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Research Article

Investigation of Potential Molecular Targets of *Zanthoxylum acanthopodium* in Ovarian Cancer Using Network Pharmacology Assessments

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Abstract
Ovarian cancer is a serious disease that affects the ovaries, and its early detection is challenging due to vague symptoms often dismissed as minor ailments. Currently, natural sources have gained attention for their potential role in anticancer treatment. This study aimed to utilize network pharmacology to explore the potential targets and mechanisms of *Zanthoxylum acanthopodium* in the treatment of ovarian cancer. This study utilized the KNApSAcK and Swiss Target Prediction to identify active compounds and target genes. Additionally, ovarian cancer-specific target genes were sourced from the GEO database. To identify possible key target genes, the network interaction between protein-protein using the STRING database and visualized them in Cytoscape. Subsequent analysis using Gene Ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways enabled us to focus on primary therapeutic targets. Our investigation into *Zanthoxylum acanthopodium* revealed 10 active compounds that pass Lipinski rule of five and oral bioavailability with acceptable pharmacokinetic profiles, 88 therapeutic targets, and identified 5 hub genes: SRC, CCNB2, MMP9, PTGS2, and PTPRC, which are strongly associated with ovarian cancer progression. Pathway enrichment analysis highlighted several pathways significantly related to the pathogenesis of ovarian cancer. This study elucidates the therapeutic potential and mechanisms of action of *Z. acanthopodium* as a promising candidate for ovarian cancer treatment. However, further research, including both *in vitro* and *in vivo* studies, is necessary to understand its molecular mechanisms comprehensively.

Keywords: gene ontology, KEGG, network pharmacology, ovarian cancer, *Zanthoxylum acanthopodium*

1. INTRODUCTION

Ovarian cancer is a large tumor that originates from the female gonads or ovaries, whose work involves generating eggs and hormones with a significant health concern due to its high incidence and mortality rates among women [1]. Each year, thousands of women are diagnosed with this disease, often at an advanced stage when it has already spread, making it more difficult to treat [2] [3]. Ovarian cancer treatment is effective but faces significant challenges, particularly with drug resistance and severe side effects [4]. Treatments such as chemotherapy and radiation often cause nausea, fatigue, organ damage, and hearing loss, limiting the dosage or duration of therapy and impacting overall treatment success [4][5]. Additionally, these techniques are highly invasive, have a high rate of recurrence, and show low long-term effectiveness, underscoring the urgent need to find new therapies [5]. Nature offers a wealth of potential sources for treating cancer, with many plants, fungi, and marine organisms containing bioactive compounds that have demonstrated anticancer properties [6]. One potential natural source is *Zanthoxylum acanthopodium* (ZA) which is an indigenous Southeast Asian spice that mostly grows in the highlands of North Sumatra, Indonesia. The plant possesses a rich composition of biologically active components like flavonoids, alkaloids, and essential oils which contribute to potential pharmacological activities [7]. It has been shown to possess anti-microbial, anti-arthritic, anti-inflammatory, anti-cancer, and anti-oxidant properties indicating its potential use in therapy [7]-[11]. By being biochemically diverse and well-known for traditional medicine, ZA is a valuable biodiversity reservoir for designing new anti-cancer drugs. However further research is required on this medicinal plant for the mechanism of its action and efficacy towards ovarian cancer.

One way to study the potency of plants as anti-cancer agents is by using a network pharmacology

Table 1. Drug likeness properties of active compounds in ZA. Key physicochemical properties, including molecular weight, hydrogen bond donors/acceptors, and lipophilicity (logP), assessed based on Lipinski's Ro5 and bioavaibility score.

No	Compounds	Molecular weight	Log P	Rotatable bonds	H-bond acceptors	H-bond donors	Lipinski violations	Bioavailability score
1	(+)-Sesamin	354.35	3.46	2	6	0	0	0.55
2	Eudesmin	386.44	3.85	6	6	0	0	0.55
3	(+)-Epieudesmin	386.44	3.82	6	6	0	0	0.55
4	Tambulin	344.32	3.11	4	7	2	0	0.55
5	Dictamine	199.21	2.38	1	3	0	0	0.55
6	Skimmianine	259.26	2.78	3	5	0	0	0.55
7	Aesculetin dimethyl ether	206.19	2.23	2	4	0	0	0.55
8	(+)-Lirioresinol B	418.44	3.52	6	8	2	0	0.55
9	Gossypetin 7,4'-dimethyl ether	346.29	2.65	3	8	4	0	0.55
10	Gossypetin 7,4'-dimethyl ether 8-glucoside	508.43	2.37	6	13	7	3	0.17
11	Platydesmine	259.30	2.57	2	4	1	0	0.55

approach [12]. Network pharmacology is a developing area that unravel the complex web of interactions between drugs and biological systems to understand the intricate interactions between drugs and biological systems [13]. This method allows for the simultaneous examination of multiple targets and pathways, resulting in a more complete understanding of how plant extracts function as therapeutic agents. It can be used to identify combinations of different compounds in plants that could improve therapeutic outcomes [13]. Network pharmacology also predicts probable beneficial effects or drug side effects, thereby improving both effectiveness and safety profile of plant-based drugs [14]. Several investigations have been reported for using network pharmacology in studying natural product potency against several cancers such as lung cancer, liver cancer, cervical cancer, etc. [15]-[18]. This study utilized network pharmacology to investigate the anti-ovarian cancer properties and action mechanisms of ZA.

2. MATERIALS AND METHODS

2.1. Data Preprocessing and Differential Expression (DE) Gene Analysis of Targets Related to Ovarian Cancer

Gene expression data for ovarian cancer and normal ovarian tissue were obtained from the Gene Expression Omnibus (GEO) with identifiers GSE189553 and GSE223426 [19]-[21]. The data underwent preprocessing steps including filtration, batch correction, and normalization. Genes with expression levels below ten counts per million (CPM) were excluded [22]. To mitigate batch effects from different datasets, Combat-seq was utilized [23]. Data normalization was performed using the trimmed mean of M-values (TMM) from the EdgeR package [24][25]. All preprocessing was conducted in RStudio version 4.3.1. To identify genes associated with disease conditions, differential expression analysis was carried out using the EdgeR package. Gene expression profiles of ovarian cancer tissues were compared to those of normal ovarian tissues, with normalization performed using the trimmed mean of M-values (TMM) to adjust for differences in sequencing depth. Genes were defined as differentially expressed if they met the significance thresholds of

P-value < 0.01, false discovery rate (FDR) < 0.05, and an absolute log fold change (LFC) greater than 1. The selection of these thresholds was based on standard practices in transcriptomics studies to ensure stringent identification of differentially expressed genes while minimizing false positives. The FDR control was applied using the Benjamini-Hochberg (BH) method, which adjusts p-values to reduce the risk of Type I errors due to multiple comparisons. This ensures that reported significant genes have a low probability of being false positives, thereby enhancing the robustness of our findings.

2.2. Investigation of Active Compounds of ZA and Their Potential Targets

The chemical components of ZA were sourced from the KNApSAcK Family web database (https://www.knapsackfamily.com/KNApSAcK/) [26]. To identify potential active compounds of ZA, Lipinski violations and bioavailability scores were obtained from the SwissADME database (http://www.swissadme.ch/index.php) and used as selection criteria [27]. Potential ZA targets were identified using the SwissTargetPrediction database (http://swisstargetprediction.ch/) [28]. Initially, the canonical SMILES structures of ZA active compounds were obtained from PubChem. These structures were then input into the search box of the SwissTargetPrediction platform. The species was set to *Homo sapiens* to ensure relevance to human biology.

2.3. Drug Likeness and Pharmacokinetic Studies of the Active Compound from ZA

The prediction of drug-likeness properties of Lipinski violation (log P, molecular weight (MW), rotatable bonds, H-bond donors, and H-bond acceptors), bioavailability score, and pharmacokinetic toxicity profiles were performed by inputting the canonical SMILES from each compound into the free access web server of SwissADME tool (http://www.swissadme.ch/) [27].

2.4. Establishment of Venn Diagram and Compounds-Targets Network

Both upregulation and downregulation targets from the ovarian cancer database of GEO were intercepted with targets from ZA using Venny 2.1,

Table 2. Pharmacokinetic profiles of selected active compounds from ZA. ADME properties, including absorption, distribution, metabolism, and excretion parameters, for evaluating potential bioavailability and toxicity.

Compounds	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	log Kp (cm/s)
(+)-Sesamin	High	Yes	No	No	Yes	No	-6.56
(+)-Eudesmin	High	Yes	No	No	No	No	-6.57
(+)-Epieudesmin	High	Yes	No	No	No	No	-6.57
Tambulin	High	No	No	Yes	No	Yes	-6.17
Dictamine	High	Yes	No	Yes	No	No	-5.46
Skimmianine	High	Yes	No	Yes	Yes	Yes	-5.87
Aesculetin dimethyl ether	High	Yes	No	Yes	No	No	-6.34
(+)-Lirioresinol B	High	No	Yes	No	No	No	-7.27
Gossypetin 7,4'-dimethyl ether	High	No	No	Yes	No	Yes	-6.67
Platydesmine	High	Yes	Yes	Yes	No	No	-6.11

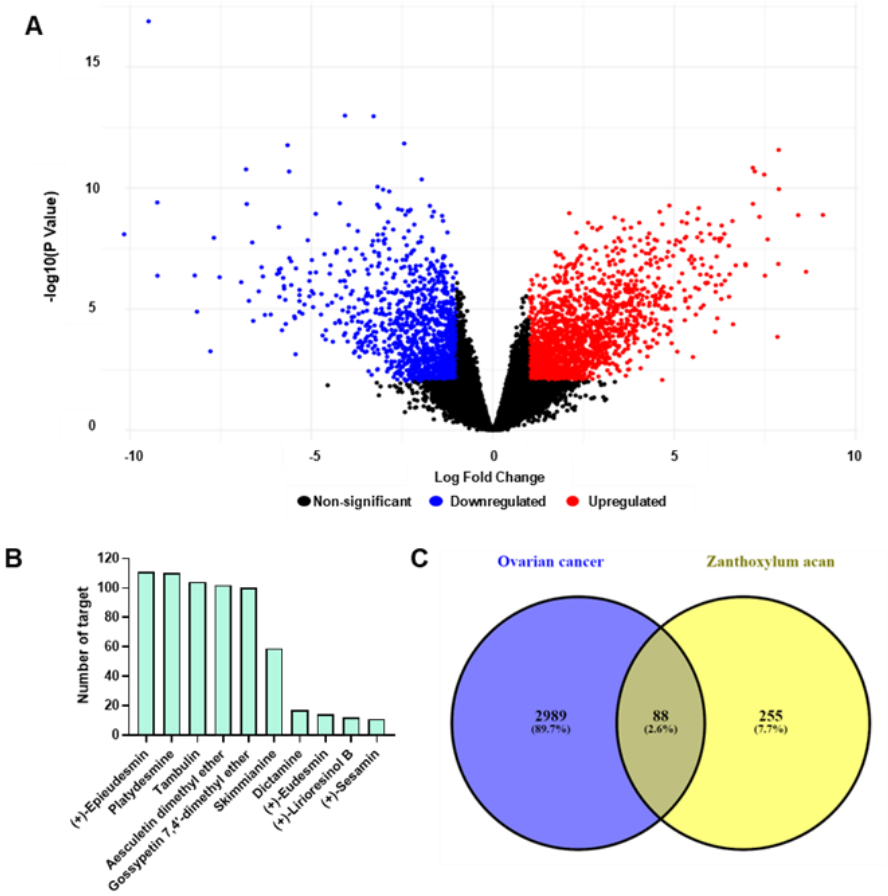

Figure 1. Identification of potential targets of ZA in ovarian cancer. (A) Volcano plot showing differentially expressed genes (DEGs) in ovarian cancer patients. Red dots represent significantly upregulated genes, while blue dots indicate downregulated genes. (B) Distribution of predicted targets for each bioactive compound in ZA, illustrating their potential interactions. (C) Venn diagram displaying 88 overlapping targets between ovarian cancer-related genes and ZA-associated targets, highlighting possible therapeutic connections.

(https://bioinfogp.cnb.csic.es/tools/venny/). The overlapping targets were imported into Cytoscape version 3.10.2 (https://cytoscape.org/) to build the compounds-target network [29].

2.5. Protein-Protein Interaction and Network Construction

To analyze the underlying mechanism of interacting genes, the common target genes of ZA and ovarian cancer were utilized. Data were imported into the STRING database (https://string-db.org/) to construct the protein-protein interaction (PPI) network [30]. A strong interaction was ensured with a cut-off confidence score of 0.7 and a 5% FDR stringency, specifying "*Homo sapiens*" as the species of interest. In the network, proteins are represented by nodes, and their interactions are shown by edges. Potential targets were constructed according to the number of degrees that identified the five primary targets.

2.6. Analysis of Gene Ontology and Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathway Enrichment Analysis

The biological functionality of the genes was investigated through gene ontology (GO) enrichment analyses using the 'clusterProfiler' package in R. The GO analysis encompassed three domains of Molecular Function (MF), Cellular Component (CC), and Biological Process (BP). Cnetplot was crafted using clusterProfiler [31] and visualized through the online platform Bioinformatics (https://www.bioinformatics.com.cn, accessed 10 July 2024), to visualized the GO and KEGG pathway enrichment.

3. RESULTS AND DISCUSSIONS

3.1. Pharmacokinetic and Active Component Screening

Table 1 shows the results of the database search for ZA compounds. A total of eleven compounds were discovered. To identify potential bioactive compounds, we applied a systematic selection process based on Lipinski's Rule of Five (Ro5) and bioavailability predictions. Only compounds with a MW of ≤ 500 Da, hydrogen bond donors ≤ 5, hydrogen bond acceptors ≤ 10, and an octanol-water partition coefficient (LogP) ≤ 5 were considered. In addition, the bioavailability scores must be > 0.5, as this threshold is indicative of good oral absorption. Among them, 10 compounds were deemed "Qualified" based on the screening results for Lipinski violations and oral bioavailability scores. The ten possible active components extracted at the end of the process are (+)-sesamin, (+)-eudesmin, (+)-epieudesmin, tambulin, dictamine, skimmianine, aesculetin dimethyl ether, (+)-lirioresinol B, gossypetin 7,4'-dimethyl ether, and platydesmine. Lipinski's rule violations and oral bioavailability scores are crucial in the search for novel drugs because they determine a compound's propensity to be an orally active drug [32]. Lipinski's Ro5 measures molecular characteristics such as log P, molecular weight, and hydrogen bond donors and acceptors to assess a molecule's drug-likeness and chances for effective absorption. High oral bioavailability indicates how well a drug is absorbed into the systemic circulation, affecting its efficacy and safety [33]. Early assessment of these parameters optimizes the overall pharmacokinetic profile, identifying potential issues during the early stages of drug development. These compounds performed

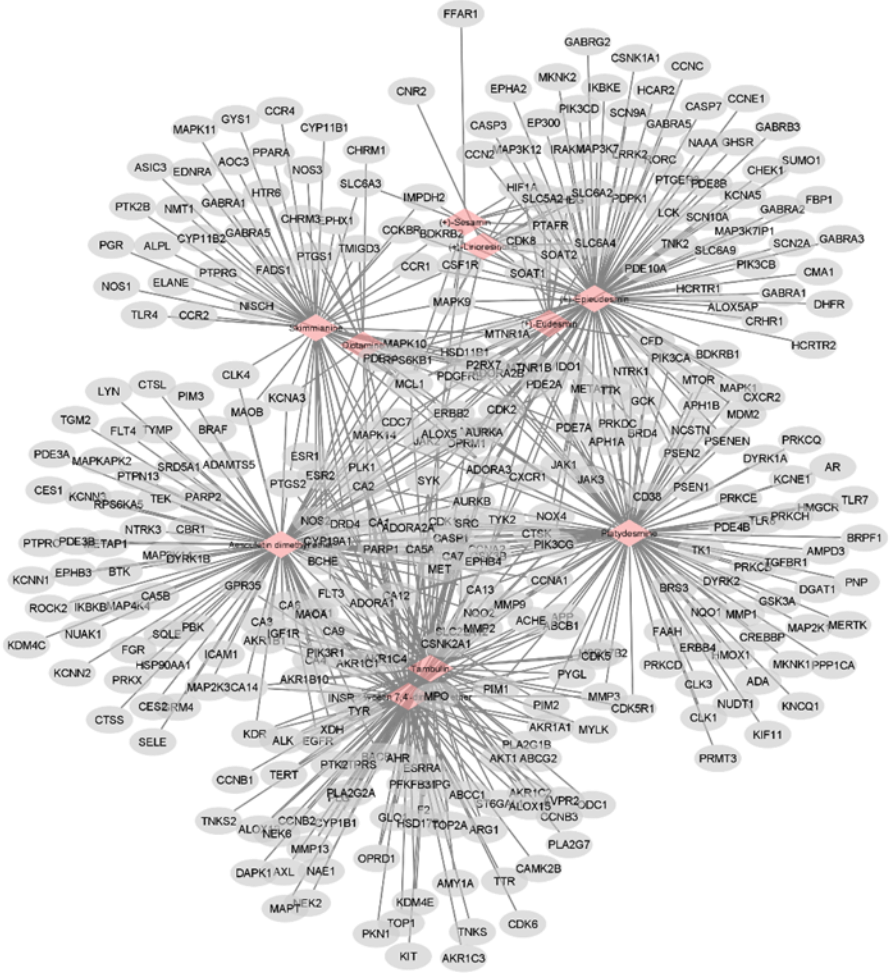

Figure 2. Interaction network between active compounds in ZA and their predicted targets in ovarian cancer. Grey nodes represent predicted protein targets, while cream-tan nodes indicate active compounds, providing insights into the molecular basis of ZA's potential therapeutic effects.

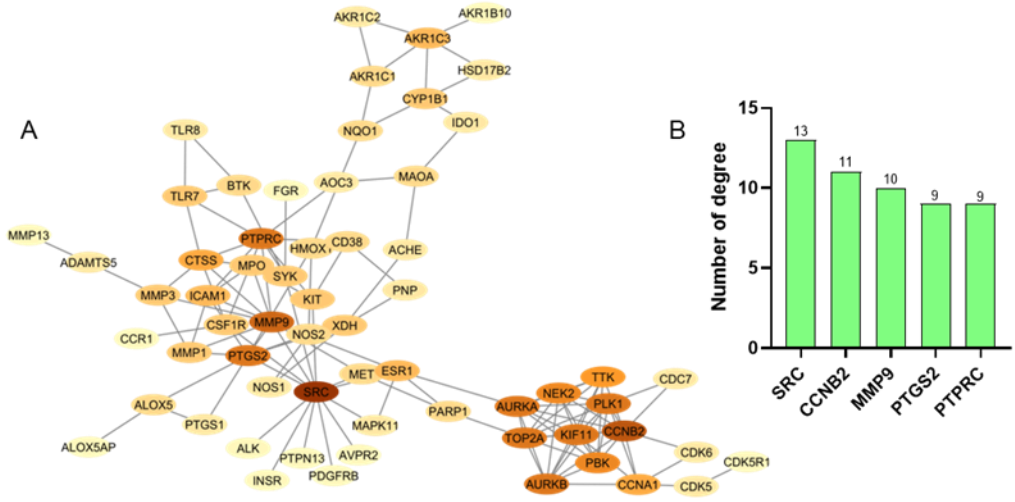

Figure 3. Protein-protein interaction (PPI) network of ZA-associated targets in ovarian cancer. (A) Central cluster of the PPI network, where node colors from dark orange to light yellow reflect variations in interaction strength, with darker shades indicating higher connectivity. (B) The five most influential target proteins ranked by the number of direct connections, identifying key regulators in ZA's mode of action.

well in most analyses of pharmacokinetic parameters (Table 2), which include absorption, distribution, metabolism, and excretion. Passing these parameters indicates a balanced pharmacokinetic profile, enhancing the drug's overall efficacy and safety [32][33]. This increases the likelihood of successful outcomes in preclinical and clinical trials, ultimately leading to the development of a viable therapeutic agent. Hence, ZA's active ingredients can be considered potential safe medications for human use.

3.2. Screening of Potential Targets for Ovarian Cancer and ZA

From the Gene Expression Omnibus database, specifically from datasets GSE189553 and GSE223426, a total of 3077 targets were obtained from the comprehensive analysis of differentially expressed genes (DEGs) associated with ovarian cancer that are potentially involved in the onset and advancement of ovarian cancer. According to the target screenings, 343 potential targets were identified for the 10 active molecules of ZA. This step is crucial in understanding the molecular interactions and the therapeutic potential of ZA against ovarian cancer. The intersection of these datasets is visualized in Figure 1(c) using a Venn diagram, which highlights the overlapping genes between the DEGs associated with ovarian cancer and the targets of ZA. A total of 88 intersecting genes were identified, representing probable anti-ovarian cancer targets of ZA. This intersection suggests a targeted therapeutic pathway where ZA could exert its effects on ovarian cancer.

3.3. Construction of the Compound-Target Regulatory Networks and Protein-Protein Interaction Network

To elucidate the mechanism by which ZA treats ovarian cancer, a compound-target interaction network was developed, as depicted in Figure 2. This network comprises 10 active compounds and 88 target proteins, which interact with each other. The analysis revealed that multiple components targeted several common proteins, indicating that the active compounds in ZA might exert a synergistic effect on various targets. To enhance visualization and deepen understanding of the mechanisms underlying these targets, the protein-protein interactions (PPI) of the target genes were analyzed using STRING v12. A high-confidence interaction threshold was set with a score greater than 0.7. The resulting PPI network, shown in Figure 3(a), consists of 70 nodes and 130 edges, representing the primary clusters of interacting target proteins. The PPI analysis suggests that proto-oncogene tyrosine-protein kinase Src (SRC), cyclin B2 (CCNB2), matrix metalloproteinase-9 (MMP9), prostaglandin-endoperoxide synthase 2 (PTGS2), and protein tyrosine phosphatase receptor type C

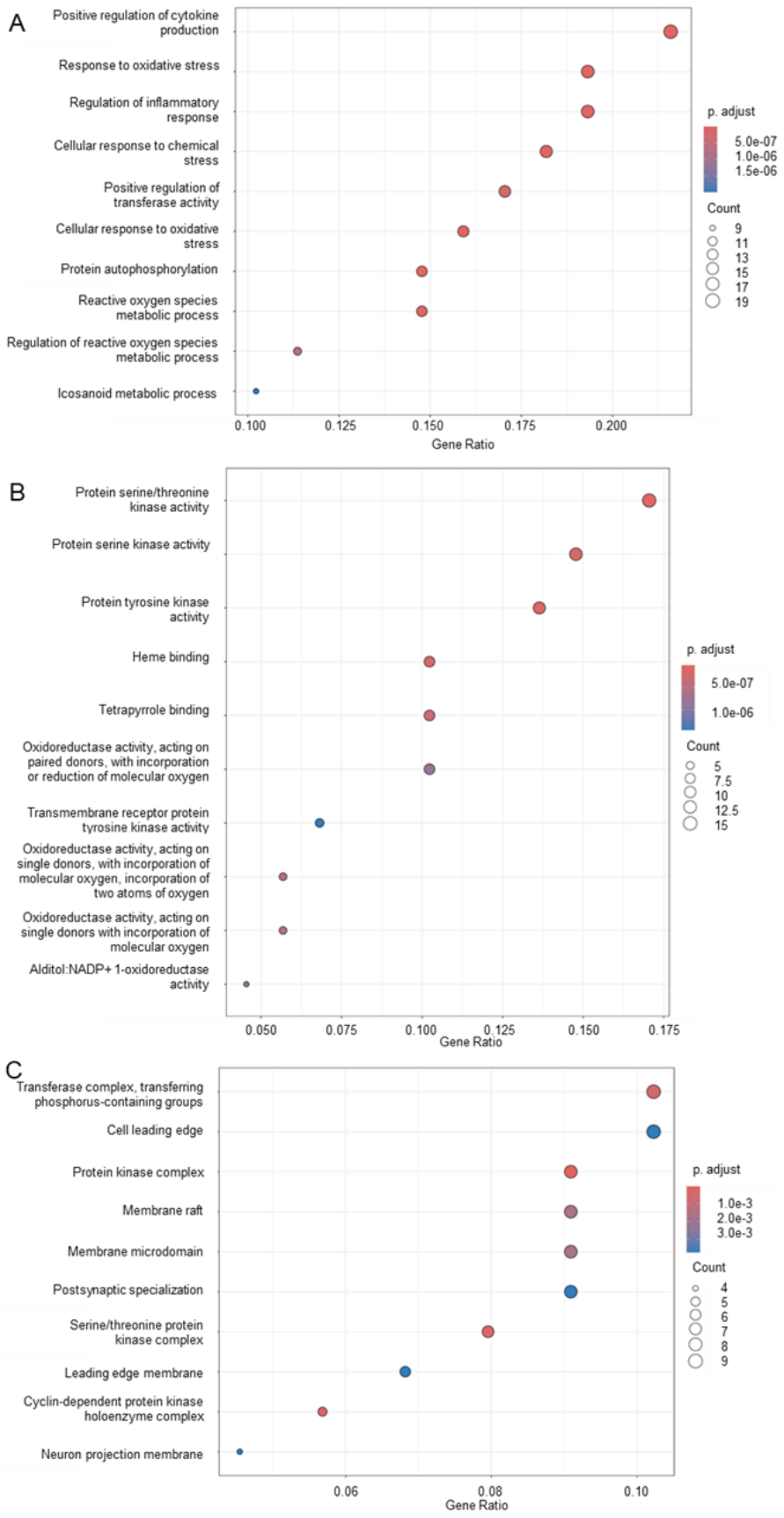

Figure 4. Gene Ontology (GO) enrichment analysis of ZA-related targets. (A) Functional enrichment of biological processes. (B) Molecular function classification. (C) Cellular component distribution. Dot size represents the number of associated genes, while color intensity indicates statistical significance, with darker hues corresponding to lower p-adjusted values.

(PTPRC) are critical targets due to their significant involvement in ovarian cancer pathways (Figure 3 (b)).

The PPI network analysis revealed that SRC, CCNB2, MMP9, PTGS2, and PTPRC exhibit high degrees of connectivity, indicating their central roles in ovarian cancer signaling. Among them, SRC acts as a hub protein with multiple direct interactions, suggesting its potential role as a master regulator in oncogenic pathways. SRC is a non-receptor tyrosine kinase that is often overexpressed or hyperactivated in ovarian cancer [34]. It promotes cancer cell proliferation, survival, and invasion by modulating various signaling pathways, including those involved in cell adhesion and motility [35]. CCNB2 is a cell cycle regulator crucial for mitosis. Overexpression of CCNB2 has been linked to increased cell division and poor prognosis, indicating its role in driving uncontrolled tumor progression. Inhibition of CCNB2 can disrupt the normal cell cycle progression, leading to suppression of cancer cell growth and enhanced apoptosis [36].

MMP9 is an enzyme that breaks down extracellular matrix components, facilitating the spread and infiltration of cancer cells [37]. Elevated MMP9 levels in ovarian cancer tissues are associated with enhanced tumor aggressiveness and the capacity to invade nearby tissues [38]. MMP9 inhibitors and RNA interference techniques have shown decreased tumor invasiveness and improved survival in animal studies. It suggested that focusing on MMP9 could open new avenues for effective ovarian cancer treatment [39][40].

PTGS2, or COX-2, is an enzyme that plays a key role in generating prostaglandins that promote inflammation and tumor growth [41]. A notable example of a COX-2 inhibitor used in ovarian cancer research is celecoxib [42]. Celecoxib is a targeted COX-2 inhibitor, designed to home in precisely on the COX-2 enzyme, which is often upregulated in ovarian cancer and contributes to tumor progression through increased production of inflammatory prostaglandins. By inhibiting COX-2, Celecoxib reduces the levels of prostaglandins such as PGE2, thereby decreasing inflammatory signals

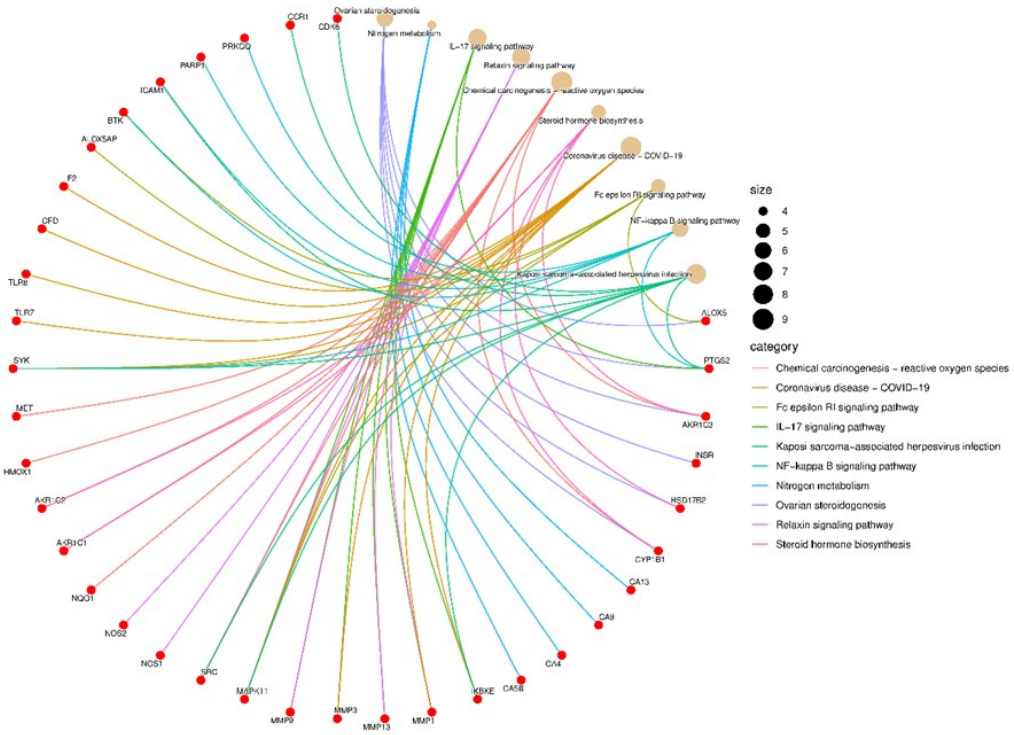

Figure 5. KEGG pathway analysis of ZA-associated targets. Network visualization of enriched pathways using cnetplot, illustrating the connection between ZA-associated genes and key signaling pathways in ovarian cancer. This analysis provides insights into the potential mechanisms through which ZA may exert its biological effects.

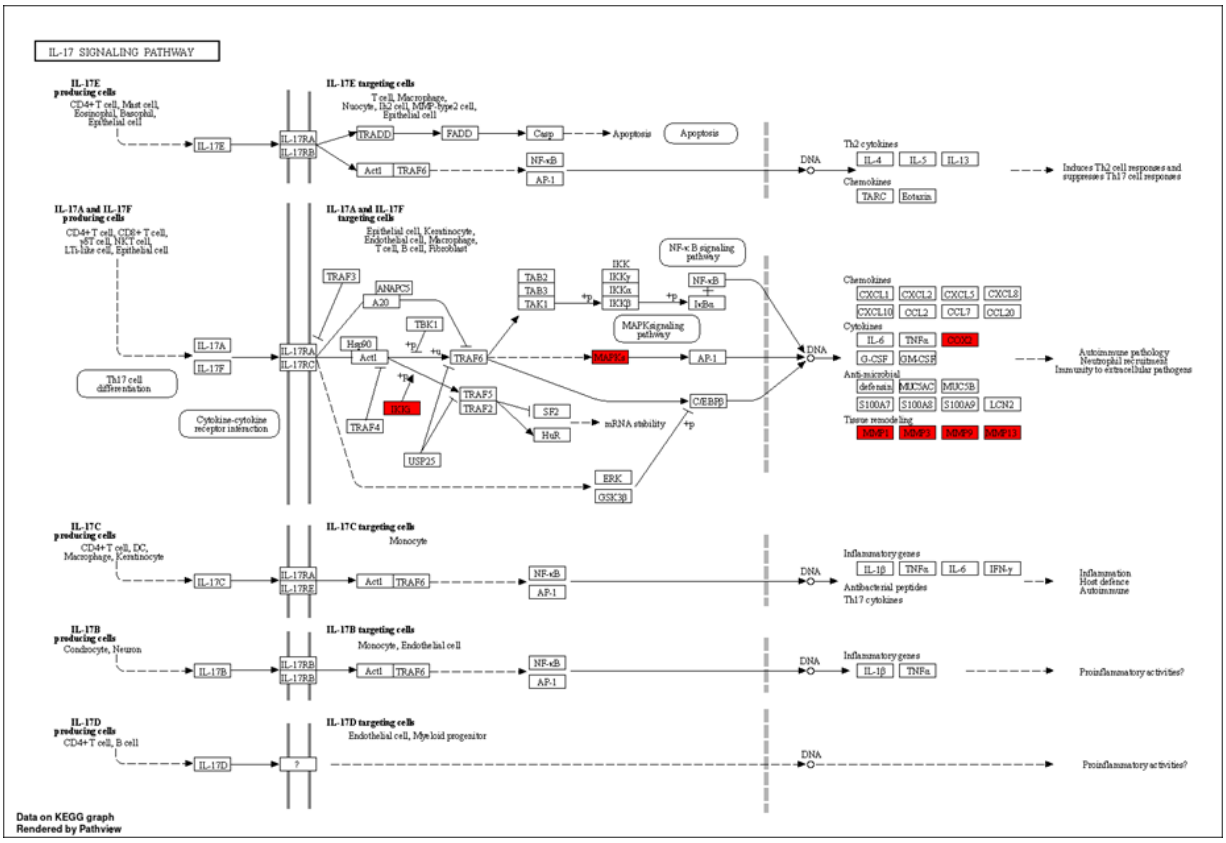

Figure 6. IL-17 signaling pathway as a potential mechanism of ZA action against ovarian cancer. ZA-related targets are highlighted within the red box.

that promote tumor growth and survival. This inhibition further halts the growth of new blood vessels, cutting off the lifeline that tumors need to expand and spread [41][42]. Elevated PTGS2 levels are often observed in ovarian cancer and support the inflammatory microenvironment that supports tumor progression [43].

PTPRC is a receptor-like phosphatase involved in cellular signaling and regulation. PTPRC is essential for regulating the activation and function of immune cells, like T cells and B cells, which responsible as the key controller in the immune response [44]. In ovarian cancer, inhibiting PTPRC can alter immune cell signaling and enhance anti-tumor immune responses [45]. This could potentially improve the body's ability to target and destroy cancer cells. Its altered expression in ovarian cancer can affect various signaling pathways related to cell growth and migration, potentially influencing cancer development and response to treatment. From a network topology perspective, these findings suggest that SRC, CCNB2, and MMP9 function as central nodes, meaning their inhibition could disrupt multiple downstream pathways, making them promising therapeutic targets. The presence of cross-talk between immune regulation (PTPRC), inflammation (PTGS2), and proliferation (SRC, CCNB2) further highlights the complexity of ovarian cancer signaling and provides potential intervention points for combination therapy.

3.4. Enrichment Analysis of Intercepted Targets

To verify the biological characteristics of the selected 88 targets in ovarian cancer, GO enrichment analysis was performed using the clusterProfile package, focusing on biological processes (BP), molecular functions (MF), and cellular compartments (CC). The BP results revealed significant enrichment in processes such as positive regulation of cytokine production, cellular response to chemical and oxidative stress, protein autophosphorylation, regulation of the inflammatory response, reactive oxygen species metabolism, and icosanoid metabolism (Figure 4 (a)). For MF, the analysis highlighted activities including protein tyrosine kinase activity, protein serine/threonine kinase activity, heme binding,

tetrapyrrole binding, oxidoreductase activity, alditol+ 1-oxidoreductase activity, and transmembrane receptor protein tyrosine kinase activity (Figure 4(b)). In terms of CC, the enriched terms included protein kinase complexes, serine/threonine protein kinase complexes, cyclin-dependent protein kinase holoenzyme complexes, transferase complexes, membrane rafts, membrane microdomains, cell leading edges, leading edge membranes, neuron projection membranes, and postsynaptic specializations (Figure 4(c)).

Using KEGG analysis, a gene-pathway network was constructed, identifying the top ten pathways associated with the mechanism of ZA against ovarian cancer. These pathways, significantly enriched with a P value, are displayed in Figure 5. They include ovarian steroidogenesis, nitrogen metabolism, the IL-17 signaling pathway, the relaxin signaling pathway, chemical carcinogenesis due to reactive oxygen species, steroid hormone biosynthesis, coronavirus disease (COVID-19), the Fc epsilon RI signaling pathway, the NF-kappa B signaling pathway, and Kaposi sarcoma-associated herpesvirus infection. Figure 6 illustrates the predicted targets of the IL-17 signaling pathway, which includes six genes. ZA could potentially target these genes for the treatment of ovarian cancer.

In this study, we employed a computational approach to identify potential molecular targets of ZA against ovarian cancer. While these findings provide valuable insights, experimental validation through *in vitro* and *in vivo* studies is essential to confirm the predicted interactions and therapeutic relevance. *In vitro* assays, such as cell viability, apoptosis, and gene expression studies, could help verify the biological effects of the identified compounds, while in vivo models would provide a more comprehensive understanding of their pharmacokinetics and efficacy. Future studies should focus on these validation strategies to bridge the gap between computational predictions and clinical applications, ensuring the translational potential of ZA-derived compounds.

4. CONCLUSIONS

In conclusion, ZA predominantly targets key proteins including SRC, CCNB2, MMP9, PTGS2, and PTPRC, and additionally influences various other pathways involved in ovarian cancer treatment. The network pharmacology study provides a robust theoretical foundation for the use of ZA and offers a comprehensive understanding of its mechanisms in combating ovarian cancer. These findings revealed strong interactions between ZA's active constituents and cancer-related targets, particularly within the PI3K-AKT and MAPK signaling pathways, suggesting potential anti-proliferative and anti-metastatic effects. Furthermore, the compound-target-pathway network highlighted the multitarget nature of ZA, supporting its potential in modulating multiple biological processes relevant to tumor progression. Our next steps will involve conducting animal and cell-based studies to confirm that the active ingredients in ZA effectively engage the critical targets for treating ovarian cancer.

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Conflicts of Interest

The authors declare no conflict of interest.

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