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Dimocarpus longan phytocompounds possess anticancer activity by specifically targeting breast cancer biomarkers via computational biology tools

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***Abstract*---**Worldwide, breast cancer (BC) is the most common cancer among women. Natural plant compounds with anticancer potential can block BC biomarkers, but they must be chosen carefully to avoid adverse side effects. In this research, the interaction between the BC biomarkers and plant compounds from Dimocarpus Longan was studied using a molecular docking approach. Twenty plant constituents from longan and two target proteins considered involved in BC (1ERR: Estrogen receptor and 3D90: Progesterone receptor) were obtained from the PubChem database and RCSB Protein Data Bank (PDB) respectively. They were docked using the SwissDock server. Then, the drug-likeness of the plant compounds that demonstrated interaction was evaluated. The results show that 1ERR and 3D90 had the lowest binding affinity with the L-epicatechin at the value of -9.5 and -8.3 kcal/mol respectively. These proteins had the most stable interaction with their plant compounds. The toxicity prediction analysis revealed that L-epicatechin is not safe to use as a drug due to AMES toxicity. All of the ten compounds had low binding scores, indicating that they had good interactions. Therefore, α-terpineol was chosen to use as a safe drug. The findings of this study should aid pharmaceutical researchers in identifying longan-based medications.

***Keywords*---**breast cancer biomarkers, dimocarpus longan, docking, toxicity, binding affinity.

Introduction

Breast cancer is the most frequent cancer among women with an estimated 1.67 million new cases reported each year. It is the most common cancer in women both in more and also less developed regions whereas in less developed regions are reported to have slightly more cases compared to more developed regions. Breast cancer also ranks as the fifth cause of death from cancer overall (522,000 deaths). Based on the Section of Cancer Surveillance, World Health Organization (WHO, (2015) even though breast cancer is the most frequent cause of cancer death among women in less developed regions (324,000 deaths, 14.3% of total), it is now also the second cause of cancer death even in more developed regions (198,000 deaths, 15.4%) (GLOBOCAN, 2019; Tsu *et al.*, 2013; WHO, 2020; Nordqvist, 2017). While tremendous strides have been made in the diagnosis and management of cancer growth, there are still major gaps and scope for development. Perhaps, there are a variety of unwanted harmful consequences during chemotherapy. Natural treatments can eliminate harmful negative impacts, such as the use of plant-derived products in cancer care. A few herbal drugs are has been used to cure cancer.

Dimocarpus Longan belongs to Sapindaceae family. The most common name for *Dimocarpus Longan* is longan. The longan fruit is native to southern China, in the provinces of Kwangtung, Kwangsi, Schezwan and Fukien (Morton and Miami, 1987) which can be found between an elevation of 500 and 1,500 ft (150-450m). The longan tree is commonly grown in former Indochina (Thailand, Cambodia, Laos, Vietnam, and Taiwan). Longan trees also grow in Malaysia and the Philippines (Morton and Miami, 1987). Polysaccharides, flavonoids, alkaloids, and carotenoids are the principal functional metabolites in longan fruit, which have great nutritional and therapeutic properties. Longan has pharmaceutical properties such as anti-oxidative, anti-obesity, anticancer, anti-aging, anti-tyrosinase, anti- immunomodulatory, anti-anxiety and anti-bacterial activities. It also prevents chronic diseases such as diabetes, hypertension, cardiovascular-related diseases, kidney-related diseases, etc. Longan fruit plays roles in enhancing memory, promoting blood metabolism, relieving insomnia, preventing amnesia, neuroprotection, digestion, strengthening up the body immune system, etc (Shahrajabian *et al.*, 2019; Yi *et al.*, 2015; Hsu *et al.*, 1985; Lin *et al.*, 2012).

Bioinformatics tools such as molecular modeling, dynamics simulation, docking, pharmacokinetics and toxicity studies aid in developing substrate-based drugs (SBD) and comprehending the protein-protein interaction between cancer cell line protein (target protein) and plant compound (ligand). To establish the interactive effects among phytochemicals and the subsequent targets, the structure-based strategy depends on established structural details. Unique ligands could be logically designed to provoke medicinal benefits, getting the benefit of the three-dimensional structure of the proteins. By identifying and improving the initial lead molecules, SBD may also offer crucial research into potential drug design and production. In order to control particular cellular behaviors, the high-affinity ligand selectively controls approved drug targets, finally producing the desired pharmacological and therapeutic results (Suhaibun *et al.*, 2020; Yu and MacKerell, 2017). According to Elengoe and Loganathan study (2021), it has been demonstrated that retinoblastoma (Rb) was docked successfully with ferulic acid

(PubChem ID: 445858) and quercetin (PubChem ID: 5280343), respectively, using the SwissDock server. Rb had the best binding affinity with ferulic acid (-6.6 kcal/mol) and quercetin (-7.8 kcal/mol). Based on Pharm *et al.*, (2021) study, it has been reported that Withanone and withaferin A from the plant extract of Withania somnifera show the best binding affinity with the target protein, PDB ID: 3N8E (mortalin). Autodock 4.2.6 was used to study the interaction between the plant compounds and target protein. Zubair and his colleagues (2016) carried out a study on molecular docking between 62 plant constituents from Begonia plant species and EGFR-TK (target protein) using computational biology tools such as open babel, SPORES, and PLANTS1.2 software under Fedora Linux operation system. The results show that cyanidin 3-(6"-(Z)-p-coumarylsophoroside) (phyto-compound) had the lowest binding energy with the EGFR-TK at the value of -120.2330. In this research, the interaction between the breast cancer biomarkers such as estrogen receptor (ER) and progesterone receptor (PR) and the twenty phytochemicals from the longan plant was studied using molecular docking, pharmacokinetics and toxicity analysis tools.

Materials and Methods

Search of Phytocompound/ligand

Plant compounds were used as ligands. They were identified via a literature review search. The literature review was performed using different types of electronic databases such as Google Scholar, Science Direct, Elsevier, etc. The phytoconstituents were retrieved based on their medicinal activities in humans. Twenty phytocompounds were then selected and the three-dimensional structures of the selected phytocompounds were retrieved from the PubChem database in sdf format (Kim *et al.*, 2016).

Preparation of Ligand

The retrieved twenty plant compounds (neohesperidin, hesperetin 5-O-glucoside, nobiletin, diosmin, avicularin, nicotiflorin, isotrifoliin, biorobin, spiraeoside, L-epicatechin, piperidine, α-terpineol, lysopc 18:1, o-phosphocholine, betaine, ellagic acid, procyanidin A2, L-glutamic acid, L-aspartic acid and citric acid) in sdf format from the PubChem database; were prepared using the DS 4.0 'Prepare 'ligand' technique, which deleted duplicates, counted tautomers/isomers, inserted hydrogen bonds, and minimized energy using the CHARMm force field (Chemistry at Harvard Macromolecular Mechanics) (Brooks *et al.*, 2009). Retrieved ligands are screened using Lipinski's Rule of Five which provides a standardized requirement or criteria that a ligand should pass in order to be suitable for drugs design. It establishes criteria for drug-like qualities and focuses on medication bioavailability (Lipinski, 2004; Veber *et al.*, 2002; Jagtap *et al.*, 2020). The requirement for a ligand to pass in order for it to be suitable for drugs will be screened on the basis of molecular weight should be equal or less than 500 daltons (MW ≤500 daltons), the number of hydrogen bond donors should be equal or less than 5 (HBD ≤5), the number of hydrogen bond acceptors should be equal or less than 10 (HBA ≤10), number of rotatable bonds should be equal or less than 10 (RB ≤10) and lop value should be equal or less than 5 (LogP ≤5) and polar surface area (PSA≤140Å^2) (Rodrigues *et al.*, 2020; Tantawy *et al.*, 2020;

Govindharaj *et al.* 2020). These ligands are screened to prepare for molecular docking with breast cancer target proteins.

Identification and Retrieval of Breast Cancer Target Proteins

The most common molecular target proteins (ER and PR) which play a vital role in breast cancer metastasis were chosen from the Therapeutic Target Database (TTD- and Potential Drug Target Database (PDTD) for the aim of molecular docking analysis. The three-dimensional (3D) models of target proteins (1ERR (ER) and 3D90 (PR) were obtained from RCSB Protein Data Bank (PDB) and downloaded in pdb format (Berman *et al.*, 2003). Both 3D target protein models were publicly available. They were chosen based on the presence of one or more active sites for docking with plant compounds/ligands. They should contain a high count of active site residues.

Preparation of Target Proteins and Identification of Active Sites

The selected target proteins were prepared using the DS 4.0 'Prepare protein' technique, which deleted duplicates, counted tautomers/isomers, and inserted hydrogen bonds. To obtain a strong binding affinity of our compound, the active site of the protein has been determined by DS Visualizer. It also searched for the poseview molecular interactions between the crystal structure of target protein and inhibitor which are displayed in PDB (Berman *et al.*, 2003). A grid box was developed to cover the selected protein-binding site and to permit the ligand to move freely. It also included all the important functional residues.

Molecular Docking

The docking of the target protein with its relevant phyto-component was performed using SwissDock (Grosdidier *et al.*, 2011). The model of the target protein-phyto-component complex was viewed using DS 4.0. The binding energy, number of hydrogen bonds and hydrogen bond distance between the target protein and phyto-component were recorded (Parmar *et al.*, 2021; Alam *et al.*, 2021; Ikwu *et al.*, 2020; Aggarwal and Verma, 2020).

Prediction of Pharmacokinetic (PK) Properties Docking

The computational biology tool ADME descriptors assist in the estimation of pharmacokinetic parameters and the assessment of molecular quality based on drug absorption, distribution, metabolism, and excretion. When administered simultaneously, the intensity and time course of PK (ADME) qualities determine the flow of drugs into, through, and out of the body. This technique reduces the cost of new medication development as well as the risk of clinical failure. In the early stages of medication research, pharmacokinetic factors help to identify the integrity and efficacy of plant components. The early-stage pharmacokinetics features of the ten screened plant substances in this research investigation were assessed using the SwissADME server (Daina *et al.*, 2017). It's a free web-based server tool that can help you figure out the pharmacokinetics and drug-like properties of tiny molecules like plant constituents.

Prediction of toxicity

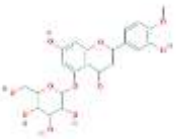
The toxicity of a substance can be evaluated by measuring the chemical substance degree of toxicity in humans or animals and the potential risk that may pose harmful effects that will risk damage to an organ. Therefore, toxicity prediction is a vital step in the drug design process before undergoing drug-trial. In this study, the prediction of toxicity was evaluated using AdmetSAR 2.0 web-based server (Yang *et al.*, 2019).

Results and Discussions

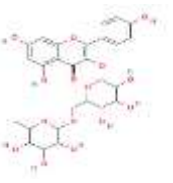
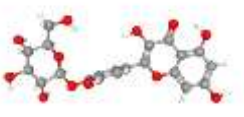
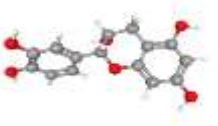
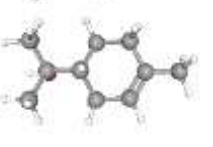
Obtain Plant Compounds of Dimorcarpus Longan

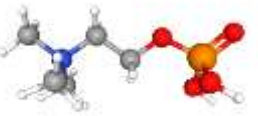
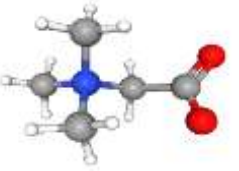
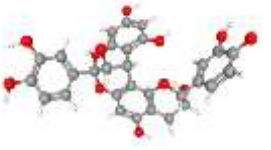
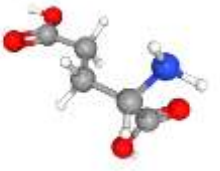
The phytocompounds of *Dimorcarpus Longan* obtained from the PubChem database were shown in Table 1. They were saved in 3D format. Each of the phytocompound varies in molecular weight.

Table 1
Phytocompounds of *Dimorcarpus Longan* retrieved from the PubChem

No	PubChem ID	Bioactive Compound	Chemical Formula	Molecular Weight (Dalton)	3D Structure
1	442439	Neohesperidin	$C_{28}H_{34}O_{15}$	610.6	
2	18625123	Hesperetin 5-O-glucoside	$C_{22}H_{24}O_{11}$	464.4	
3	72344	Nobiletin	$C_{21}H_{22}O_8$	402.4	
4	5281613	Diosmin	$C_{28}H_{32}O_{15}$	608.5	

14394

5	5490064	Avicularin	$C_{20}H_{18}O_{11}$	434.3	
6	5318767	Nicotiflorin	$C_{27}H_{30}O_{15}$	594.5	
7	5280804	Isotrifoliin	$C_{21}H_{20}O_{12}$	464.4	
8	12313332	Biorobin	$C_{27}H_{30}O_{15}$	594.5	
9	5320844	Spiraeoside	$C_{21}H_{20}O_{12}$	464.4	
10	72276	L-Epicatechin	$C_{15}H_{14}O_6$	290.27	
11	8082	Piperidine	$C_5H_{11}N$	85.15	
12	442501	α-Terpineol	$C_{10}H_{18}O$	154.25	
13	53480465	LysoPC 18:1	$C_{26}H_{52}NO_7P$	521.7	

14	1014	O-Phosphocholine	$C_5H_{15}NO_4P$	184.15	
15	247	Betaine	$C_5H_{11}NO_2$	117.15	
16	5281855	Ellagic acid	$C_{14}H_6O_8$	302.19	
17	124025	Procyanidin A2	$C_{30}H_{24}O_{12}$	576.5	
18	33032	L-Glutamic acid	$C_5H_9NO_4$	147.13	
19	5960	L-Aspartic acid	$C_4H_7NO_4$	133.1	
20	311	Citric acid	$C_6H_8O_7$	192.12	

Identification and Retrieval of Breast Cancer Target Proteins

The two most important target proteins (ER and PR) in breast cancer metastasis were identified from the PDTD and TTD databases. The 3D structures of target proteins were obtained from the RCSB PDB web server including PDB-ID: 1ERR (ER) and PDB-ID: 3D90 (PR). The server provides the x-ray crystallographic structure of the retrieved proteins. In addition, the presence of an active site for

each retrieved protein was considered for molecular docking with selected phytocompounds.

Phytocomponents Screening and Pharmacokinetics (PK) Analysis

Selected phytocomponents (ligands) obtained from the PubChem database was screened using Lipinski's Rule of 5. In drug discovery, Lipinski's Rule of 5 can predict the ability and strength of absorption and permeation. According to the Rule of 5, poor absorption and permeation are more likely when there are more than 5 hydrogen bond donors (HBD ≤5), 10 hydrogen bond acceptors (HBA ≤10), the molecular weight is greater than 500 (MW ≤500 daltons), and if the calculated Log P is greater than 5 (LogP ≤5). Based on this set of standards, the pharmacokinetics evaluation of the selected ligands/phytocompounds was performed. Out of the twenty ligands that were screened, ten ligands (nobiletin, L-epicatechin, piperidine, α-terpineol, O-phosphocholine, betaine, ellagic acid, L-glutamic acid, L-aspartic acid, and citric acid) pass the evaluation test. The ten selected ligands show no violation towards Lipinski's Rule of 5 where these ligands have less than 5 hydrogen bond donors, less than 10 hydrogen bond acceptors, the molecular weight of less than 500 and calculated Log P is less than 5 which indicates that these compounds have good absorption and permeation which possess the chemical and physical properties to be orally active drugs and is able to proceed for docking. The other ten ligands (neohesperidin, hesperetin 5-O-glucoside, diosmin, avicularin, nicotiflorin, isotrifoliin, biorobin, spiraeoside, lysoPC 18:1, and procyanidin A2) shows violation towards the Lipinski's Rule of 5. These ligands violated at least one of Lipinski's Rule of 5. The list of pharmacokinetics properties of the selected ligands was shown in Table 2 where ligands that have violated the Rule of 5 were highlighted in grey while the one that passes the Rule of 5 was highlighted in white.

Table 2
List of pharmacokinetics properties, molecular weight (MW), hydrogen bond donor (HBD), hydrogen bond acceptor (HBA), partitioning coefficient (LogP), number of rotatable bond (RB), number of heavy atoms, number of aromatic heavy atoms, polar surface area (PSA), synthetic accessibility (SA), gastrointestinal (GI) absorption, and Lipinski's Rule of 5 of all plant compounds

Bioactive Compound	PubChem ID	MW (≤500)	HBD (≤5)	HBA (≤10)	LogP (≤5)	RB (≤10)	No. of Heavy Atoms	No. of Arom. Heavy Atoms	PSA (<140 A^2)	SA	GI	LR
Neohesperidin	442439	610.6	8	15	2.57	7	43	12	234.29	Moderate	Low	NO
Hesperetin 5-O-glucoside	18625123	464.4	6	11	1.88	5	33	12	175.37	Moderate	Low	NO
Nobiletin	72344	402.4	0	8	3	7	29	16	85.59	Easy	High	YES
Diosmin	5281613	608.5	8	15	3.05	7	43	16	238.20	Moderate	Low	NO
Avicularin	5490064	434.3	7	11	1.86	4	31	16	190.28	Moderate	Low	NO

Nicotiflorin	5318767	594.5	9	15	2.79	6	42	16	249.20	Moderate	Low	NO
Isotrifoliin	5280804	464.4	9	12	0.94	4	33	16	210.51	Moderate	Low	NO
Biorobin	12313332	594.5	9	15	2.79	6	42	16	249.20	Moderate	Low	NO
Spiraeoside	5320844	464.4	8	12	1.45	4	33	16	210.51	Moderate	Low	NO
L-Epicatechin	72276	290.27	5	6	1.47	1	21	12	110.38	Easy	High	YES
Piperidine	8082	85.15	1	1	1.70	0	6	0	12.03	Easy	Low	YES
α-Terpineol	442501	154.25	1	1	2.51	1	11	0	20.23	Easy	High	YES
LysoPC 18:1	53480465	521.7	1	7	0.59	25	35	0	114.93	Moderate	Low	NO
O-Phosphocholine	1014	184.15	2	4	-2.54	4	11	0	76.57	Easy	High	YES
Betaine	247	117.15	0	2	-2.19	2	8	0	40.13	Easy	Low	YES
Ellagic Acid	5281855	302.19	4	8	0.79	0	22	16	141.34	Easy	High	YES
Procyanidin A2	124025	576.5	9	12	1.80	2	42	24	209.76	Moderate	Low	NO
L-Glutamic Acid	33032	147.13	3	5	0.41	4	10	0	100.62	Easy	High	YES
L-Aspartic Acid	5960	133.1	3	5	-0.14	3	9	0	100.62	Easy	High	YES
Citric Acid	311	192.12	4	7	-1.49	5	13	0	132.13	Easy	Low	YES

Table 3
Binding affinity score between phytocompound and target protein (breast cancer marker protein)

Compound Name	Pubchem ID	1ERR	3D90
Nobiletin	72344	-6.7	-7.9
L-Epicatechin	72276	-9.5	-8.3
Piperidine	8082	-4.1	-4.2
α-Terpineol	442501	-6.0	-6.1
O-Phosphocholine	1014	-4.5	-4.8
Betaine	247	-3.8	-3.8
Ellagic Acid	5281855	-8.2	-8.0
L-Glutamic Acid	33032	-4.7	-4.9
L-Aspartic Acid	5960	-4.5	-5.0
Citric Acid	311	-5.2	-5.5

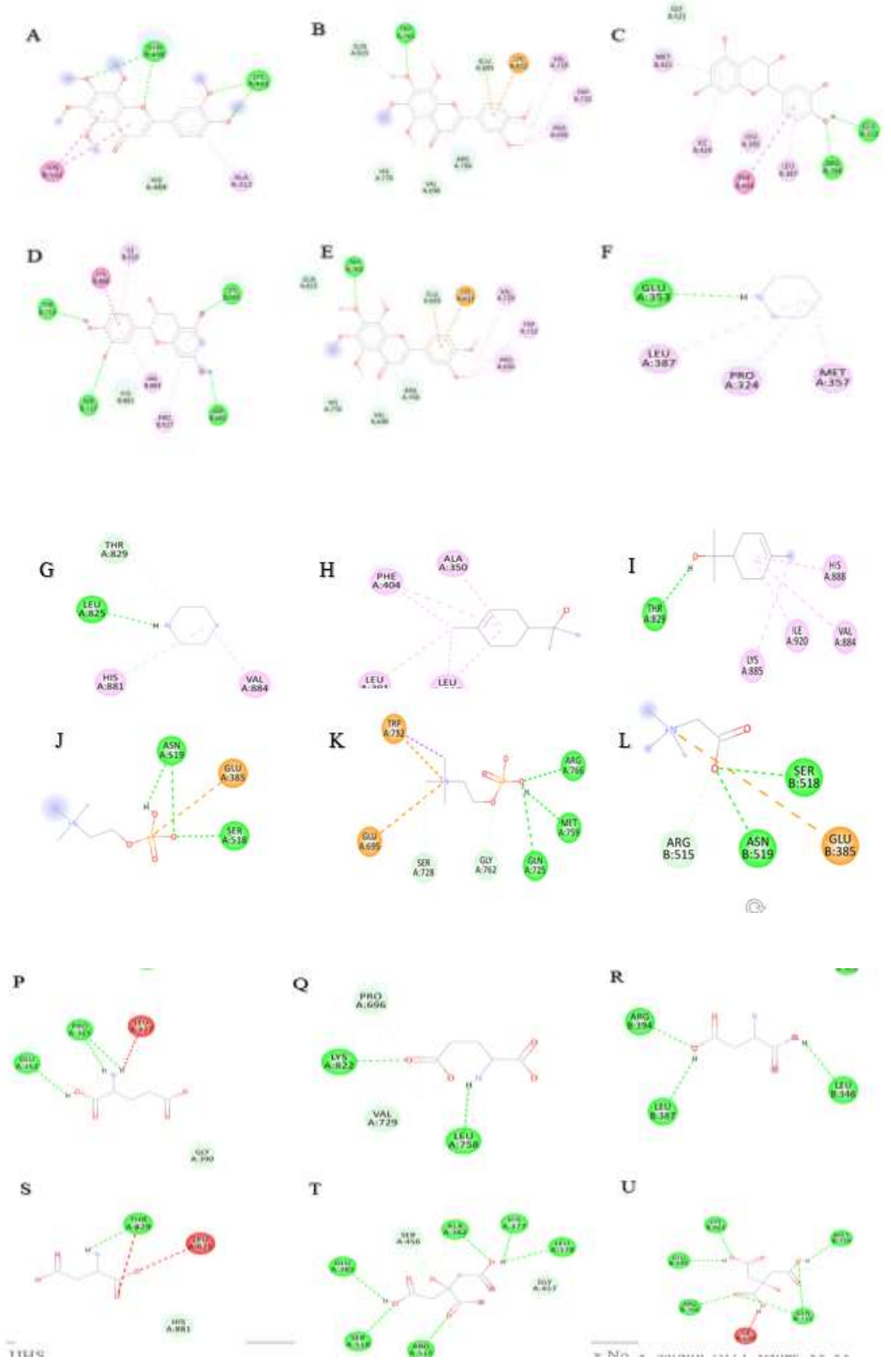

A
B
C
D
E
F
GLU A:353
LEU A:387
PRO A:324
MET A:357
G
THR A:829
LEU A:825
HIS A:881
VAL A:884
H
PHE A:404
ALA A:350
LEU
LEU
I
HIS A:888
THR A:829
ILE A:920
VAL A:884
LYS A:885
J
ASN A:519
GLU A:385
SER A:518
K
TRP A:732
ARG A:766
GLU A:695
MET A:759
SER A:728
GLY A:762
GLN A:725
L
SER B:518
ARG B:515
ASN B:519
GLU B:385
P
Q
PRO A:696
LYS A:822
VAL A:729
LEU A:756
R
ARG B:394
LEU B:347
LEU B:346
S
THR A:829
LEU A:825
HIS A:881
T
SER A:456
U

Figure 1. The interaction of 1ERR with (A) nobiletin, (C) L-epicatechin, (E) piperidine, (G) α-terpineol, (I) O-phosphocoline, (K) betaine, (M) ellagic acid,(O) L-glutamic acid, (Q) L-aspartic acid and (S) citric acid; interaction of 3D90 with (B) nobiletin, (D) L-epicatechin, (F) piperidine, (H) α-terpineol, (J) O-phosphocoline, (L) betaine, (N) ellagic acid,(P) L-glutamic acid, (R) L-aspartic acid and (T) citric acid

Table 4
List of hydrogen bond interactions between target proteins (1ERR and 3D90) and ligands (plant compounds)

Target protein	Ligand	Residues	Distance (Å)	Bond Category	Bond Type
1ERR	Nobiletin	GLN498	2.90	Hydrogen	Conventional Hydrogen
		GLN498	2.89	Hydrogen	Conventional Hydrogen
		LYS481	2.60	Hydrogen	Conventional Hydrogen
		LYS481	2.29	Hydrogen	Conventional Hydrogen
		LYS481	2.08	Hydrogen	Conventional Hydrogen
		LYS481	3.06	Hydrogen	Carbon Hydrogen
		HIS488	2.55	Hydrogen	Carbon Hydrogen
		ALA312	4.79	Hydrophobic	Pi-Alkyl
		HIS501	5.68	Hydrophobic	Pi-Pi T-shaped
		HIS501	5.26	Hydrophobic	Pi-Pi T-shaped
3D90	Nobiletin	TRP765	2.18	Hydrogen	Conventional Hydrogen
		GLN815	3.78	Hydrogen	Carbon Hydrogen
		HIS770	3.25	Hydrogen	Carbon Hydrogen
		VAL698	2.17	Hydrogen	Carbon Hydrogen
		ARG766	3.02	Hydrogen	Pi-Donor Hydrogen
		ARG766	5.09	Hydroponic	Pi-Alkyl
		ARG766	5.16	Hydrophobic	Pi-Alkyl
		GLU695	4.32	Hydrophobic	Pi-Anion
		GLU695	3.36	Hydrogen	Carbon Hydrogen
		LYS822	4.48	Hydrophobic	Pi-Cation
		VAL729	4.62	Hydrophobic	Alkyl
		TRP732	4.67	Hydrophobic	Pi-Alkyl
		TRP732	5.18	Hydrophobic	Pi-Alkyl
		PRO696	3.80	Hydrophobic	Alkyl
		PRO696	5.23	Hydrophobic	Pi-Alkyl
1ERR	L-epicatechin	GLU353	1.73	Hydrogen	Conventional Hydrogen
		ARG394	1.97	Hydrogen	Conventional

					Hydrogen
		GLY521	2.96	Hydrogen	Carbon Hydrogen
		PHE404	5.12	Hydrophobic	Pi-Pi T-shaped
		LEU387	4.47	Hydrophobic	Pi-Alkyl
		LEU391	4.72	Hydrophobic	Pi-Alkyl
		ILE424	4.60	Hydrophobic	Pi-Alkyl
		MET421	4.32	Hydrophobic	Pi-Alkyl
3D90	L-epicatechin	TYR753	2.42	Hydrogen	Conventional Hydrogen
		SER757	2.63	Hydrogen	Conventional Hydrogen
		ASP882	2.51	Hydrogen	Conventional Hydrogen
		LYS885	1.98	Hydrogen	Conventional Hydrogen
		LYS885	4.97	Hydrophobic	Pi-Alkyl
		HIS881	3.01	Hydrogen	Carbon Hydrogen
		HIS888	5.40	Hydrophobic	Pi-Pi T-shaped
		ILE920	5.14	Hydrophobic	Pi-Alkyl
		VAL884	5.17	Hydrophobic	Pi-Alkyl
		PRO927	5.03	Hydrophobic	Pi-Alkyl
1ERR	Piperidine	GLU353	2.67	Hydrogen	Conventional Hydrogen
		LEU387	5.48	Hydrophobic	Alkyl
		PRO324	4.50	Hydrophobic	Alkyl
		MET357	4.15	Hydrophobic	Alkyl
3D90	Piperidine	LEU825	2.33	Hydrogen	Conventional Hydrogen
		THR829	3.43	Hydrogen	Carbon Hydrogen
		HIS881	5.04	Hydrophobic	Pi-Alkyl
		VAL884	4.08	Hydrophobic	Alkyl
1ERR	α-Terpineol	ALA350	4.65	Hydrophobic	Alkyl
		PHE404	4.93	Hydrophobic	Pi-Alkyl
		PHE404	5.42	Hydrophobic	Pi-Alkyl
		LEU391	3.71	Hydrophobic	Alkyl
		LEU387	4.90	Hydrophobic	Alkyl
		LEU387	4.62	Hydrophobic	Alkyl
3D90	α-Terpineol	THR829	2.10	Hydrogen	Conventional Hydrogen
		LYS885	4.32	Hydrophobic	Alkyl
		ILE920	5.09	Hydrophobic	Alkyl
		VAL884	5.29	Hydrophobic	Alkyl
		HIS888	5.31	Hydrophobic	Pi-Alkyl
1ERR	O-Phosphocholine	ASN519	3.04	Hydrogen	Conventional Hydrogen
		ASN519	2.48	Hydrogen	Conventional Hydrogen
		GLU385	3.90	Hydrophobic	Attractive Charge
		SER518	1.97	Hydrogen	Conventional Hydrogen

3D90	O-Phosphocholine	ARG766	2.22	Hydrogen	Conventional Hydrogen
		MET759	2.18	Hydrogen	Conventional Hydrogen
		GLN725	2.88	Hydrogen	Conventional Hydrogen
		GLY762	2.28	Hydrogen	Carbon Hydrogen
		SER728	3.41	Hydrogen	Carbon Hydrogen
		GLU695	4.62	Hydrophobic	Attractive Charge
		TRP732	3.72	Hydrophobic	Pi-Sigma
		TRP732	4.95	Hydrophobic	Pi-Cation
1ERR	Betaine	SER518	2.69	Hydrogen	Conventional Hydrogen
		SER518	2.90	Hydrogen	Carbon Hydrogen
		GLU385	5.26	Hydrophobic	Attractive Charge
		ASN519	2.74	Hydrogen	Conventional Hydrogen
		ARG515	2.58	Hydrogen	Carbon Hydrogen
3D90	Betaine	GLN725	2.70	Hydrogen	Conventional Hydrogen
		GLN725	3.66	Hydrogen	Carbon Hydrogen
		SER728	3.76	Hydrogen	Carbon Hydrogen
		GLY762	3.04	Hydrogen	Carbon Hydrogen
		GLU695	5.14	Hydrophobic	Attractive Charge
1ERR	Ellagic acid	ARG394	2.63	Hydrogen	Conventional Hydrogen
		GLU353	1.86	Hydrogen	Conventional Hydrogen
		MET388	2.60	Hydrogen	Carbon Hydrogen
		MET388	4.98	Hydrophobic	Pi-Alkyl
		PHE404	5.32	Hydrophobic	Pi-Pi T-shaped
		PHE404	5.65	Hydrophobic	Pi-Pi T-shaped
		PHE404	4.95	Hydrophobic	Pi-Pi T-shaped
		LEU391	5.35	Hydrophobic	Pi-Alkyl
		LEU387	5.02	Hydrophobic	Pi-Alkyl
		MET421	5.40	Hydrophobic	Pi-Alkyl
		LEU346	5.38	Hydrophobic	Pi-Alkyl
		LEU346	4.50	Hydrophobic	Pi-Alkyl
		ALA350	5.05	Hydrophobic	Pi-Alkyl
		ALA350	5.00	Hydrophobic	Pi-Alkyl
3D90	Ellagic acid	ILE896	2.52	Hydrogen	Conventional Hydrogen
		SER898	2.98	Hydrogen	Conventional Hydrogen
		SER898	2.76	Hydrogen	Conventional Hydrogen
		PHE895	1.91	Hydrogen	Conventional Hydrogen
		SER898	2.46	Hydrogen	Conventional Hydrogen

		PHE905	2.75	Hydrogen	Conventional Hydrogen
		ARG899	2.97	Hydrogen	Carbon Hydrogen
		ARG899	5.10	Hydrophobic	Pi-Alkyl
		ARG899	5.01	Hydrophobic	Pi-Alkyl
		PHE895	4.59	Hydrophobic	Pi-Pi Stacked
		PHE895	5.61	Hydrophobic	Pi-Pi Stacked
		PHE895	4.87	Hydrophobic	Pi-Pi Stacked
1ERR	L-Glutamic acid	GLU353	2.26	Hydrogen	Conventional Hydrogen
		PRO325	2.57	Hydrogen	Conventional Hydrogen
		PRO325	2.43	Hydrogen	Conventional Hydrogen
		GLY390	2.68	Hydrogen	Carbon Hydrogen
		LEU327	2.35	Hydrophobic	Donor-Donor
3D90	L-Glutamic acid	LYS822	2.04	Hydrogen	Conventional Hydrogen
		LEU758	2.04	Hydrogen	Conventional Hydrogen
		VAL729	2.52	Hydrogen	Carbon Hydrogen
		PRO696	3.10	Hydrogen	Carbon Hydrogen
1ERR	L-Aspartic acid	ARG394	2.14	Hydrogen	Conventional Hydrogen
		LEU387	2.55	Hydrogen	Conventional Hydrogen
		LEU346	2.34	Hydrogen	Conventional Hydrogen
3D90	L-Aspartic acid	THR829	1.95	Hydrogen	Conventional Hydrogen
		THR829	2.93	Hydrophobic	Acceptor-Acceptor
		HIS881	3.00	Hydrogen	Carbon Hydrogen
		LEU825	2.78	Hydrophobic	Acceptor-Acceptor
1ERR	Citric acid	GLU385	2.86	Hydrogen	Conventional Hydrogen
		SER518	2.76	Hydrogen	Conventional Hydrogen
		SRG515	2.95	Hydrogen	Conventional Hydrogen
		ALA382	2.30	Hydrogen	Conventional Hydrogen
		ALA382	2.85	Hydrogen	Carbon Hydrogen
		HIS377	1.98	Hydrogen	Conventional Hydrogen
		LEU378	2.51	Hydrogen	Conventional Hydrogen
		SER456	2.53	Hydrogen	Carbon Hydrogen
		GLY457	2.70	Hydrogen	Carbon Hydrogen

3D90	Citric acid	GLN725	3.06	Hydrogen	Conventional Hydrogen
		GLN725	2.51	Hydrogen	Conventional Hydrogen
		ARG766	2.59	Hydrogen	Conventional Hydrogen
		GLU695	2.16	Hydrogen	Conventional Hydrogen
		LYS822	2.23	Hydrogen	Conventional Hydrogen
		MET759	2.54	Hydrogen	Conventional Hydrogen
		MET759	2.73	Hydrogen	Conventional Hydrogen
		ILE699	1.49	Hydrophobic	Donor-Donor

Docking Analysis

In this study, the interaction between the target protein (breast cancer marker protein) and ligand (plant compound) was determined using the SwissDock server. The best interaction was selected based on the lowest binding energy for each target protein-ligand complex because breast cancer marker protein had the most stable intermolecular interaction with the phytocomponent. 1ERR protein and 3D90 had the lowest binding affinity with the L-epicatechin (PubChem ID: 72276) at the value of -9.5 and -8.3 kcal/mol respectively (Table 3). 1ERR interacted with L-epicatechin at the residues ARG394, GLU353 and GLY521 through hydrogen bond lengths 1.97 Å, 1.73 Å and 2.96 Å respectively (Table 4). 3D90 had four hydrogen bonds with L-epicatechin at the residues TYR753, SER757, ASP882 and LYS885. The hydrogen bond lengths were 2.42 Å, 2.63 Å, 2.51 Å and 1.98 Å respectively.

Toxicity evaluation of plant compounds

By using AdmetSAR 2.0 web server, an *in silico* test for toxicity was performed on the chosen phytocompound to evaluate the negative effects that it may possess. Table 5 shows the result of drug-induced hERG toxicity, AMES toxicity, carcinogenicity (CGT), P-glycoprotein inhibitor (PGI), fish toxicity (FT), *Tetrahymena pyriformis* toxicity (TP), honeybee toxicity (HB), hepatotoxicity (HP), plasma protein binding (PPB), and rat lethal dose (LD_{50}) obtained from the server.

Table 5
Toxicity test on selected phytocompounds

Plant Compounds	hERG Toxicity	AMES Toxicity	CGT	PGI	FT	TP	HB	HP	PPB	RAT (LD_{50})
Betaine	NO	NO	NO	0.9838	NO	0.02	YES	NO	0.376	0.6371
Citric Acid	NO	NO	NO	0.9870	NO	-0.443	YES	NO	0.22	0.8407
Ellagic Acid	NO	NO	NO	0.9413	YES	1.664	NO	YES	0.993	0.6020
L-Aspartic Acid	NO	NO	NO	0.9874	NO	-0.593	NO	NO	0.194	0.5911
L-Epicatechin	NO	YES	NO	0.9411	NO	0.929	YES	NO	1.034	0.6433
L-Glutamic										

Acid	NO	NO	NO	0.9922	NO	-0.709	NO	NO	0.104	0.6349
Nobiletin	YES	NO	NO	0.9512	YES	0.865	YES	YES	1.055	0.6245
O-Phosphocholine	NO	NO	YES	0.9651	NO	0.28	YES	NO	0.658	0.5117
Piperidine	NO	NO	NO	0.9875	NO	-0.429	NO	NO	0.655	0.7407
α-Terpineol	NO	NO	NO	0.9843	YES	-0.468	YES	NO	0.652	0.6381

Based on the result obtained from *in silico* toxicity test of the selected plant compounds using AdmetSAR 2.0 web server, ellagic acid, L-epicatechin, nobiletin, and O-phosphocholine were identified to possess properties that may cause harmful effects to humans. Ellagic acid was identified to have hepatotoxicity which may cause harm to the liver. However, ellagic acid could still be used for drug design and by low dosage administration to reduce the harmful effects it may cause on the liver. O-phosphocholine was identified to have carcinogenicity properties and therefore this compound is not suitable for drug design since the compound has the ability and tendency to produce cancer. On the other hand, nobiletin was identified to possess hERG (human ether-à-go-go-related gene) toxicity and hepatotoxicity whereas according to Garrido *et al.*, 2020 study. hERG toxicity is one of the most frequent adverse side effects and may cause cardiac side effects to humans. Furthermore, L-epicatechin was identified to have Ames toxicity which is similar to carcinogens where it may cause cancer. Betaine, citric acid, L-aspartic acid, L-glutamic acid, piperidine and α-terpineol did not show any properties that may cause harmful effects to humans and therefore these compounds are suitable for drug design.

The advancement of technology enabled researchers to now have a new approach in drug design by applying and developing advance computational biology tools capable of storing, obtaining and interpreting complex biological data. Computational biology tools such as molecular dynamics simulation, molecular docking and molecular modeling are able to assist in generating 3D structure of protein structure and analyzing active sites of the specific protein to determine the protein-ligand complex interaction which is important to aid researchers to better understand the mechanisms of cancer target proteins and modulate the functions to eliminate cancer activities in humans. Scientists discovered that medicinal plants were the most effective cancer treatment. The new chemicals were identified and purified from the plant extracts. Plant chemicals have anticancer properties. As a result, in the substrate based drug design (SBDD) technique, plant molecules are employed as ligands. Drug design tools help plant chemicals enter the system biology era.

A study was conducted by Roy *et al.*, 2016 on garlic phytocompounds that possess anticancer activity by specifically targeting breast cancer biomarkers. There were twelve compounds (SACS, SAC, pCA, Phloroglucinol, Kaempferol, Isobutyl isothiocyanate, Quercetin, γGSAC, SAMC, FA, Taurine, Apigenin) from garlic that was successfully docked with the target protein and shows good interaction between phytocompound and target protein with binding energies ranging from -66.84 kcal/mol to -168.57 kcal/mol. Target protein and phytocompound interaction was formed through hydrogen bonds. Understanding this interaction will assist researchers in the development of the structure-based drug for cancer treatment.

Mani *et al.*, 2021 study stated that there is an urgent need to explore alternative therapies for the treatment of cancer that are safer with minimal side effects. Their study utilizes the natural anticancer properties contained in traditional medicinal herbs to formulate naturally-derived drugs. Molecular docking studies were conducted by studying the interaction between aloin which is a bioactive compound contained in aloe vera which is known to exhibit an anticancerous effect on different types of cancer and cancer biomarkers (eg. estrogen and progesterone receptors). The result of the study shows that aloin interaction is much better with estrogen receptor compared to progesterone receptor with the binding affinity of -8.0 kcal/mol. This indicates that aloin may become a potential anticancer treatment for breast cancer by targeting estrogen receptors.

Based on *in silico* study by Balogun *et al.*, 2021 on anticancer phytocompound in mango (*Mangifera indica*), structural bioinformatics technique via molecular docking, they found out that compound neratinib with a docking score -8.601 kcal/mol has the most stable interaction with the target protein. The pharmacokinetic model of *Mangifera indica* shown in this study indicates that the ligands are promising therapeutic agents which could be developed for breast cancer treatment.

Anticancer potential of isolated phytocompounds from *Macaranga denticulate* against breast cancer was studied by Zaheed and his colleagues (2016) where compound 3-acetylaleuritolic acid, β-sitosterol, macarangin, oleanic acid, scopoletin and stigmasterol were docked with estrogen receptor alpha with docking score of -4.482, -5.795, -6.647, -2.406, -6.569, and -5.822 respectively. Out of the six compounds, macarangin was shown to be the best compound for selective inhibitors of the estrogen receptor.

Molecular docking analysis of cianidanol from *Gingko biloba* (Arannilewa *et al.*, 2018) revealed that it had binding energy of -8.2 kcal/mol with breast cancer target protein. The reliability of the docking score was validated using the online web server ChEMBL database. The docking studies and ADMET evaluation of cianidanol showed that this ligand plays a critical role in the inhibition of HER2 which is overexpressed in aggressive female breast cancer (Suryasa et al., 2021).

In this study, the toxicity prediction analysis revealed that L-epicatechin is not safe to use as a drug due to AMES toxicity. However, ten compounds were found to be active against the targets after docking and ADMET analysis. All of the ten compounds had low binding scores, indicating that they had good interactions. 1ERR-α-terpineol and 3D90-α-terpineol complex had the lowest negative value for binding energy (-6.0 and -6.1 kcal/mol respectively) excluding L-epicatechin (PubChem ID: 72276) and ellagic acid (PubChem ID: 5281855) (Table 3). Therefore, α-terpineol (PubChem ID: 442501) was chosen to use as a safe drug. The findings of this study should aid pharmaceutical researchers in identifying longan-based medications.

Conclusion

In this study, based on the *in silico* toxicity test result, phytocompounds such as betaine, citric acid, L-aspartic acid, L-glutamic acid, piperidine and α-terpineol

from longan fruit (*Dimocarpus longan*) possess anticancer activities which can be used in drug design for the treatment of cancer by specifically targeting breast cancer biomarkers (estrogen and progesterone receptors). The selected plant compounds had a strong and stable interaction with the target proteins based on their lowest docking score which indicates a stable interaction that will aid in enhancing or decreasing the particular activity of the target protein. However, this study revealed that α-terpineol (PubChem ID: 442501) could be potentially used as the most suitable and safe drug for breast cancer treatment. This *in silico* study of anticancer properties of plant compounds by targeting breast cancer biomarkers will aid in the development of a new and effective drug for breast cancer treatment.

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