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Network Pharmacology and Molecular Docking to Explore Potential Drug Targets and Bioactive Compounds of *Brucea javanica*, *Centipeda minima*, and *Lithospermum erythrorhizon* in the Treatment of Triple Negative Breast Cancer

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ABSTRACT

Background & Objective: Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer with limited therapeutic options. In this regard, Chinese herbal medicines, including *Brucea javanica (BJ)*, *Centipeda minima (CM)*, and *Lithospermum erythrorhizon (LE)* have exhibited anti-TNBC effects in both cell culture and mouse models, yet, a comprehensive understanding of their mechanisms of action remains elusive. Our study employed a network pharmacology approach and molecular docking to elucidate the potential pivotal pathways, drug targets, and most efficacious active constituents of these medications in the treatment of TNBC.

Materials & Methods: The active compounds and their corresponding target genes were obtained from the TCMSP database. The potential target genes associated with TNBC were also collected from DisGENet. The PPI network was established in the STRING database. The gene ontology and pathway enrichment analyses were conducted using the DAVID platform. AutoDock Vina was used for molecular docking.

Results: The AGE-RAGE signaling pathway in diabetic complications was identified as the top key signaling pathway. The therapeutic effects of *CM*, *BJ*, and *LE* involved a variety of biological processes, primarily the positive regulation of gene expression and cell proliferation, as well as the negative regulation of the apoptotic process. It has previously been observed that AGEs promote and increase the proliferation, invasion, and migration of breast cancer cell lines. The top target proteins included AKT1, TP53, CASP3, and VEGFA. The top active ingredients identified were stigmasterol, beta-sitosterol, nobiletin, and quercetin for *CM*, acetylshikonin for *LE*, and beta-sitosterol for *BJ*, as determined by the disease-drug-compound-target network analysis. The docking results showed good binding affinities ranging from -9 to -6 kcal/mol for all the docked complexes.

Conclusion: *CM*, *BJ*, and *LE* can treat TNBC through a multi-target and multi-pathway mechanism, regulating key cancer signaling pathways and the apoptotic process. This network pharmacology approach provided a new basis for subsequent experimental validation and further exploration of the role of these herbal drugs in treating TNBC.

Keywords: Network Pharmacology, Docking, *Brucea javanica*, *Centipeda minima*, *Lithospermum erythrorhizon*, Triple Negative Breast Neoplasms

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1. Introduction

Breast cancer (BC) is the most prevalent malignancy in women worldwide (1). According to the American Cancer Society, in 2023, near 298,000 new cases of invasive breast cancer are diagnosed in the US, and about 44,000 women died from this cancer. Triple-negative breast cancer (TNBC) is an aggressive subtype that accounts for about 10-15% of all breast cancer cases. It is known by the lack of estrogen and progesterone receptors (ER and PR) and also not making any or too much of the human epidermal growth factor receptor 2 (HER2) (2). TNBC has remained an unmet medical challenge due to a high rate of early relapse, visceral metastasis, and limited molecular targets and therapeutic options. Patients with TNBC cannot receive hormone or anti-HER2 therapies, and chemotherapy remains the main adjuvant treatment method, although many tumors still resist it and relapse (3).

Therefore, there is an urgent need to develop novel treatment regimens and drug targets for TNBC, although this is a difficult process due to the high heterogeneity of TNBC subtypes. However, various ongoing projects and clinical trials are underway to discover new targeted therapies. For instance, there are some clinical trials that aim to target the epidermal growth factor receptor (EGFR), androgen receptor (AR), estrogen receptor ER-A36, and PARP (4). In recent years, Traditional Chinese Medicine (TCM) has been widely used and accepted as an alternative and complementary treatment for cancer, which has shown beneficial effects with less serious side effects than common chemodrugs. In the case of breast cancer, several anti-BC herbal drugs have been discovered, although some of the action mechanisms of these compounds have not been elucidated yet. More than 20 herbal alkaloids have been shown to inhibit the growth of mammary cancer cell lines. From these alkaloids, berbamine and camptothecin have demonstrated strong inhibition of breast cancer cell growth (5). Flavonoids (polyphenols) are another group of herbal drugs with potential anti-tumor properties in breast cancer cells. Resveratrol, curcumin, silibinin, Kaempferol, and baicalin are among the most well-known flavonoids with anti-carcinogenic activities for breast cancer, both *in vitro* and *in vivo* (6).

Brucea javanica (*BJ*), with the Chinese name of Ya Dan Zi, *Centipeda minima* (*CM*) with the Chinese name of E Bu Shi Cao, and *Lithospermum erythrorhizon* (*LE*) with the Chinese name of Zi Cao, are from the Chinese herbal drugs that have been examined most recently in the treatment of TNBC in cell lines and mouse models. However, the mechanism of action of their bioactive components on TNBC-related signaling pathways and their potential therapeutic targets have not been completely studied. Chen et al (7) showed the inhibitory effect of *BJ* seed extract on MDA-MB-231 TNBC cell line proliferation. Moreover, no noticeable toxicity was reported in other organs such as the liver, small intestine, and kidneys (7). Luo et al (8) also investigated the anti-cancer effects of *Bruceine D from BJ* on the MDA-MB-231 TNBC cell line (8). They observed altered expression of vimentin, E-cadherin, and β-catenin, which are associated with the epithelial to mesenchymal transition (EMT), as well as proteins related to the PI3K/AKT signaling pathway.

Centipeda minima is another herbal medicine belonging to the Asteraceae family, which was mostly well-known for its anti-allergy and asthma and anti-malaria efficacy in TCM. Its main chemical constituents include flavonoids, Sesquiterpenoids, sterols, monophenols, saponins, and fatty acids (9). Lee et al (10) conducted the first study on the anti-cancer activity of CM in TNBC cell lines and a mouse model. They reported that *CM* significantly reduces cell proliferation and inhibits cell migration and invasion in TNBC cells (10). *Lithospermum erythrorhizon* is another herbal drug belonging to the Boraginaceae family, which is mainly cultivated in China and some other Asian countries. Shikonin (a main constituent of *LE*) can effectively inhibit the activity of TNF-α and block its pre-mRNA splicing (11).

Network pharmacology has been extensively utilized in recent years to investigate the mechanisms of action of traditional Chinese medicines and identify potential drug targets. It works by applying computer algorithms and pharmacological databases to screen for effective drug targets and the involved signaling pathways, analyzing the network of herbal drug active compounds and their target genes. As no previous study was performed to holistically explore the action mechanisms and potential bioactive ingredients of *BJ*, *CM*, and *LE* in the treatment of TNBC by systems pharmacology approach, in this paper, we have conducted a network pharmacology study followed by molecular docking to discover the most effective bioactive compounds and potential drug targets of *BJ*, *CM,* and *LE* and the most significant signaling pathways, biological processes, and molecular functions, affected by these herbal drugs in TNBC treatment.

2. Materials and Methods

2.1 Acquisition of active ingredients and target genes of *BJ, CM* and *LE*

The active ingredients and potential target genes of the herbal drugs, *BJ*, *CM,* and *LE*, were obtained from the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) (https://tcmsp-e.com/). The active ingredients were selected based on ADME (absorption, distribution, metabolism, and excretion) parameters with the following thresholds: Drug-likeness (DL) ≥ 0.18, Oral bioavailability (OB) ≥ 30%, CACO-2 cell permeability ≥ 0, H-bond donor ≤ 5, and H-bond acceptor ≤ 10. However, OB% and DL are the most important parameters in the development of new

drugs. The target genes of the herbal drugs were also collected from the TCMSP platform.

2.2 Acquisition of known target genes of TNBC and their target miRs

TNBC-associated target genes were retrieved from the DisGeNET (https://www.disgenet.org/) and Malacards (https://www.malacards.org/) databases after removing duplicate genes. The target miRs for the top degree genes in the network were derived from TargetScanHuman v.8.0 database (https://www.targetscan.org/).

2.3 Construction and analysis of the protein–protein and Disease-Drug-Compound-Target gene interaction networks

The common genes between the target genes of the herbal medicines and TNBC were retrieved by overlapping the genes in Venny v.2.1 platform (https://bioinfogp.cnb.csic.es/tools/venny/). After selecting the overlapping target genes, a protein-protein interaction network of the common genes was constructed using the STRING database (https://string-db.org/) and was visualized and analyzed in Cytoscape v3.2.1 software by the network analyzer. The Cytohubba plugin in Cytoscape showed a network of the top 10 target genes with highest degree and betweenness centrality scores. A network of disease-herbal drugs-active compounds-target genes was also constructed in Cytoscape software to reveal the top highly connected bioactive ingredients of the selected herbal drugs.

2.4 Gene ontology (GO), pathway enrichment analysis and Construction of Drug-Target gene-Signaling pathway network

We performed Gene Ontology (GO) and KEGG pathway enrichment analyses to deeply explore the biological processes (BP), molecular functions (MF), involved cellular components (CC), and the key signaling pathways regarding the therapeutic effects of *BJ*, *CM*, and *LE* on TNBC. The GO and pathway analyses were conducted using the functional annotation tools of DAVID. Bonferroni-corrected p-values less than 0.05 were considered for the selection of the significant ontology and pathway terms. Then, the results of the KEGG pathway enrichment was visualized as a drug-target genes-signaling pathway network in the Cytoscape software.

2.5 Molecular Docking

Molecular docking was performed to evaluate the binding affinity for compound-target gene interactions. The 3D structures of the ligands were obtained from the PubChem database and downloaded as sdf files. The 3D structures of the hub proteins were retrieved from the rcsb database (https://www.rcsb.org/) as pdb files. The preparation of the ligand and target proteins were carried out by AutoDock Tools v.4. The ligand preprocessing included adding gasteiger charges and adding atoms by root selection in the torsion tree. The output was saved as pdbqt files. Protein preprocessing included omission of crystal water molecules, removal of co-crystallized small molecules that had occupied the binding sites, adding hydrogen atoms, adding total kollman charges, and assigning atom types. The results were saved as pdbqt files. Energy minimization and calculating RMSD were performed using Swiss-PDBViewer 4.0 (http://www.expasy.org/spdbv/) and UCSF Chimera 1.8 software. Ligands and proteins in pdbqt format were then uploaded to the AutoDock Vina wizard v.1.2.0 following by determining the grid box for each protein based on their key binding sites. The binding affinities were recorded as Kcal/mol values. The interaction results were interpreted and visualized in BIOVIA Discovery Studio 2016 software (https://discover.3ds.com/) and Python Molecular Viewer 1.5.6.

3. Result

3.1 Acquisition of the active ingredients and target genes of BJ, CM, and LE; Acquisition of target genes of TNBC

A total of 31 bioactive compounds (out of 226 compounds) were obtained from the TCMSP database based on the ADME threshold. These items included 2 ingredients from *BJ*, 20 from *CM*, and 11 compounds from *LE*, followed by elimination of 2 duplicates. Table 1 provides detailed descriptions of these active ingredients. The number of target genes for these herbal drugs was 1551, including 106 for *BJ*, 1001 for *CM*, and 444 for *LE*, resulting in 343 unique genes after removing duplicates. There were 1605 target genes for TNBC based on DisGENet and Malacards databases after removing duplicates. For DisGENet database, only genes with scores more the 0.01 were considered.

3.2 Identification of common target genes and analysis results of the protein-protein interaction network; Identification of the target miRs

After overlapping 1605 TNBC target genes and 343 herbal drugs therapeutic target genes, a total of 135 common genes were identified. The Venn diagram and the network of drug-disease common genes are shown in Figure 1. The PPI network of the common genes/proteins was established through the STRING database which included 135 nodes and 2643 edges. The average node degree, average local clustering coefficient, and PPI enrichment p-value were 39.2, 0.669, and 1.0e-16 respectively. This network was imported into Cytoscape software. Other network parameters included network diameter of 4, radius of 2, centralization of 0.554, shortest path of 17822, density of 0.297, and heterogeneity of 0.650. The PPI network is visualized in Figure 1, part C. The top 10 hub nodes based on degree and betweenness centrality were extracted from the PPI network by Cytohubba plugin and are visualized as networks in Figure 1, parts D and E. The top high degree proteins included AKT1, TP53, MYC, CASP3, VEGFA, STAT3, HIF1A, IL6, PTEN, and TNF. The top bottleneck nodes with the highest betwenness centralities also included AKT1, TP53, and FOS. The detailed characteristics of the hub nodes are provided in Table 2. The target miRs for the

top degree genes including AKT1, TP53, CASP3, and VEGFA were as follows: hsa-miR-520a-3p, hsa-miR-520b-3p, hsa-miR-302c-3p, and hsa-miR-302e-3p for AKT1, hsa-miR-122-5p for TP53, hsa-miR-98-5p and hsa-let-7-5p for CASP3, and hsa-miR-205-5p for VEGFA.

3.3 Gene Ontology and KEGG pathway enrichment analysis results

To further explore the mechanism of action of *BJ*, *CM*, and *LE* on TNBC, we entered the common target genes into the DAVID database. Interestingly, the enrichment analysis results showed that although these three herbal drugs have almost different active ingredients, but they exert their action on TNBC cells through the same key pathways and cellular processes. The gene ontology and pathway enrichment results are shown in Figure 2. The KEGG pathway results enriched 105 terms according to the Bonferroni-corrected p-values<0.05. The top significant key pathways included AGE-RAGE signaling pathway in diabetic complications (p-val= 7.25E-28), PI3K-AKT signaling pathway (p-val= 2.33E-19), p53 signaling pathway (p-val= 4.30E-15), MAPK signaling pathway (p-val= 1.34E-14), IL-17 signaling pathway (p-val= 2.76E-14), TNF signaling pathway (p-val= 5.53E-14), apoptosis (p-val= 1.38E-13), HIF-1 signaling pathway (p-val= 6.63E-12), FoxO signaling pathway (p-val= 1.42E-11), C-type lectin receptor signaling pathway (p-val= 6.22E-10), Relaxin signaling pathway (p-val= 1.82E-08), and Sphingolipid signaling pathway (p-val= 7.49E-08). The top enriched biological processes included positive regulation of gene expression (p-val= 7.87E-22), negative regulation of apoptotic process (p-val= 3.26E-18), positive regulation of transcription from RNA polymerase II promoter (p-val= 4.09E-18), positive regulation of cell proliferation (p-val= 1.09E-16), signal transduction (p-val= 1.74E-11), response to lipopolysaccharide (p-val= 1.64E-10), aging (p-val= 2.01E-10), protein phosphorylation (p-val= 7.27E-10), cellular response to hypoxia (p-val= 1.24E-09), inflammatory response (p-val= 4.63E-09), and MAPK cascade (p-val= 1.10E-08). The top 5 molecular functions were related to enzyme binding (p-val= 5.80E-17), protein binding (p-val= 1.48E-12), RNA polymerase II transcription factor activity ligand-activated sequence-specific DNA binding (p-val= 5.52E-11), protein kinase binding (p-val= 1.35E-10), and protein serine/threonine/tyrosine kinase activity (p-val= 1.50E-07). The top 5 cellular components that were enriched were chromatin (p-val=4.50E-11), macromolecular complex (p-val=8.58E-11), nucleoplasm (p-val= 1.67E-10), nucleus (p-val= 2.61E-09), and cytoplasm (p-val=4.08E-09). Figure 3, part A shows the network of the top significant signaling pathways and their involved target genes that are affected by *BJ*, *CM*, and *LE*, in the treatment of TNBC.

3.4 Construction and analysis of the Disease-Drug-Compound-Target gene interaction network

After removing 7 compounds without target genes, the disease-drug-compound-target network contained 141 nodes and 366 edges, including 3 herbs, 24 active compounds, and 113 genes. The network is illustrated in Figure 3, part B. The hub active ingredients are represented by larger pink circles. Accordingly, quercetin, luteolin, nobiletin, beta-sitosterol, stigmasterol, acetylshikonin, and 1-[(Z)-2-(3,5-dimethoxyphenyl)vinyl]-3,5-dimethoxybenzene were the top 7 highest degree active compounds in this network. Detailed information about these compounds is provided in Table 3. The top 5 active ingredients were selected as potential drugs to perform molecular docking.

3.5 Molecular docking results: Identification of the most effective active ingredients and their target proteins

The network pharmacology approach has demonstrated that the primary bioactive compounds found in herbal medications for the treatment of TNBC, namely, stigmasterol, nobiletin, and quercetin (derived from *CM*), beta-sitosterol (from both *CM* and *BJ*), and acetylshikonin (from *LE*), are capable of interacting with the top 4 targetable target proteins, AKT1, TP53, CASP3, and VEGFA. The 3D chemical structures of target proteins were obtained from rcsb PDB x-ray crystals with less than 2.5 Å resolution. The PDB ID for the selected structures of AKT1, TP53, CASP3, and VEGFA were 6HHG, 7B4N, 5IBP, and 5O4E respectively. These structures were docked to five candidate bioactive compounds (stigmasterol, beta-sitosterol, nobiletin, quercetin, and acetylshikonin). We considered a binding score $\leq$ -5 Kcal/mol as an acceptable binding energy in the docking results. Undoubtedly, the more negative the energy, the stronger the binding affinity between the ligand and the target protein. Table 4 shows the binding affinity energies (Kcal/mol) for the docked complexes. As can be seen, AKT1 has the most negative binding affinity, ranging from -9.1 kcal/mol for stigmasterol to -8 kcal/mol for nobiletin. The highest binding affinities were related to VEGFA interaction with nobiletin, which was -5.2 kcal/mol. According to Table 4, all the binding scores are good and acceptable. The molecular docking results showed reliable binding conformations for all complexes. However, we also considered the number of hydrogen and hydrophobic bonds in each complex to select the best interacting compound-target pairs. Accordingly, the complex of AKT1 with quercetin and acetylshikonin with binding energies of -8.7 and -8.5 kcal/mol, TP53 with beta-sitosterol and quercetin with binding energies of -6.9 and -6.7 kcal/mol, CASP3 with nobiletin and quercetin with binding energies of -6.4 and -6.6 kcal/mol and VEGFA with quercetin and stigmasterol with binding energies of -6.2 and -6.8 kcal/mol were the best protein-ligand complexes. The interacting sites of these complexes are shown in Figure 4. The interacting amino acids at the binding site of each complex are also detailed in Table 4. Consequently, the most effective target gene for *BJ* was identified as TP53, which interacts with beta-sitosterol, while AKT1, which interacts with acetylshikonin, was determined to be the most effective target gene for *LE*. Furthermore, AKT1, TP53, CASP3,

and VEGFA are all capable of interacting with the active compounds from *CM*.

Table 1. Detailed information of the active components of the selected herbal drugs. ([1]Molecular weight, [2]Oral bioavailability, [3]CACO-2 cell permeability, [4]Drug-likeness, [5]H-bond donors, [6]H-bond acceptors)

Mol ID	Molecule name	MW[1]	OB%[2]	CACO-2[3]	DL[4]	Hdon[5]	Hacc[6]
MOL000358	beta-sitosterol	414.79	36.91	1.32	0.75	1	1
MOL000006	luteolin	286.25	36.16	0.19	0.25	4	6
MOL011723	florilenalin angelic acid	346.46	105.11	0.16	0.39	1	5
MOL011726	senecioylplenolin	344.44	90.22	0.35	0.37	0	5
MOL011718	Arnicolide D	332.43	85.85	0.21	0.33	0	5
MOL009042	Helenalin	262.33	77.01	0.06	0.19	1	4
MOL011722	arnicolide C	334.45	76.91	0.48	0.32	0	5
MOL011728	(1R,3aR,5R,5aS,8aR,9S,9aS)-9-hydroxy-1,5,8a-trimethyl-3a,4,5,5a,6,7,9,9a-octahydro-1H-azuleno[7,6-d]furan-2,8-dione	266.37	70.36	0.2	0.19	1	4
MOL011694	Plenolin	264.35	68.26	0.24	0.19	1	4
MOL005828	nobiletin	402.43	61.67	1.05	0.52	0	8
MOL007415	[(2S)-2-[[(2S)-2-(benzoylamino)-3-phenylpropanoyl]amino]-3-phenylpropyl] acetate	444.57	58.02	0.32	0.52	2	6
MOL011724	florilenalin isobutyrate	348.48	55.53	0.24	0.38	1	5
MOL004961	Quercetin der.	330.31	46.45	0.39	0.33	3	7
MOL000098	quercetin	302.25	46.43	0.05	0.28	5	7
MOL000449	Stigmasterol	412.77	43.83	1.44	0.76	1	1
MOL011716	[2-hydroxy-2-(2-hydroxy-4-methylphenyl)-3-(2-methylpropanoyloxy)propyl] 2-methylpropanoate	338.44	43.19	0.24	0.2	2	6
MOL000596	[(3S,4aR,6aR,6aR,6bR,8aR,12S,12aR,14aR,14bR)-4,4,6a,6b,8a,12,14b-heptamethyl-11-methylene-1,2,3,4a,5,6,6a,7,8,9,10,12,12a,13,14,14a-hexadecahydropicen-3-yl] acetate	468.84	43.08	1.36	0.74	0	2
MOL011704	1-[(Z)-2-(3,5-dimethoxyphenyl)vinyl]-3,5-dimethoxybenzene	300.38	41.69	1.14	0.21	0	4
MOL006554	Taraxerol	426.8	38.4	1.37	0.77	1	1
MOL000359	sitosterol	414.79	36.91	1.32	0.75	1	1
MOL011727	[(3S,4aR,6aR,6aR,6bR,8aR,12S,12aR,14aR,14bR)-4,4,6a,6b,8a,12,14b-	665.26	33.84	1.48	0.3	0	2

Mol ID	Molecule name	MW[1]	OB%[2]	CACO-2[3]	DL[4]	Hdon[5]	Hacc[6]
	heptamethyl-11-methylene-1,2,3,4a,5,6,6a,7,8,9,10,12,12a,13,14,14a-hexadecahydropicen-3-yl] hexadecanoate						
MOL007719	Arnebin 7	272.32	73.85	0.74	0.18	2	4
MOL007714	1-methoxyacetylshikonin	344.39	73.09	0.24	0.29	1	6
MOL007722	Isoarnebin 4	288.32	64.79	0.06	0.2	3	5
MOL007716	acetylshikonin	330.36	62.39	0.3	0.27	2	6
MOL007734	5-[(E)-5-(3-furyl)-2-methyl-pent-2-enyl]-2,3-dimethoxy-p-benzoquinone	316.38	61.8	0.92	0.24	0	5
MOL007715	[(1R)-1-(5,8-dihydroxy-1,4-dioxo-2-naphthyl)-4-methyl-pent-3-enyl] propanoate	344.39	54.64	0.25	0.29	2	6
MOL001494	Mandenol	308.56	42	1.46	0.19	0	2
MOL002372	(6Z,10E,14E,18E)-2,6,10,15,19,23-hexamethyltetracosa-2,6,10,14,18,22-hexaene	410.8	33.55	2.07	0.42	0	0
MOL002883	Ethyl oleate (NF)	310.58	32.4	1.4	0.19	0	2
MOL007735	Des-O-methyllasiodiplodin	278.38	30.12	0.83	0.2	2	4

Table 2. The top hub/bottleneck proteins in the PPI network.

Gene symbol	Protein name	Closeness centrality	Degree	Betweenness centrality
AKT1	RAC-alpha serine/threonine-protein kinase	0.8562	114	0.0666
TP53	Cellular tumor antigen p53	0.8154	107	0.0425
MYC	Myc proto-oncogene protein	0.7696	98	0.0276
CASP3	Caspase-3	0.774	97	0.0297
VEGFA	Vascular endothelial growth factor A	0.7696	96	0.0213
HIF1A	Hypoxia-inducible factor 1-alpha	0.7527	93	0.0239
STAT3	Signal transducer and activator of transcription 3	0.7486	93	0.0191
IL6	Interleukin-6	0.7486	91	0.0236
PTEN	Phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase PTEN	0.7365	90	0.0263
TNF	Tumor necrosis factor	0.7445	90	0.0182
FOS	Proto-oncogene c-Fos	0.6989	79	0.03106

Table 3. The top highest degree active ingredients resulted from the Drug-Compound-Target gene interaction network, sorted based on drug-likeness value.

Active compound	Degree	Betweenness Centrality	OB%	DL	Herbal Drug
Stigmasterol	11	0.01262587	43.83	0.76	*Centipeda M*
beta-sitosterol	17	0.02306243	36.91	0.75	*Centipeda M, Brucea J*
nobiletin	19	0.01803005	61.67	0.52	*Centipeda M*
quercetin	84	0.22455227	46.43	0.28	*Centipeda M*
acetylshikonin	10	0.00733778	62.39	0.27	*Lithospermum E*
Luteolin	34	0.03893934	36.16	0.25	*Brucea J*
1-[(Z)-2-(3,5-dimethoxyphenyl)vinyl] -3,5-dimethoxybenzene	10	0.00872179	41.69	0.21	*Centipeda M*

Table 4. Docking binding affinities of the top degree active ingredients with their potential target proteins and the interacting amino acids in each complex.

Protein	Ligand	Binding Affinity (Kcal/mol)	#H-BONDS	Interacting Amino Acids		
				Conventional H-bond	Carbon H-bond	Van Der Waals
AKT1	Stigmasterol	-9.1	0			GLU85-GLU17-THR82-ARG273-ASP274-ASN54-GLN79-THR81-LEU264-ASP292-LEU210
	Beta-sitosterol	-8.6	1	GLU17		LEU210-ASP292-GLN79-LYS179-THR82-GLY294-ASP274-LEU295-LEU264-ARG273-VAL271-CYS310
	Nobiletin	-8	1	ASN54	GLN79-GLU85-ASP274-TYR272-LYS297	GLU17-VAL270-GLY294-THR82-CYS310
	Quercetin	-8.7	3	ASP274-ASP292-GLY294		GLU17-THR82-LYS179-LEU295-PHE293-THR291-TYR272-GLN79-ASN54-TYR326
	Acetylshikonin	-8.5	4	TYR18-ARG273-ASP292-ASN54		GLU17-VAL271-VAL270-TRP80-THR81-THR82-ASP274
TP53	Stigmasterol	-6.9	1	SER269		THR102-PHE113-GLY112-GLN144-PRO128-ASN131-PHE270-ASN268
	Beta-sitosterol	-6.9	2	THR102-SER269		GLY112-PHE113-PRO128-GLN144-ASN131-PHE270-ASN268

Protein	Ligand	Binding Affinity (Kcal/mol)	#H-BONDS	Interacting Amino Acids		
				Conventional H-bond	Carbon H-bond	Van Der Waals
	Nobiletin	-6.1	1	ASN131	ASN268-PRO128-LEU111	GLY112-PHE113-HIS115-GLN144-THR102-ARG110-SER269-PHE270
	Quercetin	-6.7	3	ASN131-SER269		THR102-LEU111-ARG110-PHE113-GLY112-TYR126-PRO128-ASN268-PHE270
	Acetylshikonin	-6.4	1	SER269		THR102-LEU111-PHE113-GLY112-ASN131-ASN268-PHE270
CASP3	Stigmasterol	-7.9	1	SER251		MET61-GLY122-GLU123-GLY156-THR166-ARG207-PHE252
	Beta-sitosterol	-7.2	1	GLU123		ARG207-LEU168-SER205-THR62-MET61-GLY122-PHE128
	Nobiletin	-6.4	5	HIS121-ARG207-SER251	SER205-ASP253	ARG64-GLY122-CYS163-TYR204-PHE250
	Quercetin	-6.6	3	THR62-GLU123	TRP206	GLY60-PHE128-GLY122-ARG207-SER205-TYR204
	Acetylshikonin	-6.6	2	GLY122-ARG207	CYS163	HIS121-THR166-GLU123-PHE128
VEGFA	Stigmasterol	-6.8	1	GLU103		GLN22-ASN62-LYS101-CYS102
	Beta-sitosterol	-6.3	0			GLN22-HIS27-CYS26-PRO28-ASN62-LYS101-CYS102
	Nobiletin	-5.2	1	GLN22	CYS26-CYS102	TYR21-HIS27-PRO28-ASN62
	Quercetin	-6.2	6	CYS57-CYS61-GLU64-LYS107	GLY58	GLY59-ASP63-LEU66-GLU67
	Acetylshikonin	-5.6	2	ASN62		MET18-TYR21-GLN22-CYS26

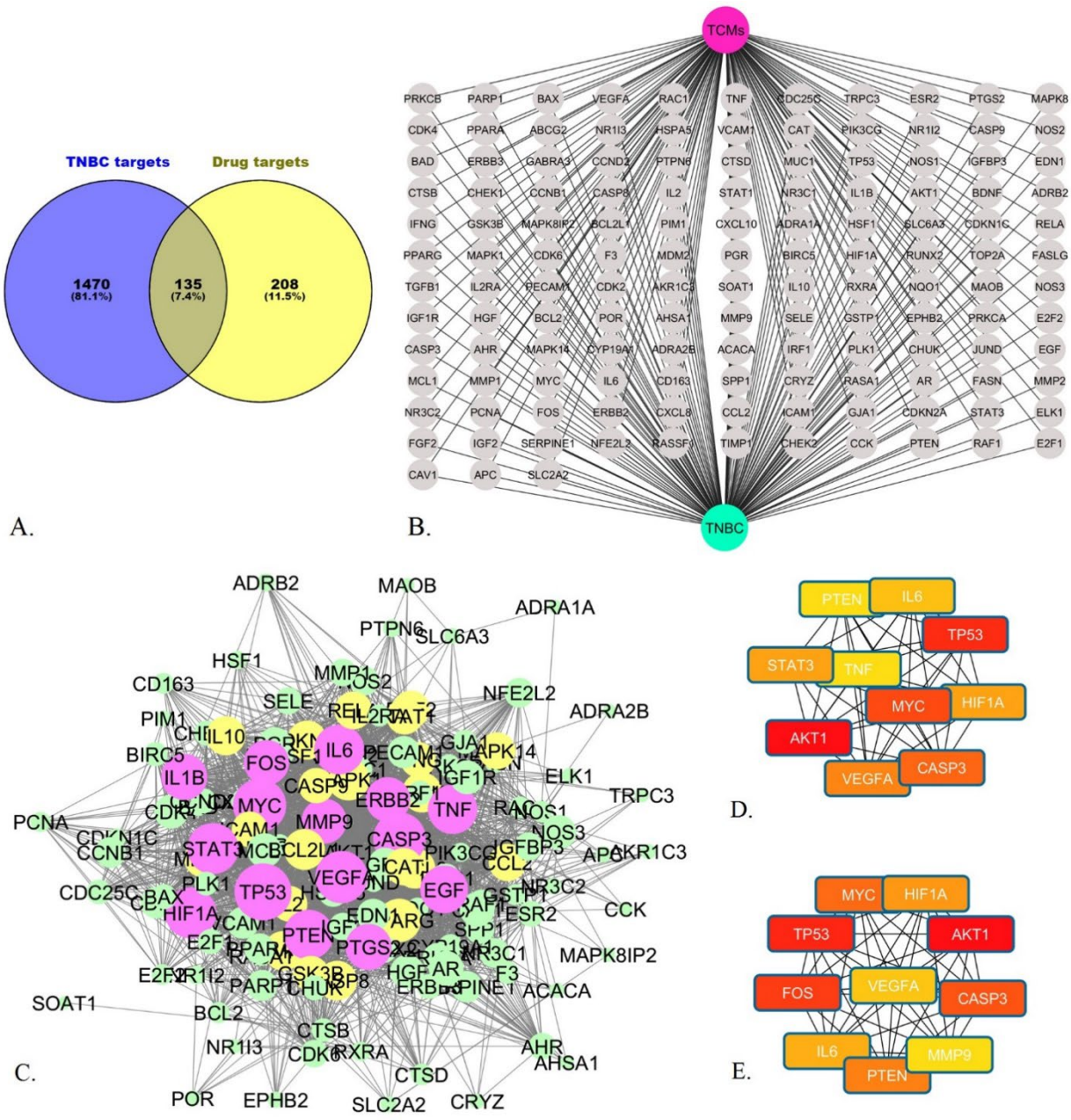

Figure 1. A) Venn diagram showing the overlapped genes between TNBC and herbal drugs; B) Network of drug-disease-common genes; C) The protein-protein interaction network of the common proteins between TNBC and herbal drugs target genes; D) A network of top 10 hub nodes with the highest degrees; E) A network of top 10 hub nodes with the highest betweenness centrality values (TCMs: Traditional Chinese Medicines, TNBC: Triple-negative Breast Cancer) (**Designed by Authors, 2025**).

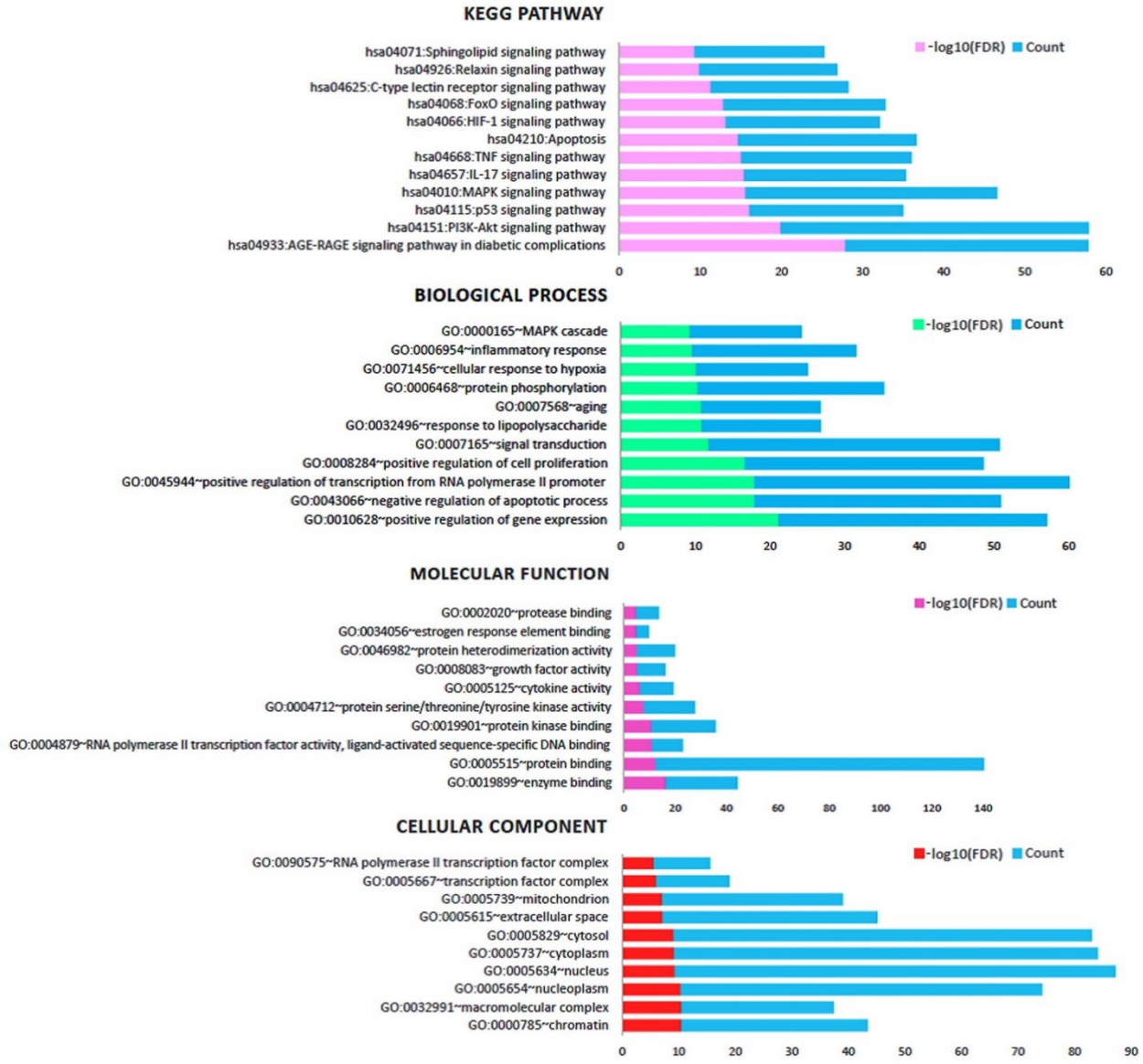

Figure 2. KEGG pathway enrichment and gene ontology (GO) results including biological process, molecular function and cellular component analysis results from DAVID database. (**Designed by Authors, 2025**).

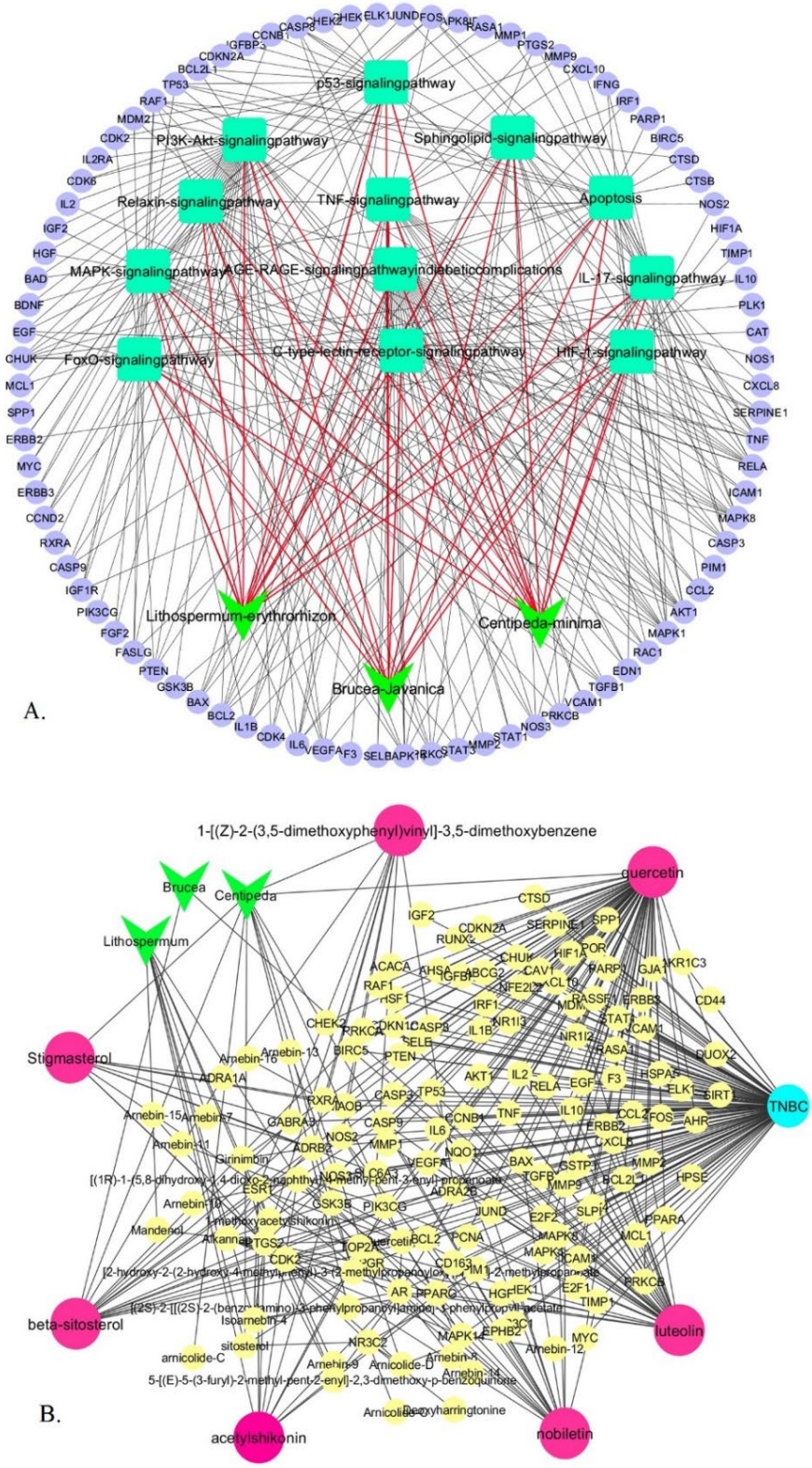

Figure 3. A) The top key pathways that are affected by *BJ*, *CM* and *LE* in TNBC treatment. The involved genes in each pathway are also shown. B) Disease-Drug-Compound-Target gene interaction network. The hub compounds are shown as pink circles. Yellow circles denote network target genes and other active ingredients. Green signs show herbal Chinese medicines. (**Designed by Authors, 2025**).

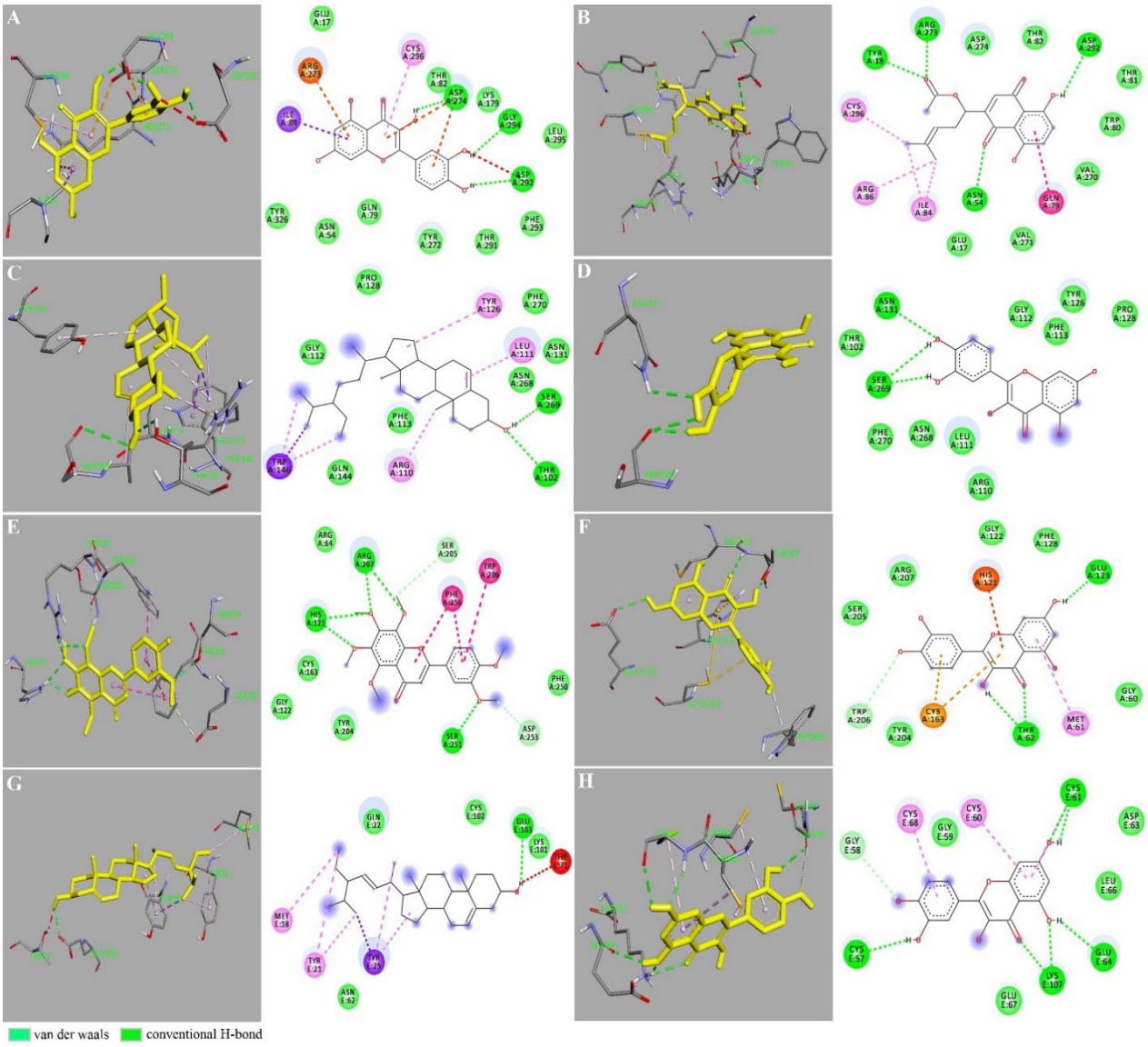

Figure 4. The 3D and 2D views of the molecular docking results showing the target proteins interacting residues with the active compounds for the top 2 best complexes for each target protein (A:AKT1-Quercetin, B:AKT1-Acetylshikonin, C:TP53-beta-sitosterol, D:TP53-Quercetin, E:CASP3-Nobiletin, F;CASP3-Quercetin, G:VEGFA-Quercetin, H:VEGFA-Stigmasterol). (**Designed by Authors, 2025**).

4. Discussions

The herbal drugs *Brucea javanica*, *Centipeda minima,* and *Lithospermum erythrorhizon* have been used in recent years for the treatment of TNBC, both in cell line and animal model studies. In the present study, we integrated network pharmacology and molecular docking to identify the most effective bioactive compounds of these herbal drugs in treating TNBC and their potential protein targets. Moreover, the most significantly enriched pathways and Gene Ontology terms regarding the effect of these herbal medicines on TNBC were presented. TNBC is an aggressive type of breast cancer with a poor prognosis. Due to the failure of anti-hormonal and anti-HER2 therapies, the development of complementary and alternative targeted drugs is urgently needed. Interestingly, although these three herbal drugs have almost different active ingredients, the enrichment analysis results showed that they exert their action on TNBC through the same key KEGG signaling pathways and the same ontology processes. The pathway enrichment analysis results showed that the AGE-RAGE signaling pathway in diabetic complications, PI3K-AKT signaling pathway, p53 signaling pathway, MAPK signaling pathway, IL-17 signaling pathway, TNF signaling pathway, apoptosis, HIF-1 signaling pathway, FoxO signaling pathway, C-type lectin receptor signaling pathway, Relaxin signaling pathway, and Sphingolipid signaling pathway were the most significant among others.

The AGE-RAGE signaling pathway in diabetic complications was the top KEGG pathway. Recent investigations have shown that there is an increased possibility of developing breast cancer in diabetic patients

(12). AGEs denote Advanced Glycation Endproducts. It was observed that AGEs promote and increase proliferation, invasion, and migration of MDA-MB-231 breast cancer cell lines. These AGEs exert their effect by increasing the expression of their receptors, RAGEs, and the ERK signaling protein (13). RAGEs are also overexpressed in cancer cells. Radia et al (14) demonstrated that siRNAs targeting the RAGE receptors resulted in decreased breast cancer cell proliferation (14). In this regard, AGEs have been proposed as putative drug targets for the treatment of patients with both diabetes and breast cancer (15). The PI3K-AKT signaling pathway is another significant pathway affected by *BJ*, *CM*, and *LE*. The involvement of this pathway in various cancers, including breast cancer, has been widely accepted (16). Chen et al (7) observed altered expression of proteins related to autophagy and PI3K/AKT/mTOR signaling pathway in MDA-MB-231 TNBC cell line treated with *BJ* extract (7). Luo et al (8) also reported altered expression of proteins involved in the PI3K/AKT signaling pathway in the MDA-MB-231 cell line affected by Bruceine D from *BJ* (8). In the case of *Centipeda minima,* Lee et al (10) suggested that it may act through the inhibition of the *PI3K/AKT/mTOR, EGFR, NF-κ*B, and STAT3 signaling pathways in breast cancer (10). Other major signaling pathways affected by these herbal drugs were the TP53 and MAPK signaling pathways. These two pathways are extensively shown to be involved in breast cancer pathology. TP53 gene mutations are associated with more aggressive breast cancer subtypes and worse overall survival. The MAPK pathway is also involved in the invasion and migration of breast cancer cells (17). Therefore, it can be concluded that *BJ*, *CM*, and *LE* may act on breast cancer cells by reducing the migration and invasion of cancer cells through suppression of these pathways. The other pathways mentioned above in the KEGG enrichment analysis are also from the most important pathways in different cancer types.

Analysis of the disease-drug-compound-target gene interaction network revealed that quercetin, luteolin, nobiletin, beta-sitosterol, stigmasterol, acetylshikonin, and 1-[(Z)-2-(3,5-dimethoxyphenyl)vinyl]-3,5-dimethoxybenzene were the top high-degree bioactive components of the herbal drugs. By sorting these hub nodes based on their drug-likeness property, the top five active compounds included stigmasterol, beta-sitosterol, nobiletin, quercetin, and acetylshikonin, with drug-likeness of 0.76, 0.75, 0.52, 0.28, and 0.27, respectively. Their oral bioavailability percent were also 43.83, 36.91, 61.67, 46.43, and 62.39, respectively. We selected these active components to dock with AKT1, TP53, CASP3, and VEGFA, which are potential key targetable hub/bottleneck proteins for TNBC. Stigmasterol was a key chemical component of *CM*. Stigmasterol (C29H48O) is a phytosterol, a steroid derived from tetracyclic triterpenes, which have a similar structure to cholesterol. Stigmasterol and its derivatives are emerging as potential candidates for novel anticancer drugs (18). It has been observed that stigmasterol can trigger the PI3K/AKT/mTOR and JAK/STAT signaling pathways through the activation of certain pro-apoptotic proteins, thereby suppressing chemoresistance in various cancers. Previous cell line and mouse model studies identified Bcl-2, Bcl-xl, and VEGF as possible targets for stigmasterol in breast cancer, which showed a reduction in their expression (19). The anti-tumor efficacy of stigmasterol in combination with chemotherapeutics on breast cancer cell lines was also reported by Gautam et al (20) who delivered the drug via nanohybrid phytoliposomes to MDA-MB-231 cells (20). It was also demonstrated that the combination of stigmasterol and beta-sitosterol has an immunoregulatory effect, resulting in reduced cytokine secretion and the activation of immune cells (21).

Beta-sitosterol is another active ingredient from *CM* and *BJ*. Its structure is similar to that of cholesterol, with an additional ethyl group. It is not synthesized in the human body and is only obtained from plant sources, such as wheat, rice, corn, nuts, and olive oil. It is observed that beta-sitosterol from the leaves of the medicinal plant, *Acalypha wilkesiana*, induces apoptosis in the MCF-7 breast cancer cell line (22). Nobiletin was another significant active compound in our results, which is found in *CM*. Several studies have also demonstrated the enhanced cytotoxic effects of chemotherapeutic agents, such as vinblastine and doxorubicin, when combined with nobiletin. It can also ameliorate the chemoresistance by inhibiting CXCR4, a key regulator of cancer stem cells. It was observed that nobiletin can induce G2/M arrest in TNBC cells by downregulating the AKT and MAPK signaling pathways (23).

Quercetin, a natural flavonoid, was another key compound in our results, which was present in *CM*. Quercetin has been proposed as a potential chemopreventer that plays a role in various cancer-related processes such as apoptosis, oxidative stress, tumor growth, and cancer cells metastasis (24). It is involved in several pathways and can negatively modulate the PI3K-AKT, MAPK, NF-kB, and mTOR signaling pathways (25). There are several studies on the therapeutic efficacy of quercetin in breast cancer. Tao et al (26) found that quercetin can prevent cell invasion and proliferation in breast cancer cells by activating the caspase-3 pathway and downregulating EGFR (26). It can reduce the migration of TNBC cells by regulating the β-catenin signaling pathway. It was also demonstrated that quercetin can reverse resistance to cisplatin in the MDA-MB-468 TNBC cell line by inhibiting the cytochrome P450 1B1 enzyme (27, 28).

Acetylshikonin was another bioactive compound in our results, which is a key ingredient of *Lithospermum erythrorhizon*. Shikonin and its derivatives have shown great potential in cancer treatment. Acetylshikonin is a naphthoquinone compound with anti-inflammatory, anti-bacterial, and anti-tumor effects. The proposed mechanisms for the anti-cancer activities of shikonin primarily include the induction of reactive oxygen species (ROS), inhibition of the EGFR pathway, activation of the PI3K/AKT signaling pathway, and induction of

necroptosis and apoptosis (29). Previous studies have demonstrated that shikonins exhibit anti-TNBC activity by inhibiting the IMPDH2 enzyme. It was also reported that shikonin can reverse the epithelial-to-mesenchymal transition by suppressing β-catenin signaling and consequently inhibit the metastasis of TNBC cells (30). Docking of these bioactive compounds against AKT1, TP53, CASP3, and VEGFA hub proteins showed acceptable results. Among the formed complexes, the interaction of AKT1 with stigmasterol, beta-sitosterol, quercetin, and acetylshikonin had the most negative binding energies with near -9 kcal/mol. The other binding affinities were all around -7 to -6 ckal/mol. These results show that stigmasterol, beta-sitosterol, nobiletin, quercetin, and acetylshikonin can act as potential drug targets for TNBC treatment by targeting AKT1, TP53, CASP3, and VEGFA.

Limitations and Future Directions

From a systematic viewpoint, our research investigated the molecular and pharmacological mechanisms of the Chinese herbal medicines Brucea javanica, Centipeda minima, and Lithospermum erythrorhizon in addressing triple-negative breast cancer. Nevertheless, this study has some limitations. A more extensive database of TCM target genes is required, which enhances the reliability of the network pharmacology analysis results. Similar to other analyses in network pharmacology, while the intersection of potential targets for these herbal medications and TNBC enhances the reliability of the virtual screening results in this study, it is important to note that some targets outside of this intersection may play a crucial role in the treatment or diagnosis of TNBC, a challenge that is frequently encountered in virtual screening.

Currently, network pharmacology depends on various databases for the mining of bioactive compounds. Although these databases are curated, they may exhibit inconsistencies arising from multiple sources of information and experimental data. One approach to address this issue is to utilize contemporary, high-throughput techniques for chemical identification of active ingredients such as modern mass spectrometry methods. Despite the integration of network pharmacology and molecular docking results, we remain unable to fully comprehend the precise therapeutic mechanisms of these herbal compounds. A thorough understanding of their impact on TNBC relies on the collaborative advancement of multiple disciplines. Further *in vivo* and clinical studies are required to confirm the mechanisms revealed by our research. Furthermore, additional research is necessary to investigate the potential toxicity of these herbal compounds.

5. Conclusion

In conclusion, the results of this study, consistent with previous experimental results, demonstrate the potential of the Chinese herbal medicines *Brucea javanica*, *Centipeda minima*, and *Lithospermum erythrorhizon* in the treatment of triple-negative breast cancer. Network studies, gene ontology analysis, and pathway enrichment revealed the key mechanisms and signaling pathways underlying the anti-tumor effects of *BJ*, *CM*, and *LE*. The target proteins were involved in various cellular processes, including the regulation of gene expression, the regulation of the apoptotic process, the regulation of transcription from RNA polymerase II promoters, the regulation of cell proliferation, signal transduction, the cellular response to hypoxia, the inflammatory response, and the MAPK cascade. The AGE-RAGE signaling pathway in diabetic complications, PI3K-AKT, p53, and MAPK were also the top key signaling pathways related to the effect of these herbal compounds on TNBC. The network pharmacology approach revealed that the main bioactive compounds of the herbal drugs in TNBC treatment, stigmasterol, nobiletin, and quercetin (from CM), beta-sitosterol (from CM and BJ), and acetylshikonin (from LE), could act on multiple drug targets, including AKT1, TP53, CASP3, and VEGFA. However, the best docked complexes included AKT1 with quercetin and acetylshikonin, TP53 with beta-sitosterol and quercetin, CASP3 with nobiletin and quercetin, and VEGFA with quercetin and Stigmasterol. Therefore, the best target gene for *BJ* was TP53, which acts on beta-sitosterol; the best target gene for LE was AKT1, which acts on acetylshikonin. Additionally, AKT1, TP53, CASP3, and VEGFA could all act on *CM* active compounds. Among the formed complexes, interaction of AKT1 with stigmasterol, beta-sitosterol, quercetin, and acetylshikonin had the most negative binding energies with near -9 kcal/mol. Given the inadequate accuracy and comprehensiveness of the databases throughout the network pharmacology investigation and because the study lacked negative controls, it remains essential to conduct biological experiments and thorough evidence-based medical validation in subsequent phases to guarantee the reliability of the study, especially in the case of docking outcomes. The results of this study provide a basis for further research on the clinical application of these herbal medicines in the treatment of TNBC. However, these results not only need to be verified by *in vitro* and *in vivo* studies, but also need to be translated into clinical trials and human trials in the future. Undoubtedly, other possible cellular processes and pathways involved in the mechanism of action of these herbal medicines will be revealed in the future.

6. Declarations

6.1 Acknowledgments

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6.2 Ethical Considerations

This study does not include any research involving human or animals. Ethics code: IR.SBMU.RETECH.REC.1401.830.

6.3 Authors' Contributions

R.FY, A.AO contributed to the conception and design of the study. All the authors contributed to data collection, statistical analysis, and interpretation of the data. R.FY and A.AO wrote the paper draft. All the authors reviewed and approved the final manuscript.

6.4 Conflict of Interest

The authors declare that they have no known conflict of interests or personal relationships that could have appeared to influence the work reported in this paper.

6.5 Fund or Financial Support

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6.6 Using Artificial Intelligence Tools (AI Tools)

The authors did not use any generative AI and AI-assisted technologies during the preparation of this paper.

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