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Systematic Study on the Mechanism of Tanshinone IIA Based on Bioinformatics

Xing Gao[1], Xuehui Wang[1], Yihui Li[1], Hailing Ding[1], Keming Li[1,2], Shaoyang Hou[3], Xinchao Wang[3], Zhaobin Fan[3]*

1.Qilu Institute of Technology, #3028 Jingshi East Road, Jinan City, Shandong Province, 250200, China
2.Shandong Xiehe University, #6277 Jiqing Road, Licheng District, Jinan City, Shandong Province, 250109, China
3.Heze University, #2269 Daxue Road, Mudan District, Heze City, Shandong Province, 274015, China
Corresponding author: Zhaobin Fan

Abstract: Objective: Tanshinone IIA, one of the most abundant liposoluble components isolated from the traditional Chinese medicine Salvia miltiorrhiza, exhibits significant biological activities in anti-inflammatory, antibacterial, and antitumor effects. This study aims to systematically explore the mechanism of Tanshinone IIA through bioinformatics. **Methods:** We utilized the TCMSP database to retrieve the oral bioavailability (OB) and drug-likeness (DL) of Tanshinone IIA. The gene chip numbered GSE85871 was downloaded from the GEO database, and differential genes were analyzed using R language to identify potential targets of Tanshinone IIA. After obtaining these targets, GO analysis and KEGG pathway analysis were performed using the DAVID 6.8 database. Diseases related to Tanshinone IIA were explored through the CTD database. Finally, Cytoscape was employed to construct a visual network of multiple targets, pathways, and diseases associated with Tanshinone IIA. **Results:** Tanshinone IIA demonstrated good drug efficacy with an OB value of 49.89% and a DL value of 0.4. A total of 132 potential targets were identified, primarily exhibiting gene co-expression and physical interaction in the PPI network. These targets were enriched in biological processes and pathways such as ovarian steroidogenesis, cell cycle, and steroid hormone biosynthesis. Tanshinone IIA was found to be relevant in the treatment of diseases including breast tumors, hypertension, atherosclerosis, gliomas, vascular system injuries, left ventricular hypertrophy, leukemia, and hearing loss. **Conclusion:** Utilizing bioinformatics approaches, we systematically analyzed the possible molecular mechanisms of Tanshinone IIA, providing potential targets and insights into its pharmacological mechanisms and treatment strategies

Keywords: Salvia Miltiorrhiza; Tanshinone IIA; Bioinformatics; Mechanism of Action
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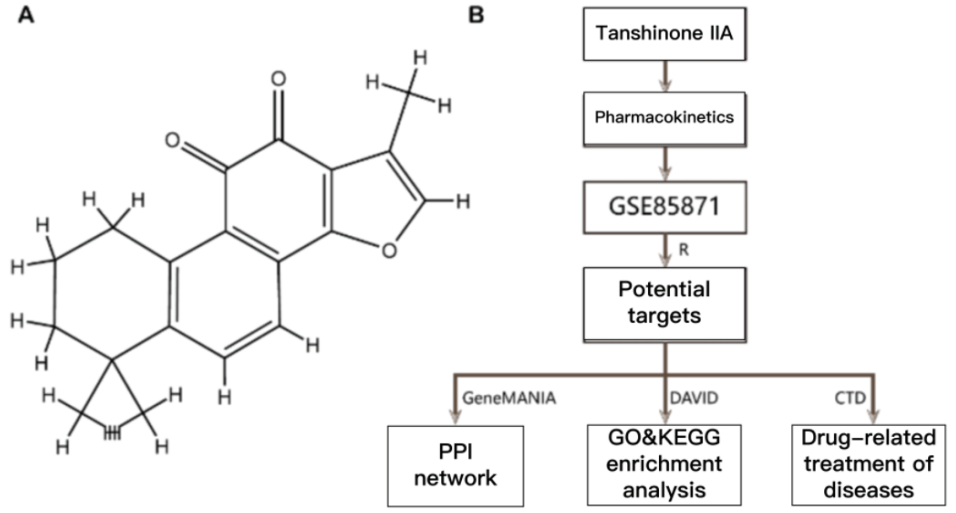
Salviae Miltiorrhizae, first recorded in “Shennong’s Herbal Classic”, is bitter in taste and slightly cold in nature, pertaining to the heart and liver meridians. Its medicinal parts mainly consist of dried roots and tubers, which have been widely used in the treatment of vascular diseases [1]. Tanshinone IIA, one of the significant bioactive components of Salviae Miltiorrhizae, belongs to the category of liposoluble phenanthrenequinone compounds. It exerts protective effects on the heart and nerves, possesses anticancer and antibacterial properties [2-4]. However, there has been no systematic analysis of the complex mechanism of action of tanshinone IIA.

In this study, we innovatively employed the TCMSP database to comprehensively evaluate the pharmacological parameters

of tanshinone IIA. By screening potential targets of tanshinone IIA, we constructed and analyzed a protein-protein interaction (PPI) network. Additionally, we conducted enrichment analysis of Gene Ontology (GO) terms and Kyoto Encyclopedia of Genes and Genomes (KEGG) signaling pathways. We also searched for diseases and targets associated with tanshinone IIA and established a "component-target-pathway-disease" network. This approach provides valuable data support for further in-depth research or the development and utilization of Salviae Miltiorrhizae and tanshinone IIA.

Figure 1: Chemical structure of Tanshinone IIA and a roadmap of its predicted mechanism. (A) Chemical structure diagram of Tanshinone IIA (PubChem CID: 164676); (B) Flowchart illustrating the pharmacological mechanism of action of Tanshinone IIA.



1.Materials and Methods

1.1 Evaluation of Pharmacokinetic Parameters

The Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) is a computational systems biology and medicine platform for evaluating the pharmacology of Chinese herbal medicines [5]. This database encompasses not only chemical substances, target and drug-target networks, related drug-target networks, but also pharmacokinetic properties of natural compounds such as oral bioavailability, drug-likeness, Caco-2 permeability, half-life, and blood-brain barrier (BBB) penetration of some chemical components in Chinese medicine [6]. OB, calculated using the internal model OBioAvail 1.1 in the TCMSP database, represents one of the most crucial pharmacokinetic properties of oral medications and plays a significant role in the efficiency of systemic drug administration. DL, which relies on molecular descriptors and the tavioto coefficient in the database, is a qualitative concept primarily used in drug design to evaluate the drug-likeness of compounds. In this study, "tanshinone IIA" was used as a search term to evaluate the pharmacokinetic parameters of tanshinone IIA at the molecular level.

1.2 Screening of Potential Targets

The raw data for the gene chip with the related number GSE85871 and the platform annotation file GPL571 for tanshinone IIA were downloaded from the Gene Expression Omnibus (GEO). The GSE85871 dataset contains gene expression profile information for MCF7 cells treated with 102 different Chinese medicinal molecules [7], including two samples of tanshinone IIA and six blank control samples. Normalization and differentially expressed gene screening were performed using the Affy and limma packages in R. Quality control was conducted using fold change (FC) and P-value, with standards set at $P < 0.01$ and $|\log2FC| \geq 1$. The gplots package was utilized to create a cluster diagram, and the plot package was used to generate a volcano plot.

1.3 Construction of PPI Network

GeneMANIA is primarily used to generate hypotheses about gene function, analyze gene lists, and prioritize genes for functional testing [8]. The results of the differentially expressed genes mentioned above were organized, and GeneMANIA was

employed to construct a PPI network, analyzing the targets and their roles and relationships within the network.

1.4 Enrichment Analysis of GO and KEGG Signaling Pathways

The Database for Annotation, Visualization, and Integrated Discovery (DAVID) is a web-based software toolkit that effectively aids in understanding the interactive relationships in gene expression data and provides systematic information about genes of interest [9]. DAVID database was used to perform GO and KEGG signaling pathway enrichment analysis on potential targets, and the ggplot2 package was used to create an enrichment analysis bubble chart.

1.5 Retrieval of Related Therapeutic Diseases

The Comparative Toxicogenomics Database (CTD) is a powerful, publicly available database that enhances understanding of the health effects of environmental exposures [10]. CTD integrates various information about chemicals, including chemical structures, curated interacting genes and proteins, curated and inferred disease relationships, and rich pathway and functional annotations. In this study, “tanshinone IIA” was used as a search term to retrieve related therapeutic diseases.

2.Results

2.1 Pharmacokinetic Parameters

Through the TCMSP database, we conducted an in-depth study on the critical characteristics related to the pharmacokinetics of tanshinone IIA, including OB, DL, Caco-2, BBB, and the five rules of Lipinski’s rule of five (MW, AlogP, TPSA, Hdon, HACC). The results are presented in Table 1. It is worth noting that tanshinone IIA has an OB value of 49.89% and a DL value of 0.4, indicating good drug efficacy.

Table 1: Pharmacological and Molecular Characteristics of Tanshinone IIA

MW	AlogP	Hdon	Hacc	OB (%)	Caco-2	BBB	DL	FASA-	TPSA	RBN	HL
294.37	4.66	0	3	49.89	1.05	0.7	0.4	0.31	47.28	0	23.56

2.2 Potential Drug Targets

Based on screening criteria, this study analyzed the relevant raw data with the GEO accession number GSE85871 using R language. The analysis revealed that tanshinone IIA-treated MCF7 cells could induce 132 significantly differentially expressed genes, including 85 upregulated genes and 47 downregulated genes. The clustering plot and volcano plot are shown in Figures 2 and 3, respectively.

2.3 PPI Network

The intrinsic mechanism of drug regulation is often not determined by a single target or pathway but is commonly modulated by multiple targets and pathways. By organizing the aforementioned differentially expressed gene results and using GeneMANIA to construct a PPI network, it was revealed that among the 132 target proteins and their interacting proteins, 76.27% share similar co-expression characteristics, 14.91% exhibit physical interactions, and 3.83% possess co-localization relationships. Other results, including genetic interactions, pathways, predictions, and shared protein domains, are illustrated in Figure 4.

2.4 GO and KEGG Enrichment Analysis

To further categorize the biological functions of the potential targets of tanshinone IIA, GO and Pathway enrichment analyses were conducted using DAVID 6.8. The results indicated that the biological processes (BP) of the potential targets were significantly enriched in processes such as nuclear division, negative regulation of DNA-templated transcription, positive regulation of nuclear protein export from the nucleus, cellular response to hydrogen peroxide, and cell cycle arrest mediated by P53-class mediator resulting from DNA damage and signal transduction, as shown in Figure 5A. Changes in cellular components (CC) were primarily focused on the nucleus, nucleoplasm, cytosol, membrane, and CHOP-ATF3 complex, as illustrated in Figure 5B. Variations in molecular functions (MF) were predominantly manifested in protein binding, transcription factor activity, sequence-specific DNA binding, zinc ion binding, poly(A) RNA binding, and histone-lysine N-methyltransferase activity, as depicted in Figure 5C. KEGG pathway analysis revealed that the enrichment of potential targets was primarily observed in ovarian steroidogenesis, cell cycle, and steroid hormone biosynthesis, as shown in Figure 5.

Figure 2: Cluster diagram of differentially expressed genes in Tanshinone IIA-related datasets

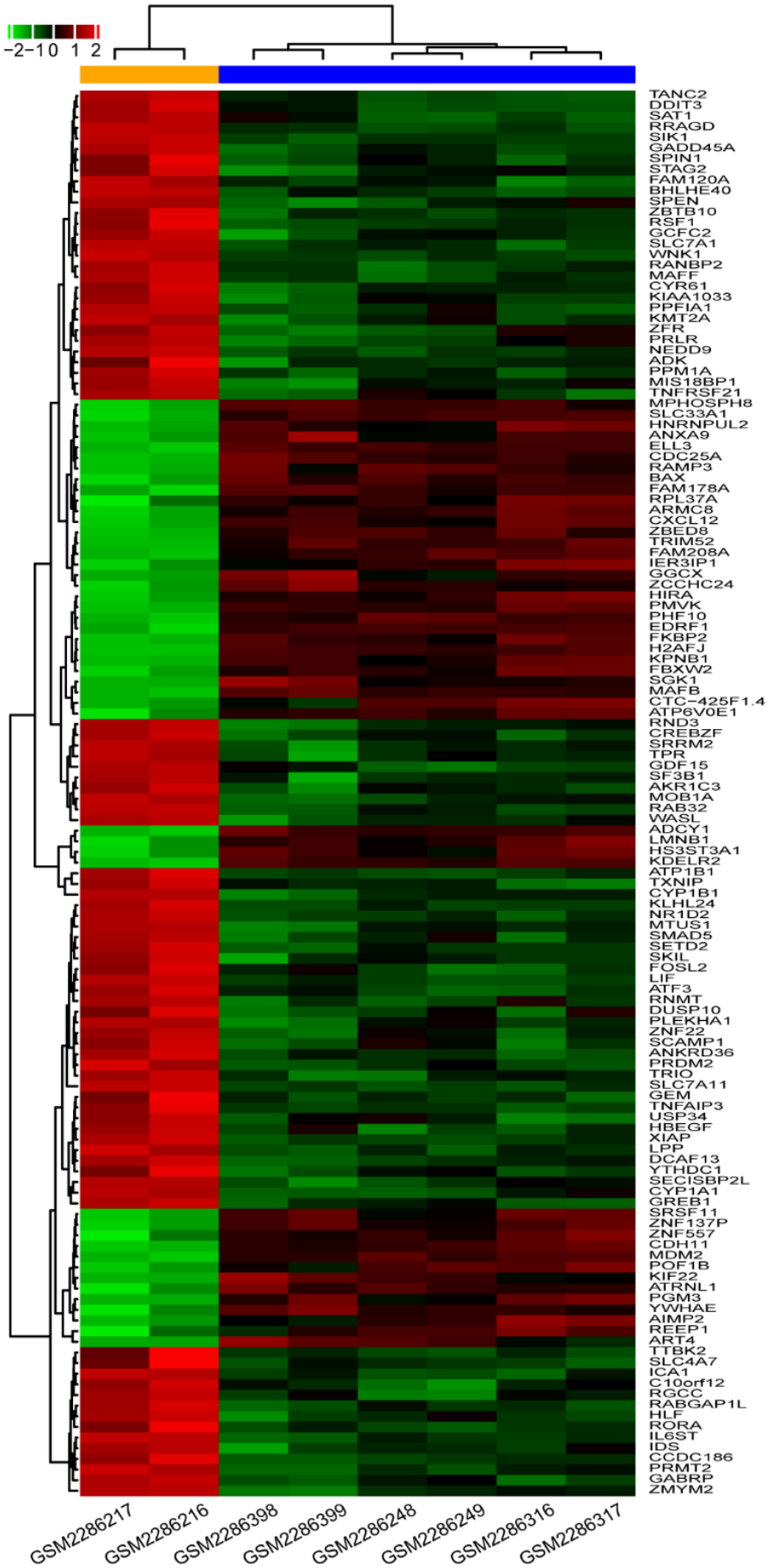


Figure 3: Volcano plot of differentially expressed genes in Tanshinone IIA-related datasets

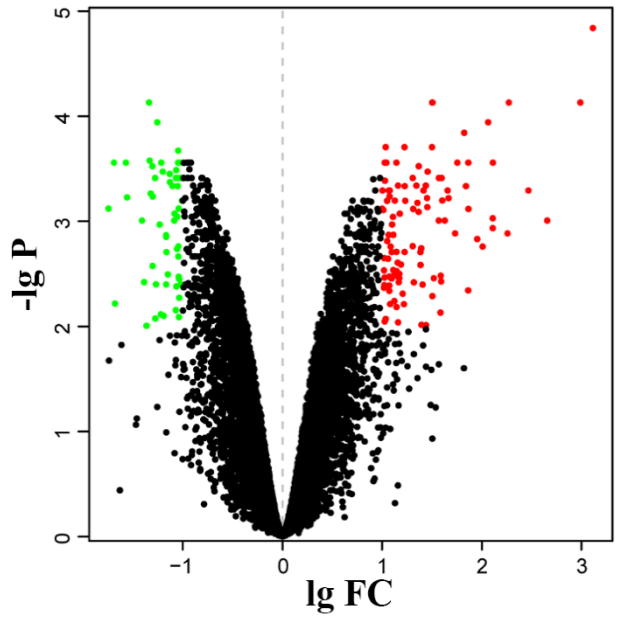


Figure 4: PPI network diagram of potential targets of Tanshinone IIA(Black nodes represent target proteins submitted as query terms in the search, gray circles represent genes associated with the query genes, and different connection colors represent different correlations)

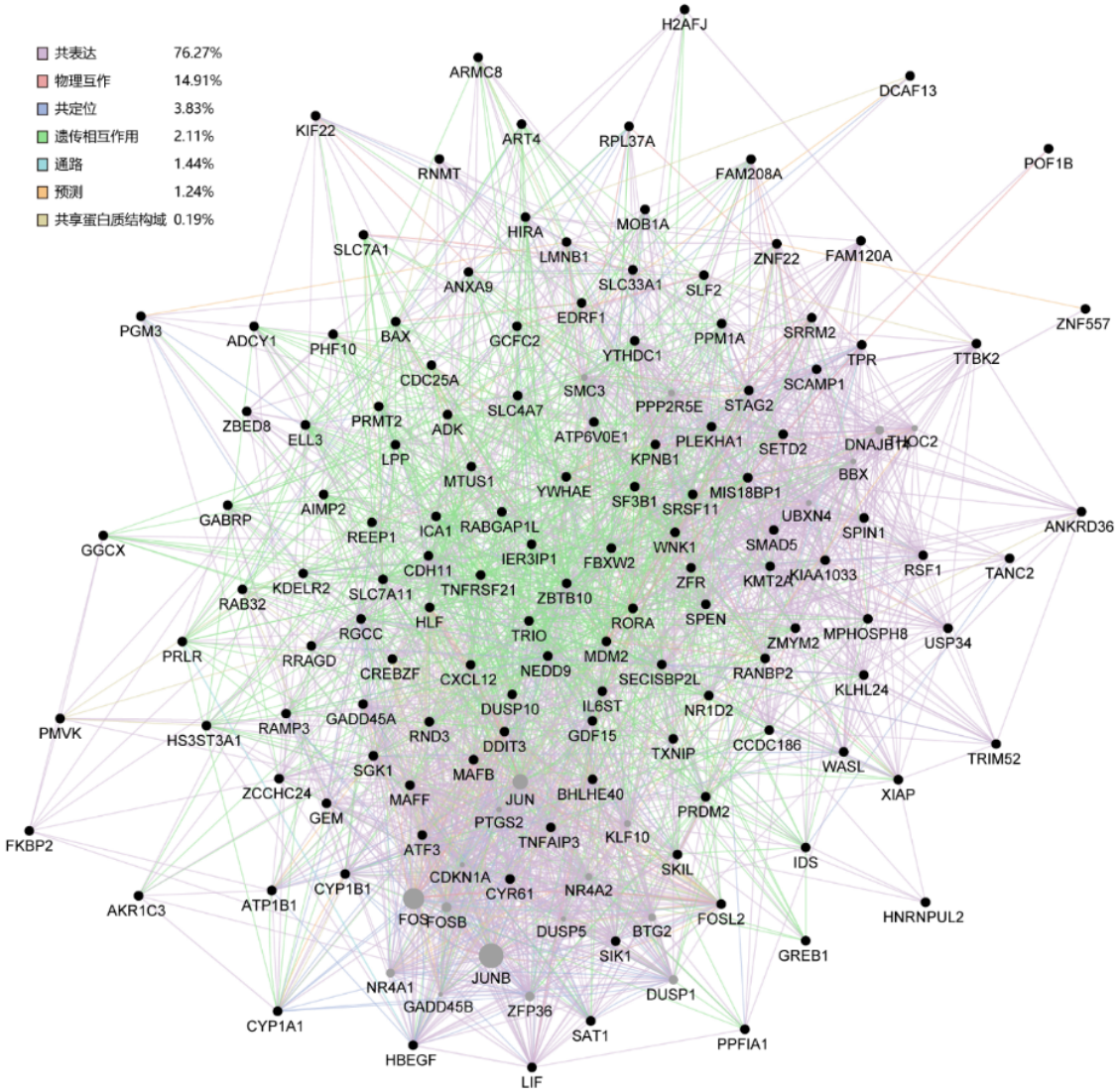
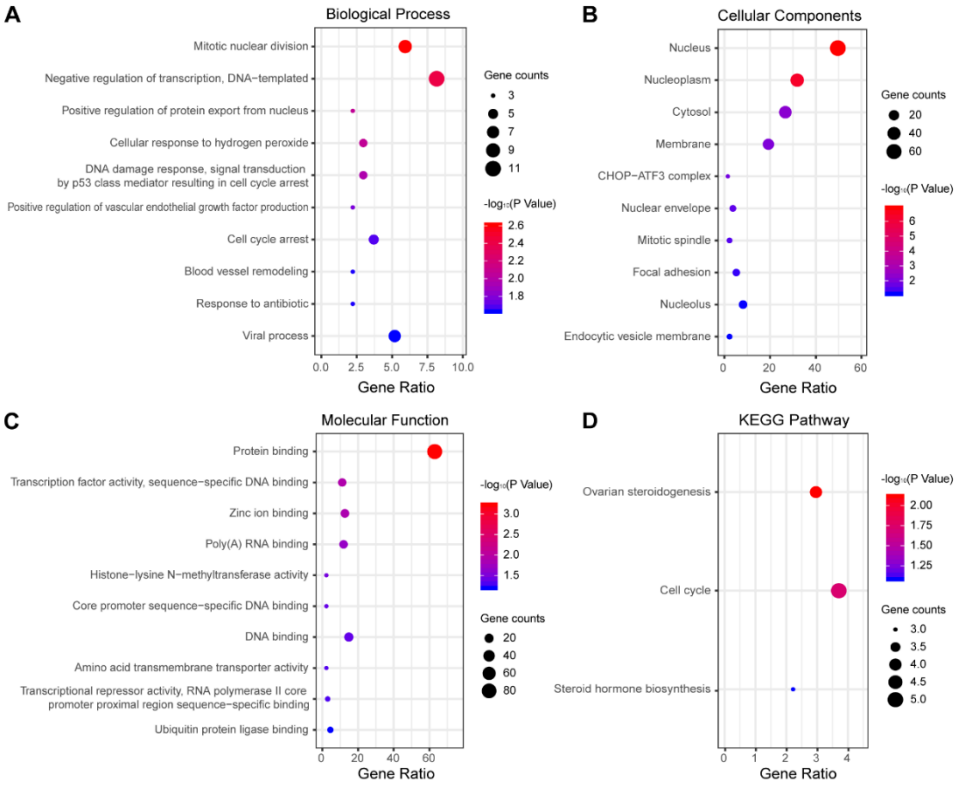


Figure 5: Bubble diagram of GO function and KEGG pathway analysis of potential targets of Tanshinone IIA



2.5 Diseases Related to Therapeutic Applications

The diseases with direct evidence of treatment by tanshinone IIA, retrieved from the CTD database, primarily include breast neoplasms, hypertension, atherosclerosis, gliomas, vascular system injuries, left ventricular hypertrophy, leukemia, and hearing loss. These are summarized in Table 2.

Table 2: Associated Therapeutic Diseases and Their Respective Targets and Scores

Diseases	Associated Targets	Scores
Breast tumor	AHR、BAX、BCL2、BIRC5、CASP8、CDKN1B、CST6、CTNNB1、CXCL8、CYP1A1、CYP3A4、DDIT3、EDNRB、ETS2、FOS、GRB7、GSTP1、HIST1H1C、HMOX1、IL1B、IL6、KRAS、MAP3K1、MMP1、MMP9、NFKBIA、NOS2、NOS3、PARP1、PTGS2、RARB、RB1、RELA、SPP1、TNF、TNFSF10、TP53	81.64
Hypertension	AGT、AHR、BCL2、CD36、CYP1A1、DUSP5、EDN1、EDNRA、FOS、GSK3B、GSTP1、HMOX1、IL1B、IL6、INPPL1、MMP9、NOS2、NOS3、NR3C1、OLR1、PPARG、PTGS2、RELA、TLR4、TNF、TP53	46.65
Atherosclerosis	AGT、AHR、IL6、MMP1、NOS2、NOS3、PARP1、PPARG、PTGS2、TLR4、TNF、VEGFA	29.93
Glioma	GSTP1、PTGS2、SPP1、TNF、TNFSF10、TP53	14.22
Vascular system injury	HMOX1、SPP1、TNF	10.74
Left ventricular hypertrophy	AGT、AHR、EDN1、MYC	9.38
Leukemia	VEGFA	3.12
Hearing loss	TLR4	3.11

3.Discussion

One of the significant reasons for the high cost of late-stage drug development failures is unfavorable pharmacokinetics and toxicity profiles. The adoption of methods such as predicting and simulating pharmacokinetics, metabolism, and toxicity endpoints can simplify and accelerate the drug discovery process to some extent. Currently, this approach is gaining increasing favor and attention from relevant researchers [11].

OB represents the percentage of an orally administered drug that reaches systemic circulation without alteration, indicating the convergence of pharmacokinetic processes. High oral bioavailability is often a critical indicator in determining the drug-like properties of bioactive molecules as therapeutic agents. DL, established based on the analysis of physicochemical properties or/and structural features of existing small molecule drugs and/or drug candidates, is a qualitative concept used in drug design to estimate how "drug-like" a compound is expected to be. This estimation aids in optimizing pharmacokinetic and drug properties, such as solubility and chemical stability. The TCMSP database suggests reference standards as OB: ≥30%; DL ≥0.18. As evident from Table 1, the properties of tanshinone IIA meet these requirements, indicating that it is a promising candidate for drug discovery.

In this study, the dataset with the accession number GSE85871 from the GEO database was selected. This dataset encompasses the gene expression profiles established after treating MCF7 cells with tanshinone IIA. Through R language analysis, 132 significantly differentially expressed genes were identified, including 85 upregulated genes and 47 downregulated genes. These differential genes can be considered, to some extent, as potential targets of tanshinone IIA, and the pharmacological effects of some of these potential targets have been established in the literature. According to the research results of XU et al. [12], tanshinone IIA can effectively increase the expression of hypoxia-inducible factors, thereby upregulating VEGF expression, improving cardiac function, protecting myocardium, and exerting anti-myocardial hypertrophy effects. Zhou et al. [13] demonstrated that tanshinone IIA could reduce neuronal damage and protect against cerebral ischemia-reperfusion injury by decreasing the expression levels of NF-κB and IκB genes and proteins in a rat model of ischemia-reperfusion. Wang et al. [14] found that tanshinone IIA downregulates the expression of VEGF and β-catenin genes and proteins, inhibits the growth of subcutaneous xenografts of human colorectal cancer in nude mice, and suppresses microvessel formation, thereby exhibiting antitumor effects.

To better understand the functions of the potential targets of tanshinone IIA, GO and KEGG signaling pathway analyses were performed using DAVID 6.8. The potential targets were mainly enriched in biological processes such as nuclear division, negative regulation of DNA-templated transcription, positive regulation of nuclear protein export, and KEGG signaling pathways including ovarian steroidogenesis, cell cycle, and steroid hormone biosynthesis. In this study, by searching the CTD, eight diseases with direct therapeutic evidence for tanshinone IIA were identified, including breast tumors, hypertension, atherosclerosis, gliomas, vascular system injuries, left ventricular hypertrophy, leukemia, and hearing loss. As shown in Table 2, there is a significant overlap between the targets supported by the literature for these diseases and the differential genes screened in this study, further corroborating the feasibility of the research approach.

The enrichment of KEGG pathways, particularly the cell cycle and steroid hormone biosynthesis, underscores the multifaceted mechanisms by which Tanshinone IIA (Tan IIA) exerts its therapeutic effects against diseases such as breast cancer. The cell cycle pathway, a critical hub for cancer progression, is tightly regulated by genes like TP53, BCL2, and CDKN1B, which were identified as key targets in this study. Tan IIA likely inhibits breast tumor growth by modulating these targets to induce cell cycle arrest. For instance, TP53, a tumor suppressor gene frequently dysregulated in cancers, promotes cell cycle arrest or apoptosis in response to DNA damage. Our data revealed upregulation of TP53 and downregulation of anti-apoptotic BCL2, suggesting that Tan IIA triggers pro-apoptotic signaling and halts uncontrolled proliferation in breast cancer cells. Furthermore, the downregulation of CDKN1B (p27), a cyclin-dependent kinase inhibitor, may disrupt cyclin-CDK complexes, thereby blocking G1/S phase transition and impeding tumor cell division.

Additionally, the steroid hormone biosynthesis pathway, enriched in this study, provides insights into Tan IIA's potential efficacy against hormone-dependent breast cancers. Estrogen receptor (ER)-positive breast cancers rely on steroid hormones for growth, and Tan IIA may interfere with this dependency by targeting enzymes like CYP19A1 (aromatase), which

catalyzes estrogen synthesis. Although not explicitly listed in our target results, the overlap between steroidogenic pathways and genes such as CYP3A4 (involved in hormone metabolism) implies indirect regulation of estrogen levels. By suppressing steroid hormone production or signaling, Tan IIA could attenuate ER-driven tumor proliferation.

In summary, this study evaluated the pharmacokinetic parameters of tanshinone IIA using the TCMSP database, identified its potential targets through high-throughput microarray data, and conducted further biological functional studies. The results suggest that tanshinone IIA may possess multiple functions, including nuclear division, ovarian steroidogenesis, cell cycle, and steroid hormone biosynthesis, which are closely related to its antitumor, anti-atherosclerotic, ischemia-reperfusion protective, and anti-inflammatory effects. Tanshinone IIA emerges as a highly potential drug candidate; however, further research is needed to determine its precise pharmacological effects and mechanisms of action.

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no

Conflict of Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

Reference

[1] Kang, Y., & Gao, M. (2019). Current status and progress in mechanistic studies of Salvia miltiorrhiza in the treatment of coronary heart disease. Liaoning Medical Journal, 33(2), 85–88.

[2] Su, M., Qin, Y., Lou, Y., et al. (2019). Study on the angiogenic effect of sodium tanshinone IIA sulfonate in vitro and in vivo. Drugs & Clinic, 34(4), 934–940.

[3] Ning, J., He, C., & Huang, J. (2019). Study on the anti-inflammatory effect of tanshinone IIA in vitro and in vivo. Drugs & Clinic, 34(2), 292–298.

[4] Tian, Q. (2018). Meta-analysis of tanshinone IIA as adjunctive therapy for chronic heart failure [Master's thesis, Nanchang University].

[5] Ru, J., Peng, L., Wang, J., et al. (2014). TCMSP: A database of systems pharmacology for drug discovery from herbal medicines. Journal of Cheminformatics, 6(1), 13.

[6] Xu, X., Zhang, W., Huang, C., et al. (2012). A novel chemometric method for the prediction of human oral bioavailability. International Journal of Molecular Sciences, 13(6), 6964–6982.

[7] Mostafavi, S., Ray, D., Wardefarley, D., et al. (2008). GeneMANIA: A real-time multiple association network integration algorithm for predicting gene function. Genome Biology, 9(Suppl 1), 1–15.

[8] Huang, D. W., Sherman, B. T., & Lempicki, R. A. (2009). Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nature Protocols.

[9] Davis, A. P., King, B. L., Mockus, S., et al. (2013). The Comparative Toxicogenomics Database: Update 2011. Nucleic Acids Research, 41(Database issue), D1104–D1114.

[10] Lipinski, C. A., Lombardo, F., Dominy, B. W., et al. (2012). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Advanced Drug Delivery Reviews, 64(1–3), 4–17.

[11] Van De Waterbeemd, H., & Gifford, E. (2003). ADMET in silico modelling: Towards prediction paradise? Nature Reviews Drug Discovery, 2(3), 192–204.

[12] Xu, W., Yang, J., & Wu, L.-M. (2009). Cardioprotective effects of tanshinone IIA on myocardial ischemia injury in rats. Die Pharmazie, 64(5), 332.

[13] Zhou, L., Liu, Y., Wang, F., et al. (2013). Effects of tanshinone IIA on the activity of NF-κB and IκB in the brain tissue of I/R rats. Chinese Medicinal Materials, 36(7), 1136–1139.

[14] Wang, Y., Liu, X., Zhou, L., et al. (2013). Inhibitory effect of tanshinone IIA on angiogenesis in nude mice with human intestinal cancer. Chinese Journal of Experimental Traditional Medical Formulae, 19(3), 167–171.