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Mechanism of Ginsenoside Rg3 in Endometriosis Based on Network Pharmacology

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ABSTRACT: Endometriosis (EMs) is a highly prevalent disease among women of reproductive age, and current therapeutic options are limited by high recurrence rates and significant adverse effects. This study employed network pharmacology and molecular docking techniques to investigate the mechanism of Ginsenoside Rg3 against EMs. A total of 114 intersection targets between the drug and the disease were identified, and core nodes such as ALB, AKT1, and EGFR were screened through the PPI network. Enrichment analysis suggested that its effects are concentrated in signaling pathways like PI3K-Akt and MAPK, regulating cell proliferation, invasion, and matrix remodeling processes. Molecular docking verified stable binding of core targets with Ginsenoside Rg3 (binding energy ≤ -9 kcal/mol). Analysis via the GEO database revealed that MMP9 is specifically highly expressed in EMs lesions, while the expression of targets such as AKT1 and EGFR is significantly upregulated. The study indicates that Ginsenoside Rg3 primarily exerts anti-inflammatory and anti-invasive effects through multi-target and multi-pathway mechanisms, demonstrating potential to inhibit the progression of EMs, thereby providing a theoretical basis for the clinical application of Ginsenoside Rg3 in the treatment of EMs.

KEY WARDS: *Endometriosis; Ginsenoside Rg3; Network Pharmacology; Molecular Docking*

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I. INTRODUCTION

Endometriosis (EMs) is an estrogen-dependent chronic inflammatory disease characterized by complex pathogenesis. Its primary manifestation is the presence of active endometrial tissue (including glands and stroma) outside the uterine cavity, such as on the ovaries, pelvic peritoneum, and rectovaginal septum. These ectopic lesions undergo recurrent cyclic bleeding, inflammatory infiltration, and fibrotic proliferation corresponding with the menstrual cycle, leading to the destruction of pelvic anatomy and adhesion formation. EMs is one of the most common gynecological diseases in women of reproductive age, with a global incidence rate showing an increasing trend year by year, estimated at approximately 5%–10% [1][2][3]. Clinically, patients often present with progressive secondary dysmenorrhea, chronic pelvic pain, dyspareunia, and abnormal bleeding symptoms such as menorrhagia and prolonged menstruation [4]. Particularly severe is that about 30%–50% of patients suffer from infertility, making it one of the main causes of female reproductive dysfunction [5][6].

Currently, Western medical strategies for EMs are mainly limited to surgical resection of lesions and pharmacological hormone therapy. Surgery aims to directly remove visible lesions; however, although it can alleviate symptoms in the short term, the surgical trauma is considerable, and it is difficult to completely clear microscopic and occult micro-lesions, resulting in a persistently high postoperative recurrence rate [7]. Clinical drug treatments for EMs mostly involve oral contraceptives, high-efficiency progestins, or Gonadotropin-Releasing Hormone Agonists (GnRH-a) [8]. The core mechanism of these drugs is to artificially induce a "pseudo-menopause" state by suppressing the hypothalamic-pituitary-ovarian axis via negative feedback, thereby reducing systemic estrogen levels to inhibit endometrial growth. However, long-term use is often accompanied by irreversible bone loss, severe vasomotor symptoms (hot flashes and night sweats), liver

function impairment, and rebound recurrence after drug withdrawal. Furthermore, the drug-induced low-estrogen state limits their long-term application in patients with urgent fertility demands [9].

Given the high risks, hazards, and side effects associated with current Western medical treatments for Endometriosis (EMs), exploring lead compounds from the treasure trove of Chinese herbs that possess natural origins, low toxicity, and high-efficiency biological activity has become a cutting-edge hotspot in reproductive medicine and translational pharmacology. Traditional Chinese Medicine (TCM) holds unique advantages in disease treatment. Its emphasis on "treatment based on syndrome differentiation" and "holistic concept" allows for the systematic regulation of the neuro-endocrine-immune network by harmonizing Qi and blood, activating blood circulation to resolve stasis, and softening hard masses to dissipate nodules. This enables multi-link and multi-target improvement of the internal microenvironmental imbalance, featuring mild and durable effects, minimal side effects, and stable long-term efficacy [10][11]. As the main active ingredient of the traditional precious herb Panax ginseng, ginsenosides have attracted considerable academic attention due to their extensive pharmacological activities. Among them, Ginsenoside Rg3, a specific tetracyclic triterpenoid saponin monomer, has been confirmed not only to significantly inhibit the release of inflammatory mediators such as prostaglandin E2 by blocking classic inflammatory signaling pathways like NF-κB and MAPK, thereby improving the characteristic chronic inflammatory microenvironment of EMs [12][13][14]. The known pharmacological characteristics of Ginsenoside Rg3 align highly with the intricate pathophysiological mechanisms of EMs. Therefore, in-depth exploration of the therapeutic potential of Ginsenoside Rg3 against EMs and its multi-effect molecular regulatory network involving "anti-inflammation, anti-angiogenesis, and anti-invasion," will not only provide a promising natural, low-toxicity candidate drug for EMs clinical treatment but also offer strong evidence to support the understanding of the modern scientific connotation of Traditional Chinese Medicine.

II. MATERIAL AND METHODS

2.1 Acquisition of Common Targets for Ginsenoside Rg3 and EMs

Using "Ginsenoside Rg3" as the search term, reverse target prediction was performed in the SuperPred database (https://prediction.charite.de) [15] and the PharmMapper database (https://www.lilab-ecust.cn/pharmmapper/index.html) [16] to obtain potential protein targets. Subsequently, these targets were imported into the UniProt database [17] for standardization, restricted to the species Homo sapiens, to uniformly map all protein names to official gene symbols (Gene Symbol). Unannotated, non-human, or null entries were removed. Alias discrepancies for the same gene across different databases were consolidated using the primary gene names recommended by UniProt, followed by manual verification to ensure the uniqueness and accuracy of the drug target list.

Using "Endometriosis" as the keyword, gene targets reported to be associated with the occurrence, development, or treatment of the disease were retrieved from the TTD (https://ttd.idrblab.cn) [18] and GeneCards (https://www.genecards.org) [19] databases. To ensure comprehensiveness, results from both databases were merged and deduplicated. Entries based solely on text mining, lacking experimental support, or with low evidence levels were excluded to form the final EMs-related target dataset.

The standardized drug targets and disease targets were imported into the Venny 2.1.0 online tool (https://bioinfogp.cnb.csic.es/tools/venny/). A Venn diagram was plotted, and the intersection was calculated to obtain the common targets. These intersecting genes were used for subsequent protein-protein interaction (PPI) network construction and functional enrichment analysis.

2.2 Construction of the Protein-Protein Interaction (PPI) Network

The obtained common targets of Ginsenoside Rg3 and Endometriosis (EMs) were imported into the STRING database (https://cn.string-db.org) [20]. In the "Multiple Proteins by Names / Identifiers" module, the list of intersecting genes was inputted (one gene per line), with the species set to Homo sapiensfor automatic recognition. Network parameters were configured as follows: network type was set to "full STRING network"; the required confidence score was set to "high confidence" (≥0.700); FDR stringency was set to "medium" (5%); and no limit was placed on the number of interactors to obtain the most complete interaction profile.

The generated interaction file in TSV format was imported into Cytoscape v3.8.0 software for network visualization. Nodes represented protein targets, and edges represented functional associations between proteins. The Degree Centrality algorithm was used to calculate the connectivity of each node. Node color and size were mapped to degree values to visually highlight core targets and their interaction intensity within the network.

2.3 GO and KEGG Enrichment Analysis

The list of intersecting target genes for Ginsenoside Rg3 and EMs was formatted (one gene symbol per line) and uploaded to the Metascape online bioinformatics analysis platform [21]. In the functional annotation module, Gene Ontology (GO) functional enrichment analysis was initiated, including Biological Process (BP), Cellular Component (CC), and Molecular Function (MF). Concurrently, Kyoto Encyclopedia of Genes and

Genomes (KEGG) pathway enrichment analysis was performed to comprehensively analyze the biological functions of the targets. Parameters were kept at default system settings except for the significance threshold, which was set to a P-value < 0.01, and the minimum overlap was set to ≥ 3 to filter for reliable enrichment results.

Upon completion of automated calculations, significantly enriched GO Terms and KEGG Pathways were exported as structured CSV files. These data were imported into the Weishengxin online visualization platform (https://www.bioinformatics.com.cn). Based on presentation requirements, appropriate chart templates were selected: Bubble Charts were used to visualize the gene ratio and enrichment degree of terms; Bar charts were used to compare the significance of different pathways; and Network Diagrams were used to illustrate the complex regulatory relationships between key pathways and core targets. This workflow systematically elucidates the potential biological functions and signal transduction mechanisms by which Ginsenoside Rg3 intervenes in EMs.

2.4 Molecular Docking

First, the standard 3D structural information of "Ginsenoside Rg3" was retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov) [22], downloaded, and saved as the ligand small molecule for docking. Subsequently, the protein sequences of core targets screened from the PPI network were mapped to the RCSB PDB database (https://www.rcsb.org) [23] to retrieve and download corresponding high-resolution X-ray crystal structures (Resolution ≤ 3.0 Å). Entries containing native ligands or co-crystal structures were prioritized as docking templates.

In the AutoDock Vina (http://vina.scripps.edu/) software environment, the ligand structure of Ginsenoside Rg3 was topologically optimized, hydrogen atoms were added, and excess solvent molecules were removed from the receptor-ligand system. After docking, the generated result files (Docking Log File) were imported into BIOVIA Discovery Studio 2019 software. The molecular visualization module was used to analyze hydrogen bonding, hydrophobic interactions, and electrostatic complementarity between the ligand and receptor amino acid residues in the binding conformation. The LibDock module (http://accelrys.com/products/discovery-studio/) was invoked to calculate the LibDock Score based on polar contacts and surface contact area. This allowed for the ranking and verification of binding affinity between key targets and Rg3, ensuring the reliability of the screening results.

2.5 Validation of Key Target Expression Using GEO Database

This study utilized the GEO database (https://www.ncbi.nlm.nih.gov/geo/) to evaluate the transcriptional expression changes of selected core targets under actual pathological conditions. Within GEO Datasets, the species was restricted to Homo sapiens, and the retrieval type was limited to "Expression profiling by array" or "High-throughput sequencing." Public datasets containing ectopic lesions and normal endometrial tissues were screened using the keyword "Endometriosis." Inclusion criteria were: clear sample distinction between EMs patient lesion tissues and healthy control endometrium, sample size n≥3per group, and complete raw data that had undergone standardization.

Eligible series data were imported into the GEO2R analysis module. Thex-axis represented the control group and EMs patients, while the y-axis represented the log2-transformed gene expression values. Using log_2FC and P-values as criteria for differential expression, the mRNA transcription levels of key targets in EMs versus controls were systematically compared.

III. RESULTS AND DISCUSSIONS

3.1 Acquisition of Common Targets for Ginsenoside Rg3 and EMs

Using "Ginsenoside Rg3" as the keyword, screening was performed in the SuperPred and PharmMapper databases. After merging the results and removing duplicates, 322 potential targets related to Ginsenoside Rg3 were obtained. Subsequently, using "Endometriosis" as the keyword, 1,626 disease-related targets were retrieved from the TTD and GeneCards databases. By integrating the drug targets and disease targets, a total of 114 intersecting targets were identified as the potential therapeutic targets of Ginsenoside Rg3 against endometriosis.

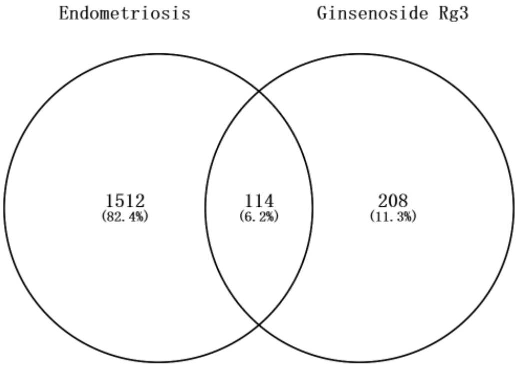

Figure 1. Venn diagram of intersection targets of Ginsenoside Rg3 and Endometriosis.

3.2 Construction of the Protein-Protein Interaction (PPI) Network

The 114 common targets shared by Ginsenoside Rg3 and Endometriosis were imported into the STRING database to construct the PPI network. A higher Degree value indicates a higher density of connections among targets and more interactions with other targets, suggesting a greater probability that the target is a core hub. The visualization resulted in a network comprising 141 nodes and 1,415 edges. Among these, ALB, AKT1, EGFR, STAT3, MMP9, CASP3, and ESR1 exhibited relatively high Degree values, measuring 77, 71, 71, 70, 69, 64, and 63, respectively. Molecular docking was subsequently employed to further analyze the interactions between Ginsenoside Rg3 and these specific targets. Larger nodes in the network indicate higher Degree values; notably, the major targets depicted in Figure 3 are closely associated with key signaling pathways, such as PI3K-Akt and MAPK.

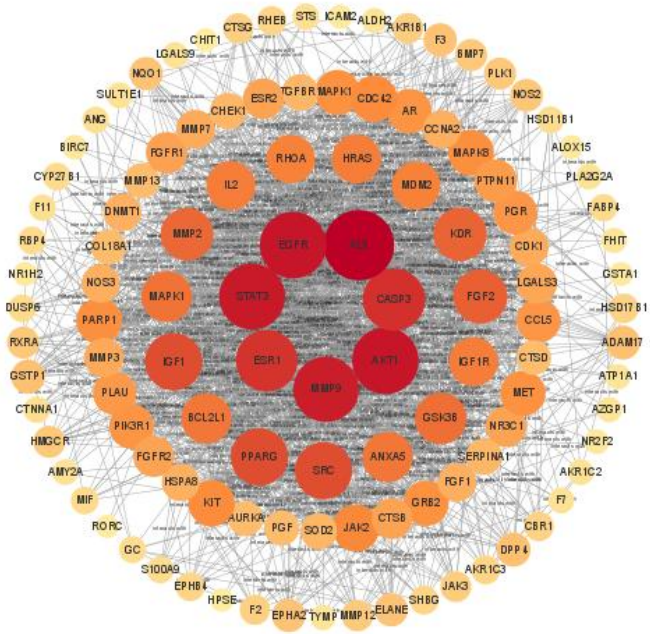

Figure 2. PPI network of potential therapeutic targets of Ginsenoside Rg3 for Endometriosis.

3.3 GO and KEGG Enrichment Analysis

KEGG pathway enrichment analysis involved 259 signaling pathways. The top 10 signaling pathways ranked by p-value are displayed in Figure 3A, including PI3K–Akt signaling pathway, MAPK signaling pathway, receptor activation, reactive oxygen species (ROS), focal adhesion, proteoglycans in cancer, Ras signaling pathway, lipid and atherosclerosis, Rap1 signaling pathway, EGFR tyrosine kinase inhibitor resistance, prostate cancer, endocrine resistance, AGE–RAGE signaling pathway in diabetic complications, relaxin

signaling pathway, breast cancer, FoxO signaling pathway, estrogen signaling pathway, signaling pathways regulating pluripotency of stem cells, and prolactin signaling pathway.

GO enrichment analysis yielded 4,344 entries for Biological Process (BP), 369 entries for Cellular Component (CC), and 724 entries for Molecular Function (MF). The top 10 entries for each category were selected for visualization (Figure 3B). BP included positive regulation of cell motility, enzyme-linked receptor protein signaling pathway, and cellular response to hormone stimulus. CC comprised the extracellular matrix, external encapsulating structure, and secretory granule lumen. MF involved phosphotransferase activity, kinase activity, and protein kinase activity.

KEGG pathway enrichment highlighted significant enrichment in pathways related to cancer pathways, signal transduction, chemical carcinogenesis, and oxidative stress, suggesting that Ginsenoside Rg3 may exert therapeutic effects on EMs through multi-pathway regulation. Furthermore, GO enrichment analysis investigated molecular functions, cellular components, and biological processes, indicating that modulating kinase and phosphatase activities to transmit signals, participating in extracellular matrix remodeling, or vesicle transport could be the potential mechanisms by which Ginsenoside Rg3 treats endometriosis.

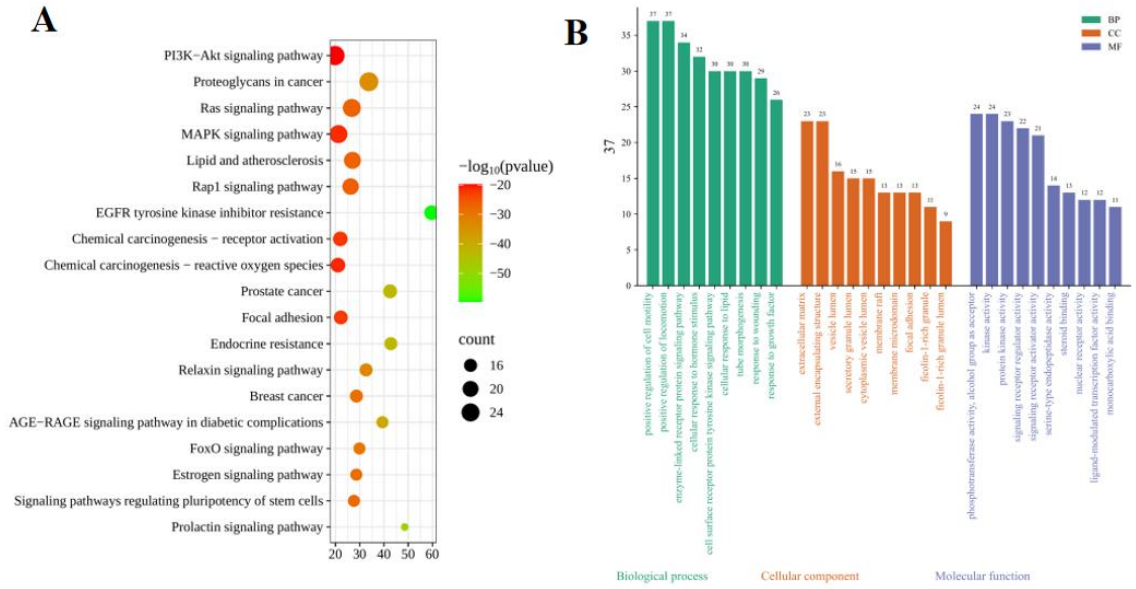

Figure 3. Enrichment analysis of intersecting targets: (A) KEGG pathway enrichment analysis for Endometriosis and Ginsenoside Rg3; (B) GO enrichment analysis of Ginsenoside Rg3 in Endometriosis.

3.4 Molecular Docking

Molecular docking was performed to evaluate the binding affinity between Ginsenoside Rg3 and the strongly correlated drug-disease nodes (Degree > 60) within the PPI network, aiming to identify EMs targets with favorable binding properties. Based on binding free energy calculations, seven targets—ALB, AKT1, EGFR, STAT3, MMP9, CASP3, and ESR1—exhibited binding affinities lower than -9 kcal/mol with Ginsenoside Rg3. Lower binding free energy indicates a more stable binding conformation, confirming that these seven core targets bind effectively to Ginsenoside Rg3.

ALB transports various endogenous and exogenous substances, interferes with endocrine signaling pathways, and participates in the systemic effects of endocrine-disrupting chemicals on cancer progression [24]. AKT1, a serine/threonine kinase, serves as a key effector in the PI3K signaling pathway; it promotes cell survival and proliferation by phosphorylating downstream substrates, establishing itself as a critical node in targeted cancer therapy. EGFR, a receptor tyrosine kinase, drives oncogenic pathways such as MAPK and PI3K upon activation; its overexpression or mutation is closely linked to tumor invasion and targeted therapy resistance [25]. STAT3 undergoes phosphorylation and translocates into the nucleus upon stimulation by cytokines and growth factors, where it regulates the transcription of genes related to proliferation and apoptosis resistance; its sustained activation facilitates the initiation and progression of various solid tumors [26]. MMP9, a member of the matrix metalloproteinase family, promotes tumor invasion, metastasis, and angiogenesis by degrading extracellular matrix components, acting as a key executor in the remodeling of the tumor microenvironment [27]. CASP3 is a core effector molecule in the apoptotic cascade, responsible for cleaving specific substrates to execute programmed cell death; its functional inactivation often leads to chemoresistance

and tumor progression [28]. ESR1 encodes estrogen receptor alpha (ERα), which mediates the transcriptional regulation of estrogen signaling pathways; its expression level is closely associated with the sensitivity to endocrine therapy and the prognosis of hormone-dependent tumors [29].

Table 1. Binding energies of Ginsenoside Rg3 with Endometriosis targets.

Targets	Protein names	PDB ID	Resolution (Å)	Binding affinity (kcal/mol)	LibDock scores
ALB	Albumin	1N5U	1.90	-11	111.720
AKT1	RAC-alpha serine/threonine-protein kinase	3O96	2.70	-11.9	无
EGFR	Epidermal growth factor receptor	3BEL	2.30	-10.7	148.846
STAT3	Signal transducer and activator of transcription 3	6NJS	2.70	-9.7	128.581
MMP9	Matrix metalloproteinase-9	5I12	1.59	-11.1	203.067
CASP3	CASPASE-3	2J33	2.00	-10	170.371
ESR1	ESTRADIOL RECEPTOR	1QKT	2.20	-10.1	无

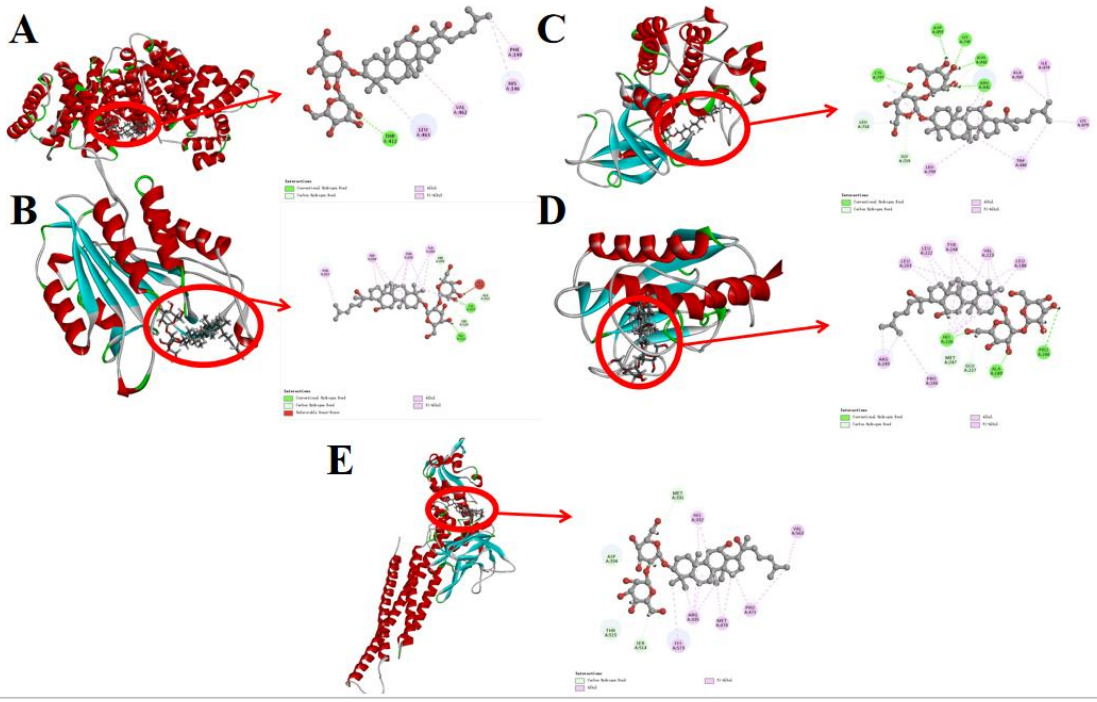

Figure 4. Molecular docking validation of core targets: (A) ALB, (B) EGFR, (C) STAT3, (D) MMP9, and (E) CASP3.

3.5 Validation of Key Target Expression

The GEO database, which integrates gene expression data from endometriosis and normal endometrial tissues detected by microarray and RNA-Seq technologies (curated by NCBI) and encompasses multidimensional clinical phenotype information, was utilized to analyze the transcriptional level differences of the seven Ginsenoside Rg3 target genes between EMs and normal tissues, as well as their underlying molecular regulatory mechanisms. As shown in Figure 5, the median expression levels of STAT3, AKT1, ALB, EGFR, and MMP9 in patients were slightly higher than those in the control group. Conversely, the median expression levels of ESR1 and CASP3 in patients were slightly lower than those in controls. Notably, a P-value < 0.05 for CASP3 indicated a statistically significant difference in expression between the two groups, suggesting its potential involvement in the apoptosis inhibition mechanisms associated with EMs. Furthermore, ESR1 exhibited an extremely significant difference ($P < 0.001$) between EMs patients (Patient) and the control group (Control), which aligns with the estrogen-dependent pathological characteristics of endometriosis.

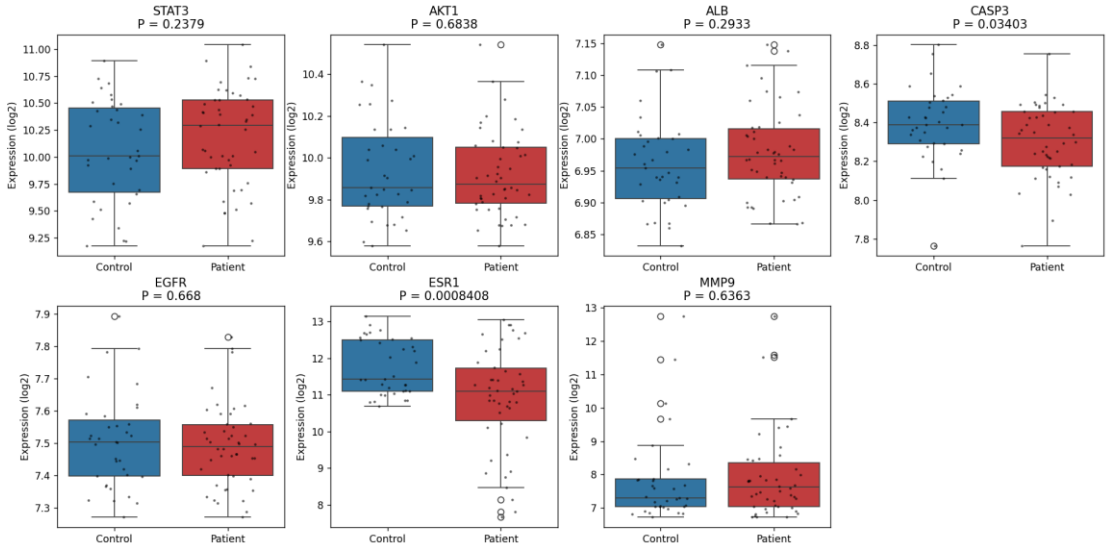

Figure 5. mRNA transcriptional levels of core target genes in EMs and normal tissues.

IV. DISCUSSION AND CONCLUSIONS

In this study, we employed a strategy combining network pharmacology predictions with validation using the GEO database to systematically identify the potential targets of Ginsenoside Rg3 in the intervention of endometriosis (EMs). Differential expression analysis based on the GEO dataset revealed that among the seven candidate proteins screened, only ESR1 (P=0.0008408, P<0.001) and CASP3 (P=0.03403, P<0.05) exhibited statistically significant differences between EMs patients and the control group. The remaining targets (e.g., EGFR, MMP9, AKT1) showed no significant differences (P>0.05). These results suggest that ESR1 and CASP3 may serve as the key molecular nodes through which Ginsenoside Rg3 exerts its anti-EMs effects.

From a pathological perspective, ESR1, a core subtype of the estrogen receptor, is closely associated with the estrogen-independent progression of EMs and the aberrant proliferation of ectopic endometrium. The significant downregulation of ESR1 observed in the patient group suggests that Ginsenoside Rg3 may restore the negative regulation of estrogen signaling by modulating ESR1 expression or activity, thereby inhibiting the excessive proliferation of ectopic lesions. Conversely, CASP3 acts as the terminal effector molecule in the apoptotic pathway; its reduced expression reflects impaired apoptosis within EMs lesions. If Ginsenoside Rg3 can reverse the downregulation of CASP3, it is expected to reactivate programmed cell death in ectopic cells, curbing the sustained growth of the lesions.

Notably, although network pharmacology predicted potential regulatory roles for targets such as EGFR and MMP9, they did not exhibit significant differences in this GEO dataset. This discrepancy may stem from: (1) temporal/spatial heterogeneity between transcriptional levels and protein activity; (2) bias related to sample size or the dataset itself; or (3) hierarchical regulation of targets (e.g., post-translational modifications or non-coding RNA interference). Therefore, the significant differences observed in ESR1 and CASP3 provide a more reliable entry point for subsequent mechanistic studies.

Molecular docking results further supported that Ginsenoside Rg3 forms stable bindings with ESR1 and CASP3 (binding energy ≤−9kcal/mol), indicating that it can directly act on these two targets at the molecular level to exert regulatory effects. In summary, this study progressively focused on ESR1 and CASP3—from bioinformatics prediction to clinical sample validation—providing a more precise molecular target framework for understanding the mechanism by which Ginsenoside Rg3 intervenes in EMs.

By integrating network pharmacology, molecular docking, and validation via the GEO database, this study identifies ESR1(P<0.001) and CASP3(P<0.05) as the key molecular targets through which Ginsenoside Rg3 intervenes in endometriosis (EMs). The therapeutic effect of Ginsenoside Rg3 against EMs is likely achieved by restoring estrogen signaling homeostasis through the modulation of ESR1 and promoting the apoptosis of ectopic cells via the activation of CASP3. These findings provide a more focused molecular basis for subsequent experimental validation and clinical translation. Consequently, ESR1 and CASP3 can be regarded as priority candidate targets for the development of adjuvant therapeutic strategies for EMs.

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