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ARTICLE

Ampelopsin Inhibits Breast Cancer Glucose Metabolism Reprogramming Based on Network Pharmacology and Molecular Docking

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ABSTRACT

Background: Breast cancer (BC) is the most frequent type of gynecology tumors with high morbidity and mortality. Ampelopsin, the main active compound of *Ampelopsis grossedentata*, exerts an anti-tumor effect on a variety of cancers. However, the anti-cancer role of ampelopsin in BC remains unclear. The aim of this study is to explore the mechanism of ampelopsin against breast cancer. **Materials and Methods:** The target genes of ampelopsin in the treatment of breast cancer were determined and analyzed by network pharmacology and molecular docking. Cytoscape software was used to identify the core target genes and construct a protein–protein interaction (PPI) network. Discovery Studio software was used to perform the molecular docking of ampelopsin and core genes and glycolytic metabolic enzymes. **Results:** In total, 25 potential target genes of ampelopsin were screened out. The core target genes of ampelopsin against breast cancer were *AKT1*, *ESR1*, *ESR2*, *NCOA1*, *HSP90AA1*, *NCOA2*, *BECN1*, *COMT*, *HMOX1*, and *CDK6*, with AKT1, ESR1 and ESR2 considered as the key target proteins. Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis showed that ampelopsin inhibited breast cancer via modulating the estrogen signaling pathway, apoptosis regulation, carbohydrate metabolism, and inflammation. Molecular docking analysis showed that ampelopsin possessed a stable binding ability to regulate the three target proteins and glycolytic metabolic enzymes such as ALDOA and LDHA. **Conclusions:** Ampelopsin may inhibit the proliferation of breast cancer cells by acting on AKT and estrogen-related glucose metabolic pathways and inhibiting the enzymes involved in glycolysis and oxidative phosphorylation.

KEYWORDS

Ampelopsin; breast cancer; glycolysis; network pharmacology; molecular docking

Nomenclature

ALDOA	aldolase
BC	breast cancer
COX7RP	cytochrome C oxidase subunit 7α-related polypeptide
CTD	comparative toxicogenomics database

ECM	extracellular matrix
ER	estrogen receptor
ETCM	Encyclopedia of Traditional Chinese Medicine
GO	Gene Ontology
HK2	hexokinase 2
HR	hormone receptor
KEGG	Kyoto Encyclopedia of Genes and Genomes
LDHA	lactate dehydrogenase A
MCT	monocarboxylic acid transporter
OXPHOS	oxidative phosphorylation
PFKL	liver phosphofructokinase
PK	pyruvate kinase
PPI	protein–protein interaction
PR	progesterone receptor
TCA	tricarboxylic acid
TNBC	triple-negative breast cancer

1 Introduction

Breast cancer (BC) is the most common type of cancers and the leading cause of cancer-related deaths among women [1]. Clinical treatments for BC fall under the radiotherapy, surgical resection, chemotherapy, immunotherapy, and hormonal therapy [2]. Most breast cancers express hormone receptors (HR) such as the estrogen receptor α (ERα) and progesterone receptor (PR), whereas others express human epidermal growth factor receptor 2 (HER2). HR- and HER2-positive cancers can be treated with endocrine therapy and anti-HER2 molecules (such as Trastuzumab), respectively [3]. Triple-negative breast cancer (TNBC) is a subtype of BC that lacks ERα, PR, and HER2 expression, accounting for 15%–20% of BC cases. Owing to the lack of relevant receptors, TNBC is often unresponsive to targeted therapy. Currently, conventional chemotherapy and surgical resection are the mainstays for the treatment of TNBC. However, inherent or acquired drug resistance in all BC types leads to treatment failure [4,5]. Thus, there is an urgent need to develop new and alternative BC therapies.

Cancer cells undergo metabolic changes to satisfy their energy requirements for increased proliferation, migration, and invasion. Multiple metabolic pathways in cancer cells, such as glycolysis, oxidative phosphorylation (OXPHOS), tricarboxylic acid (TCA) cycle, and amino acid and lipid metabolism, are reprogrammed as they undergo adaptation [6]. Although a hypoxic microenvironment generally increases glucose consumption and glycolysis, cancer cells differ from normal cells in which they prefer glycolysis even in the presence of sufficient oxygen. This phenomenon is called the Warburg effect [7]. MCF-7 (HR-positive), SKBR3 (HER2-positive), and MAD-MB-231 (TNBC) BC cells rely on glycolysis to meet approximately 20% [8,9], 50% [10], and 70% [11] of their ATP requirements, respectively. Therefore, by targeting glycolysis and related processes, researchers can discover new strategies for treating TNBC.

Ampelopsin, also known as dihydromyricetin, is the main active flavonoid in *Ampelopsis grossedentata* [12]. Modern pharmacological studies have shown that ampelopsin exhibits anti-inflammatory, antimicrobial, antioxidant, and hypoglycemic activitie [13]. Several studies have explored the anti-tumor effects of ampelopsin. For example, ampelopsin promotes apoptosis in lung adenocarcinoma [14], liver cancer [15], breast cancer [16], and ovarian cancer cells [17]. Moreover, ampelopsin could inhibit the proliferation of cholangiocarcinoma cells via regulating miR-21 [18] and promotes apoptosis of nasopharyngeal cancer cells via inhibiting the activation of NF-κB [19]. *In vivo* studies have demonstrated that ampelopsin inhibits the progression of tumors through the Wnt/β-catenin signaling

pathway [15,20]. Besides, ampelopsin can restrain the proliferation of BC stem cells by interfering with the OXPHOS in TNBC cells through the TNFα/NF-κB signaling pathway [21]. In addition, ampelopsin can inhibit the occurrence and development of TNBC by enhancing mitochondrial autophagy and endoplasmic reticulum stress through the mammalian target of rapamycin (mTOR) signaling pathway [16]. However, it is not clear whether ampelopsin inhibits the progression by regulating glycolysis.

In this study, we investigated the targets of ampelopsin against BC using network pharmacology and molecular docking to determine the potential mechanism of ampelopsin against BC and whether ampelopsin can prevent against the proliferation of tumor cells by regulating glycolysis.

2 Materials and Methods

Network pharmacology and molecular docking could provide an effective way to identify the mechanisms underlying the effects of traditional Chinese medicine and active compounds [22]. Traditional network pharmacology and molecular docking combine multiple database resources to identify core genes that can be targeted by drugs or active compounds. Thus, network pharmacology and molecular docking were employed in this study to discover the role of ampelopsin in the treatment of human breast cancer.

2.1 Target Screening of Ampelopsin

The Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMCP, https://www.tcmsp-e.com/), HERB (http://herb.ac.cn/), and Encyclopedia of Traditional Chinese Medicine (ETCM, http://www.tcmip.cn/ETCM/) databases were used to obtain the necessary information of the target genes of ampelopsin.

2.2 Potential Therapeutic Targets of Ampelopsin in BC

Information related to BC markers and target genes was collected from GeneCards (https://www.genecards.org/), MalaCards (https://www.malacards.org/), and Comparative Toxicogenomics Database (CTD, http://ctdbase.org/), using the keyword "BC". The potential targets of ampelopsin in the treatment of BC were identified by analyzing the intersection targets of ampelopsin and BC online (https://bioinfogp.cnb.csic.es/tools/venny/index.html).

2.3 Potential Protein–Protein Interactions (PPI) Network Construction and Analysis

Analysis was performed using the STRING database (https://string-db.org/) [23], and the species selected to assess PPI was "*Homo sapiens*" with a confidence degree of 0.9. The network visualization software Cytoscape [24] was used to construct the ampelopsin–BC target network, and the MCODE plug-in of Cytoscape was employed to screen the core targets. The clusters containing molecules in the network with the highest scores were considered core genes.

2.4 Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) Enrichment Analyses

The ClueGO plug-in of Cytoscape (version 3.8.2) and the Database for Annotation, Visualization and Integrated Discovery (DAVID) software (https://david.ncifcrf.gov/) were used to analyze the core target genes in the PPI network. The core targets were imported into Kyoto Encyclopedia of Genes and Genomes (KEGG) for pathway visualization in order to screen reliable biological processes, molecular functions, and signaling pathways. Results with $P < 0.05$ and $Q < 0.05$ were considered statistically significant.

2.5 Molecular Docking

Ampelopsin was used as the ligand, and the core target proteins related to glucose metabolism were used as receptors. Molecular docking verification was performed using Discovery Studio 2019 software. Discovery Studio is a life science prediction software developed by BIOVIA company that integrates classic and advanced algorithms as well as high-quality graphical interfaces from the current molecular

simulation field mainly used for binding and interaction between proteins and small molecule compounds [25]. The 3D structure of the human target protein was downloaded from the Protein Data Bank (PDB) database (https://www.rcsb.org/). PDB database provides archive-information about the 3D shapes of proteins, nucleic acids, and complex assemblies [26]. The PubChem database (https://pubchem.ncbi.nlm.nih.gov/) was used to determine the 3D structure of ampelopsin and the core target proteins [26]. Molecular Operating Environment software (MEO v2019.0102), a drug discovery software platform that integrates visualization, modeling simulation, and method development, was used to optimize the target protein structure [27]. RSMD (RSMD ≤ 4 A is reliable and RSMD ≤ 2 A is accurate), representing the accuracy parameter of the molecular docking model, and S, referring to the binding free energy [28], were used to verify the binding of ampelopsin to the target proteins and enzymes. The potential binding modes of ampelopsin, glycolytic enzymes and target proteins were predicted and analyzed using molecular docking. The interaction energy of the ligand and receptor was calculated, and the optimal receptor–ligand complex was selected for mapping.

3 Results

3.1 Potential Therapeutic Target Genes of Ampelopsin in BC

A total of 85 target genes of ampelopsin were identified in the three TCM databases, including protein molecules involved in various pathways such as glucose and lipid metabolism, cell proliferation, inflammation, and tumor microenvironment. A total of 622 BC markers and genes were retrieved from the CTD, GeneCards, and MalaCards databases. Veeny was used to analyze and compare the target genes of ampelopsin and BC (Fig. 1). Twenty-five potential intersection targets were identified and are shown in Table 1.

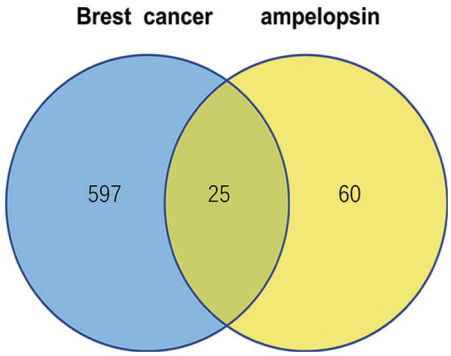

Figure 1: Ampelopsin-breast cancer target intersection

Table 1: The 25 potential ampelopsin target genes in breast cancer

Target genes				
AKT1	*ESR1*	*ESR2*	*BECN1*	*HSP90AA1*
NCOA1	*NCOA2*	*COMT*	*HMOX1*	*CDK6*
CA12	*DNMT1*	*CYP19A1*	*CYP1B1*	*CDH1*
CA9	*CXCR4*	*ESRRA*	*GPER1*	*MTOR*
AHR	*PTGS2*	*NQO2*	*PIM1*	*TOP2A*

3.2 Construction and Analysis of a PPI Network and the Central Node

The 25 intersection targets were uploaded to the STRING database. Multiple proteins were selected with a confidence interval > 0.4 and a protein-protein interaction (PPI) network was constructed. The PPI network

had 25 nodes (for the target genes in Table 1) and 102 links, with an average node degree of 8.16 (Fig. 2). The MCODE plug-in of Cytoscape was used for the cluster analysis, and the results showed ten important genes which were *AKT1*, *ESR1*, *ESR2*, *NCOA1*, *HSP90AA1*, *NCOA2*, *BECN1*, *COMT*, *HMOX1*, and *CDK6*. Cluster 1 consisted of 30 nodes and 363 edges, with an average node degree of 25.034; cluster 2 consisted of 18 nodes and 32 edges, with an average node degree of 3.592; cluster 3 consisted of 4 nodes and 5 edges, with an average node degree of 3.333. Genes such as *AKT1*, *ESR1* and *ESR2* were selected by degree to be the core targets (Fig. 3).

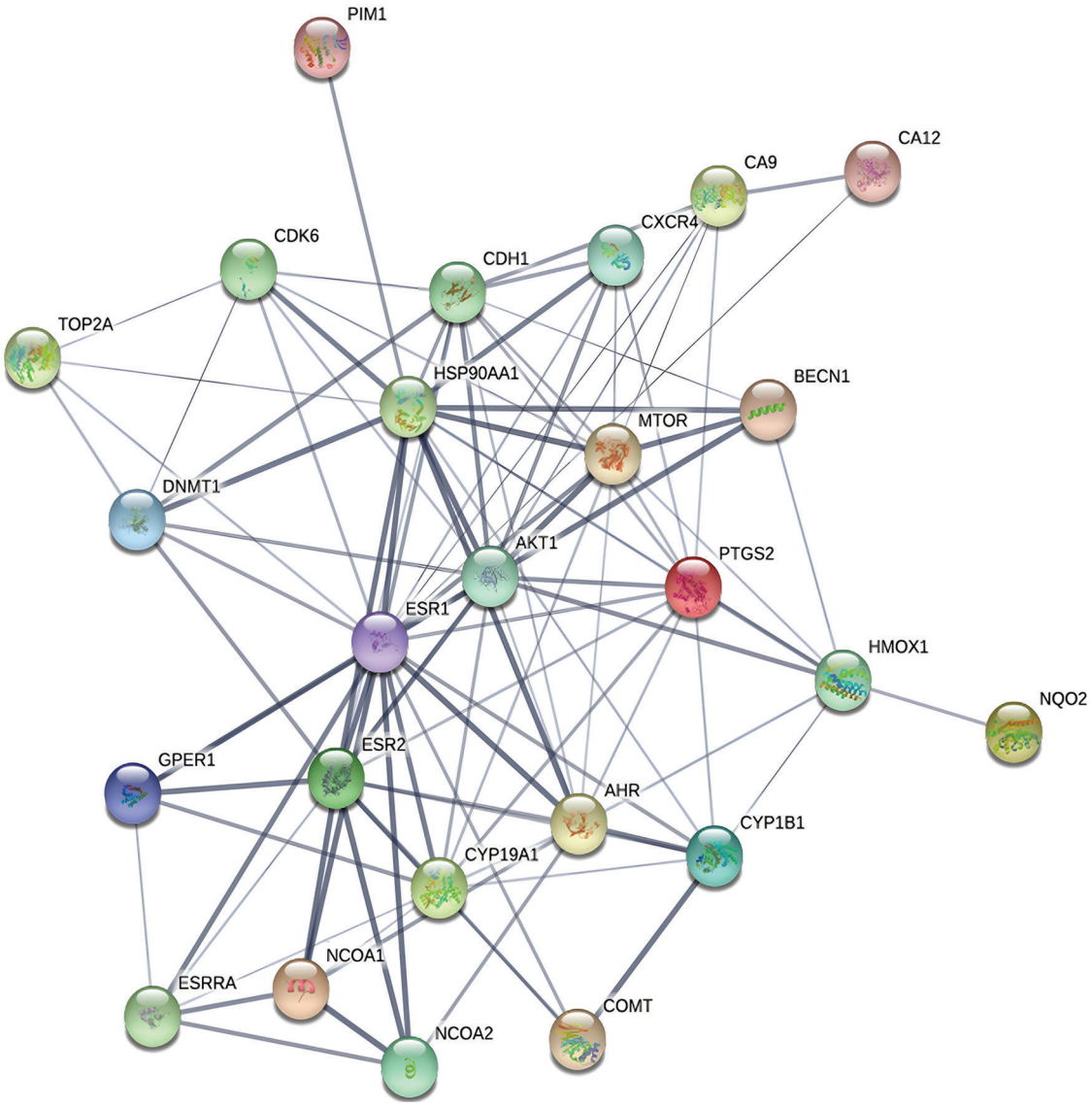

Figure 2: Protein–protein interaction network of the intersection targets

3.3 GO and KEGG Enrichment Analyses

A total of 34 biological processes of the intersection targets were identified using the GO enrichment analysis. As shown in Fig. 4, the biological processes associated with intersection target genes included cell migration in angiogenesis, activity of steroid HR, negative regulation of autophagy, and cell proliferation.

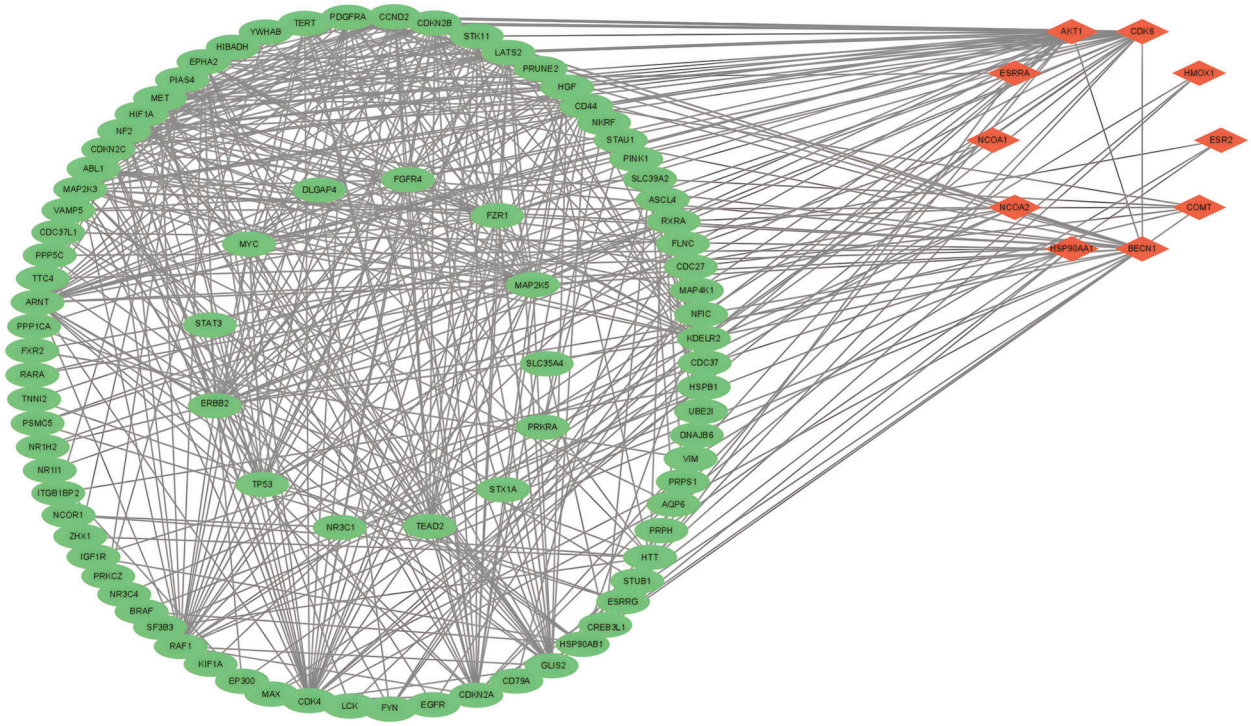

Figure 3: Cluster of MCODE cluster analysis

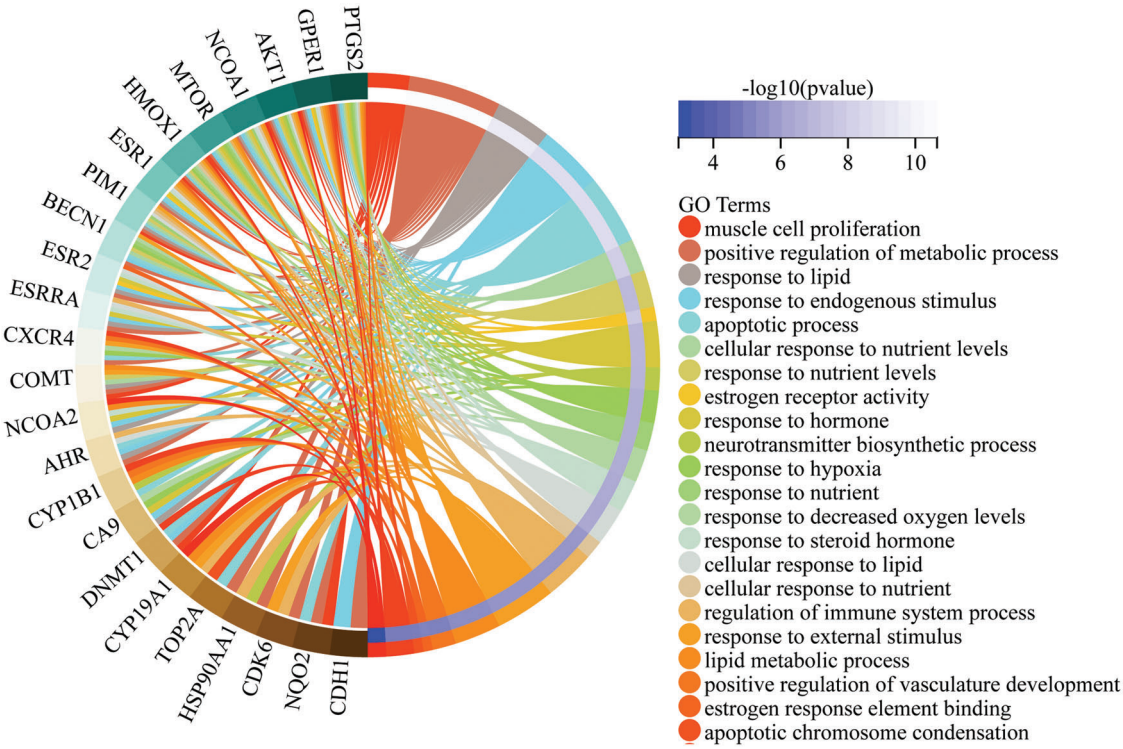

Figure 4: Gene Ontology (GO) enrichment analysis of the intersection targets

The KEGG enrichment analysis revealed several tumor-related endocrine pathways, indicating that ampelopsin could inhibit the occurrence and development of BC through the hormone-receptor pathway. The hormone signaling pathways included endocrine resistance, estrogen signaling, prolactin signaling, thyroid hormone signaling, and other pathways such as autophagy (Fig. 5 and Table 2).

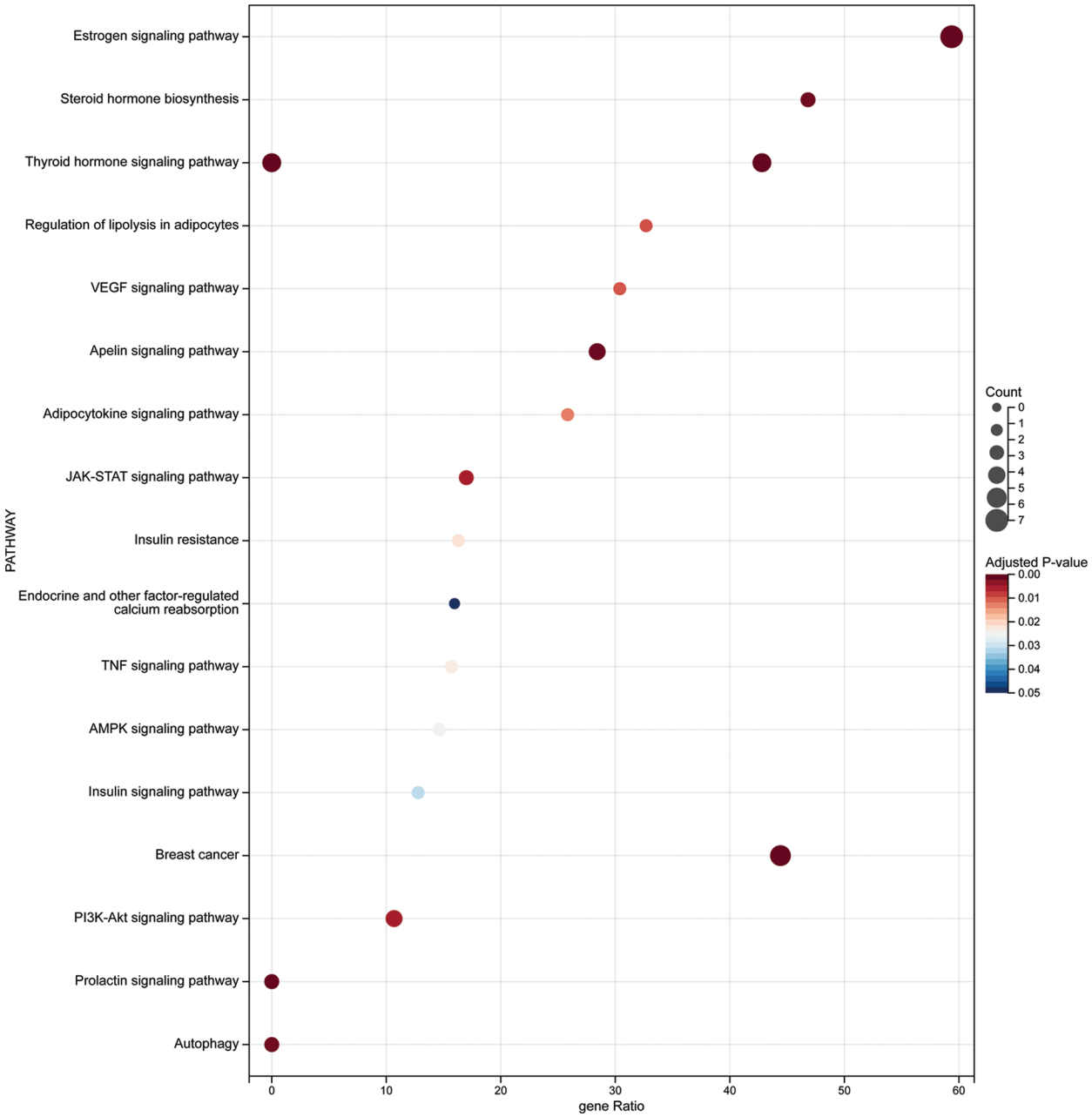

Figure 5: KEGG enrichment analysis of the intersection targets

Table 2: KEGG pathway enrichment analysis results of ampelopsin breast cancer targets

Term	*P*
hsa05200:Pathways in cancer	5.89E-07
hsa05207:Chemical carcinogenesis-receptor activation	4.24E-06
hsa04915:Estrogen signaling pathway	9.50E-06
hsa01522:Endocrine resistance	5.38E-05
hsa05224:Breast cancer	2.60E-04
hsa05206:MicroRNAs in cancer	4.48E-04
hsa05167:Kaposi sarcoma-associated herpesvirus infection	7.46E-04
hsa05163:Human cytomegalovirus infection	0.001298127
hsa04919:Thyroid hormone signaling pathway	0.002242942
hsa04371:Apelin signaling pathway	0.003327075
hsa05225:Hepatocellular carcinoma	0.005663594
hsa04929:GnRH secretion	0.008642747
hsa04917:Prolactin signaling pathway	0.01027225
hsa05218:Melanoma	0.010843564
hsa05214:Glioma	0.011726507
hsa05212:Pancreatic cancer	0.012027687
hsa05208:Chemical carcinogenesis-reactive oxygen species	0.012326602
hsa05222:Small cell lung cancer	0.017300076
hsa05215:Prostate cancer	0.019117189
hsa04659:Th17 cell differentiation	0.023385665
hsa04066:HIF-1 signaling pathway	0.023791704
hsa05165:Human papillomavirus infection	0.034853731
hsa05418:Fluid shear stress and atherosclerosis	0.037280765
hsa04140:Autophagy-animal	0.038265495
hsa05017:Spinocerebellar ataxia	0.039260337
hsa04151:PI3K-Akt signaling pathway	0.041322153
hsa05226:Gastric cancer	0.04230456
hsa04218:Cellular senescence	0.045966586

Through KEGG pathway enrichment, we concluded that metabolic enzymes in the glycolytic pathway were regulated by hormone signalings. Thus, ampelopsin might regulate glycolysis through PI3K/AKT and promote lipid metabolism through the apelin signaling pathway, which plays an important role in the regulation of autophagy in BC (Figs. 6–8).

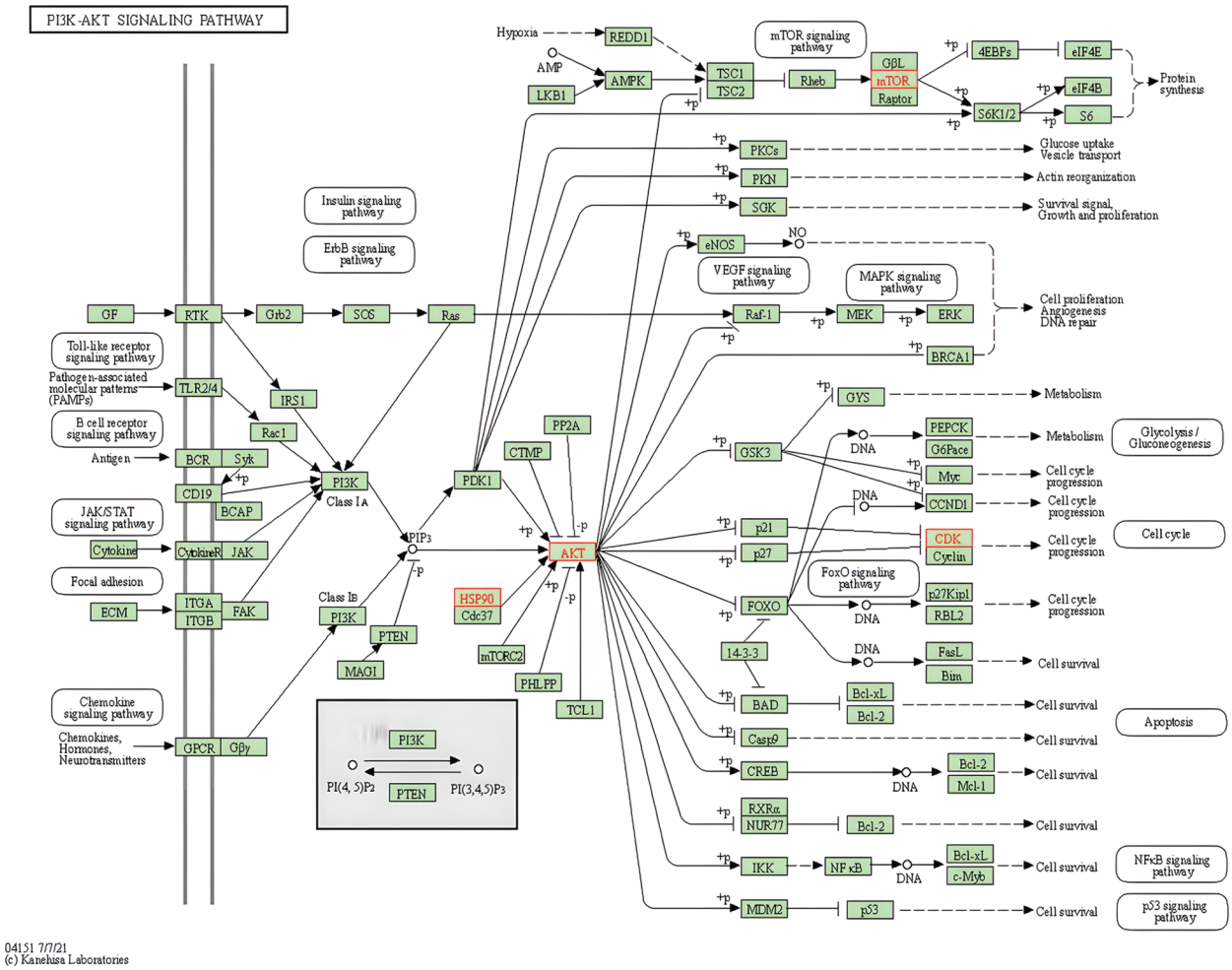

Figure 6: Potential role of ampelopsin in the PI3K/AKT signaling pathway

3.4 Molecular Docking

As shown in Figs. 2–5, ampelopsin might bind to AKT1 and other key target proteins to regulate AKT downstream signaling molecules. Glycolytic pathway is regulated by the PI3K/AKT signaling pathway. Therefore, we analyzed the effect of ampelopsin on the target proteins and metabolic enzymes involved in glycolysis. We performed molecular docking analysis using ampelopsin as the ligand and AKT1, ESR1, ESR2, and glycolytic metabolic enzymes such as hexokinase 2 (HK2), liver phosphofructokinase (PFKL), aldolase (ALDOA), pyruvate kinase (PK), lactate dehydrogenase A (LDHA), and cytochrome C oxidase subunit 7α-related polypeptide (COX7RP) as the receptors.

The binding of ampelopsin to the core target proteins and enzymes related to glycolytic pathway was determined (Table 3 and Fig. 9). Our results indicated that ampelopsin had a high affinity for its targets, such as ESR1 and ESR2 ($S < -6$ kcal/mol and RMSD < 2), and a moderate affinity for AKT1. Docking with enzymes related to glycolytic pathway showed that the binding of ampelopsin to ALDOA and LDHA was stable and strong ($S < -6$ kcal/mol and RMSD < 2) (Table 3 and Fig. 9). However, there was a moderate affinity between ampelopsin and some other enzymes such as HK2, PFKL, PK and COX7RP (Table 3).

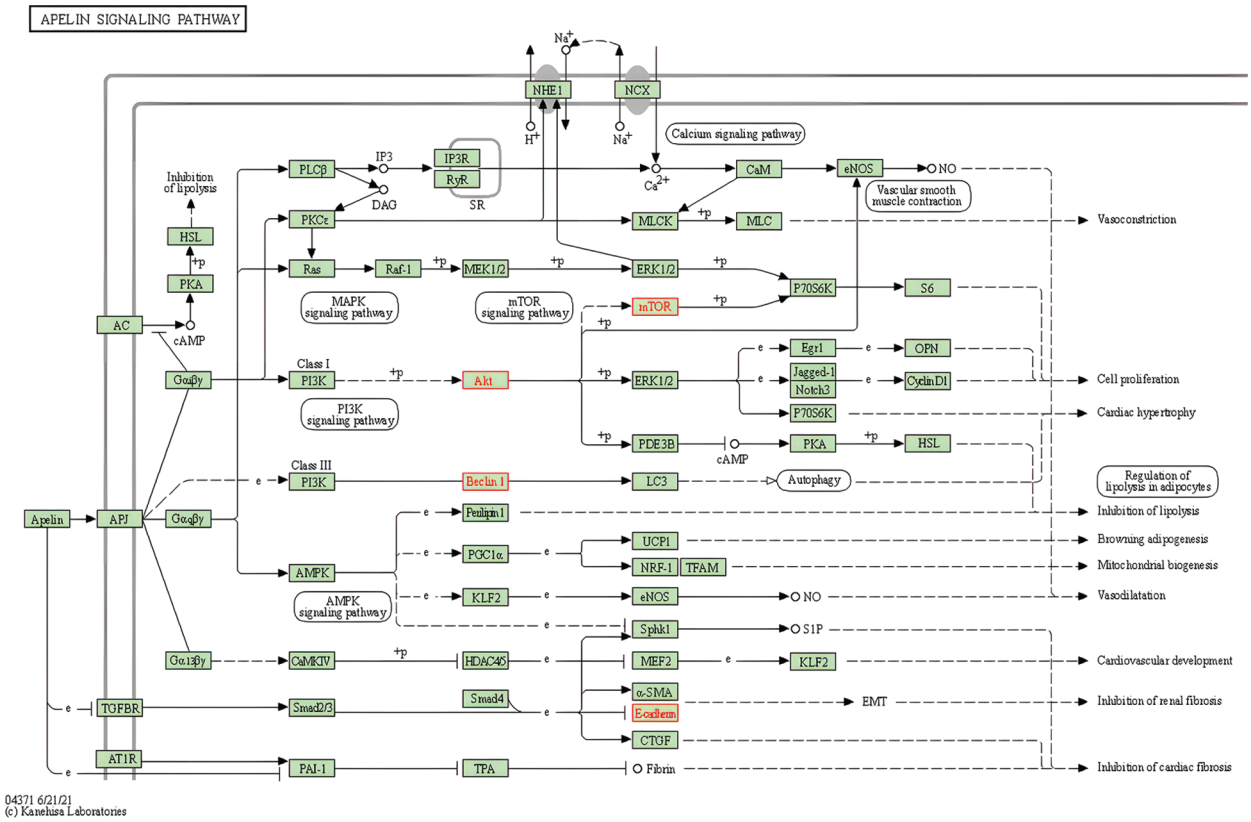

Figure 7: Potential role of ampelopsin in the apelin signaling pathway

4 Discussion

In this study, we have evaluated the therapeutic role of ampelopsin in the treatment of BC. Our results indicated the following: **(1)** there were 25 potential targets of ampelopsin in BC; **(2)** the target genes of ampelopsin were *AKT1*, *ESR1*, *ESR2*, *NCOA1*, *HSP90AA1*, *NCOA2*, *BECN1*, *COMT*, *HMOX1*, and *CDK6*, with AKT1, ESR1, and ESR2 considered as the core target proteins; **(3)** ampelopsin inhibits BC by regulating the estrogen signaling pathway, apoptosis, carbohydrate metabolism, and inflammation; **(4)** ampelopsin possesses a stable binding ability to regulate target proteins such as AKT1, ESR1, and ESR2 and the glycolytic enzymes ALDOA and LDHA.

OXPHOS and mitochondrial super-complexes exhibit an essential effect on promoting cell proliferation. Although intracellular ATP production is measured differently, the proportion of energy produced via glycolytic pathway in MAD-MB-231 cells is among 40%–70%, suggesting that glycolysis exhibits an essential effect on TNBC cells [11,29]. Previous studies have indicated that tumor cells showing the "Warburg effect" exhibit specific metabolic profiles at different times; glycolysis is the main metabolic pathway during the day. At night, however, tumor cells revert to the mitochondrial aerobic oxidation and OXPHOS pattern of normal healthy cells [30,31]. Owing to this circadian rhythm, these tumors can become cancerous at some point in time [31–33]. During the day, tumor cells undergo glycolysis in the environment even in presence of sufficient oxygen, and the overproduced lactic acid flows out of the cells through the monocarboxylic acid transporters [34]. Lactic acid changes the pH of the tumor microenvironment and promotes the decomposition of the extracellular matrix as well as the migration and invasion of tumor cells [35]. Additionally, an acidic microenvironment can increase angiogenesis and

promote tumor metastasis. Hence, glycolysis can improve the proliferation, migration, and invasion of tumor cells. Therefore, the regulation of the glycolytic pathway may be an important strategy for the treatment of breast cancer.

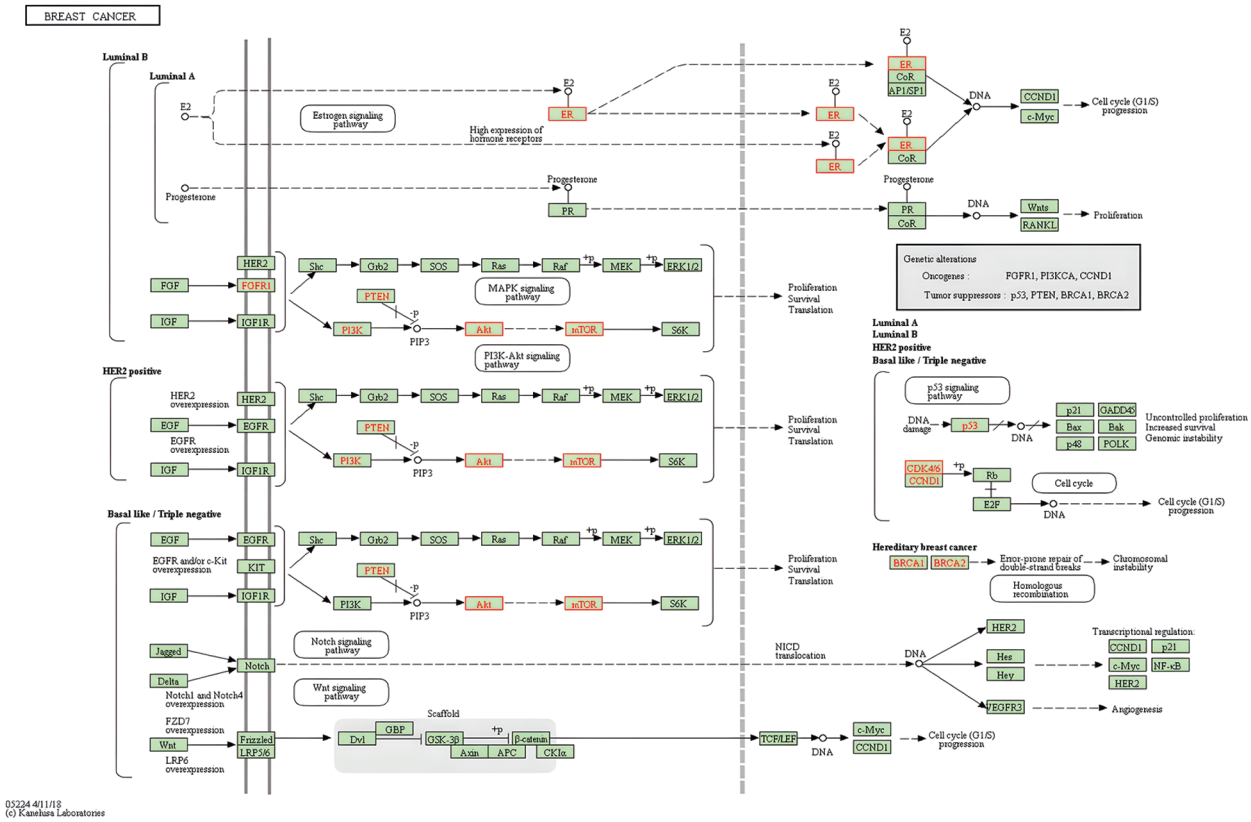

Figure 8: Potential role of the PI3K/AKT/mTOR signaling pathway in breast cancer

Table 3: Molecular docking of ampelopsin with target proteins, glycolytic enzymes and cytochrome oxidase

		Ampelopsin	
Protein	PDBID	S (kcal/mol)	RMSD
AKT1	2UVM	−5.0557	2.7668
ESR1	1A52	−7.0123	1.4790
ESR2	1L2J	−6.7558	1.9921
HK2	5HEX	−6.2292	2.0903
PFKL	AF-P17858-F1-model_v2	−5.6438	1.5113
ALDOA	6XMH	−6.0408	1.8000
PK	1T5A	−5.7481	2.4257
LDHA	LI10	−6.7856	1.6790
COX7RP	AF-O14548-F1-model_v2	−5.1073	1.1572

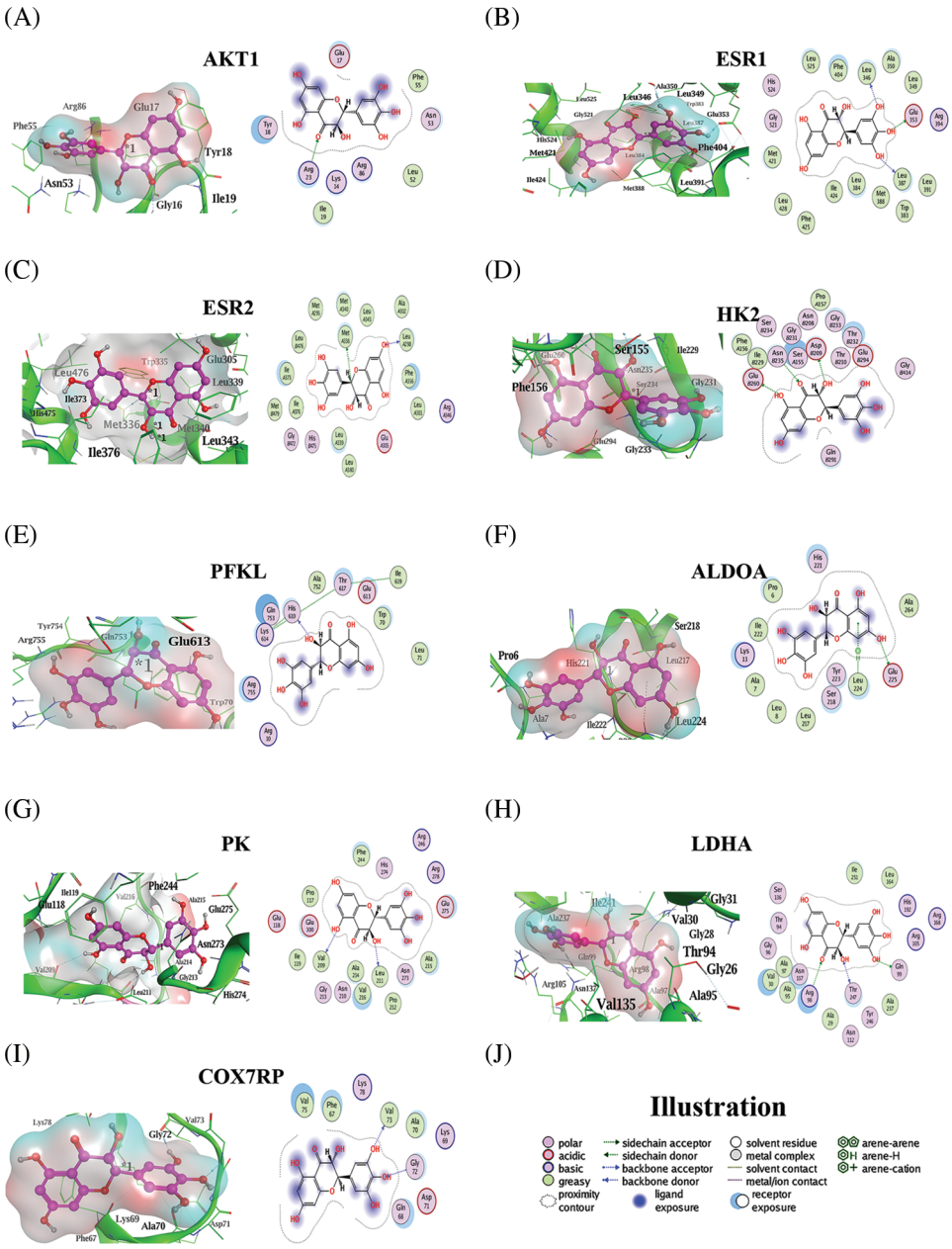

Figure 9: Molecular docking of ampelopsin with target genes, glycolytic enzymes, and cytochrome oxidase. (A–I) Molecular docking pattern of ampelopsin with AKT1 (A), ESR1 (B), ESR2 (C), HK2 (D), PFKL (E), ALDOA (F), PK (G), LDHA (H), and COX7RP (I), (J) Illustration of the ligand-receptor binding pattern. AKT1 (PKB1), Protein kinase B1; ESR, estrogen receptor gene; HK2, hexokinase 2; PFKL, liver phosphofructokinase; ALDOA, aldolase; PK, pyruvate kinase; LDHA, lactate dehydrogenase A; COX7RP, cytochrome C oxidase subunit 7α-related polypeptide

In tumor cells, multiple metabolic processes are reprogrammed to provide energy. For instance, OXPHOS is facilitated by the formation of the mitochondrial respiratory chain supercomplex (complexes I, III, and IV) [36]. Ampelopsin can promote mitochondrial autophagy in BC cells and inhibit the activity of mitochondrial supercomplexes through the PI3K/AKT/mTOR signaling pathway [21]. Glycolysis plays

an important role in promoting tumor proliferation, migration, and invasion. Therefore, it is important to elucidate the role of ampelopsin in regulating glycolysis.

In the present study, 25 potential target genes of ampelopsin were identified against BC (Table 1). The PPI network analysis suggested that *AKT1*, *ESR1*, *ESR2*, *NCOA1*, *HSP90AA1*, *NCOA2*, *BECN1*, *COMT*, *HMOX1*, and *CDK6* were the core target genes of ampelopsin against BC (Figs. 1–3 and Table 1). *AKT1* is a well-known oncogene involved in the regulation of the metabolism and proliferation of tumor cells. The estrogen receptors ESR1 and ESR2 activate the second messengers in the cells by binding to estrogen and regulating signaling pathways such as the PI3K/AKT/mTOR [37], MAPK/ERK [38] and cAMP/PKA pathways [39]. The KEGG enrichment analysis results suggested that ampelopsin could affect the development of BC by regulating the estrogen signaling pathway, cell cycle, and metabolism (Figs. 4–8 and Table 2).

HK2, the first key enzyme in the glycolytic pathway, is inhibited by the negative feedback of glucose-6-phosphate, whereas PFKL is the second rate-limiting enzyme in glycolysis and the most important rate-limiting enzyme regulating glycolysis. PFKL catalyzes the conversion of fructose-6-phosphate to fructose-1,6-diphosphate. Incidentally, fructose-2,6-bisphosphate synthesized by 6-phosphate fructokinase 2/fructose-2,6-bisphosphatase (PFK2) is the strongest allosteric activator of PFKL. The PFKL activity is significantly increased in TNBC, and it may contribute to the increased lymph node infiltration and metastasis [40]. By regulating the PI3K/AKT and cAMP/PKA signaling pathways activated by ESR1 and ESR2, ampelopsin can promote the phosphorylation of PFK2 and the hydrolysis of fructose-2,6-bisphosphate, reduce the production of fructose-2,6-bisphosphate, and inhibit the glycolytic rate-limiting enzyme PFKL [41]. As a result, ampelopsin is a potent inhibitor of TNBC cell proliferation and metastasis.

As a downstream enzyme of PFKL, ALDOA is regulated by the PI3K/AKT signaling pathway and is associated with cancer progression [42]. PK is the third key enzyme in glycolysis, and its activity is regulated by the cAMP/PKA signaling pathway. Ampelopsin activates cAMP/PKA through the estrogen signaling pathway, promoting PK phosphorylation and inactivation. LDHA catalyzes the final step of aerobic glycolysis, generating lactic acid. LDHA expression is associated with the invasion and metastasis of tumor cells [43]. Hence, ampelopsin can effectively bind to enzymes such as HK2, PFKL, ALDOA, PK, LDHA, and COX7RP, especially ALDOA and LDHA, to inhibit their activity and reduce lactic acid production and energy generation (Fig. 9 and Table 3). These results suggest that ampelopsin could inhibit the progression of BC through glycolysis regulation.

The molecular docking results confirmed the possibility of ampelopsin binding to BC core target genes (*AKT1*, *ESR1* and *ESR2*) and enzymes involved in glycolysis (HK2, PFK1, ALDOA, PK and LDHA). The findings suggested a strong binding between ampelopsin and the target proteins ESR1 and ESR2 ($S < -6$ kcal/mol and RMSD < 2) (Fig. 9 and Table 3). Moreover, ampelopsin inhibited ALDOA and LDHA by strongly binding to them ($S < -6$ kcal/mol and RMSD < 2). Furthermore, ampelopsin regulated glycolysis and OXPHOS by binding to HK2, PFK1, PK, and COX7RP (Fig. 9 and Table 3).

In this study, we used network pharmacology and molecular docking analysis to confirm that ampelopsin may inhibit BC by acting with three core genes and five glucose-metabolism regulatory enzymes. However, our study had some limitations. First, some key targets and pathways may not have been adopted in this study because of the limitations of setting screening conditions and application databases. Second, this study did not consider the influence of ampelopsin concentration on its anti-cancer activity. Third, the effects of ampelopsin on other glucose metabolism processes such as the pentose phosphate pathway, OXPHOS, glycogen synthesis and decomposition, and gluconeogenesis were not discussed. Thus, further studies are needed to determine the role of ampelopsin in regulating glycolysis and inhibiting the occurrence and development of TNBC.

In conclusion, our study provides evidence that ampelopsin inhibits glycolysis in BC cells by regulating the PI3K/AKT and cAMP/PKA signaling pathways and suppresses the activities of enzymes involved in glycolysis, thereby providing a theoretical basis and experimental support for ampelopsin treatment in breast cancer.

Authorship Statement: The authors confirm contribution to the paper as follows: Conceptualization, Lin Liu, Yunfeng Li, and Jingshan Zhao; Data curation, Lin Liu, Rong Zeng, and Wenmei Zhang; Formal analysis, Lin Liu and Rong Zeng; Funding acquisition, Lin Liu, Jingshan Zhao, Guohong Zhang and Yunfeng Li; Investigation, Jingshan Zhao and Yunfeng Li; Methodology, Lin Liu; Supervision, Jingshan Zhao and Yunfeng Li; Writing–original draft, Lin Liu; Writing–review & editing, Rong Zeng, Jingshan Zhao, Guohong Zhang and Yunfeng Li. All authors reviewed the results and approved the final version of the manuscript.

Ethics Approval and Informed Consent Statement: Not applicable.

Availability of Data and Materials: The data generated and/or analyzed in this study can be found at: TCMSP (https://old.tcmsp-e.com/tcmsp.php), HERB (http://herb.ac.cn/), ETCM (http://www.tcmip.cn/ETCM/), GeneCards (https://www.genecards.org), MALACards (https://www.malacards.org), CTD (http://ctdbase.org/), Cytoscape software (version 3.8.2), STRING database (https://string-db.org/), DiscoveryStudio, PDH database (http://www.rcsb.org/), and PubChem database (https://pubchem.ncbi.nlm.nih.gov/).

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