16	-2.99
Sitosterol	NA	III	1.25	-4.13
Taxifolin	NA	II	1.02	-2.99

The evaluation of carcinogenicity is an essential aspect of the safety assessment of potential drug candidates. Carcinogenicity refers to the ability of a substance to induce cancer. During drug development, extensive studies are conducted to assess the potential carcinogenic effects of compounds. These studies typically involve in vitro tests, animal studies, and epidemiological data analysis. In this study, all the ligands show absence of carcinogenicity (Table 6). Acute oral toxicity is a crucial consideration in drug discovery as it assesses the potential adverse effects of a compound when ingested orally. It provides important information about the safety profile of a drug candidate and helps guide decision-making during preclinical development. Oral acute toxicity is classified into high, moderate, slight and non-toxic. 1 ligand show high, 2 moderate, 4 are slightly toxic while 1 is non-toxic (Table 6). The water solubility of a drug is a critical parameter in drug discovery and development, as it can significantly impact the drug's pharmacokinetics, formulation, and overall therapeutic efficacy. The data obtained for water solubility is well correlated with that of Ali solubility (Table 5). Plasma protein binding is a crucial factor in drug discovery and development as it affects the pharmacokinetics, distribution, and efficacy of a drug in the body. Results show that most of the compounds have remarkable plasma protein binding properties. It is imperative to note that despite remarkable pharmacokinetic profiles demonstrated by certain compounds some few compounds also exhibit poor pharmacokinetic profiles but are considered safe for human use. Some compounds such as Bryophyllum A, shows poor pharmacokinetic profile but is considered safe for human use due while Bryophyllum B show good pharmacokinetic profile but is considered unsafe for human use due to reproductive effect as a result of low toxicity profile (Rahman *et al.*, 2022) . However, Bryophyllum B was predicted to act as a potential therapy for atherosclerosis disease (Yuniwati, 2022). Other reported compounds of BP that demonstrate remarkable pharmacokinetic profiles include; kaemferol, acaecetin, luteolin and patuletin (Ogidigo *et al.*, 2018).

Conclusion

Among eight different ligands, Apigenin emerged as the most promising candidate, displaying the highest binding score (- 6.5) and forming crucial hydrogen bonds with Asp 863 and Met 801. This suggests a robust and specific binding affinity to the HER2 protein. Bryophyllin A also exhibited a strong binding score (- 6.3) and formed a significant hydrogen bond with Met 901. This interaction underscores its potential as a HER2 inhibitor. Catechin, despite a slightly lower binding score (-5.9), demonstrated meaningful interactions by forming hydrogen bonds with Ser 728, Arg 849, and Asn 850. Emodin, Quercetin, and Taxifolin, with moderate binding scores (- 6.2, -6.4, and -6.0, respectively), all interacted via hydrogen bonds with Asp 863 and Met 801. These ligands may warrant further exploration. Islandicin formed a hydrogen bond with Gly 787 and Leu 786, complementing its binding score of -6.1. Sitosterol, with the lowest binding score (- 5.3), still displayed a binding interaction through hydrogen bonds with Asp 863 and Met 801.

Overall, Apigenin and Bryophyllin A exhibit the most promising binding affinities and hydrogen bond interactions with HER2, making them strong candidates for further investigation as potential

HER2 inhibitors or modulators. In conclusion, this molecular docking study provides valuable insights into potential ligands for HER2 targeting. Further research and experimentation are warranted to validate these findings.

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