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Exploring the Therapeutic Potential of Secondary Metabolites from *Pogostemon cablin* (Aceh Patchouli Oil) as Anti-Breast Cancer Agents: A Network Pharmacology, ADMET, and Molecular Docking Approach

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Abstract

Breast cancer remains a major global health challenge with increasing incidence and mortality. Limitations of long-term therapies have driven the search for safer and more effective anticancer agents. Aceh patchouli oil (*Pogostemon cablin* Benth.) is rich in bioactive compounds, such as terpenoids and sesquiterpenes, with potential anticancer activity; however, its molecular mechanisms remain unclear. This study employed an *in silico* approach integrating network pharmacology, molecular docking, and ADMET evaluation to assess the multitarget potential of patchouli oil compounds against breast cancer. A total of 714 common targets between patchouli oil compounds and breast cancer-related proteins were identified, with AKT1 and EGFR identified as key targets involved in the PI3K/AKT, MAPK, Ras, and estrogen signaling pathways. Docking results indicated that several bioactive compounds could interact with AKT1 and EGFR, including one compound showing a stronger binding affinity toward EGFR than the control compound. ADMET evaluation revealed generally favorable drug-likeness profiles. These findings support the potential of Aceh patchouli oil as a

multitarget anti-breast cancer candidate and warrant further in vitro and in vivo validation.

Keywords: Breast cancer, Pogostemon cablin, Aceh patchouli oil, Network pharmacology, Molecular docking, ADMET

1 Introduction

Breast cancer represents one of the most serious global health challenges and is projected to continue increasing in both incidence and mortality worldwide, thereby imposing a significant health and economic burden.[1] Currently, various therapeutic modalities for breast cancer are available, including chemotherapy, hormone therapy, targeted therapy, and immunotherapy; however, limitations remain for long-term treatment, such as systemic toxicity, drug resistance, and tumor molecular heterogeneity.[2, 3] In addition, the high cost of prolonged treatment often leads to financial toxicity, which can adversely affect patients' psychological well-being.[4] These limitations have driven the search for alternative therapeutic agents that are safer and more effective.[3, 5]

Natural products have long served as an important source for the development of anticancer agents, particularly for breast cancer, due to their ability to modulate multiple molecular targets and key cancer-related signaling pathways.[6, 7] One natural product with promising potential is Aceh patchouli oil (Pogostemon cablin Benth.), an aromatic plant rich in secondary metabolites such as terpenoids and sesquiterpenes. These compounds have been reported to exhibit antioxidant, anti-inflammatory, and anticancer activities.[8] However, the molecular mechanisms underlying the effects of P. cablin secondary metabolites on breast cancer have not yet been fully elucidated, highlighting the need for systematic investigation to evaluate its therapeutic potential.[8, 9]

Advances in science and technology have led to the development of network pharmacology approaches, which enable the systematic mapping of multi-target interactions between bioactive compounds and disease-related proteins. This approach provides a comprehensive understanding of the molecular mechanisms involved in complex diseases such as breast cancer.[10] In addition, molecular docking and ADMET prediction have become essential computational tools for evaluating binding affinity, as well as the pharmacokinetic and safety profiles of candidate compounds, prior to experimental validation.[11]

Based on the research workflow illustrated in Fig. 1, this study explored the anti-breast cancer potential of P. cablin using a comprehensive in silico approach integrating multiple computational methods. Network pharmacology was employed to identify proteins involved in breast cancer-related signaling pathways, molecular docking was used to investigate interactions between P. cablin compounds and breast cancer-associated target proteins, and ADMET profiling was conducted to assess the drug-likeness and safety properties of the compounds. Collectively, these approaches

were applied to evaluate P. cablin as a potential multitarget candidate for breast cancer therapy.

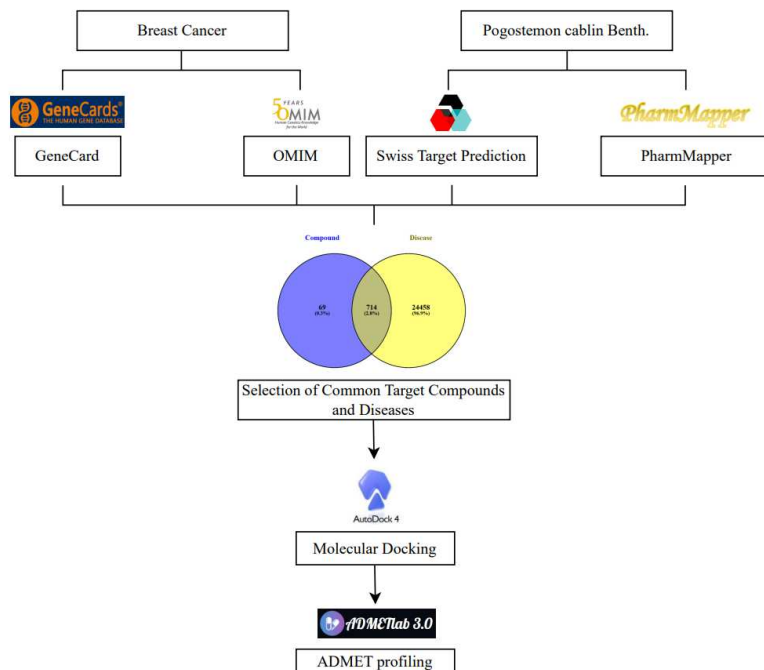


Fig. 1 Research Workflow

2 Results

2.1 Identification of Breast Cancer Molecular Targets through Network Pharmacology

Protein target data from the 31 test compounds were obtained from the SwissTargetPrediction and PharmMapper databases. After the removal of duplicated proteins using the Venny 2.1 tool, a total of 510 compound target proteins were obtained from the SwissTargetPrediction database and 391 target proteins from the PharmMapper database. Construction of a Venn diagram revealed 118 common protein targets shared by both databases, as shown in Fig. 3A. Breast cancer-related protein targets were obtained from the GeneCards and OMIM databases. After removing duplicated entries, 20,514 protein targets were identified from the GeneCards database and 5,963 protein targets from the OMIM database. A Venn diagram analysis revealed 1,305 common protein targets between these two databases, as shown in Fig. 3B. Subsequently, a Venn diagram comparing compound-related and disease-related targets

identified 714 common protein targets, hereafter referred to as common targets, as shown in Fig. 3C.

To further visualize the interaction between bioactive compounds, potential protein targets, and breast cancer, a compound-target-disease network was constructed, as shown in Fig. 2. The network illustrates the multi-component and multi-target characteristics of Pogostemon cablin B., in which 31 bioactive compounds interact with multiple breast cancer-related protein targets. Several targets, including EGFR, AKT1, ESR1, TNF, IL6, CASP3, SRC, HSP90AA1, and ALB, were connected to multiple compounds, indicating their potential central roles in the pharmacological effects of Pogostemon cablin B. against breast cancer.

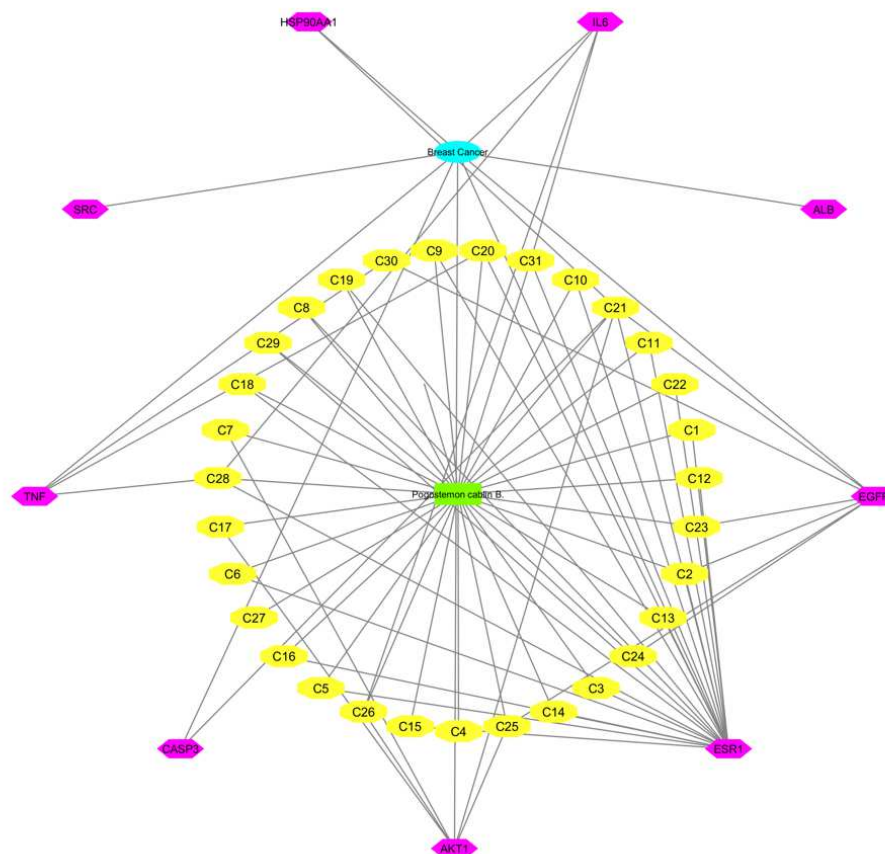


Fig. 2 Compound-target-disease network of Pogostemon cablin B. against breast cancer

2.2 Protein-Protein Interaction (PPI) Network Analysis and Key Target Identification

The 714 common targets were used to construct a protein-protein interaction (PPI) network using the STRING database, and the resulting TSV file was analyzed using Cytoscape software. Proteins not connected to the main network were removed, resulting in a network consisting of 706 interconnected proteins. Degree-based filtering was then applied to the main network. Proteins with a degree value greater than or equal to 180 were selected, yielding nine proteins that were subsequently defined as key targets, as shown in Fig. 3D. The nine key targets were subjected to Gene Ontology (GO) enrichment analysis in the biological process (BP) category and KEGG pathway analysis using the SRplot database. In the BP category, as shown in Fig. 3E, the key targets were significantly enriched in biological processes related to the regulation of cell proliferation, cell cycle progression, and apoptosis. Additional enriched processes included MAPK signaling, hormonal responses (including steroid hormone and estradiol responses), mammary gland epithelial development, regulation of microRNA, and responses to reactive oxygen species. KEGG pathway analysis, as shown in Fig. 3F, revealed significant enrichment in multiple cancer-related signaling pathways. The most enriched pathways included pathways in cancer, breast cancer, and the PI3K-Akt, MAPK, and Ras signaling pathways. Pathways related to hormonal regulation, such as the estrogen signaling pathway and the ErbB signaling pathway, were also highly enriched. In addition, inflammatory and immune-related pathways, including IL-17, TNF, and JAK-STAT signaling pathways, as well as hypoxia- and angiogenesis-related pathways such as the HIF-1 and VEGF signaling pathways, showed significant enrichment. Among the 15 KEGG pathways analyzed, two proteins demonstrated extensive involvement across the majority of pathways, namely AKT1, which was involved in 13 pathways, and EGFR, which was involved in 11 pathways. Based on this extensive pathway involvement, AKT1 and EGFR were selected for further molecular docking analysis.

2.3 Binding Affinity of Pogostemon cablin Compounds toward AKT1 and EGFR

Molecular docking analysis was performed between AKT1 and EGFR proteins and all test compounds, as well as the control compounds. The docking results were expressed as binding affinity values and used to compare the interactions of test compounds with those of the controls. For the AKT1 protein, binding affinity values of the test compounds ranged from -4.3 to -7.2 kcal/mol, as presented in Table 1. The compound C13 showed the strongest binding affinity among the test compounds (-7.2 kcal/mol), although this value was lower than that of the control compound capivasertib (-8.7 kcal/mol). For the EGFR protein, binding affinity values of the test compounds ranged from -4.2 to -8.2 kcal/mol, as shown in Table 1. The compound C28 exhibited the strongest binding affinity among the test compounds (-8.2 kcal/mol), which was higher than that of the control compound gefitinib (-7.8 kcal/mol).

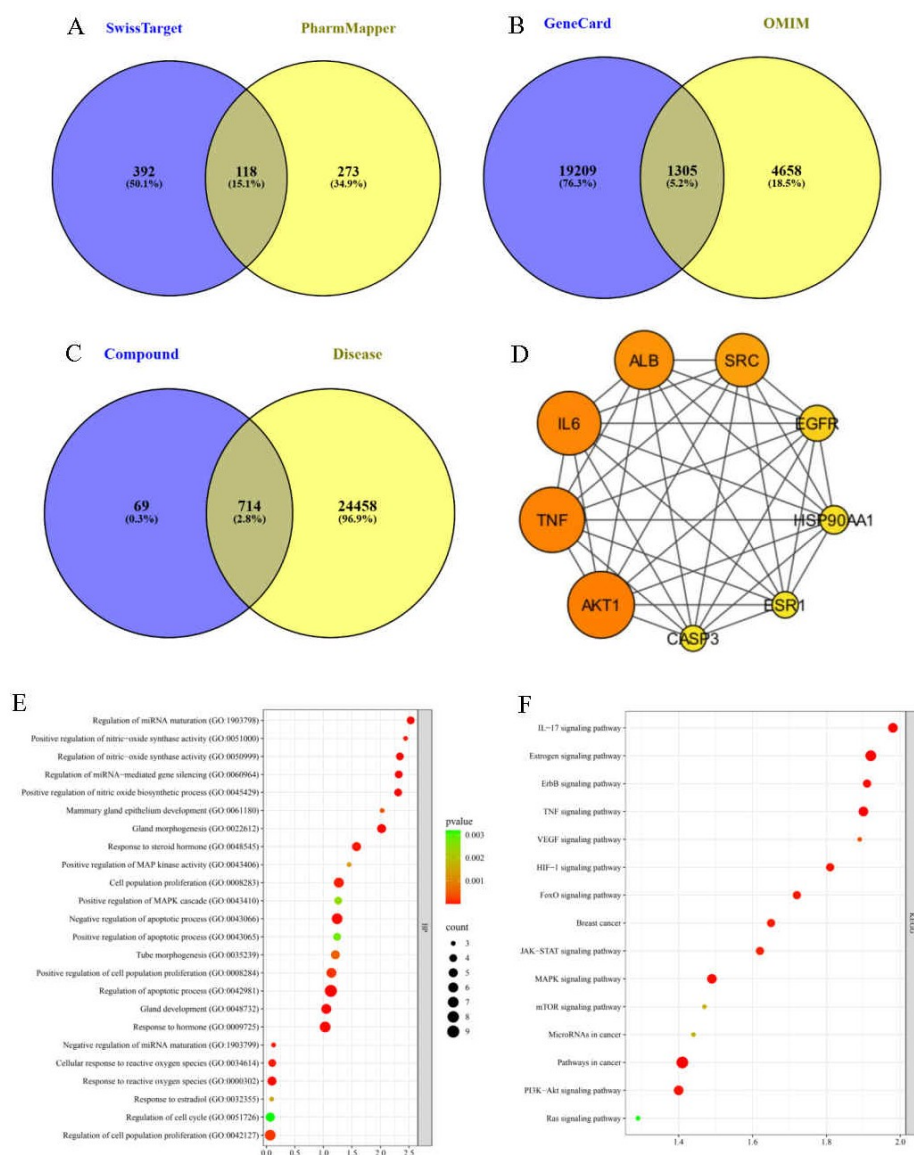


Fig. 3 Identification of potential targets through network pharmacology analysis. (A) Venn diagram of compound target databases. (B) Venn diagram of disease target databases. (C) Venn diagram of the intersection between compound- and disease-related targets. (D) Network of nine key targets obtained based on degree filtering. (E) Enrichment bubble plot of Gene Ontology (GO) biological process analysis. (F) Enrichment bubble plot of KEGG pathway analysis.

Table 1 Molecular docking binding affinity of bioactive compounds against Capivasertib and Gefitinib targets

Ligand	Binding Affinity (Kcal/mol)	
	AKT1	EGFR
Capivasertib (Control)	-8.7	-
Gefitinib (Control)	-	-7.8
C1	-4.8	-5.2
C2	-4.3	-4.2
C3	-6.4	-6.4
C4	-6.4	-6.5
C5	-6.5	-7.3
C6	-6.6	-6.8
C7	-6.4	-7.0
C8	-6.7	-6.9
C9	-6.5	-6.4
C10	-6.2	-6.4
C11	-4.7	-5.1
C12	-6.1	-5.7
C13	-7.2	-7.1
C14	-6.2	-6.5
C15	-6.4	-6.7
C16	-6.5	-6.9
C17	-6.5	-6.7
C18	-6.4	-6.8
C19	-6.8	-7.1
C20	-6.1	-5.8
C21	-6.1	-6.6
C22	-5.3	-4.9
C23	-5.6	-5.8
C24	-7.0	-7.1
C25	-6.3	-7.0
C26	-6.1	-6.2
C27	-5.7	-5.3
C28	-6.1	-8.2
C29	-5.9	-5.3
C30	-6.4	-5.2
C31	-5.7	-5.5

2.4 Molecular Interaction Patterns of Active Compounds at the AKT1 and EGFR Binding Sites

Docking results were visualized using Discovery Studio 2021 to analyze two-dimensional (2D) interaction patterns of the ligand–protein complexes. For the AKT1 protein, the control compound capivasertib formed three hydrogen bonds, six hydrophobic interactions, and thirteen van der Waals interactions, as shown in Fig.

4A. In contrast, the best-performing test compound formed seven hydrophobic interactions and seven van der Waals interactions, without forming hydrogen bonds, as shown in Fig. 4B. Several amino acid residues were shared between the test compound and capivasertib, including LEU156, VAL164, ALA177, GLY157, GLU234, THR291, and ALA230. Hydrophobicity mapping revealed that capivasertib occupied a predominantly hydrophilic binding pocket, indicated by a bluish-colored region (Fig. 4E), whereas the test compound was located in a hydrophobic pocket, indicated by a brownish-colored region (Fig. 4F). For the EGFR protein, the control compound gefitinib formed three hydrogen bonds, five hydrophobic interactions, and eleven van der Waals interactions, as shown in Fig. 4C. The best-performing test compound formed eight hydrophobic interactions and seven van der Waals interactions, without forming hydrogen bonds, as shown in Fig. 4D. Shared amino acid residues between the test compound and gefitinib included ALA719, VAL702, ASP831, and GLY772. Hydrophobicity analysis indicated that both compounds were located within hydrophobic binding pockets, as shown in Fig. 4G-H.

2.5 Evaluation of the ADMET Profile of Bioactive Compounds from Aceh Patchouli Oil

2.5.1 Drug-Likeness and Physicochemical Properties

Evaluation of drug-likeness based on Lipinski’s Rule of Five indicated that 30 out of 31 compounds fulfilled all criteria (as shown in Table 2). Physicochemical analysis showed that the compounds were small molecules with an average molecular weight of 241.04 Da. The compounds exhibited relatively high lipophilicity, with an average logP value of 4.38. The average numbers of hydrogen bond donors and acceptors were 0.52 and 1.26, respectively, while the average topological polar surface area (TPSA) was 21.57 Å². These results indicate relatively consistent physicochemical characteristics among the majority of the test compounds.

2.5.2 ADMET Properties

Absorption prediction indicated moderate permeability based on Caco-2 and MDCK cell models. Only three compounds were predicted to have a high probability of human intestinal absorption. P-glycoprotein analysis showed that 17 compounds were predicted to act as P-gp inhibitors, while four compounds were predicted to be P-gp substrates. In terms of distribution, all compounds exhibited high plasma protein binding, with an average value of 91.37%, resulting in a low free drug fraction (Fu) with an average value of 9.07%. Blood–brain barrier penetration was predicted for 15 compounds, whereas the remaining compounds showed limited potential to penetrate the central nervous system (as shown in Table 2). Metabolism analysis indicated that most compounds were predicted to interact with cytochrome P450 enzymes. Specifically, 28 compounds were predicted to act as CYP2C8 inhibitors, 25 compounds as CYP2B6 inhibitors, and 22 compounds as substrates for CYP2C19. The average plasma clearance value was 9.41 mL/min/kg, and the average elimination half-life was 1.13 hours. Toxicity prediction indicated that all compounds were predicted to be non-toxic in terms of acute oral toxicity. Drug-induced liver injury risk was predicted for 6.4% of

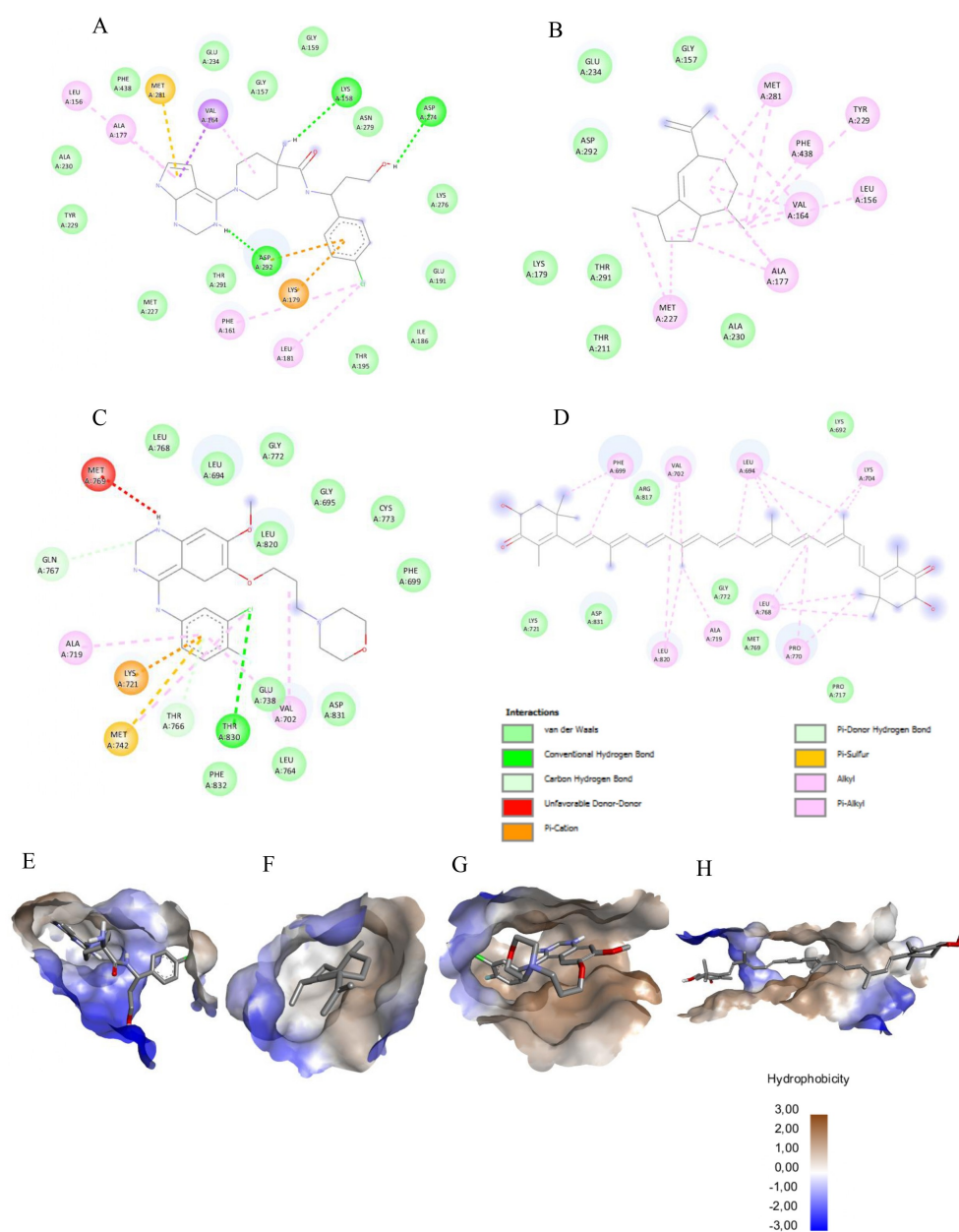


Fig. 4 Two-dimensional (2D) interaction diagrams and hydrophobicity maps of selected ligands with target proteins. (A) 2D interaction of capivasertib with AKT1. (B) 2D interaction of C13 with AKT1. (C) 2D interaction of gefitinib with EGFR. (D) 2D interaction of C28 with EGFR. (E) Hydrophobicity map of capivasertib-AKT1 complex. (F) Hydrophobicity map of C13-AKT1 complex. (G) Hydrophobicity map of gefitinib-EGFR complex. (H) Hydrophobicity map of C28-EGFR complex.

the compounds. In addition, 22 compounds were predicted to have potential carcinogenicity, and 16 compounds showed predicted risks of neurotoxicity. Most compounds were predicted not to inhibit the hERG channel, with only a small proportion showing potential inhibitory effects (as shown in Table 3).

Table 2 Druglikeness and Physicochemical, Absorption, and Distribution Profiles

Comp.	Druglikeness and Physicochemical						Absorption				Distribution			
	MW (g/mol)	logP	nHA	nHD	TPSA ($\text{\AA}^2$)	Lipinski Rules	Caco2	MDCK	HIA	P-gp Sub/Inh	PPB (%)	Fu (%)	VDss	BBB
C1	136.13	4.271	00.00	00.00	0.0	Accepted	-4.665	-4.797	- - -	- -/+ + +	92.60	7.20	0.452	-
C2	130.14	2.597	01.00	01.00	20.23	Accepted	-4.941	-4.684	+	+ + / - -	78.90	25.10	0.109	+ +
C3	204.19	4.088	00.00	00.00	0.0	Accepted	-4.555	-4.628	- - -	- / + +	95.20	7.30	0.394	- -
C4	204.19	5.219	00.00	00.00	0.0	Accepted	-4.685	-4.984	- - -	- - - / - -	98.20	2.30	0.185	+ + +
C5	204.18	4.197	00.00	00.00	0.0	Accepted	-4.644	-4.644	- - -	+ / + +	95.5	4.5	0.292	- -
C6	204.19	4.468	00.00	00.00	0.0	Accepted	-4.568	-4.626	- - -	- / + + +	94.2	7.90	0.383	- -
C7	218.17	3.606	01.00	00.00	17.07	Accepted	-4.653	-4.525	- - -	- - - / + + +	94.5	6.0	0.220	+ +
C8	238.19	2.619	02.00	02.00	40.46	Accepted	-4.829	-4.598	- - -	- - / - -	72.7	28.0	-0.011	+ +
C9	220.18	4.498	01.00	00.00	12.53	Accepted	-4.811	-4.931	- - -	- - - / + +	96.90	4.40	0.609	+ + +
C10	220.18	3.024	01.00	00.00	12.53	Accepted	-4.533	-4.840	- - -	- - - / + + +	96.30	4.10	0.517	+
C11	140.12	2.746	01.00	00.00	12.53	Accepted	-4.625	-4.797	- - -	- - - / +	63.00	31.60	0.181	+ + +
C12	222.20	3.434	01.00	01.00	20.23	Accepted	-4.752	-4.563	- - -	+ / - - -	94.60	4.70	0.559	- - -
C13	204.19	4.512	00.00	00.00	0.0	Accepted	-4.71	-4.626	- - -	+ / - - -	98.1	1.9	0.481	+ + +
C14	220.18	4.173	01.00	00.00	12.53	Accepted	-4.886	-4.595	- - -	- - / + + +	89.1	13.8	0.344	+ +
C15	220.18	4.409	01.00	00.00	12.53	Accepted	-4.812	-4.876	- - -	- - - / + +	95.4	6.6	0.367	- -
C16	220.18	4.251	01.00	00.00	12.53	Accepted	-4.725	-4.953	- - -	- - - / + +	96.5	5.1	0.550	+ +
C17	218.17	3.347	01.00	00.00	17.07	Accepted	-4.55	-4.751	- - -	- - - / +	98.10	1.80	0.089	+ + +
C18	222.20	3.752	01.00	01.00	20.23	Accepted	-4.672	-4.957	- - -	- - - / + +	97.30	3.80	0.407	+ +
C19	220.18	4.235	01.00	00.00	12.53	Accepted	-4.672	-4.957	- - -	- - - / + +	97.30	3.80	0.407	+ +
C20	152.12	2.397	01.00	01.00	20.23	Accepted	-4.455	-4.688	- -	- - - / - - -	44.00	53.00	-0.049	+ + +
C21	224.10	3.325	04.00	01.00	67.51	Accepted	-4.665	-4.797	- - -	- - - / + +	92.60	7.20	0.452	-
C22	536.59	10.298	01.00	01.00	20.23	Rejected	-5.123	-5.006	+ + +	- - - / - - -	105.80	0.10	3.189	- - -
C23	296.31	07.46	01.00	01.00	20.23	Accepted	-5.028	-4.601	- - -	- - - / - - -	80.00	14.70	0.065	- - -
C24	236.18	1.732	02.00	01.00	37.30	Accepted	-4.657	-4.499	- - -	- - - / -	85.00	16.80	0.462	- -
C25	260.14	3.309	03.00	00.00	39.44	Accepted	-4.93	-4.762	- - -	- - - / +	94.70	4.80	0.411	+ +
C26	206.17	3.563	01.00	00.00	17.07	Accepted	-4.455	-4.723	- - -	- - - / -	94.30	6.70	0.486	+ + +
C27	256.24	6.648	02.00	01.00	37.30	Accepted	-5.096	-4.803	+ +	- - - / - - -	98.00	1.70	0.592	- - -
C28	596.39	4.375	4.375	02.00	74.60	Accepted	-5.045	-4.807	- - -	- / + + +	94.70	5.50	0.388	- - -
C29	282.26	6.748	02.00	01.00	37.30	Accepted	-5.093	-4.728	- - -	- - - / - - -	99.10	0.30	-0.780	- - -
C30	280.24	5.778	02.00	01.00	37.30	Accepted	-5.071	-4.721	- - -	- - - / - - -	97.10	2.30	-0.443	- - -
C31	278.22	6.664	02.00	01.00	37.30	Accepted	-5.071	-4.823	- - -	- - - / - - -	98.00	1.30	-0.462	- - -

Note: MW: g/mol; TPSA: $\text{\AA}^2$; HIA: %.

Table 3 Metabolism (Substrate/Inhibitor), Excretion, and Toxicity Profiles

Comp.	Metabolism (Substrate/Inhibitor)					Excretion		Toxicity							
	1A2	2C19	2C9	2D6	3A4	CL	T _{1/2}	AMES	DILI	RatTox	Skin	Carci	Geno	Neph	Neur
C1	---/-	+++/-	---/-	+++/-	---/-	10.596	1.267	0.066	0.324	0.128	0.72	0.6	0.0	0.023	0.714
C2	---/-	---/+	---/-	---/-	---/-	10.631	1.152	0.128	0.058	0.136	0.79	0.244	0.0	0.244	0.131
C3	+++/-	+++/-	+++/-	+++/-	+++/-	9.008	0.164	0.469	0.423	0.402	0.572	0.798	0.165	0.395	0.55
C4	---/-	+++/-	---/-	+++/-	---/-	11.691	0.805	0.248	0.309	0.232	0.263	0.655	0.005	0.051	0.584
C5	+++/-	+++/-	+++/-	+++/-	+++/-	9.258	0.258	0.654	0.493	0.336	0.873	0.794	0.146	0.49	0.577
C6	+/+	+++/-	---/-	---/-	+++/-	10.126	0.488	0.499	0.375	0.304	0.6	0.784	0.205	0.527	0.634
C7	---/-	+++/-	+++/-	---/-	---/-	10.364	1.037	0.418	0.3	0.536	0.698	0.688	0.718	0.231	0.564
C8	---/-	---/-	+++/-	---/-	---/-	9.011	1.029	0.459	0.087	0.215	0.983	0.901	0.219	0.504	0.068
C9	---/-	+++/-	+++/-	+++/-	---/-	14.628	1.093	0.401	0.247	0.406	0.249	0.693	0.016	0.089	0.538
C10	---/-	+++/-	---/-	---/-	---/-	11.491	1.199	0.556	0.278	0.552	0.815	0.715	0.334	0.208	0.618
C11	---/-	+++/-	+++/-	+++/-	+++/-	10.063	0.915	0.628	0.162	0.539	0.644	0.657	0.089	0.27	0.524
C12	+++/-	+++/-	---/-	---/-	+++/-	15.047	1.324	0.48	0.143	0.245	0.649	0.773	0.066	0.417	0.072
C13	+++/-	+++/-	+++/-	---/-	---/-	10.515	0.586	0.203	0.505	0.472	0.466	0.537	0.022	0.173	0.658
C14	---/-	+++/-	---/+	---/-	+++/-	14.022	1.56	0.547	0.15	0.733	0.856	0.467	0.477	0.197	0.397
C15	+/+	+++/-	---/-	---/-	---/-	11.37	1.057	0.578	0.298	0.417	0.419	0.717	0.079	0.146	0.39
C16	---/-	+++/-	+++/-	+++/-	---/-	17.696	1.652	0.381	0.308	0.288	0.121	0.634	0.006	0.082	0.54
C17	---/-	+++/-	---/-	+++/-	---/-	8.473	0.823	0.22	0.406	0.25	0.55	0.793	0.006	0.017	0.646
C18	---/-	---/-	---/-	---/-	+++/-	14.375	1.809	0.449	0.081	0.243	0.717	0.739	0.059	0.471	0.098
C19	---/-	+++/-	---/-	+++/-	---/-	14.328	1.273	0.385	0.222	0.403	0.085	0.615	0.01	0.048	0.522
C20	---/-	---/-	+++/-	+++/-	---/-	7.982	2.227	0.326	0.17	0.218	0.27	0.477	0.001	0.15	0.319
C21	+++/-	+++/-	+++/-	---/-	---/-	3.718	0.918	0.0066	0.446	0.444	0.544	0.666	0.575	0.089	0.096
C22	+/+	+/+	+++/-	+++/-	---/-	4.254	5.826	0.003	0.066	0.54	1.0	0.13	0.0	0.06	0.0
C23	---/-	+++/-	---/+	---/-	+/+	6.931	0.324	0.245	0.019	0.086	0.999	0.475	0.0	0.369	0.072
C24	---/-	+++/-	---/-	---/-	+/+	8.184	1.246	0.538	0.112	0.396	0.94	0.882	0.632	0.736	0.318
C25	+/+	+/+	+++/-	+++/-	+/+	9.43	0.686	0.341	0.321	0.577	0.488	0.556	0.375	0.054	0.509
C26	+++/-	+++/-	+++/-	---/-	+++/-	8.433	0.32	0.457	0.168	0.501	0.707	0.619	0.323	0.363	0.54
C27	---/-	---/-	+++/-	+++/-	---/-	3.77	0.932	0.047	0.188	0.124	0.909	0.27	0.0	0.236	0.03
C28	+++/-	+/+	+++/-	---/-	---/-	4.941	0.885	0.89	0.716	0.833	0.992	0.896	0.996	0.996	0.996
C29	---/+	---/-	+++/-	+++/-	---/-	3.597	0.875	0.02	0.034	0.028	0.996	0.075	0.0	0.239	0.019
C30	---/+	+++/-	---/+	+++/-	+/+	3.344	0.921	0.188	0.146	0.113	0.956	0.183	0.0	0.496	0.067
C31	---/-	---/-	+++/-	+++/-	---/-	4.574	0.368	0.428	0.0	0.049	1.0	0.183	0.0	0.297	0.025

Note: Metabolism presented as Substrate/Inhibitor; symbols: (+) sub/inh, (-) non-sub/inh. CL: CLplasma; T_{1/2}: half-life; AMES: mutagenicity; DILI: liver injury; RatTox: acute toxicity; Neph: nephrotoxicity; Neur: neurotoxicity.

3 Materials and Methods

3.1 Network Pharmacology

The test compounds consisted of 31 bioactive compounds identified from GC-MS analysis of Aceh patchouli oil extract (*Pogostemon cablin* Benth.). The chemical structures of the 31 bioactive compounds are presented in Fig. 5. The SMILES structures of the compounds were retrieved from the PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>). These SMILES structures were used to predict compound targets using the SwissTargetPrediction database (<https://www.swisstargetprediction.ch/>) and PharmMapper (<https://www.lilab-ecust.cn/pharmmapper/>). Breast cancer-related proteins were identified from the GeneCards (<https://www.genecards.org/>) and OMIM (<https://www.omim.org/>) databases using the keyword "breast cancer". Common targets were identified using the Venny 2.1 tool (<https://bioinfogp.cnb.csic.es/tools/venny/>) and subsequently used to construct a target interaction network via the STRING database (<https://string-db.org/>). Degree-based filtering of the network was then performed using Cytoscape software.

3.2 Molecular Docking

Two breast cancer-related proteins identified from the network pharmacology analysis, AKT1 and EGFR, were selected for molecular docking analysis. The three-dimensional (3D) structures of the bioactive compounds from *P. cablin*, as well as the control compounds gefitinib and capivasertib, were downloaded in SDF format from the PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>). All compound structures were energy-minimized using Open Babel in PyRx 0.9 and saved in PDBQT format. The 3D structures of AKT1 and EGFR were obtained from the RCSB Protein Data Bank (<https://www.rcsb.org/>). Protein preparation, including the removal of water molecules and native ligands and the determination of active site coordinates, was performed using Discovery Studio 2021 software. The prepared protein structures were saved in PDB format. The prepared ligands and protein structures were then imported into PyRx 0.9 for docking analysis. Docking results were visualized using Discovery Studio 2021.

3.3 ADMET Profiling

ADMET profiling was performed using the ADMETlab 3.0 database (<https://admetlab3.scbdd.com/>) based on the SMILES data of each test compound. The ADMET prediction results were exported in CSV format for further analysis.

4 Discussion

The in silico approach employed in this study provides a systematic overview of the potential of Aceh patchouli oil (*Pogostemon cablin* Benth.) as a candidate anti-breast cancer agent. The identification of 714 common targets between patchouli oil compounds and breast cancer-related proteins indicates that compounds derived from

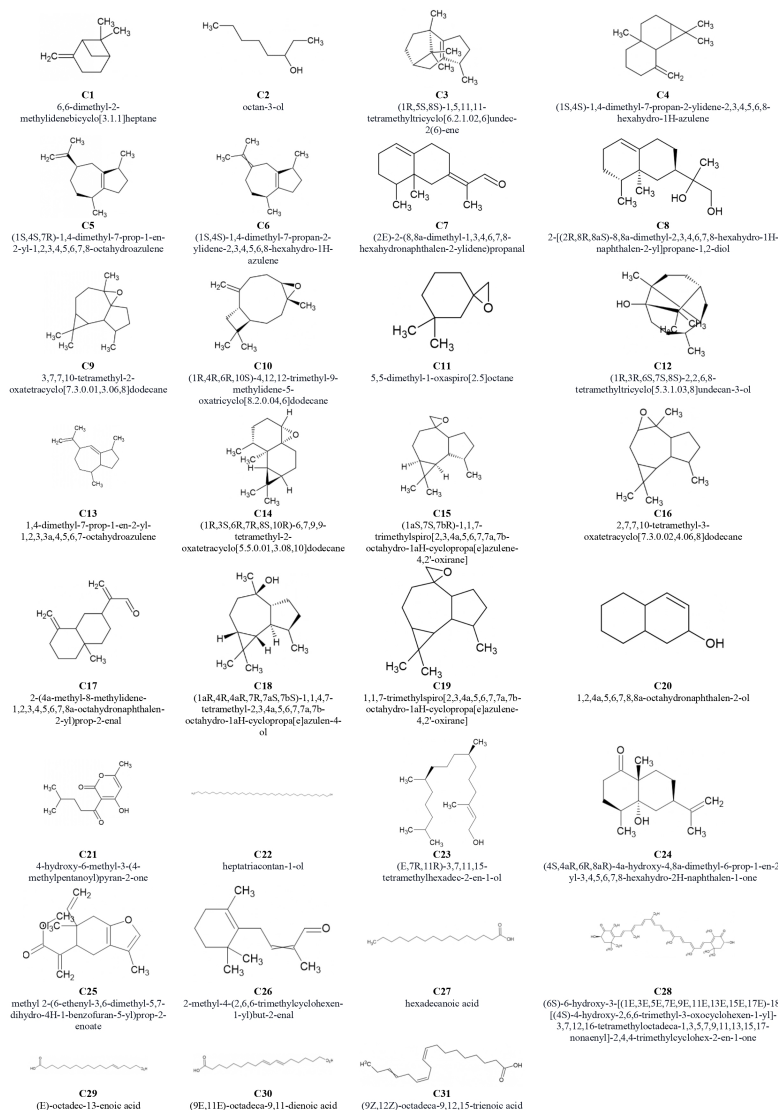


Fig. 5 Chemical structures of the 31 bioactive compounds identified from GC-MS analysis of Aceh patchouli oil (*Pogostemon cablin* Benth.)

Aceh patchouli oil are capable of interacting with complex molecular networks involved in breast cancer progression. These findings are consistent with the concept of network pharmacology, which emphasizes that natural compounds generally exert therapeutic effects through multitarget mechanisms rather than single-target actions.[12–16] This approach is considered particularly suitable for complex diseases such as cancer, which involve diverse molecular alterations and interconnected signaling pathways.[17, 18]

Protein–protein interaction network analysis demonstrated that most of the identified common targets were interconnected within a single major network, indicating functional relationships among proteins implicated in breast cancer pathogenesis. Degree-based filtering identified nine key targets with high connectivity, suggesting that these proteins play central roles within the molecular network. Among these targets, AKT1 and EGFR emerged as the most prominent proteins, showing involvement in nearly all enriched KEGG pathways. This finding suggests that AKT1 and EGFR function as major hubs linking multiple breast cancer–related signaling pathways. These results are in line with previous studies reporting that the EGFR and PI3K/AKT signaling pathways represent critical molecular axes regulating cell proliferation, survival, migration, invasion, and therapeutic resistance in breast cancer.[19–23]

Aberrant activation of EGFR has been reported across various breast cancer subtypes and is frequently associated with increased tumor aggressiveness and poorer prognosis.[24, 25] Similarly, AKT1, a key component of the PI3K/AKT pathway, plays an essential role in regulating cell survival and metabolic signaling. Dysregulation or excessive activation of AKT1 can promote tumor growth and reduce the sensitivity of cancer cells to chemotherapy and targeted therapies currently in clinical use.[26–28] Therefore, the identification of AKT1 and EGFR as key targets further supports the biological relevance of the findings derived from the network pharmacology analysis conducted in this study.

Gene Ontology enrichment analysis in the biological process category revealed that the key targets were significantly enriched in processes associated with the regulation of cell proliferation, cell cycle progression, and apoptosis. These processes represent fundamental hallmarks of cancer and reflect the imbalance between proliferative and cell death signals that underlies tumor development. Enrichment in hormonal responses, including steroid hormone and estradiol responses, further highlights the close association between the identified molecular targets and breast cancer pathophysiology, which is strongly influenced by hormonal regulation.[29–31] In addition, enrichment related to mammary gland epithelial development suggests that these targets may be involved in regulating breast tissue differentiation, which can be disrupted during malignant transformation.

At the signaling pathway level, KEGG pathway analysis demonstrated strong enrichment in pathways in cancer and breast cancer, as well as in the PI3K-Akt, MAPK, and Ras signaling pathways. These pathways are widely recognized as central regulators of cancer cell growth, survival, and adaptation to various cellular stresses, including oxidative stress and anticancer treatment.[21, 29, 32, 33] Moreover, enrichment of the estrogen signaling pathway and the ErbB signaling pathway further underscores the role of EGFR as an upstream regulator capable of activating multiple downstream signaling cascades, including PI3K/AKT and MAPK, in breast cancer.[24, 25, 30] The involvement of inflammatory and immune-related pathways, such as IL-17, TNF, and JAK-STAT, as well as hypoxia- and angiogenesis-related pathways, including HIF-1 and VEGF, suggests that patchouli oil compounds may also influence the tumor microenvironment, which plays an important role in tumor growth and metastasis.[34–36]

The selection of AKT1 and EGFR for molecular docking analysis was based on their extensive involvement across the majority of enriched KEGG pathways. Docking results demonstrated that bioactive compounds from patchouli oil exhibited varying binding affinities toward both targets. For AKT1, although the strongest-binding test compound showed a lower binding affinity compared to the control compound capivasertib, the obtained values indicate that this compound is capable of interacting with the AKT1 binding site. This suggests potential inhibitory activity, although further structural optimization may be required to enhance interaction strength and stability.[37–39]

In contrast, for the EGFR target, one test compound exhibited a binding affinity that exceeded that of the control compound gefitinib. This finding indicates that certain components of patchouli oil possess promising potential to modulate EGFR activity. Previous studies have reported that terpenoid and sesquiterpene compounds from essential oils can interact with receptor tyrosine kinases and inhibit the EGFR/MAPK signaling pathway, thereby suppressing cancer cell proliferation and survival.[40–42] The alternative binding modes observed for these natural compounds may provide potential advantages in overcoming resistance to existing EGFR inhibitors.[43–45]

Further analysis of molecular interactions revealed that both test and control compounds shared several binding residues on AKT1 and EGFR, indicating that the test compounds occupy binding pockets similar to those of the reference inhibitors. The predominance of hydrophobic and van der Waals interactions suggests that complex stability is largely mediated by non-covalent forces, which are commonly observed in interactions between natural products and protein targets. This interaction pattern may explain the differences in binding affinity compared to synthetic inhibitors, which are typically designed to form strong and specific hydrogen bonds.[46, 47]

Evaluation of the ADMET profiles provides preliminary insight into the feasibility of patchouli oil compounds as drug candidates. Most compounds satisfied Lipinski’s Rule of Five, indicating favorable drug-likeness. However, relatively high lipophilicity and low TPSA values suggest that these compounds are hydrophobic, which may enhance membrane permeability but could also present challenges related to solubility. Absorption predictions indicated moderate permeability, with only a small proportion of compounds showing high predicted intestinal absorption, suggesting that structural optimization may be required to improve oral bioavailability.[48–50]

High plasma protein binding and low free drug fractions indicate that most compounds may be widely distributed in systemic circulation, although only a limited fraction would be available in the free form. Predicted blood–brain barrier penetration for some compounds suggests potential central nervous system exposure, which may represent either a therapeutic opportunity or a safety concern depending on the clinical context. Extensive predicted interactions with cytochrome P450 enzymes indicate that hepatic metabolism is likely to be the primary elimination pathway, but also highlight the potential for drug–drug interactions that should be considered during further development.[51–53]

Overall, the integration of network pharmacology, molecular docking, and ADMET evaluation demonstrates that Aceh patchouli oil exhibits potential as a natural

product-based anti-breast cancer agent with a multitarget mechanism of action, particularly through modulation of the EGFR/PI3K/AKT signaling axis. Although these *in silico* findings provide a strong scientific foundation, further validation through *in vitro* and *in vivo* studies is necessary to confirm the biological activity, molecular mechanisms, and safety profiles of the identified compounds before progression to preclinical and clinical development.

5 Conclusion

This study demonstrates that bioactive compounds derived from Aceh patchouli oil (*Pogostemon cablin* Benth.) exhibit potential as anti-breast cancer agents through a multitarget mechanism of action. Network pharmacology analysis identified multiple molecular targets associated with breast cancer, with AKT1 and EGFR emerging as key hub proteins involved in the majority of enriched signaling pathways. These findings indicate that the therapeutic effects of patchouli oil compounds may be mediated through the modulation of interconnected molecular networks rather than single-target inhibition.

Molecular docking analysis revealed that the tested compounds showed varying binding affinities toward AKT1 and EGFR. Although the binding affinity of the most active compound against AKT1 was lower than that of the reference inhibitor capivasertib, the interaction results suggest a potential ability to modulate AKT1 activity. In contrast, one compound demonstrated a binding affinity toward EGFR that exceeded that of the reference inhibitor gefitinib, highlighting its potential as a promising EGFR-modulating agent.

ADMET prediction further supported the feasibility of the identified compounds as drug candidates, as most compounds satisfied Lipinski's Rule of Five and exhibited acceptable pharmacokinetic profiles. However, limitations related to lipophilicity, plasma protein binding, and predicted metabolic interactions indicate that further optimization may be required to improve bioavailability and safety profiles.

Overall, the integration of network pharmacology, molecular docking, and ADMET analysis provides *in silico* evidence supporting the potential of Aceh patchouli oil as a source of bioactive compounds for breast cancer therapy. Nevertheless, experimental validation through *in vitro* and *in vivo* studies is required to confirm the anticancer activity, molecular mechanisms, and safety of these compounds before further development.

Supplementary information. Not applicable

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Declarations

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- Conflict of interest

The authors have declared no Competing interests

- Ethics approval and consent to participate
Not applicable
- Consent for publication
The manuscript is approved by all authors for publication
- Data availability
All data generated and analyzed during this study are available from the corresponding author.
- Author contribution
All authors contributed to the study conception and design. Concepts and ideas were developed by YR and WA. Material preparation, design, and experimental studies were performed by YR, WA, and MR. Data acquisition and literature search were carried out by YR, WA, MR, SFD, FY, NT, PRR, ASS, and FMA. Data analysis were conducted by YR, WA, MR, SFD, FY, and NT. The intellectual content was defined by YR, WA, MR, SFD, FY, NT, and PRR. The first draft of the manuscript was prepared by all authors. Manuscript editing was performed by YR, WA, and SFD, while manuscript review and final approval were provided by YR, WA, MR, SFD, FY, and NT.

References

- [1] Freihat O, Sipos D, Kovacs A. Global burden and projections of breast cancer incidence and mortality to 2050: A comprehensive analysis of GLOBOCAN data. *Frontiers in Public Health*. 2025;13:1622954.
- [2] Gautam S, Maurya R, Vikal A, Patel P, Thakur S, Singh A, et al. Understanding drug resistance in breast cancer: Mechanisms and emerging therapeutic strategies. *Medicine in Drug Discovery*. 2025;p. 100210.
- [3] Andrade de Oliveira K, Sengupta S, Yadav AK, Clarke R. The complex nature of heterogeneity and its roles in breast cancer biology and therapeutic responsiveness. *Frontiers in Endocrinology*. 2023;14:1083048.
- [4] Ehsan AN, Wu CA, Minasian A, Singh T, Bass M, Pace L, et al. Financial toxicity among patients with breast cancer worldwide: a systematic review and meta-analysis. *JAMA network Open*. 2023;6(2):e2255388–e2255388.
- [5] Wang B, He X, Dutta S, Chen S, Liang J, Huang W, et al. New progress and challenges of targeted therapies for breast cancer. *Annals of Palliative Medicine*. 2025;14(4):34352–34552.
- [6] Sun X, Liu K, Lu S, He W, Du Z. Targeted therapy and immunotherapy for heterogeneous breast cancer. *Cancers*. 2022;14(21):5456.
- [7] Alqathama A. Natural products as promising modulators of breast cancer immunotherapy. *Frontiers in Immunology*. 2024;15:1410300.

- [8] Zhang J, Wu Y, Li Y, Li S, Liu J, Yang X, et al. Natural products and derivatives for breast cancer treatment: From drug discovery to molecular mechanism. *Phytomedicine*. 2024;129:155600.
- [9] Mrisho II, Musazade E, Chen H, Zhao H, Xing J, Li X, et al. Unlocking the Therapeutic Potential of Patchouli Leaves: A Comprehensive Review of Phytochemical and Pharmacological Insights. *Plants*. 2025;14(7):1034.
- [10] Fatima S, Farzeen I, Ashraf A, Aslam B, Ijaz MU, Hayat S, et al. A comprehensive review on pharmacological activities of pachypodol: A bioactive compound of an aromatic medicinal plant *Pogostemon cablin* Benth. *Molecules*. 2023;28(8):3469.
- [11] Ismail NZ, Khairuddean M, Abubakar S, Arsad H. Network pharmacology, molecular docking and molecular dynamics simulation of chalcone scaffold-based compounds targeting breast cancer receptors. *Journal of Biomolecular Structure and Dynamics*. 2025;43(7):3242–3257.
- [12] Hopkins AL. Network pharmacology: the next paradigm in drug discovery. *Nature chemical biology*. 2008;4(11):682–690.
- [13] Shao L, Bo Z. Traditional Chinese medicine network pharmacology: theory, methodology and application. *Chinese Journal of Natural Medicines*. 2013;.
- [14] Nogales C, Mamdouh ZM, List M, Kiel C, Casas AI, Schmidt HH. Network pharmacology: curing causal mechanisms instead of treating symptoms. *Trends in pharmacological sciences*. 2022;43(2):136–150.
- [15] Zhang Gb, Li Qy, Chen Ql, Su Sb. Network pharmacology: a new approach for Chinese herbal medicine research. *Evidence-Based Complementary and Alternative Medicine*. 2013;2013(1):621423.
- [16] Yuan H, Ma Q, Cui H, Liu G, Zhao X, Li W, et al. How can synergism of traditional medicines benefit from network pharmacology? *Molecules*. 2017;22(7):1135.
- [17] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *cell*. 2011;144(5):646–674.
- [18] Barabasi AL, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. *Nature reviews genetics*. 2011;12(1):56–68.
- [19] Kallergi G, Agelaki S, Kalykaki A, Stournaras C, Mavroudis D, Georgoulas V. Phosphorylated EGFR and PI3K/Akt signaling kinases are expressed in circulating tumor cells of breast cancer patients. *Breast cancer research*. 2008;10(5):R80.

- [20] Yuan Y, Long H, Zhou Z, Fu Y, Jiang B. PI3K–AKT-Targeting breast cancer treatments: Natural products and synthetic compounds. *Biomolecules*. 2023;13(1):93.
- [21] Li H, Prever L, Hirsch E, Gulluni F. Targeting PI3K/AKT/mTOR signaling pathway in breast cancer. *Cancers*. 2021;13(14):3517.
- [22] Miricescu D, Totan A, Stanescu-Spinu II, Badoiu SC, Stefani C, Greabu M. PI3K/AKT/mTOR signaling pathway in breast cancer: from molecular landscape to clinical aspects. *International journal of molecular sciences*. 2020;22(1):173.
- [23] Davis NM, Sokolosky M, Stadelman K, Abrams SL, Libra M, Candido S, et al. Deregulation of the EGFR/PI3K/PTEN/Akt/mTORC1 pathway in breast cancer: possibilities for therapeutic intervention. *Oncotarget*. 2014;5(13):4603.
- [24] Masuda H, Zhang D, Bartholomeusz C, Doihara H, Hortobagyi GN, Ueno NT. Role of epidermal growth factor receptor in breast cancer. *Breast cancer research and treatment*. 2012;136(2):331–345.
- [25] Yarden Y, Pines G. The ERBB network: at last, cancer therapy meets systems biology. *Nature Reviews Cancer*. 2012;12(8):553–563.
- [26] Mundi PS, Sachdev J, McCourt C, Kalinsky K. AKT in cancer: new molecular insights and advances in drug development. *British journal of clinical pharmacology*. 2016;82(4):943–956.
- [27] Hoxhaj G, Manning BD. The PI3K–AKT network at the interface of oncogenic signalling and cancer metabolism. *Nature Reviews Cancer*. 2020;20(2):74–88.
- [28] Manning BD, Toker A. AKT/PKB signaling: navigating the network. *Cell*. 2017;169(3):381–405.
- [29] Hanahan D. Hallmarks of cancer: new dimensions. *Cancer discovery*. 2022;12(1):31–46.
- [30] Yager JD, Davidson NE. Estrogen carcinogenesis in breast cancer. *New England Journal of Medicine*. 2006;354(3):270–282.
- [31] Briskin C, O’Malley B. Hormone action in the mammary gland. *Cold Spring Harbor perspectives in biology*. 2010;2(12):a003178.
- [32] Yang X, Wu H. RAS signaling in carcinogenesis, cancer therapy and resistance mechanisms. *Journal of Hematology & Oncology*. 2024;17(1):108.
- [33] Dhillon AS, Hagan S, Rath O, Kolch W. MAP kinase signalling pathways in cancer. *Oncogene*. 2007;26(22):3279–3290.

- [34] Gl S. HIF-1 and mechanisms of hypoxia sensing. *Curr Opin Cell Biol.* 2001;13:167–171.
- [35] SI G. Immunity, inflammation, and cancer. *Cell.* 2010;140:883–899.
- [36] Korn T, Bettelli E, Oukka M, Kuchroo V. IL-17 and Th17 cells. *Annual review of immunology.* 2009;27:485–517.
- [37] Yassin Adam A M, Nabila A K, Mohamed S N, Ashraf A A, Kamal M D. Synthesis of some new pyrimidine-based pyrene/benzochromene hybrids as EGFR kinase inhibitors in HCT-116 cancer cells through apoptosis. *RSC Advances.* 2025;15(37):30683–30696.
- [38] Noor MAA, Haq MM, Chowdhury MAR, Tayara H, Shim H, Chong KT. In Silico Exploration of Novel EGFR Kinase Mutant-Selective Inhibitors Using a Hybrid Computational Approach. *Pharmaceuticals.* 2024;17(9).
- [39] Hassan D, Menges C, Testa J, Bellacosa A. AKT kinases as therapeutic targets. *Journal of experimental & clinical cancer research : CR.* 2024;43:313.
- [40] Tu Sn, Hu F, Zhang J, Cai H, Yang J. Research progress on the signaling pathway mechanism of terpenoids against breast cancer. *Discover Oncology.* 2025;16:433.
- [41] Shi A, Liu L, Li S, Qi B. Natural products targeting the MAPK-signaling pathway in cancer: overview. *Journal of Cancer Research and Clinical Oncology.* 2024;150.
- [42] Mohamed Abdoul-Latif F, Ainane A, Houmed Aboubaker I, Mohamed J, Ainane T. Exploring the Potent Anticancer Activity of Essential Oils and Their Bioactive Compounds: Mechanisms and Prospects for Future Cancer Therapy. *Pharmaceuticals.* 2023;16(8).
- [43] Li X, Gaohui Z, Qiyao P, Xiuyang L, Xinrong Z, Wanping Z, et al. Natural products combating EGFR-TKIs resistance in cancer. *European Journal of Medicinal Chemistry Reports.* 2025;13:100251.
- [44] Alrumaihi F, Rahmani AH, Prabhu SV, Kumar V, Anwar S. The Role of Plant-Derived Natural Products as a Regulator of the Tyrosine Kinase Pathway in the Management of Lung Cancer. *Current Issues in Molecular Biology.* 2025;47(7).
- [45] Alamri AM, Assiri AA, Yousuf A, Khan NU. Exploring Nigella Sativa’s medicinal capacity against skin cancer pathways using network pharmacology and molecular docking. *Scientific Reports.* 2025;15:34609.
- [46] Asiamah I, Obiri S, Tamekloe W, Armah F, Borquaye L. Applications of Molecular Docking in Natural Products-Based Drug Discovery. *Scientific African.* 2023;20:e01593.

- [47] Othman B, Beigh S, Albanghali M, Sindi A, Shanawaz M, Ibahim M, et al. Comprehensive pharmacokinetic profiling and molecular docking analysis of natural bioactive compounds targeting oncogenic biomarkers in breast cancer. *Scientific Reports*. 2025;15.
- [48] Odhiambo D, Omosa L, Njagi E, Kithure J, Wekesa E. In-silico Pharmacokinetics ADME/Tox Analysis of phytochemicals from genus *Dracaena* for their therapeutic potential. *Scientific African*. 2025;29:e02796.
- [49] Pires DEV, Blundell TL, Ascher DB. pkCSM: Predicting Small-Molecule Pharmacokinetic and Toxicity Properties Using Graph-Based Signatures. *Journal of Medicinal Chemistry*. 2015;58(9):4066–4072.
- [50] Benet L, Hosey C, Ursu O, Oprea T. BDDCS, the Rule of 5 and drugability. *Advanced Drug Delivery Reviews*. 2016;101.
- [51] Lee J, Beers J, Lanphier R, Jackson K. A Review of CYP-Mediated Drug Interactions: Mechanisms and In Vitro Drug-Drug Interaction Assessment. *Biomolecules*. 2024;14:99.
- [52] Vargas R, Martinez-Martinez N, Lizano C, Pacheco-Molina J, Garcia E, Perez-Lozano M, et al. Advancing through the blood-brain barrier: mechanisms, challenges and drug delivery strategies: Review paper. *ADMET and DMPK*. 2025;p. 2988.
- [53] Wanat K. Biological barriers, and the influence of protein binding on the passage of drugs across them. *Molecular Biology Reports*. 2020;47.