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Exploring the Molecular Mechanism of Phenethyl Alcohol Glycoside's Anti-Cervical Cancer Activity Based on Network Pharmacology

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Abstract. Cervical cancer is one of the most common and most threatening malignant tumors of the female reproductive system worldwide, with an incidence markedly higher than that of endometrial and ovarian cancers. There is an urgent need for multi-target, low-toxicity therapeutic strategies. This study, based on network pharmacology integrated with experimental validation, systematically investigates the molecular mechanisms by which phenylethanoid glycosides (PhGs: echinacoside, acteoside, isoacteoside, and 2-acetylacteoside) act against cervical cancer. Overlapping targets between PhGs and cervical cancer were screened using databases such as SwissTargetPrediction and GeneCards; a protein–protein interaction (PPI) network was constructed with STRING to identify hub genes. Target expression was verified using the GEPIA and HPA databases, and GO/KEGG enrichment analyses were performed via Metascape. Finally, CCK-8, colony-formation, Transwell, and ELISA assays were employed to verify the effects of PhGs on the proliferation, migration, and inflammatory cytokine secretion of HeLa and SiHa cervical cancer cells. In total, 27 common targets were identified, of which 15 were hub genes (e.g., CASP3, MMP9, AKT1). KEGG enrichment indicated that PhGs mainly regulate the PI3K–Akt, MAPK, mTOR, VEGF, and IL-17 signaling pathways. Experimental results confirmed that PhGs inhibit cervical cancer cell proliferation, colony formation, and migration in a concentration-dependent manner. In summary, by coordinately controlling key targets related to apoptosis (CASP3), metastasis (MMP9), inflammation (TNF/IL-6), and the PI3K–Akt/MAPK pathways, PhGs suppress the progression of cervical cancer, and their multi-target mechanism provides a theoretical basis for the development of adjuvant therapeutics for this disease.

Keywords: Phenylethanoid Glycosides; Cervical Cancer; Network Pharmacology; Molecular Mechanism.

1. Introduction

Cervical cancer ranks among the four most common malignant tumors affecting women worldwide, with its incidence and mortality rates being particularly high in China. According to the latest 2024 data from the National Cancer Center, new cervical cancer cases in China exceed 100,000 per year and deaths exceed 14,000, far higher than the levels reported in the United States. In addition to population size, this disparity is closely related to the low coverage of HPV vaccination and the incomplete screening system in China (Burd, 2003). Persistent infection with high-risk human papillomavirus (HPV) is the principal etiologic factor in cervical carcinogenesis. Current treatments include surgery for early disease, radiotherapy for intermediate and advanced stages, and chemotherapy for advanced or high-risk patients (Olusola, Banerjee, Philley, & Dasgupta, 2019). Although these modalities can effectively control early lesions, patients with late-stage or recurrent disease still face daunting challenges of therapeutic resistance and metastasis, which severely limit efficacy as well as quality of life and survival. Therefore, there is an urgent need to explore safe and effective novel anti-cervical cancer agents (Bedell, Goldstein, Goldstein, & Goldstein, 2020).

Natural products, by virtue of their multi-target and low-toxicity properties, are an important source for anticancer drug discovery. Phenylethanoid glycosides (PhGs) are a class of water-soluble active constituents widely distributed in medicinal plants and abundant in traditional Chinese materia medica such as *Cistanche*, *Rehmannia*, and *Ligustrum lucidum* (Xue, & Yang, 2016). Previous studies have shown that PhGs possess anti-inflammatory, antioxidant, and antitumor potential *(Tian, Li, Lin, Qiu, Zhu, Li, Tao, Wang, Ren, & Chen, 2021)*. However, most of these findings are validations of

isolated targets, and a systematic exploration of the mechanisms of PhGs in cervical cancer remains lacking. Given that the occurrence and development of cervical cancer typically involve complex regulation across multiple targets and pathways, reliance on single-target studies is insufficient to reveal the complete pharmacological network of action (Nogales, Mamdouh, List, Kiel, Casas, & Schmidt, 2022).

Phenylethanoid glycosides (PhGs) are a class of water-soluble active constituents widely distributed in medicinal plants and abundant in traditional Chinese materia medica such as *Cistanche*, *Rehmannia*, and *Ligustrum lucidum (Kite, 2020)*. Modern pharmacological research indicates that PhGs exert antioxidant, anti-inflammatory, and immunomodulatory effects, and in recent years they have been shown to display antitumor activity in multiple malignancies. For example, echinacoside and acteoside inhibit the proliferation of cervical cancer cells such as HeLa and SiHa and induce apoptosis (Li, Lin, Gu, Gao, & Tzeng, 2016) . Nevertheless, most of these results remain validations of isolated targets, and a systematic investigation of the mechanisms of PhGs in cervical cancer is still lacking. Considering that the initiation and progression of cervical cancer involve multi-target, multi-pathway regulation, single-target approaches cannot elucidate the complete pharmacological network (Yao, Wan, Zhang, Shen, Wei, Shi, Ou, Liu, Ge, Fei, & Zeng, 2024).

Accordingly, this study introduces a network-pharmacology approach to systematically elucidate the mechanisms by which PhGs act against cervical cancer: by constructing an interaction network of "PhG active constituents–potential targets–cervical cancer," identifying hub targets and key pathways, and ultimately validating, through in vitro cell experiments, the effects of these hub targets and key signaling pathways on the growth, proliferation, and migration of cervical cancer cells. This work, for the first time from a network perspective, reveals that PhGs exert anti-cervical cancer effects by modulating the multidimensional network of "HPV oncogenic proteins–host signaling–immune microenvironment," thereby overcoming the limitations of single-target studies. The results provide a scientific basis for the use of PhGs as adjuvant therapeutics or sensitizers in cervical cancer, offer a "dry–wet combined" research paradigm for systematic mechanism studies of multi-component natural products, and suggest that the identified hub targets may offer new avenues for targeted therapy of cervical cancer.

2. Materials and Methods

2.1 Prediction of Phenylethanoid Glycosides Target

The corresponding targets of the phenylethanoid glycosides echinacoside, acteoside, isoacteoside, and 2-acetylacteoside were retrieved from the SwissTargetPrediction database (http://www.swisstargetprediction.ch). The retrieved targets were converted to standard gene names using the UniProt database and deduplicated.

2.2 Prediction of cervical-cancer–related targets

Using "Cervical cancer" as the keyword and restricting the species to "Homo sapiens," disease-related targets were collected from the GeneCards database (https://www.genecards.org/), the OMIM database (https://www.omim.org/), and the DisGeNET database (https://www.disgenet.org/).

2.3 Analysis of potential anti-cervical-cancer targets of phenylethanoid glycosides

The target sets for phenylethanoid glycosides and cervical cancer were uploaded to Venny 2.1.0 (https://bioinfogp.cnb.csic.es/tools/venny) to draw Venn diagrams for visualization, and the intersecting targets—i.e., the potential targets through which phenylethanoid glycosides exert anti-cervical-cancer activity—were downloaded.

2.4 Construction of the protein–protein interaction (PPI) network for potential targets of phenylethanoid glycosides against cervical cancer and identification of hub targets

The set of potential anti-cervical-cancer targets of phenylethanoid glycosides was entered into the STRING database (https://cn.string-db.org/) using the "Multiple proteins" input mode with species limited to "Homo sapiens" to obtain the PPI network and the corresponding TSV file. After exporting the TSV file, the PPI network was constructed in Cytoscape 3.8.2, and the CytoHubba plugin was used to calculate degree values for screening hub genes.

2.5 Validation of hub-target expression levels

To validate the above bioinformatic results, the expression levels of the identified hub genes were examined across different datasets. Transcriptional expression of the hub genes in normal cervical tissue and in cervical cancer tissues of different stages was queried in the Gene Expression Profiling Interactive Analysis (GEPIA) database (http://gepia.cancer-pku.cn/), with tumor and normal samples derived from the TCGA database (https://www.genome.gov/Funded-Programs-Projects/Cancer-Genome-Atlas) and the GTEx database (https://gtexportal.org/home/), respectively. Protein expression was viewed in the Human Protein Atlas (https://www.proteinatlas.org/), which presents immunohistochemically stained tissue images, to assess hub-gene protein levels in normal cervical tissue and in cervical cancer tissues of different stages.

2.6 Functional enrichment analysis of potential anti-cervical-cancer targets of phenylethanoid glycosides

Potential targets through which phenylethanoid glycosides act against cervical cancer were entered into the Metascape database (https://www.metascape.org/gp/index.html#/main/step1) for GO functional enrichment and KEGG pathway enrichment analyses. In the analysis tool, the sequence attribute was set to "official gene symbol," the organism to "Homo sapiens," and datasets obtained from GO and KEGG enrichment were filtered with $P < 0.05$.

2.7 Network analysis of "phenylethanoid glycosides–cervical cancer–signaling pathways–targets"

The potential target set through which phenylethanoid glycosides act against cervical cancer and the top five KEGG signaling pathways were imported into Cytoscape to construct a visual network of "drug–signaling pathways–target genes–disease."

2.8 CCK-8 assay

HeLa and SiHa cells were seeded in 96-well plates at 1×10^4 cells/well. After 24 h incubation at 37 °C in a 5% CO_2 incubator to allow adherence, different concentrations of phenylethanoid glycosides (200 μM, 100 μM, 50 μM, 25 μM) were added. Drugs were removed at 24 h; untreated cells served as controls. Three replicate wells were set for each group. Then 100 μL of serum-free medium containing 10 μL CCK-8 was added to each well and incubated for ~1.5 h, after which OD values were measured at 450 nm with a microplate reader.

2.9 Colony-formation assay

HeLa and SiHa cells were seeded at 100 cells/well in 6-well plates and incubated overnight. Medium was refreshed every 2–3 days. When appropriate colony density was reached at 14 days, cells were treated with phenylethanoid glycosides at 200 μM, 100 μM, 50 μM, 25 μM for 48 h. After drug removal, cells were fixed with formaldehyde for 30 min, stained with crystal violet for 30 min, rinsed with running water, air-dried, and photographed. Images were quantified using ImageJ.

2.10 Transwell assay

A blank control and treatment groups at 200 μM, 100 μM, 50 μM, 25 μM phenylethanoid glycosides were set and incubated for 24 h. After forming a cell suspension, cells were collected by centrifugation, resuspended in DMEM basal medium, and adjusted to 5×10^4 cells/well for the upper chamber; 200 μL of serum-free basal medium was added to the upper chamber. The lower chamber received 500 μL complete medium with 10% FBS. After 24 h, cells on the lower surface were fixed with ice-cold methanol and stained with 0.1% crystal violet. Fields were observed and photographed under 100× magnification. All experiments were repeated three times.

2.11 Elisa assay

Commercial ELISA kits were used to detect interleukin-6 (IL-6) levels in the supernatants of HeLa and SiHa cells after 24 h treatment with phenylethanoid glycosides (200 μM, 100 μM, 50 μM, 25 μM). Procedures strictly followed the manufacturer's instructions.

3. Result

3.1 Analysis of potential anti-cervical-cancer targets of phenylethanoid glycosides

Targets corresponding to phenylethanoid glycosides were retrieved from the SwissTargetPrediction database and converted to standard gene names in UniProt; after deduplication, 171 drug targets were obtained. Using "Cervical cancer" as the search term, 171 disease-related targets were collected from GeneCards (https://www.genecards.org/); 799 disease-related targets were retrieved from DisGeNET (https://www.disgenet.org/); and XX disease-related targets were retrieved from OMIM (http://www.omim.org/). Venn diagrams were drawn using the Venn Diagrams online tool to identify 27 intersecting targets between phenylethanoid glycosides and cervical cancer, which were considered the potential targets by which phenylethanoid glycosides exert anti-cervical-cancer activity (Figure 1).

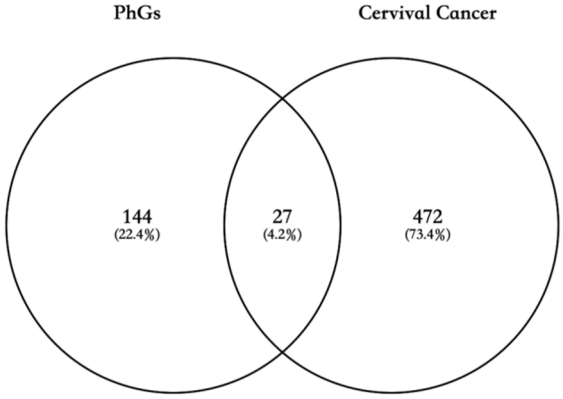

Figure 1: Potential Target Sites for Phenethyl Alcohol Glycoside's Anti-Cervical Cancer Activity

3.2 Screening of core genes for the anti-cervical-cancer activity of phenylethanoid glycosides

The 27 potential targets were input into the STRING database to obtain the protein–protein interaction (PPI) relationships, and the results were imported into Cytoscape to construct the PPI network. The network comprised **27 nodes** and **180 edges**, with a **network density of 0.513**; node size and color depth were **positively correlated with degree** (Figure 2).

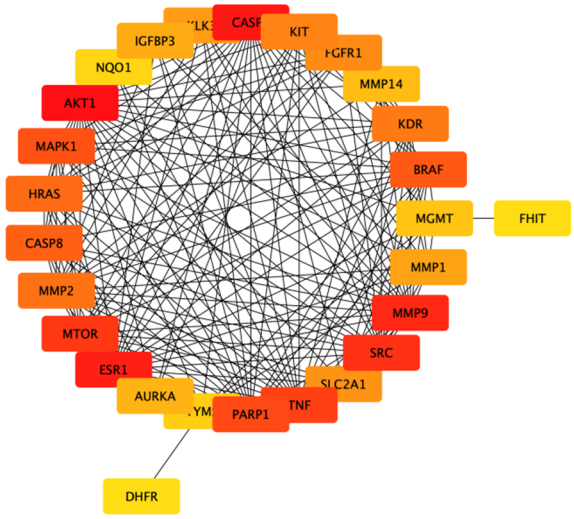

Figure 2: Potential Target Protein-Protein Interaction (PPI) Network for Phenethyl Alcohol Glycoside's Anti-Cervical Cancer Activity

The PPI network was analyzed in **Cytoscape**, and the **CytoHubba** plugin was used to identify genes with **degree values > 14** as hub genes, namely **KIT, BRAF, SRC, KDR, MMP9, MMP2, HRAS, PARP1, ESR1, CASP3, MTOR, TNF, CASP8, MAPK1,** and **AKT1** (Figure 3).

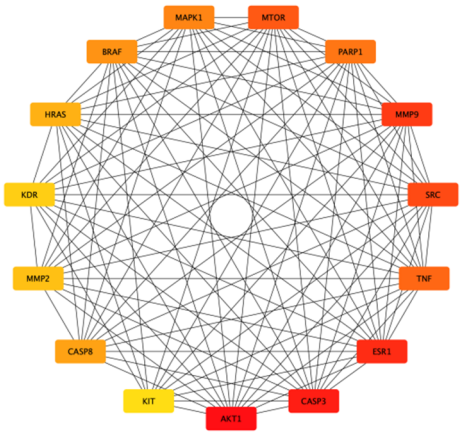

Figure 3: Protein-Protein Interaction (PPI) Network of Core Target Proteins Mediating the Anti-Cervical Cancer Activity of Phenethyl Alcohol Glycoside

3.3 Validation of hub-gene expression at the clinical level

To assess whether the identified hub genes are representative and therapeutically relevant, we first examined the transcriptomic expression of the 15 hub genes in the **GEPIA** database. The results showed that, compared with normal tissue samples, the expression levels of **CASP3, TNF,** and **MMP9** were significantly upregulated in cervical cancer tissues, whereas **KDR, KIT,** and **MMP2** were significantly downregulated (Figure 4).

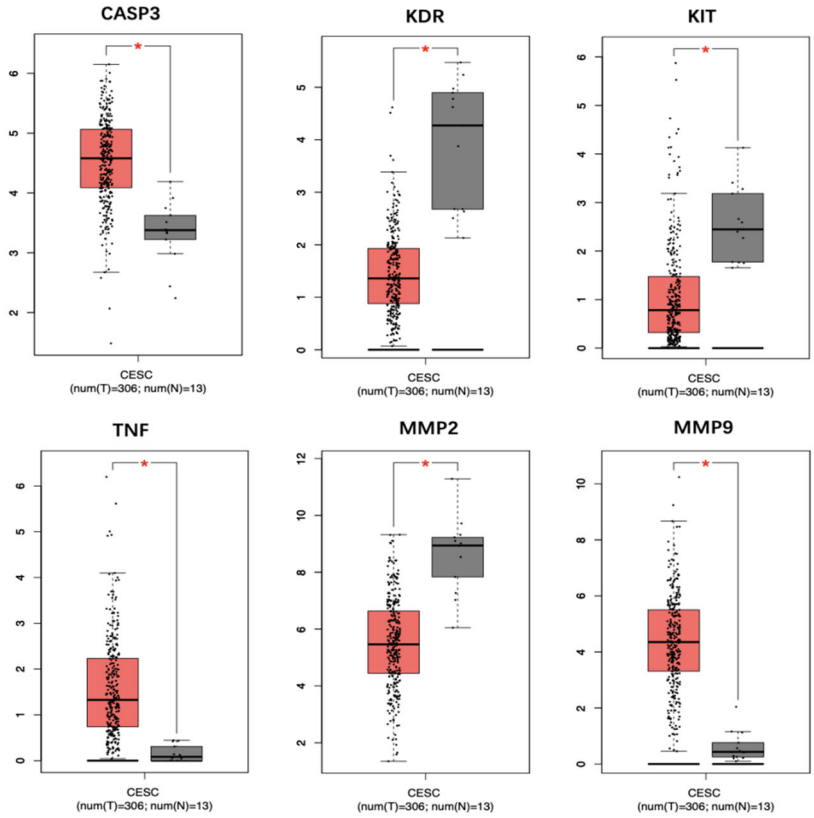

Figure 4: Expression of hub genes in cervical cancer tissue samples

3.4 Correlation between hub genes and survival time in patients with cervical cancer

The 15 hub differentially expressed genes identified by the above screening and validation are considered to participate throughout the process of malignant transformation and are closely related to the pathogenesis of cervical cancer. By examining the correlations between the expression levels of these genes and patients' survival times, their roles in disease progression can be further clarified. For patients with cervical cancer, up-regulation of the hub genes **CASP3**, **KIT** (written as **KT** in the source), and **MMP9** has a significantly detrimental impact on both **overall survival (OS)** and **progression-free survival (PFS)**, indicating increased survival risk in patients with higher expression of these genes (Figure 5). In contrast, patients with up-regulated **BRAF** expression tend to exhibit better **OS** and **RFS**, suggesting that elevated BRAF expression is associated with reduced survival risk (Figure 5).

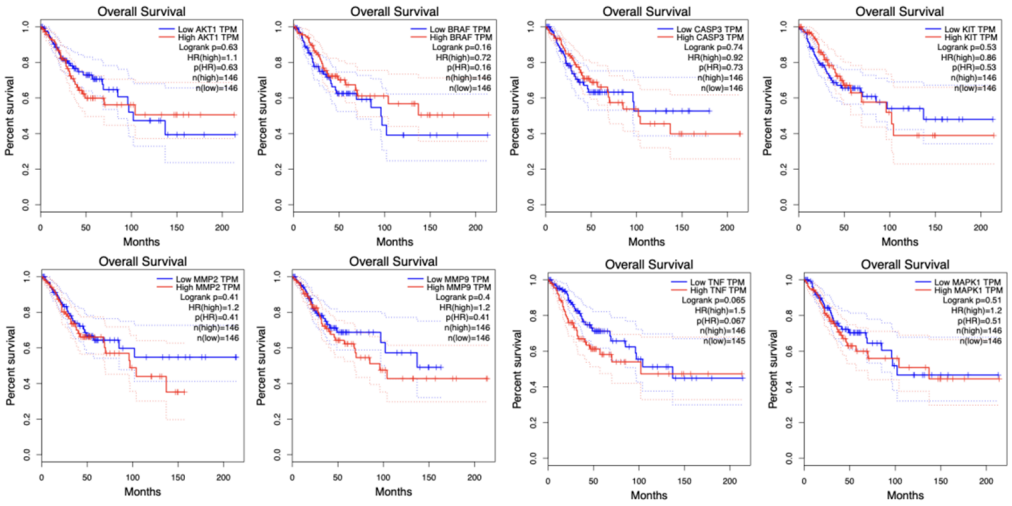

Figure 5: Survival analysis of hub genes in cervical cancer patients

3.5 Functional annotation of hub genes

GO term bar plots were obtained from the Metascape database, and the **top 16** pathways were selected for visualization (Figure 6). GO enrichment analysis indicated that the targets are mainly involved in GO terms such as **response to stimulus**, **locomotion**, **regulation of biological process**, **cellular process**, and **developmental process**.

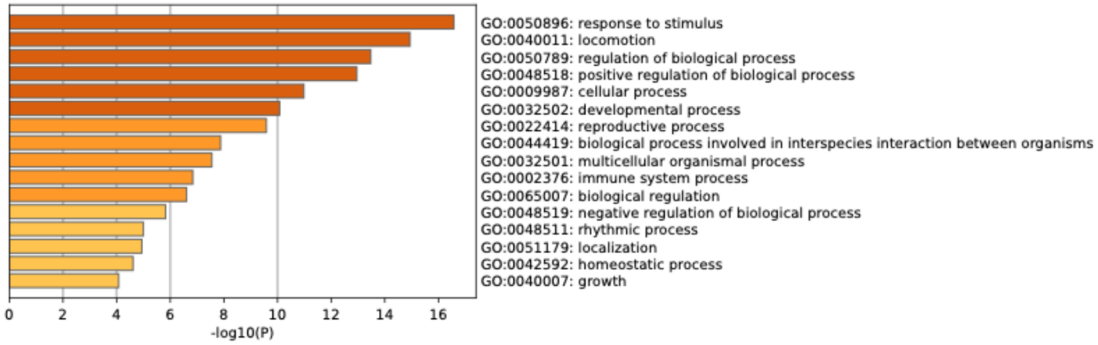

Figure 6: Gene Ontology Enrichment Analysis of Phenethyl Alcohol Glycoside's Anti-Cervical Cancer Activity

Based on the KEGG enrichment analysis, the **top seven KEGG signaling pathways** were selected for visualization (Figure 7), namely **EGFR tyrosine kinase inhibitor resistance, MAPK signaling pathway, AGE–RAGE signaling pathway, VEGF signaling pathway, mTOR signaling pathway, PI3K–Akt signaling pathway**, and **IL-17 signaling pathway**. These results indicate that the **anti-cervical cancer activity of phenylethanoid glycosides** is closely associated with these pathways.

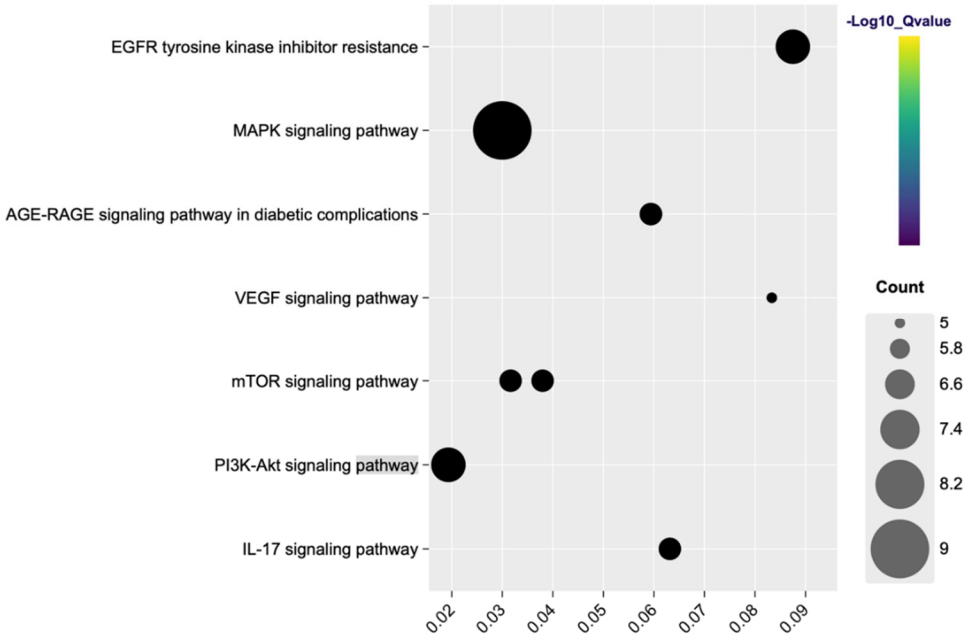

Figure 7: KEGG Gene Enrichment Analysis of Phenethyl Alcohol Glycoside's Anti-Cervical Cancer Activity

3.6 "Phenylethanoid glycosides–cervical cancer–key signaling pathways–hub targets" network analysis

The intersection targets of Phenylethanoid glycosides in exerting anti-cervical cancer activity and the targets of the top six KEGG signaling pathways were imported into Cytoscape 3.8.2 software to construct a visual network diagram of "drug-disease-signaling pathway" (Figure 8), indicating that Phenylethanoid glycosides exert anti-pathogenic bacterial activity from multiple targets and multiple pathways.

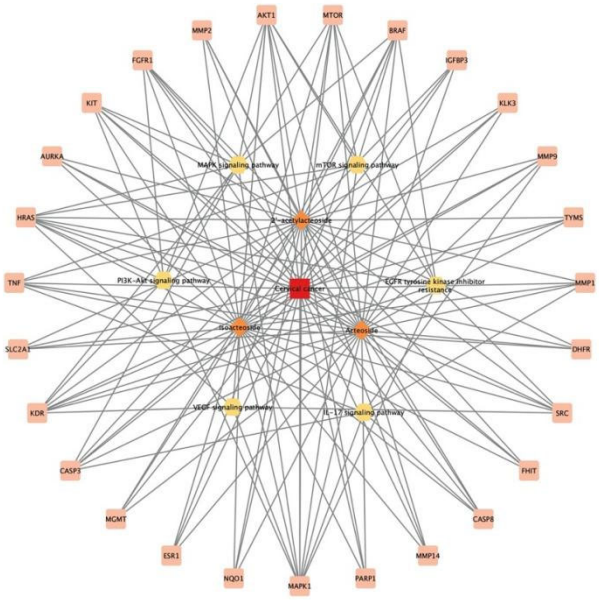

Figure 8: Network analysis of "phenylethanoid glycosides–cervical cancer–key signaling pathways–hub targets."

3.7 Phenylethanoid glycosides inhibit cervical cancer cell growth, proliferation, and colony-forming ability

The CCK-8 assay showed that, compared with the untreated control group (**0 μmol/L**), **acteoside (ACT)**, **isoacteoside (IsoACT)**, and **echinacoside (ECH)** effectively inhibited the growth and proliferation of **HeLa** and **SiHa** cells within **24 h** (Figure 9), with the inhibitory effect **increasing significantly with drug concentration**.

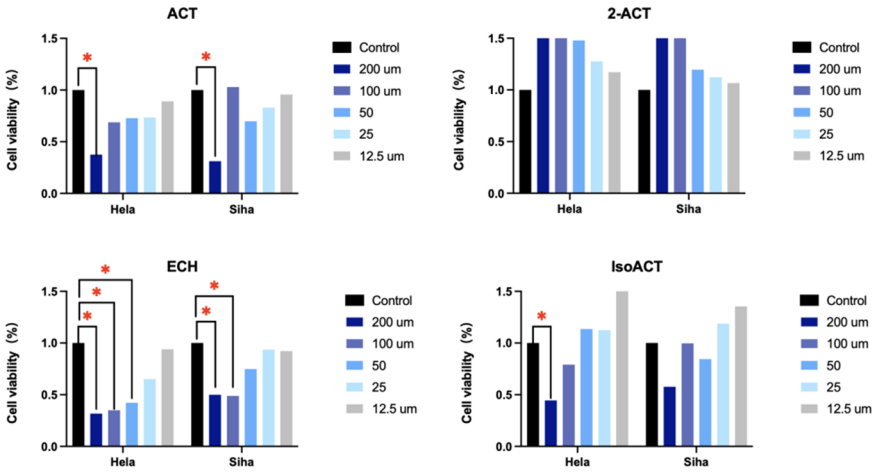

Figure 9: Analysis of Phenethyl Alcohol Glycoside's Anti-Cervical Cancer Cell Proliferation Activity

This study selected **acteoside (ACT)** and **echinacoside (ECH)** for subsequent experiments. In the colony-formation assay, compared with the control group, **200 μM ECH** and **200 μM ACT inhibited the number of colonies formed by SiHa cells** (Figure 10).

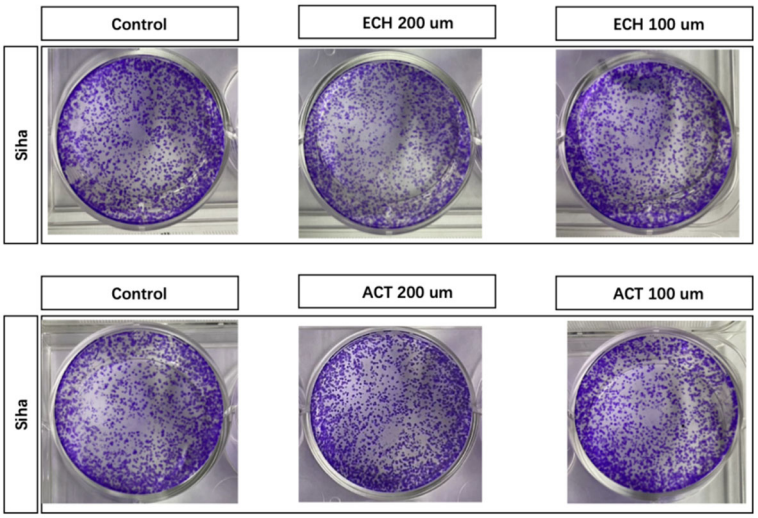

Figure 10: Analysis of Anti-Cervical Cancer Cell Monoclonal Formation Capacity of Phenethyl Alcohol Glycoside

3.8 Phenylethanoid glycosides inhibit cervical cancer cell migration

To further determine whether **acteoside (ACT)** affects the invasive capability of HeLa and SiHa cells, a **Transwell invasion assay** was performed. Compared with the control group, **200 μM ACT** significantly **suppressed the migration** of both HeLa and SiHa cells (Figure 11).

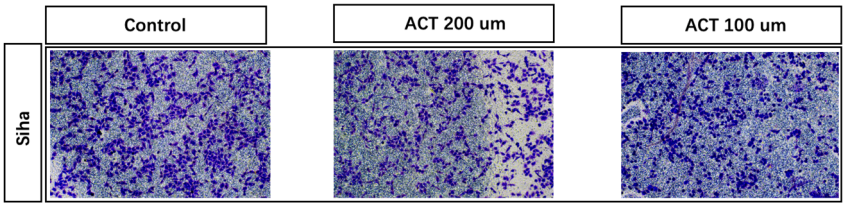

Figure 11: Analysis of the inhibitory effect of phenylethanoid glycosides on the migration of cervical cancer cells.

3.9 Phenylethanoid glycosides inhibit inflammatory cytokine secretion in cervical cancer cells

To further verify whether **acteoside (ACT)** affects the secretion of inflammatory cytokines in HeLa and SiHa cells, ELISA was used to measure **IL-6**. Compared with the control group, **200 μM ACT** reduced the secretion of IL-6 by HeLa and SiHa cells (Figure 12).

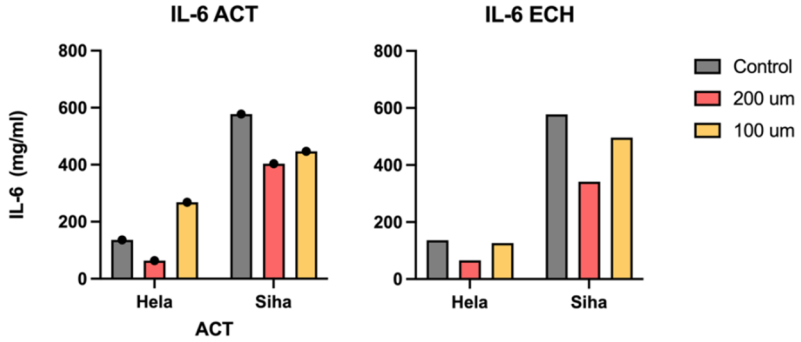

Figure 12: Analysis of the inhibitory effect of phenylethanoid glycosides on the secretion of inflammatory cytokines IL-6 of cervical cancer cells

4. Discussion

This study, for the first time, systematically elucidates the **multi-dimensional molecular mechanisms** by which phenylethanoid glycosides (PhGs) act against cervical cancer by integrating **network pharmacology** with **in vitro experimental validation**. The work not only confirms the significant inhibitory effects of PhGs on cervical cancer cell proliferation, migration, and the inflammatory microenvironment, but more importantly resolves—at the network level—the mechanism by which PhGs exert a coordinated antitumor effect through intervention in the complex network of **"HPV oncogenic proteins–host signaling–immune microenvironment."** This finding overcomes the limitations of traditional single-target studies and provides paradigm-level evidence for multi-target therapeutic strategies using natural products. By constructing a **"PhGs–targets–cervical cancer"** interaction network, we identified **15 hub targets** (including **CASP3, TNF, MMP9, AKT1, MAPK1**, etc.) whose functions span apoptosis regulation, metastatic invasion, inflammatory responses, and key oncogenic signaling nodes. These targets exhibit pronounced aberrant expression in cervical cancer tissues (**up-regulation of CASP3/MMP9, down-regulation of KDR/KIT**) and are closely associated with poor patient prognosis (e.g., shortened survival in patients with high CASP3/MMP9 expression). Notably, the regulation of these targets by PhGs is **bidirectional**: on the one hand, PhGs suppress pro-oncogenic factors (such as **MMP9**, **IL-6/IL-8**), and on the other, they activate anti-tumor pathways (such as **KDR-mediated vascular normalization**). This "multi-directional correction" is precisely the core advantage of PhGs in counteracting the complex pathological network of cervical cancer.

KEGG enrichment analysis further revealed **synergistic effects among key pathways**. PhGs simultaneously modulate the **PI3K–Akt**, **MAPK**, **mTOR**, **VEGF**, and **IL-17** pathways to form network-level regulation: inhibition of the **AKT1/mTOR axis** blocks the PI3K–Akt pathway to induce apoptosis (Yue, Liu, Liu, Li, Chang, Miao, & Zhao, 2015); down-regulation of **MMP2/9** and suppression of the **VEGF** pathway curb metastasis; and reduced secretion of **TNF/IL-6/IL-8** remodels the immune microenvironment (Johnson, O'Keefe, & Grandis, 2018). In vitro validation showed that treatment with **200 μM PhGs** significantly decreased colony-forming ability and migration of HeLa/SiHa cells and was accompanied by a sharp reduction in IL-6 secretion. This multi-pathway synergy—particularly the inhibition of the **PI3K/Akt/mTOR axis** that is persistently activated following HPV infection (a key downstream route of the **E6/E7** oncoproteins)—provides a molecular basis for PhGs to overcome HPV-related therapeutic resistance (Aguayo, Perez-Dominguez, Osorio, Oliva, & Calaf, 2023). The results link, for the first time, the anticancer mechanism of PhGs to the **host-signal hijacking** by HPV oncoproteins, revealing their potential to reverse virus-mediated malignant transformation of host cells by interfering with the **"E6–p53/PI3K"** and **"E7–pRb/mTOR"** oncogenic axes (Tommasino, & Crawford, 1995).

The clinical translational value of this study is reflected in three aspects. First, the hub targets (e.g., **CASP3, MMP9**) may serve as new loci for targeted therapy in cervical cancer, while PhGs themselves, owing to their multi-target properties, have the potential to become **radiosensitizers/chemosensitizers** or maintenance therapies for advanced patients. Second, the established **"dry–wet combined" strategy** (from network prediction to cellular functional verification) provides a reproducible paradigm for systematic mechanism studies of complex natural products(Infantino, Santarsiero, Convertini, Todisco, & Iacobazzi, 2021). Third, the ability of PhGs to regulate the **cross-network of viral proteins and host pathways** offers a new avenue for controlling the carcinogenic process driven by persistent HPV infection. Nevertheless, limitations remain: direct binding evidence between specific PhG constituents and targets requires further study via **molecular docking** or **surface plasmon resonance**; upstream–downstream regulatory relationships among hub targets need clarification through **gene knockout/overexpression**; and **animal models** are necessary to evaluate in vivo efficacy and systemic toxicity. Future work should focus on **structure optimization** of individual PhG compounds, exploration of **combination therapy** with immune checkpoint inhibitors, and in-depth analysis of their effects on **immune-cell infiltration** within the tumor microenvironment, so as to fully exploit their unique advantage in modulating the

tumor immune niche. In sum, this study not only provides a solid molecular basis for the application of PhGs in cervical cancer but also opens new directions for the development of **multi-target natural anticancer drugs**.

References

[1] Burd E. M. (2003). Human papillomavirus and cervical cancer. Clinical microbiology reviews, 16(1), 1–17. https://doi.org/10.1128/CMR.16.1.1-17.2003

[2] Olusola, P., Banerjee, H. N., Philley, J. V., & Dasgupta, S. (2019). Human Papilloma Virus-Associated Cervical Cancer and Health Disparities. Cells, 8(6), 622. https://doi.org/10.3390/cells8060622

[3] Bedell, S. L., Goldstein, L. S., Goldstein, A. R., & Goldstein, A. T. (2020). Cervical Cancer Screening: Past, Present, and Future. Sexual medicine reviews, 8(1), 28–37. https://doi.org/10.1016/j.sxmr.2019.09.005

[4] Xue, Z., & Yang, B. (2016). Phenylethanoid Glycosides: Research Advances in Their Phytochemistry, Pharmacological Activity and Pharmacokinetics. Molecules (Basel, Switzerland), 21(8), 991. https://doi.org/10.3390/molecules21080991

[5] Tian, X. Y., Li, M. X., Lin, T., Qiu, Y., Zhu, Y. T., Li, X. L., Tao, W. D., Wang, P., Ren, X. X., & Chen, L. P. (2021). A review on the structure and pharmacological activity of phenylethanoid glycosides. European journal of medicinal chemistry, 209, 112563. https://doi.org/10.1016/j.ejmech.2020.112563

[6] Nogales, C., Mamdouh, Z. M., List, M., Kiel, C., Casas, A. I., & Schmidt, H. H. H. W. (2022). Network pharmacology: curing causal mechanisms instead of treating symptoms. Trends in pharmacological sciences, 43(2), 136–150. https://doi.org/10.1016/j.tips.2021.11.004

[7] Kite G. C. (2020). Characterisation of phenylethanoid glycosides by multiple-stage mass spectrometry. Rapid communications in mass spectrometry : RCM, 34 Suppl 4, e8563. https://doi.org/10.1002/rcm.8563

[8] Li, Z., Lin, H., Gu, L., Gao, J., & Tzeng, C. M. (2016). Herba Cistanche (Rou Cong-Rong): One of the Best Pharmaceutical Gifts of Traditional Chinese Medicine. Frontiers in pharmacology, 7, 41. https://doi.org/10.3389/fphar.2016.00041

[9] Yao, J., Wan, H., Zhang, J., Shen, W., Wei, X., Shi, C., Ou, B., Liu, D., Ge, L., Fei, J., & Zeng, X. (2024). Tubuloside B, a major constituent of Cistanche deserticola, inhibits migration of hepatocellular carcinoma by inhibiting Hippo-YAP pathway. Phytomedicine : international journal of phytotherapy and phytopharmacology, 129, 155552. https://doi.org/10.1016/j.phymed.2024.155552

[10] Yue, H. W., Liu, J., Liu, P. P., Li, W. J., Chang, F., Miao, J. Y., & Zhao, J. (2015). Sphingosylphosphorylcholine protects cardiomyocytes against ischemic apoptosis via lipid raft/PTEN/Akt1/mTOR mediated autophagy. Biochimica et biophysica acta, 1851(9), 1186–1193. https://doi.org/10.1016/j.bbalip.2015.04.001

[11] Johnson, D. E., O'Keefe, R. A., & Grandis, J. R. (2018). Targeting the IL-6/JAK/STAT3 signalling axis in cancer. Nature reviews. Clinical oncology, 15(4), 234–248. https://doi.org/10.1038/nrclinonc.2018.8

[12] Aguayo, F., Perez-Dominguez, F., Osorio, J. C., Oliva, C., & Calaf, G. M. (2023). PI3K/AKT/mTOR Signaling Pathway in HPV-Driven Head and Neck Carcinogenesis: Therapeutic Implications. Biology, 12(5), 672. https://doi.org/10.3390/biology12050672

[13] Tommasino, M., & Crawford, L. (1995). Human papillomavirus E6 and E7: proteins which deregulate the cell cycle. BioEssays : news and reviews in molecular, cellular and developmental biology, 17(6), 509–518. https://doi.org/10.1002/bies.950170607

[14] Infantino, V., Santarsiero, A., Convertini, P., Todisco, S., & Iacobazzi, V. (2021). Cancer Cell Metabolism in Hypoxia: Role of HIF-1 as Key Regulator and Therapeutic Target. International journal of molecular sciences, 22(11), 5703. https://doi.org/10.3390/ijms22115703