EVALUATION OF PHYTOCONSTITUENSTS FROM CASSIA TORA BY MOLECULAR DOCKING APPROACH

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KEYWORDS
In-slico, molecular docking, cassia tora, Breast Cancer

ABSTRACT
One kind of cancer that starts in the cells of the breast tissues is called breast cancer. The compounds from the medicinal plant C. tora were utilised in this in silico investigation. The interactions of six distinct ligands with the human epidermal growth factor 2 (HER2) protein (PDB ID: 3pp0) were assessed in this investigation. Kaempferol, Rubrofusarin, Obtusin, Physcion, Crysophanol, and Brassinolide are among the ligands. Cassia tora kaempferol demonstrated a binding energy of -8.7 kcal/mol, respectively. Ala 751, Glu 770, Met 774, Phe 864, Thr 852, Thr 798, Val 734, Lys 753, Asn 850, Leu 726, Leu 796, Leu 852, and Gln 799 are all closely linked to kaempferol on the receptor's active site. The residue interacted with kaempferol, demonstrating its superior inhibitory capacity. The substances that have an anti-ulcerative action attach to the receptor as native ligands because they have the lowest binding energy. Consequently, Cassia tora's kaempferol results in a better ligand-receptor complex structure.
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INTRODUCTION

One kind of cancer that starts in the cells of the breast tissues is called breast cancer. Although it can happen to men, it mainly affects women. A lump or bulge known as a tumour is created when aberrant cells in the breast tissue grow out of control (1). Metastasis is the process by which breast cancer spreads to different areas of the body via the bloodstream or lymphatic system (2, 3). The prognosis and survival rates for individuals with breast cancer have been considerably enhanced by early identification and treatment breakthroughs (4). Although the precise causes of breast cancer remain unclear, a number of risk factors have been found. These include age (risk increases with age), hormone factors (early menstruation, late menopause, hormone replacement therapy), genetics (family history of breast cancer or carrying specific mutations like BRCA1 and BRCA2), exposure to ionising radiation, obesity, alcohol use, and more (5). Not everyone who has these risk factors will have breast cancer, even if they can raise the risk. The physical, emotional, and social impacts of breast cancer can be extensive. Physically, it may result in symptoms such nipple discharge, skin abnormalities, breast lumps, and changes in breast size or shape (6,7). Anxiety, worry, melancholy, and uncertainty are among emotional reactions to the diagnosis. Socially, it could affect everyday life and relationships. Treatment side effects, including as hormone therapy, radiation, chemotherapy, and surgery, can also be emotionally and physically taxing. The kind and stage of breast cancer, in addition to personal variables, determine the course of treatment (8). Radiation therapy, chemotherapy, targeted therapy, hormone therapy, immunotherapy, and surgery (mastectomy or lumpectomy) are common forms of treatment (9, 10).

A mix of these strategies may be used in treatment plans (8). Removing or eliminating the cancer cells, preventing recurrence, and enhancing general quality of life are the objectives (11). Certain molecular and genetic targets have been found by researchers to be involved in the initiation and progression of breast cancer. In order to stop the spread of cancer, targeted medicines target these particular chemicals, receptors, and genetic alterations (12). While some targeted medicines target overexpressed proteins like HER2, others aim to inhibit hormone receptors (such those for oestrogen or progesterone). Human epidermal growth factor receptor 2, or HER2, is a protein involved in controlling cell division and growth. The HER2 gene is overexpressed or amplified in certain breast tumours, which results in a higher HER2 protein production (13, 14). Since HER2 overexpression is linked to more aggressive tumour growth and a worse prognosis, HER2-positive breast cancer is a crucial target for breast cancer treatment. By focussing on HER2, treatment results can be enhanced and the cancer's growth slowed down. The HER2 (human epidermal growth factor receptor 2) protein is frequently employed as a target protein in molecular docking studies, particularly when examining the binding of possible ligands or therapeutic molecules (15, 16). One protein involved in controlling cell division and proliferation is called HER2 (17). The HER2 gene is overexpressed or amplified in certain breast tumours, which results in a higher HER2 protein production (11). Since HER2 overexpression is linked to more aggressive tumour growth and a worse prognosis, HER2-positive breast cancer is a crucial target for breast cancer treatment. By focussing on HER2, treatment results can be enhanced and the cancer's growth slowed down. The HER2 (human epidermal growth factor receptor 2) protein is frequently employed as a target protein in molecular docking studies, particularly when examining the binding of possible ligands or therapeutic molecules (18).

Long before the majority of modern medications were discovered, herbal treatments were utilised for millennia to cure a variety of illnesses. Consequently, herbal medicines are thought to be more culturally acceptable and to have fewer negative and antagonistic effects (19). Remarkably, drugs derived from plants are acknowledged as one of the most attractive sources of innovative treatments, showing promise in the treatment of a number of illnesses, including cancer. In the literature from throughout the world, a number of possible medicinal plants for

the treatment of peptic ulcers have been investigated and reported (20). A common technique for drug design prediction and confirmation is the in-silico approach. (20) Through Insilco research, this study makes use of Caasia tora's potential to inhibit HER2, one of the target proteins for breast cancer.

MATERIALS AND METHODS

Ligand preparation: The study made use of hundreds of phytochemicals that were extracted from the Cassia tora plant and published in the literature. The process used to prepare the ligand was similar to that described in our earlier published work (21). The PubChem database (www.pubchem.ncbi.nlm.nih.gov) provided the three-dimensional structures of the phytochemicals found in the identified plants in SDF format. Pyrex-Open Babel software was used to minimise and convert the structures to PDBQT.

Protein target preparation: The process used to prepare the protein was likewise comparable to that described in our earlier published work (22). The Protein Data Bank (https://www.rcsb.org) provided the human epidermal growth factor protein 2 (HER2) PDB structure (PDB ID: 3PP0). The protein molecule was stripped of all heteroatoms using UCF Chimaera (Version 1. 12).

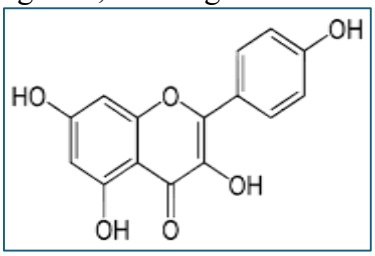
Molecular docking: Potential inhibitors of the HER2 (3pp0) protein were identified via structural-based virtual screening (23, 24). Prior to the docking process, the scoring and docking functions were verified. For additional research, phytochemicals that interacted with the residues of the 3pp0 catalytic site were chosen.

Procedure for post docking analysis: In order to perform post molecular docking analysis, the appropriate models of the ligands that bound to the 3pp0 protein's active site were re-docked using UCF Chimaera (Version 1. 12). This produced the protein-ligands complex, and the compounds that interacted with the 3pp0's key catalytic residues were then taken into consideration for post-docking studies using Discovery Studio (Version 2.0) to investigate the interactions between the proteins and ligands (25, 26, 27).

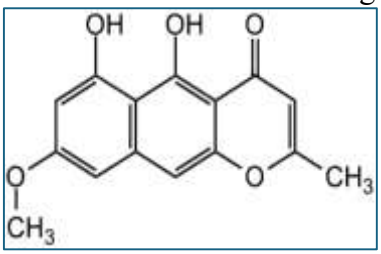
ADMET analysis: The method employed here is taken directly from our previously published work (28) The ADMETSAR (http://lmmd.ecust.edu.cn/admetsar2/) and Swiss ADME (www.swissadme.ch) servers were used to investigate the phytocompounds' toxicological and metabolic characteristics. The relevant values of the ADMET (absorption, distribution, metabolism, excretion, and toxicity) were estimated using the phytocompounds' canonical grins (29–30).

RESULTS AND DISCUSSION

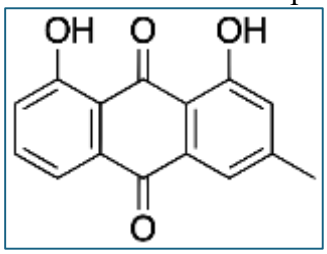
Molecular docking analysis: Fig. 2 displays the chemical structures of the chosen ligands. The medicinal plants used for the study are the source of these ligands. According to Table 1 and Figure 2, these ligands do in fact exhibit believable binding affinities to the HER2 protein.



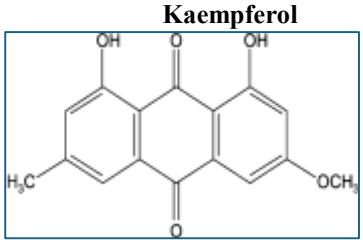
Kaempferol



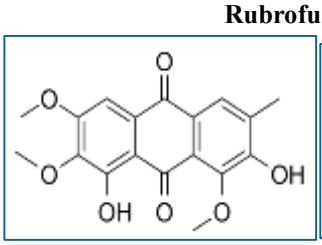
Rubrofusarin



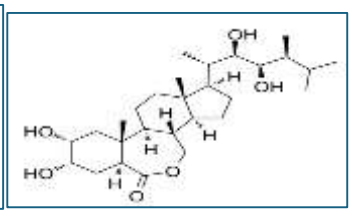
Crysophanol



Physcion



Obtusin



Brassinolide

Figure 1: Structures of the Bioactive Compound Of Cassia Tora

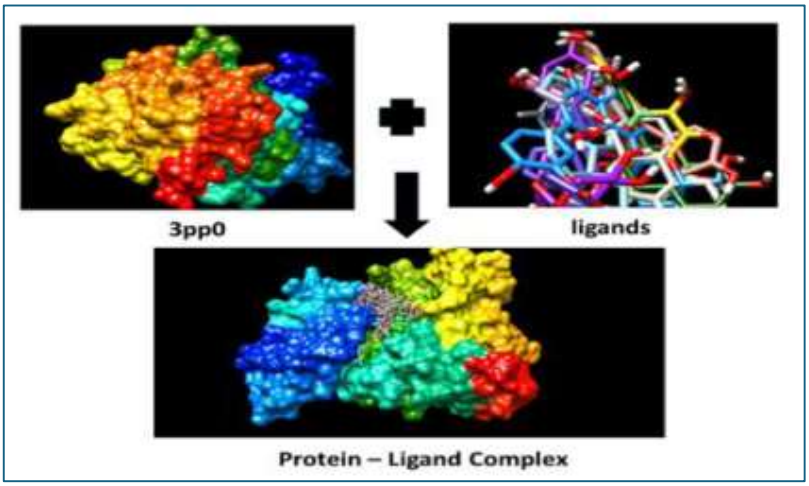


Figure 2. Protein – Ligands' Complex

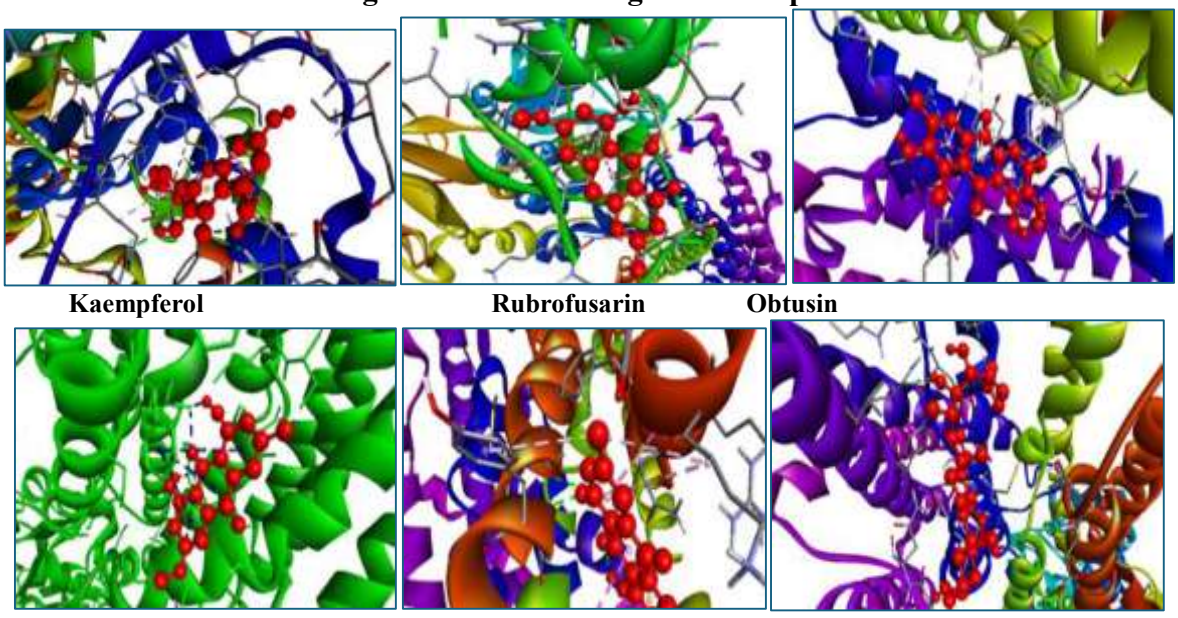


Figure 3: Depiction of HER2 (3PP0) -ligands' interactions complexes

Technically, a ligand and a protein target connect physically during molecular docking. As seen in Fig. 2, the chosen ligands in this investigation formed a protein-ligand complex by effectively and successfully bonding to the HER2 active site. When compared to the standard molecule Lapatinib, the amino acid residues Leu726, Val734, Ala751, Lys753, Thr798, Gly804, Arg849, Leu852, Thr862, and Asp863 were found to interact often. Molecular docking results usually include protein-ligand interactions, root mean square deviations (RMSD), and binding scores. Table 1 displays the protein-ligand interactions and binding scores. Fig. 3 also displays the degree of interactions that demonstrate the particular bonding between the ligands and the HER2 amino acid residue.

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

Compound name	PubChem CID	Binding score (kcal/mol)	Hydrogen bond interaction	Other interactions
Kaempferol	10134	-8.7	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

Rubrofusarin	22543	-6.3	A Asp 863, Met 901	Bryophyllin 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
Obtusin	32056	-5.9	Ser 728, Arg 849, Asn 850	Ala 730, Arg 756, Asp 845, Gly 729, Lys 798, Phe 731
Physcion	43128	-5.2	Asp 863, Met 801	Glu 770, Lys 753, Asn 850, Leu 726, Leu 785, Gln 799
Crysophanol	528532	-4.5	Gly 787, Leu 786	Leu 715, Leu 726, Leu 796, Ile 752, Thr 798, Val 750
Brassinolide	528532	-5.8	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

Analysis of root mean square deviation (rmsd) The structural similarity or difference between two molecular structures, usually a reference (in this case, the initial ligand conformation in the crystal structure 3pp0) and the docked ligand conformations, is measured by the Root Mean Square Deviation (RMSD). The ligands' RMSD values are shown in Table 2. A more accurate docking result is suggested by lower RMSD values, which show a tighter structural match between the reference and projected structures.

The docked conformations of the six ligands—Kaempferol, Rubrofusarin, Obtusin, Physcion, Crysophanol, and Brassinolide—are being compared to the reference structure of 3pp0. Following docking, the ligand's structure deviates from the initial crystallographic structure of 3pp0, as indicated by the RMSD values. The docked ligand conformations fall within an acceptable range of structural similarity to the reference structure (3pp0), according to RMSD values within the lower and upper bounds.

Although Obtusin, Physcion, Crysophanol, and Brassinolide have shown particularly encouraging results in terms of structural similarity, these RMSD values generally imply that the molecular docking simulations for these ligands against 3pp0 have produced conformations that closely resemble the crystallographic structure. To make more firm judgements regarding the binding affinities and biological significance of these ligand-protein complexes, additional verification and investigation are required, including taking binding energy and particular interactions into account.

Table 2. RMSD analysis data of phytoconstituents

S. No.	Compound name	RMSD (Å) (Upper boundary)	RMSD (Å) (Lower boundary)
1	Kaempferol	5.0675	2.493
2	Rubrofusarin	4.798	3.298
3	Obtusin	5.813	3.501
4	Physcion	6.985	1.711
5	Crysophanol	6.533	1.854
6	Brassinolide	3.654	1.656

Drug-likeness properties and ADMET screening: The inherent qualities that the ligands exhibit during molecular docking and ADMET screening are referred to as drug-likeness attributes. This characteristic includes the connection between a ligand's size, content, bonding chemistry, and chemical structure with the HER2 protein. Successful pharmacokinetic analyses of Cassia tora was performed, and the outcomes are shown in Table 3-4.

Table 3. Structural properties of phytoconstituents

Ligand	Molecular formulae	MW (g/mol)	Heavy atoms	Aromatic	Rotatable bonds	H-Bond acceptors	H-Bond donors
Kaempferol	$C_{15}H_{10}O_6$	286.23	21	12	1	**5**	3
Rubrofusarin	$C_{15}H_{12}O_5$	272.25	20	17	1	5	3
Obtusin	$C_{18}H_{16}O_7$	344.3	24	14	2	4	4
Physcion	$C_{16}H_{12}O_5$	284.26	19	11	0	4	3
Crysophanol	$C_{15}H_{10}O_4$	254.2	15	9	1	3	1
Brassinolide	$C_{28}H_{48}O_6$	480.686	34	6	2	7	2

Predicted structural characteristics included the number of heavy atoms, rotatable bonds, and hydrogen donors and acceptors. The most effective drug-like compounds are filtered using parameters such molecular weights, heavy atoms, number of aromatic rings, rotatable bonds, hydrogen bond donors, and hydrogen bond acceptors. The results are shown in Table 3. Heavy atoms in drug compounds can affect pharmacokinetics, physicochemical characteristics, and drug-target interactions, among other aspects of drug discovery. Increased molecular weight, hydrophobic interactions, electronic effects, metabolism and clearance, radiolabeling, and imaging are some of the main consequences of heavy atoms in drug development. Small molecular weights are another characteristic of molecules that are thought to be druglike. Compounds with molecular weights more than 500 g/mol are classified as large molecular weights. The various molecular weight prediction scores of the substances under investigation are shown in Table 3. The molecular weight of zero compounds is less than 500 g/mol. This demonstrates the exceptional drug-like qualities of every ligand. Four ligands have hydrogen bond acceptors above five, but all ligands have hydrogen bond donors below five. Because of their distinct chemical characteristics and interactions with biological targets, aromatic rings are essential to the drug discovery process. Additionally, aromatic rings improve metabolic stability, lipophilicity, target selectivity, and binding interactions. Table 3 shows the expected number of aromatic rings in each chemical.

The parameters for the ligands' absorption, distribution, metabolism, and excretion (ADME) characteristics are shown in Table 4. Ali solubility is the solubility parameter that describes a substance's solubility characteristics by taking into account its hydrogen bonding, polar, and dispersion forces. Because it has a direct impact on a compound's bioavailability, formulation development, and overall efficacy, solubility is a crucial consideration in drug research. According to Table 4's results, four ligands are soluble, three are moderately soluble, one is poorly soluble, and none are insoluble. This demonstrates that the majority of these chemicals have exceptional universal solubility. The brain and central nervous system (CNS) are separated from the blood circulation by the extremely selective blood-brain barrier (BBB). Although it is essential for shielding the brain from dangerous compounds, it presents a problem for the creation and discovery of new drugs. Five ligands exhibit outstanding BBB qualities, according to the results, whereas only one ligand deviates from BBB predictions (Table 4).

Table 4. ADME properties of phytoconstituents

Ligand	GI absorption	BBB permeant	Pgp substrate	Bioavailability score	Lead-likeness #violations	Ali solubility	Synthetic accessibility
Kaempferol	High	No	No	0.17	0	Moderately soluble	2.76
Rubrofusarin	High	Yes	Yes	0.45	1	Moderately soluble Soluble	5.11
Obtusin	High	No	N0	0.57	0	Soluble	3.32

Physcion	High	Yes	No	0.34	1	Moderately soluble	2.69
Crysophanol	High	Yes	No	0.51	1	Soluble	2.56
Brassinolide	High	No	No	0.51	1	Soluble	3.11

In the context of drug discovery, the term "lead-likeness" describes the collection of traits and attributes that are frequently connected to promising therapeutic candidates. These characteristics serve as a guide for determining whether a chemical is suitable for additional research as a possible therapeutic candidate. According to the results, only one ligand exhibits good lead-likeness property, whereas five ligands exhibit exceptional lead-likeness property (Table 4). Since it establishes how much a drug is absorbed from the gastrointestinal system into the bloodstream, gastrointestinal (GI) absorption is a crucial consideration in drug discovery. A drug's bioavailability and therapeutic efficacy can be strongly impacted by the effectiveness of GI absorption. The findings indicate that all of the ligands exhibit high GI absorption properties, but only one exhibits low GI absorption properties (Table 4). The percentage of a drug's prescribed dose that enters the systemic circulation, or bioavailability, is directly impacted by GI absorption. A better bioavailability, which results in a higher concentration of the medication available for distribution to target tissues, is ensured by efficient GI absorption. Low bioavailability due to poor GI absorption may require bigger dosages or different modes of administration in order to reach therapeutic levels. A membrane transporter protein called P-glycoprotein (P-gp) is essential for the distribution, absorption, and excretion of drugs. It can affect the pharmacokinetics and therapeutic efficacy of several medications and is involved in their efflux. According to the results, four ligands exhibit exceptional P-gp characteristics. All ligands exhibit bioavailability values less than 1, which translates to an excellent range for bioavailability properties, according to the results (Table 4). In drug discovery, the term "synthetic accessibility" refers to the simplicity and effectiveness of creating a chemical molecule. It is essential for assessing the viability and practicality of creating a medication candidate. The study's values fall within the permitted range of 1–10, according to the results (Table 4).

Table 5. Toxicological properties of phytoconstituents

Ligand	Carcinogenicity	Acute oral toxicity	Plasma protein binding	Water solubility
Kaempferol	NA	III	1.09	-2.77
Rubrofusarin	NA	I	1.05	-4.653
Obtusin	NA	IV	1.01	-3.112
Physcion	NA	III	1.06	-3.066
Crysophanol	NA	III	1.21	-4.326
Brassinolide	NA	II	1.02	-2.871

One crucial component of evaluating the safety of possible medication candidates is determining their carcinogenicity. The term "carcinogenicity" describes a substance's capacity to cause cancer. Extensive research is done to evaluate the possible carcinogenic effects of substances during the drug development process. Animal research, epidemiological data analysis, and in vitro testing are frequently used in these investigations. Every ligand in this investigation exhibits no carcinogenicity (Table 5). Because it evaluates a compound's possible negative effects when taken orally, acute oral toxicity is an important factor in drug research. It helps direct decision-making during preclinical development and offers crucial information about a medication candidate's safety profile. There are four categories for oral acute toxicity:

severe, moderate, minor, and non-toxic. One ligand is benign, two are moderately hazardous, four are slightly toxic, and one exhibits high toxicity (Table 5). The pharmacokinetics, formulation, and overall therapeutic efficacy of a medication can all be greatly impacted by its water solubility, making it a crucial characteristic in drug research and development. There is a strong correlation between the water solubility and Ali solubility values (Table 5). Because it influences a medication's pharmacokinetics, distribution, and effectiveness in the body, plasma protein binding is an important consideration in drug discovery and development. The majority of the compounds had exceptional plasma protein binding capabilities, according to the results.

CONCLUSION

When predicting and verifying the composition of a therapeutic candidate made from Cassia tora as an anti-cancer agent, the molecular docking simulation is incredibly helpful. Even though kaempferol interacted with the residue, it showed a strong inhibitory effect. The substances that have an anti-cancer effect bind to the receptor with the lowest binding energy and bind as native ligands. As a result, Cassia tora's kaempferol produces the optimal ligand-receptor complex configuration. To sum up, this molecular docking study offers important information on possible ligands for HER2 targeting. To confirm these results, more investigation and testing are necessary.

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