SIN-CHN SCIENTIFIC PRESS PTE.LTD.

Molecular & Cellular Biomechanics 2025, 22(5), 1636.
https://doi.org/10.62617/mcb1636

Article

Research on the anti hyperlipidemia effect and signaling pathway of Polygonum multiflorum based on network pharmacology

Jinji Wang[1], Ming Yang[1], Yuna Han[1], Zhijie Zhu[2], Xiaolei Fang[1], Xuefeng Zhuang[1], Kaixuan Zhou[3], Lijing Li[1,*], Jia Liu[1,*]

[1] College of Pharmacy, Changchun University of Chinese Medicine, Changchun 130117, China
[2] Tonghua Golden-Horse Pharmaceutical Industry Co., Ltd, Tonghua 134003, China
[3] College of Chinese Medicine, Bozhou University, Bozhou 236800, China
*** Corresponding authors:** Lijing Li, lilijing66@163.com; Jia Liu, ccliujia1002@126.com

CITATION

Wang J, Yang M, Han Y, et al. Research on the anti hyperlipidemia effect and signaling pathway of Polygonum multiflorum based on network pharmacology. Molecular & Cellular Biomechanics. 2025; 22(5): 1636. https://doi.org/10.62617/mcb1636

ARTICLE INFO

Received: 20 February 2025
Accepted: 24 March 2025
Available online: 31 March 2025

COPYRIGHT

Copyright © 2025 by author(s). *Molecular & Cellular Biomechanics* is published by Sin-Chn Scientific Press Pte. Ltd. This work is licensed under the Creative Commons Attribution (CC BY) license. https://creativecommons.org/licenses/by/4.0/

Abstract: Objective: To investigate the mechanism and signaling pathway of Polygonum multiflorum in combating hyperlipidemia based on network pharmacology. **Method:** Search traditional Chinese medicine databases and literature to screen and integrate the active ingredients and target proteins of Polygonum multiflorum. Retrieve and obtain the active ingredients and targets of Polygonum multiflorum from the TCMSP database and DrugBank database. Construct a compound target network of Polygonum multiflorum and its corresponding protein-protein interaction (PPI) network in Cytoscape software, and perform gene GO function and KEGG pathway enrichment analysis in the DAVID database. Screen out the effective ingredients and targets of Polygonum multiflorum for anti hyperlipidemia, and draw a target pathway network model. **Result:** It is predicted that the main active ingredients of Polygonum multiflorum for anti hyperlipidemia drugs are omega-hydroxyflavone-8-methyl ether, alfalfa extract, and kaempferol. They bind to three core targets, epidermal growth factor receptor (EGFR), estrogen receptor 1 (ESR1), and matrix metalloproteinase 9 (MMP9), and affect the PI3K Akt, HIF-1, and estrogen signaling pathways to play a key role in anti-hyperlipidemia. **Conclusion:** Polygonum multiflorum plays a precise role in anti hyperlipidemia by exerting the characteristics of multiple active ingredients, multiple targets, and multiple signaling pathways in order to provide a scientific basis for systematically elucidating the mechanism of Polygonum multiflorum in treating hyperlipidemia.

Keywords: Polygonum multiflorum; hyperlipidemia; network pharmacology; mechanism of action; signaling pathway

1. Introduction

Hyperlipidemia, as a disorder of lipid metabolism, is a common and frequently occurring disease in modern society, posing a serious threat to human health. With the improvement of living standards and the change of eating habits, the incidence rate of hyperlipidemia has increased year by year, which has become an important factor leading to atherosclerosis, coronary heart disease and other cardiovascular diseases [1]. Therefore, finding effective lipid-lowering drugs and exploring their mechanisms of action are of great significance for the prevention and treatment of hyperlipidemia and related diseases.

Polygonum multiflorum, as a traditional Chinese medicinal herb, has various pharmacological activities and is widely used in the prevention and treatment of diseases such as hyperlipidemia, coronary heart disease, and primary hypertension [2].

Traditional Chinese medicine believes that Polygonum multiflorum has the effects of nourishing the liver and kidneys, nourishing essence and blood, strengthening muscles and bones, and promoting hair growth [3]. Modern pharmacological studies have also confirmed [4] that Polygonum multiflorum Thunb has significant effects on lowering blood lipids and anti-atherosclerosis, showing its potential value in the treatment of hyperlipidemia [5]. In recent years, network pharmacology, as an emerging research method, has provided new perspectives and means for the analysis of drug mechanisms by integrating knowledge and technologies from multiple disciplines such as biology, chemistry, and computer science. This method can systematically analyze the complex relationship between drugs and diseases, reveal the multi-component, multi-target, and multi-pathway characteristics of drug action, and provide a scientific basis for drug development. Based on this, this study applies the theory and methods of network pharmacology to collect and analyze the chemical components and targets of Polygonum multiflorum, combined with relevant targets of hyperlipidemia, to construct a "drug target disease" network, thereby screening the key targets and signaling pathways of Polygonum multiflorum for anti-hyperlipidemia. This will help to better understand the pharmacological effects of Polygonum multiflorum and provide new ideas and strategies for the treatment of hyperlipidemia.

2. Materials and methods

2.1. Screening of active ingredients in Polygonum multiflorum and prediction of target genes

Refer to literature and use ChemDraw 16.0 software to draw the structural diagram of the compound. Save the structural diagram as an SDF format file and use PubChem (http://pubchem.ncbi.nlm.nih.gov/) Hehua Source Network (http://www.chemsrc.com/) Compare the database to obtain the chemical composition structure diagram of Polygonum multiflorum. Upload the SDF format file to the Swiss ADME platform (http://www.swissadme.ch/) Set the screening criteria as follows: Gastrointestinal absorption is "high", and at least two results are "Yes" in Lipinski, Ghose, Veber, Egan, and Muegge drug analysis. Select compounds with good oral bioavailability and similar drug structures as active ingredients. Upload the SDF files of these components to the Swiss Target Prediction platform (http://www.swisstargetprediction.ch/) And set the species as' Homo sapiens'. Collect targets with a "Probability" value exceeding 0.1 as potential targets for active ingredients.

2.2. Target collection for hyperlipidemic diseases

Search for hyperlipidemia-related targets in the disease target database using the keyword "Hyperlipidemia" from September 2023 to November 2023, including OMIM (version: October 2023); http://www.omim.org/) TTD (version: September 2023); http://db.idrblab.org/ttd/) Genecards (version: October 2023); http://www.genecards.org/) Three disease databases.

2.3. Building a "drug active ingredient potential target" network

Using R 3.5.2 software, screen the intersection of active ingredient targets and disease targets, and organize the results into an Excel file. Subsequently, import the data into Cytoscape 3.7.1 software (http://cytoscape.org/). Construct a network diagram of "drug active ingredient target disease". The nodes in the figure represent drugs, active ingredients, targets, and diseases, and the interactions between nodes are connected by edges. Use Cytoscape's Network Analysis plugin to conduct in-depth analysis of the network's topology structure.

2.4. Building PPI

Based on intersection targets, utilizing the STRING online platform (http://string-db.org/cgi/input.pl). Construct PPI and identify key node genes to reveal the interaction relationships between targets.

2.5. GO and KEGG functional enrichment analysis

Through GO functional enrichment and KEGG pathway enrichment analysis on the STRING platform, functional annotation and pathway mapping of intersecting targets were performed to clarify their potential roles in biological processes and metabolic pathways.

2.6. Molecular docking between active ingredients of Polygonum multiflorum and key targets for anti hyperlipidemia

In order to conduct preliminary molecular docking validation of the active ingredients in Polygonum multiflorum, components corresponding to multiple targets were selected, including ω-hydroxyflavon-8-methyl ether, alfalfa extract, kaempferol, and core target proteins. Retrieve the structural information of the target molecule from the PubChem database and convert it into a 3D small molecule file using Chem 3D 16.0 software. Subsequently, access the PDB database (http://www.rcsb.org/). Download the protein structure files for epidermal growth factor receptor (EGFR, PDB ID: 2ITX), estrogen receptor 1 (ESR1, PDB ID: 6VJ1), and matrix metalloproteinase 9 (MMP9, PDB ID: 6ESM). Use AutoDock 4.2.6 software to preprocess protein structures, including steps such as removing water molecules, adding hydrogen atoms, and setting charges. Docking the processed protein with small molecules of the compound, and evaluating the strength of the interaction through binding energy parameters. Finally, the docking results were visualized using PyMOL software to analyze the binding mode between the compound and the target protein.

3. Results

3.1. Active Ingredients of Polygonum multiflorum

The chemical components of Polygonum multiflorum were depicted using ChemDraw. The structures of these compounds were compared against databases such as PubChem and ChemSpider. On the Swiss Target Prediction and Swiss ADME platforms, active ingredients that did not meet the preset conditions and lacked targets were excluded, resulting in 28 eligible compounds. See **Table 1** for details.

Table 1. Active ingredients of Polygonum multiflorum.

Number	Compound	Molecular Formula	Number	Compound	Molecular Formula
PM1	2,3,5,4´-Tetrahydroxystilbene-2-0-xyloside	$C_{20}H_{22}O_9$	PM16	Emodin-1,6-dimethyl ether	$C_{17}H_{14}O_5$
PM2	Resveratrol	$C_{14}H_{12}O_3$	PM17	Digoxin Anthraquinone	$C_{16}H_{12}O_4$
PM3	Resveratrol-4'-0-B-D-glucoside	$C_{27}H_{26}O_{12}$	PM18	2-Methoxy-6-acetyl-7-methyljuglone	$C_{14}H_{12}O_5$
PM4	Dihydroresveratrol-3-0-glucoside	$C_{20}H_{24}O_8$	PM19	Medicagol	$C_{17}H_{14}O_7$
PM5	Polydatin	$C_{20}H_{22}O_8$	PM20	Apigenin	$C_{15}H_{10}O_5$
PM6	Chrysophanol	$C_{15}H_{10}O_4$	PM21	Kaempferol	$C_{15}H_{10}O_6$
PM7	Emodin	$C_{15}H_{10}O_5$	PM22	Quercetin	$C_{15}H_{10}O_7$
PM8	Physcion	$C_{16}H_{12}O_5$	PM23	Hydroquinone	$C_6H_6O_2$
PM9	Emodin-3-ethyl ether	$C_{17}H_{15}O_5$	PM24	2,6-Dihydroxybenzoic acid	$C_7H_6O_4$
PM10	Rhein	$C_{15}H_8O_6$	PM25	Gallic acid	$C_7H_6O_5$
PM11	ω-Hydroxyemodin	$C_{15}H_{10}O_6$	PM26	4-Methyl-3methoxybenzaldehyde-1-0-glucoside	$C_{13}H_{18}O_8$
PM12	ω-Hydroxyemodin-8-methyl ether	$C_{16}H_{12}O_6$	PM27	Trans-N-caffeoyltyramine	$C_{17}H_{17}O_3$
PM13	Emodin-8-methyl ether	$C_{16}H_{11}O_5$	PM28	Methyl gallate	$C_8H_8O_5$
PM14	Emodin-6,8-dimethyl ether	$C_{17}H_{14}O_5$	PM29	N-Trans-feruloyl-3-methoxytyramine	$C_{19}H_{21}O_5$
PM15	2-Acetylemodin	$C_{17}H_{13}O_6$	PM30	Schisandrin	$C_{24}H_{32}O_7$

3.2. Potential targets

Based on the targets of active ingredients obtained from the Swiss Target Prediction platform, targets with a "Probability" greater than 0.1 were screened, resulting in 338 targets for the drug's active ingredients after removing duplicates. Using the GeneCards and DisGeNET databases, 1375 targets related to hyperlipidemia were screened. Through Venn diagram analysis, the intersection targets were identified as potential targets, yielding 143 potential targets. See **Figure 1** and **Table 2** for details.

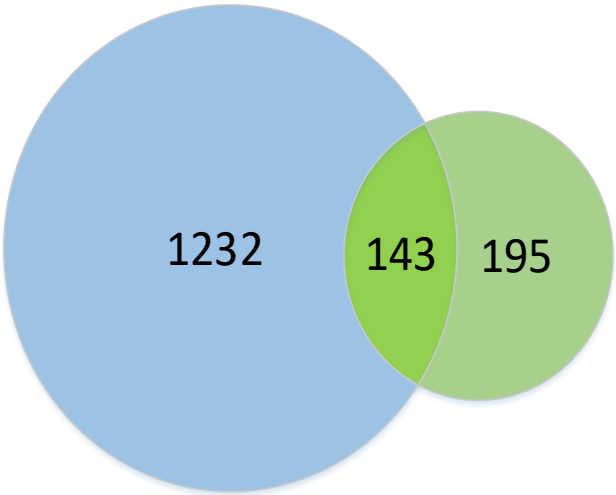

Figure 1. Venn diagram of potential targets for Polygonum multiflorum in improving hyperlipidemia.

Table 2. Potential targets of Polygonum multiflorum for improving hyperlipidemia.

Number	Potential Target	Number	Potential Target	Number	Potential Target	Number	Potential Target	Number	Potential Target
1	ABCB1	14	CASP3	27	FTO	40	MAP2K1	53	PIK3R
2	ABCC1	15	CCND1	28	GAPDH	41	MAPK1	54	PLA2G1B
3	ABCG1	16	CD38	29	GLO1	42	MAPK14	55	PLA2GA
4	ABL1	17	CFTR	30	GRM5	43	MAPK3	56	PLA2G7
5	ACE	18	CHRNA7	31	GSK3β	44	MAPK8	57	PLG
6	ACEH	19	CRHR1	32	GUSB	45	MAPT	58	PNP
7	ADA	20	CSNK2A1	33	HDAC1	46	MET	59	PPARG
8	ADK	21	CYP19A1	34	HDAC4	47	MGAM	60	PRKCA
9	ADORA1	22	CYP1A2	35	HMGCR	48	MME	61	PRKCD
10	ADORA2A	23	CYP1B1	36	HRAS	49	MMP1	62	PRKCZ
11	ADRA2A	24	CYP2C19	37	HSP90AA1	50	MMP2	63	PSEN1
12	AHR	25	CYP2C9	38	HSP0AB1	51	MMP3	64	PTGS1
13	AKR1A1	26	CYP3A4	39	HTR2C	52	MMP9	65	PTGS2

3.3. "Drug-active ingredient-potential target" network

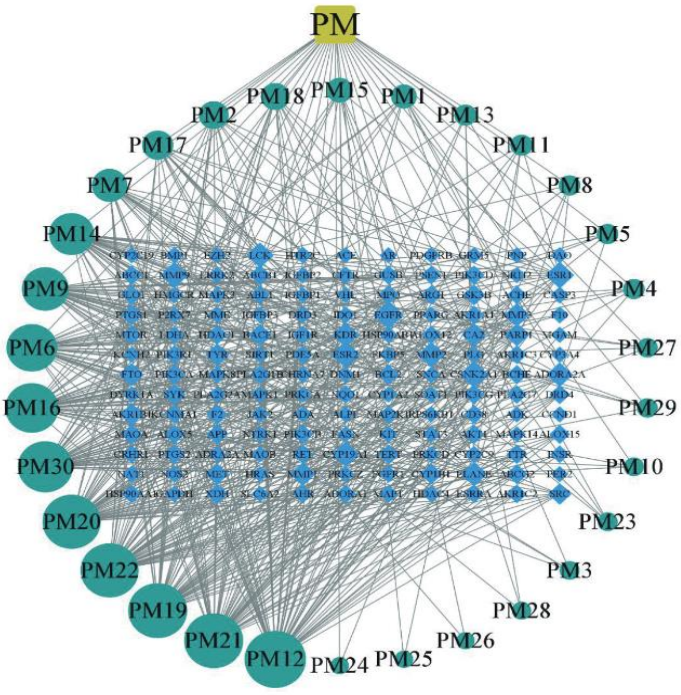

Figure 2. Drug-active ingredient-potential target network diagram.

The "Drug-Active Ingredient-Potential Target" network diagram was constructed using Cytoscape software, as shown in **Figure 2**. This network diagram comprises a total of 174 nodes, specifically including 1 drug, 30 active ingredients, and 143 targets, interconnected by 625 edges. The Degree values of these edges reflect the frequency of interactions between active ingredients and targets; higher values imply richer biological functions and stronger interactions. The analysis results show that among

the active ingredients, those with higher Degree values include ω-hydroxyemodin-8-O-methyl ether (Degree = 55), medicagol (Degree = 52), and kaempferol (Degree = 52). Potential targets with higher Degree values include EGFR (Degree = 17), ESR1 (Degree = 15), CSNK2A1 (Degree = 15), ESR2 (Degree = 15), and MMP9 (Degree = 14), suggesting high biological significance.

3.4. Construction of PPI network

PPI analysis for potential targets to obtain a STRING database for the PPI network relationship dataset. The PPI network map was successfully constructed with the visualization of the acquired data with Cytoscape software; see **Figure 3**. The network consists of 143 nodes and 1792 edges, where each node represents a potential target, and the edges are used to describe the interaction relationship between the targets. The number of edges directly reflects the strength of the association between targets, and the more the number of edges, the closer the connection between targets.

The Degree values of all nodes in the graph are ranked in high order. The results showed that the targets such as AKT 1, MAPK 3, CASP 3, EGFR, SRC, MAPK 1, ESR 1, MAPK 8, STAT 3, and MMP 9 were high. In the constructed "drug-active component-potential target" network, EGFR, ESR 1 and MMP 9 could interact with more than 14 active components, suggesting that the active components in Polygonum multiflorum can improve hyperlipidemia by acting on core targets such as EGFR, ESR 1 and MMP 9.

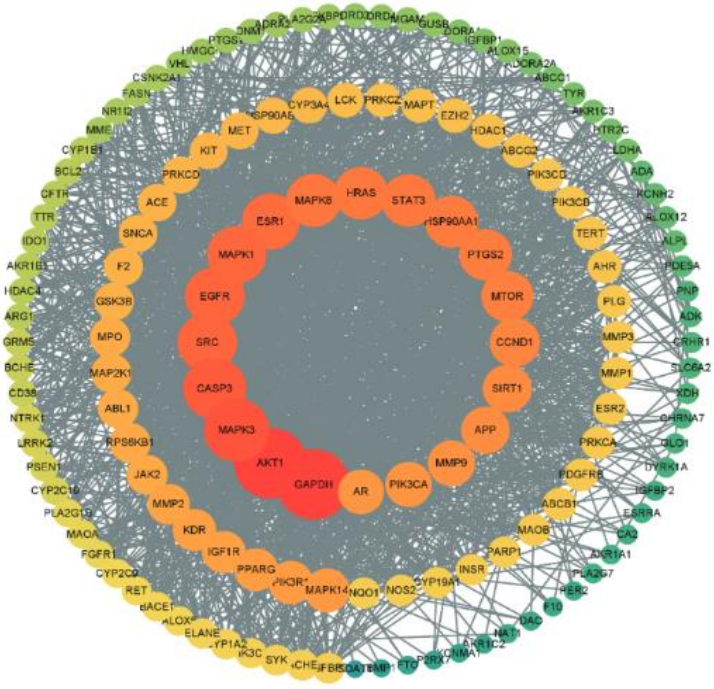

Figure 3. PPI protein-protein interaction network diagram.

3.5. GO enrichment analysis and KEGG pathway enrichment analysis

GO and KEGG pathway enrichment analysis of potential targets was performed using the DAVID database. GO analysis includes three main categories: biological process (biological processes), cell component (cellular components) and molecular

function (molecular functions). The analysis results are presented in a graph form, where the abscissa represents the entry category and the ordinate represents the number of genes, to highlight the entries with a large number of genes. The significance of the enrichment analysis was displayed by the bubble map, and the first 20 entries with $P < 0.01$ were selected for display (see **Figure 4**). In terms of KEGG pathway enrichment analysis, the top 20 pathways with the largest number of genes were prioritized, and the enrichment bars were drawn. The top 20 pathways were also ranked from small to large, and the *P*-values were selected for graphical display (see **Figure 5**). As shown in **Figure 5**, the enrichment factor (Rich Factor) reflects the proportional relationship between the number of genes in a specific pathway and the total number of genes of the pathway, and the size of its value directly indicates the degree of enrichment. The color of the dots changes from blue to red. The darker red indicates a smaller *P*-value, which is statistically significant; the size of the dots represents the number of targets involved in the pathway.

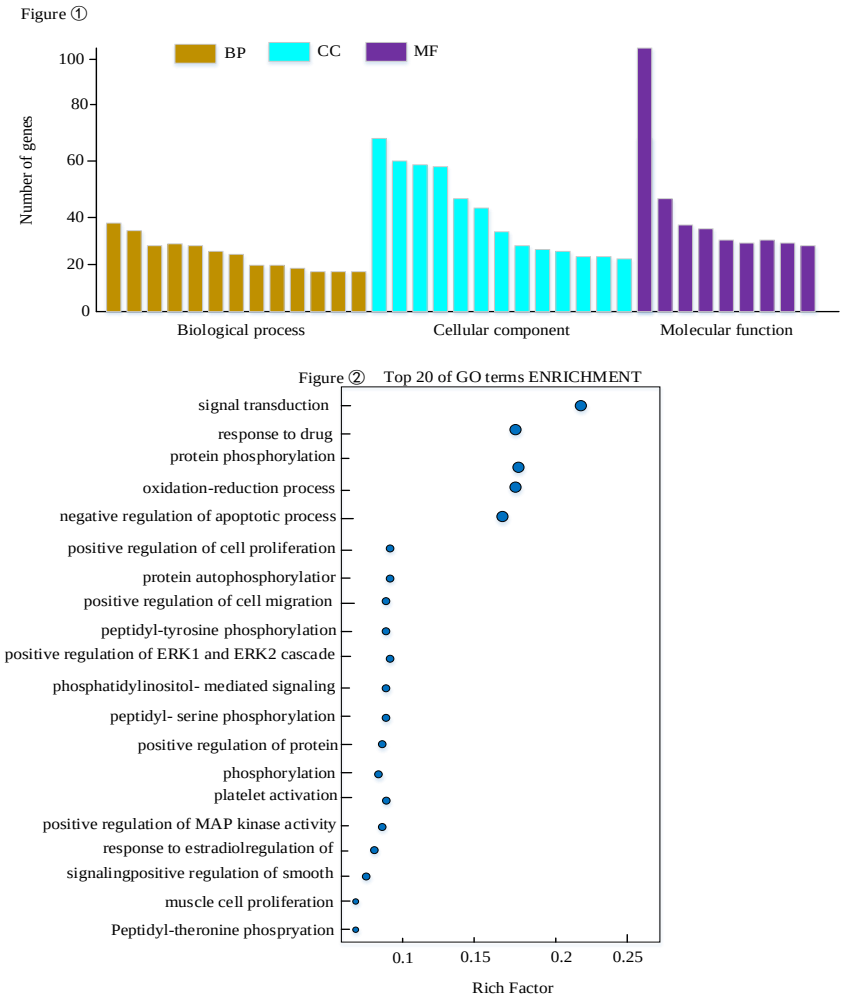

Figure 4. Results of GO enrichment analysis.

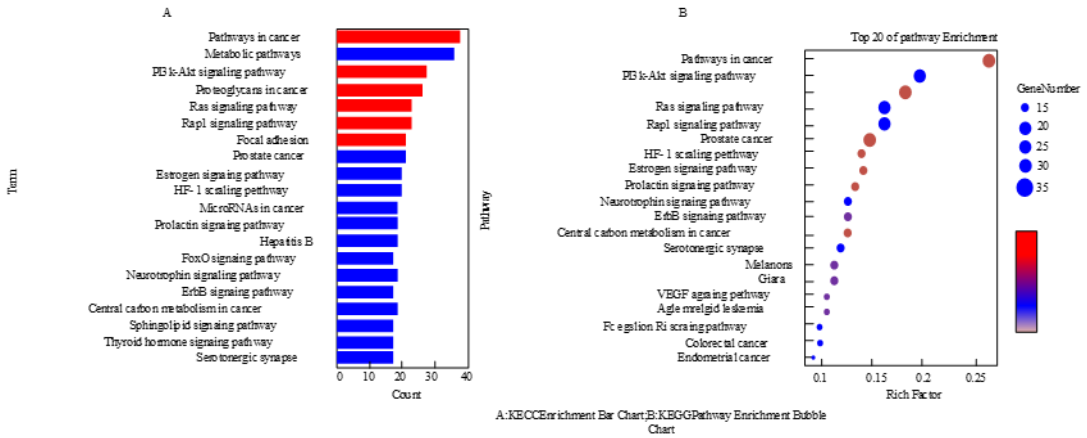

Figure 5. Results of KEGG enrichment analysis. **(A)** KECC enrichment bar chart; **(B)** KEGG pathway enrichment bubble.

The GO analysis revealed that potential targets are mainly distributed in the plasma membrane (plasma membrane), cytoplasm (cytoplasm), cell fluid (cytosol), and cell nucleus (nucleus) of the cell, and in the molecular functional level involved in protein binding (protein binding), ATP binding (ATP binding), enzyme binding (enzyme binding), and protein kinase activity (protein kinase activity) and other processes, and then deeply involved in signal transduction (signal transduction), drug response (response to drug), protein phosphorylation (protein phosphorylation), and redox processes (oxidation-reduction process). The enriched bubble map further highlights the highly enriched status of protein phosphorylation, protein binding, enzyme binding, and protein kinase activity in the three categories. A significant number of targets and prominent locations within the metabolic pathway (metabolic pathways) were verified by KEGG analysis. Combined with the analysis of **Figures 4** and **5**, it can be inferred that the regulatory mechanism of Polygonum multiflorum on hyperlipidemia may be closely related to the phosphatidylinositol 3-kinase-protein kinase B (PI3K-Akt), hypoxia-inducible factor 1 (HIF-1), and estrogen (Estrogen) signaling pathways.

3.6. Molecular docking

Molecular docking was performed between the active components of Polygonum multiflorum, namely ω-hydroxyemodin-8-O-methyl ether, medicarpin, and kaempferol, and the core targets EGFR, ESR1, and MMP9. The results are presented in **Table 3**. In the analysis of molecular docking, a binding energy lower than −5 kcal·mol^{-1} was defined as the threshold to judge whether a stable binding could form between the receptor and ligand molecules. A lower binding energy value indicates a more excellent binding effect between the receptor and ligand. A schematic diagram of the binding mode of low binding energy molecules is shown in **Figure 6**. The research results revealed that these active components exhibited stable binding characteristics with the selected core targets, forming robust docking structures.

Table 3. Binding energies (kcal·mol^{-1}) of Polygonum multiflorum active components docked with core targets.

Active Ingredients	Core Target		
	EGFR	**ESR1**	**MMP9**
ω-Hydroxyemodin-8-methyl Ether	−7.31	−5.75	−7.08
Medicarpin	−5.5	−6.4	−5.87
Kaempferol	−9.76	−9.73	−9.72

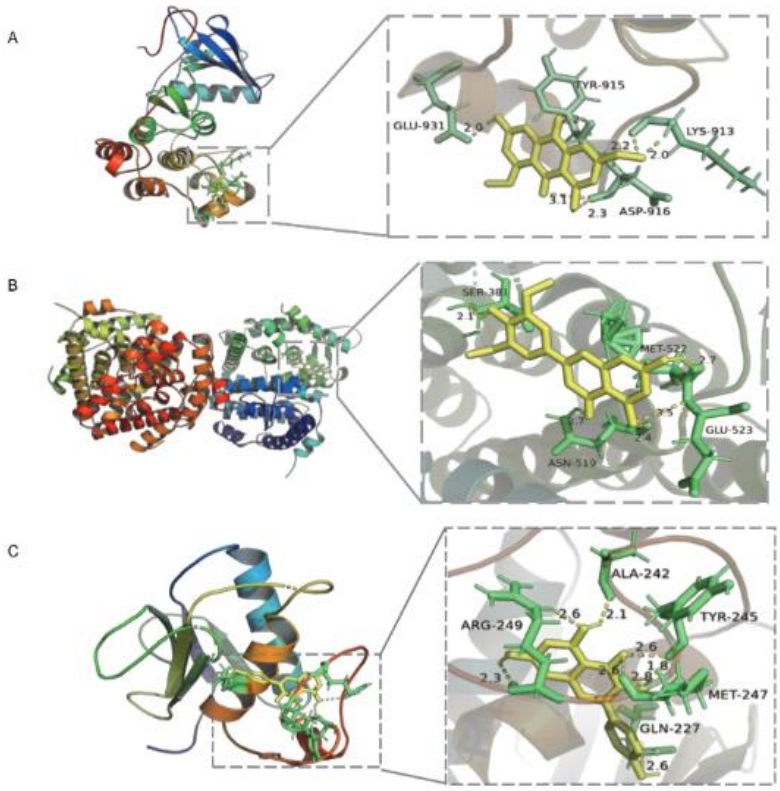

Figure 6. Schematic diagram of partial molecular docking. **(A)** ω-Hydroxyemodin-8-methyl ether molecular docking results; **(B)** Medicarpin molecular docking results; **(C)** Kaempferol molecular docking results.

4. Conclusion

Polygonum multiflorum, as a traditional Chinese medicine, has complex and diverse pharmacological effects. In order to identify the anti-hyperlipidemic active components, ChemDraw software was used to map the structure of potential compounds, and compare them through PubChem and the source network database to ensure the accuracy of the compound structure [6]. With the help of the Swiss ADME platform, compounds with excellent oral bioavailability were selected as potential active ingredients based on gastrointestinal absorption efficiency and drug-like parameters. Among the selected active ingredients, compounds such as ω-hydroxyemodin-8-methyl ether, alfalfa, and kaempferol became the focus of this study. These components are high in Polygonum multiflorum and have significant bioactive [7] in several studies. For example, ω-hydroxyemodin-8-methyl ether, as a natural polyphenol, exhibits antioxidant, anti-inflammatory, and anti-tumor

pharmacological effects [8]; alfalfa is effective in regulating blood lipid, reducing blood sugar, and enhancing immunity; and kaempferol is considered to have antioxidant, anti-inflammatory, and anti-tumor activity [9].

In the study, GeneCards and DisGeNET databases were used to collect the target information related to hyperlipidemia, and the targets with potential interaction with the active ingredients were selected through Venn diagram analysis. Among the selected potential targets, targets such as EGFR, ESR 1 and MMP 9 have attracted special attention. These targets play important roles in the pathogenesis of hyperlipidemia, and they are closely related to the development of various cardiovascular diseases and tumors. Among them, EGFR, as a transmembrane receptor, is widely involved in the process of cell growth, proliferation and differentiation, and its abnormal activation can lead to malignant cell proliferation and tumor formation [10]; ESR 1, as a nuclear receptor, mainly mediates estrogen signaling, participates in the regulation of blood lipid metabolism and vascular function [11–13]; MMP 9, as a matrix metalloproteinase, can degrade extracellular matrix and promote angiogenesis and inflammatory response [14].

To verify the interaction between the active components and the core targets, molecular dynamic simulation was further implemented in this study. Molecular dynamics simulations can dynamically observe the stability and conformational changes of the active components after binding to the target, thus providing a deeper understanding of the interaction mechanism between them. The simulation results showed that ω-hydroxyemodin-8-methyl ether, Medicago, and kaempferol could maintain a stable binding state with small conformational changes after binding to EGFR, ESR 1 and MMP 9, which further confirmed the strong binding ability between these active components and the core targets. Specifically, ω-hydroxyemodin-8-methyl ether can form strong hydrogen bonds and hydrophobic interactions with EGFR and ESR 1 [15]; alfalfa energy can form stable π-π stacking and hydrophobic interactions with EGFR and MMP 9 [16]; and kaempferol can form extensive hydrogen bonds, hydrophobic interactions and aromatic ring heaps [17] with all three targets. Suggesting that these interactions enhance the affinity between the active component and the target, which may affect the biological function of the target [18]. For example, the binding of ω-hydroxyemodin-8-methyl ether to EGFR and ESR 1 may interfere with the signaling pathways of these receptors, which in turn affect cell growth, proliferation and blood lipid metabolism [19–21]. Similarly, the interaction of Medicarpin with EGFR and MMP 9 may inhibit angiogenesis and inflammatory responses, while the extensive binding of kaempferol with all three targets may exert its pharmacological effects through multiple mechanisms [22].

This study found that the binding of these active components to the target may also function by regulating the signaling pathways associated with hyperlipemia. The PI3K-Akt signaling pathway plays a key role in regulating cell growth, proliferation, metabolism as well as survival, and its abnormal activation is closely related to the development of various diseases, including hyperlipemia. In this study, the binding of the active components of Polygonum multiflorum to targets such as EGFR and ESR 1 may affect the conduction of the PI3K-Akt signaling pathway, which subsequently regulates blood lipid metabolism [23]. Moreover, the HIF-1 signaling pathway is involved in processes such as angiogenesis, energy metabolism and inflammatory

response under hypoxia, while the estrogen signaling pathway is closely related to the development of blood lipid metabolism, vascular function and cardiovascular diseases. The combination of Polygonum multiflorum active components with key targets in these pathways such as EGFR, ESR 1 and MMP 9 may exert antihyperlipidemic effects [24] by modulating the activity of these pathways. Moreover, the estrogen signaling pathway also has important roles in lipid metabolism, energy balance, and inflammatory response. The combination of the active components of Polygonum multiflorum and the targets related to the estrogen signaling pathway may further exert its anti-hyperlipidemic effect by regulating the activity of this pathway. The results of KEGG enrichment analysis showed that PI3K-Akt, HIF-1 and estrogen signaling pathways were significantly enriched in hyperlipidemia-related targets, and these pathways were closely associated with the lipid-lowering effect of Polygonum multiflorum active components. The PI3K-Akt signaling pathway plays a central role in regulating cell metabolism and survival, and the active components of Polygonum multiflorum may reduce lipid synthesis and promote lipolysis, thus reducing blood lipid levels. The HIF-1 signaling pathway regulates energy metabolism and angiogenesis under hypoxia, and the active components of this pathway, may improve cellular energy metabolism and alleviate hypoxic damage caused by hyperlipidemia. The estrogen signaling pathway affects cardiovascular health by regulating lipid metabolism and vascular function, and the active components of Polygonum multiflorum may improve blood lipid metabolism and enhance vascular protective effects by activating or regulating this pathway. The results of GO enrichment analysis showed that the potential targets of the active components of Polygonum multiflorum were mainly enriched in biological processes such as lipid metabolism, inflammatory response and angiogenesis, which are closely related to the occurrence and development of hyperlipemia. In terms of cellular components, the targets were mainly distributed in the plasma membrane, cytoplasm and nucleus, indicating that the active components may exert lipid-lowering effects by acting on cell membrane receptors or nuclear receptors. In terms of molecular function, the targets are mainly involved in protein binding, ATP binding and enzyme activity regulation, suggesting that the active components may play lipid-lowering effects by regulating the activities of key enzymes or signaling proteins.

Numerous studies have shown that multiple drugs or interventions have also been reported to exert lipid-lowering effects through modulation of PI3K-Akt, HIF-1, and estrogen signaling pathways. Some foreign scholars show that statins reduce lipid synthesis by inhibiting the abnormal activation of the PI3K-Akt pathway and promote lipid decomposition, thus significantly reducing the blood lipid level. However, in contrast to statins, the active components of Polygonum multiflorum not only act through the PI3K-Akt pathway, but also achieve multiple lipid-lowering mechanisms by regulating HIF-1 and estrogen signaling pathways. In regard to HIF-1 signaling, metformin, as a commonly used hypoglycemic drug, was also found to ameliorate hyperlipemia-related metabolic abnormalities by inhibiting the activation of the HIF-1 pathway. However, the active ingredient of Polygonum multiflorum (e.g., kaempferol) not only inhibits the HIF-1 pathway, but also further reduces the tissue damage caused by hyperlipidemia through antioxidant and anti-inflammatory effects, which may distinguish it uniquely from other drugs. In terms of estrogen signaling,

hormone replacement therapy (HRT) regulates lipid metabolism and vascular function by supplementing exogenous estrogens, but its long-term use may increase the risk of breast cancer and cardiovascular disease. In contrast, the active ingredients of Polygonum multiflorum regulate the estrogen signaling pathway through the natural phytoestrogen-like action, which may have a higher safety profile and a lower risk of side effects.

This study also found that active components such as ω-hydroxyemodin-8-methyl ether and Medicago could reduce blood lipid levels and improve vascular function by inhibiting PI3K-Akt pathway activation. The HIF-1 signaling pathway is mainly involved in regulating processes such as cellular hypoxia adaptation and energy metabolism. In hyperlipidemic conditions, cells are often hypoxic and show abnormal energy metabolism characteristics. This study found that active components such as kaempferol could reduce blood lipid levels and improve the cellular hypoxia adaptation capacity by inhibiting HIF-1 pathway activation [25]. The estrogen signaling pathway is closely related to estrogen and is mainly involved in the regulation of blood lipid metabolism, vascular function and inflammatory response. Studies have shown that estrogen deficiency or abnormalities can lead to disturbed lipid metabolism and cardiovascular disorders. In this study, we found that active components such as ω-hydroxyemodin-8-methyl ether and Medicago could reduce blood lipid levels and improve vascular function by regulating estrogen pathway activity.

Although the network pharmacology approach provides a powerful tool to study the mechanism of action, there are some limitations in this study. First, network pharmacology research is based on a large number of databases and computational models, and the results have certain virtuality. Despite the rigorous screening and analysis of this study through multiple databases and platforms, the obtained results still require further experimental validation. Second, this study lacks in vivo and in vitro experimental validation. Although methods such as molecular docking and molecular dynamics simulation can predict interactions between active components and targets to some extent, real biological environments are complex and changeable, thus requiring further verification of these interactions by experimental means. In the future, we will continue to study the anti-hyperlipidemia mechanism of Polygonum multiflorum, and verify the results of network pharmacology studies through in vivo and in vitro experiments, so as to provide a more reliable scientific basis for the clinical application of Polygonum multiflorum.

In conclusion, this study investigated the mechanism and signaling pathway of Polygonum multiflorum comprehensively through the network pharmacology method. It is found that multiple active components in Polygonum multiflorum can form stable interactions with hyperlipidemia-related core targets, and exert anti-hyperlipidemic effects by affecting specific signaling pathways.

Author contributions: Conceptualization, JW and MY; methodology, YH; software, XF; validation, XZ, KZ and YH; formal analysis, JW; investigation, MY; resources, LL; data curation, MY; writing—original draft preparation, JW; writing—review and editing, KZ; visualization, XZ; supervision, JL; project administration, LL; funding

acquisition, ZZ. All authors have read and agreed to the published version of the manuscript.

Ethical approval: Not applicable.

Conflict of interest: The authors declare no conflict of interest.

References

1. Han Z, Zhuo F, Li F, et al. Study on the Effect and Mechanism of FXR Signaling Pathway Mediated Lipid Deposition Induced by Polygonum multiflorum Thunb. Journal of New Medicine. 2021; 52(10): 759-763.
2. Mao H, Xie L, Fan X, et al. Effects of Ethanol Extract of Polygonum multiflorum Thunb. on LPS-induced TLR4/TRIF/IRF-3 Signaling Pathway in Rats. International Journal of Pharmaceutical Research. 2016; 43(3): 496-503.
3. Wang M, Yang H, Kang S, et al. Effects of Polygonum multiflorum Thunb. Decoction on Insulin Signaling Pathway in the Liver of Aging Rats. Journal of Guizhou University of Traditional Chinese Medicine. 2020; 42(1): 17-20, 32.
4. Takatomo A, Masako T, Nobuhito G. HIF-1-dependent lipin1 induction prevents excessive lipid accumulation in choline-deficient diet-induced fatty liver. Scientific Reports. 2018; 8(1): 14230-14233.
5. Gu S, Wang T. Hepatic estrogen receptor α is critical for regulation of gluconeogenesis and lipid metabolism in males. Scientific Reports. 2017; 7(1): 1661-1667.
6. Sabroe. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific Reports. 2017; 7(15): 4271-4277.
7. Palmisano BT, Le TD, Zhu L, et al. Cholesteryl ester transfer protein alters liver and plasma triglyceride metabolism through two liver networks in female mice. Journal of Lipid Research. 2016; 57(8): 1541-1551.
8. Boehm-Cagan A, Bar R, Liraz O, et al. ABCA1 Agonist Reverses the ApoE4-Driven Cognitive and Brain Pathologies. Journal of Alzheimer's Disease: JAD. 2016; 54(3): 336-339.
9. Thomas PV, Shahnaz R, Diana N, et al. Matrix metalloproteinases in atherosclerosis: role of nitric oxide, hydrogen sulfide, homocysteine, and polymorphisms. Vascular Health and Risk Management. 2015; 11(22): 1157-1163.
10. Lin Zhu, Melissa N. Martinez, Christopher H. Emfinger, et al. Estrogen signaling prevents diet-induced hepatic insulin resistance in male mice with obesity. American Journal of Physiology. 2014; 306(5): 1188-1197.
11. Feng R, Sun J, Zhang B, et al. Effects of Polygonum multiflorum Thunb. Extract on BDNF/TrkB and Its Downstream Signaling Pathways in Rats with Attention Deficit Hyperactivity Disorder. Chinese Journal of Basic Medicine in Traditional Chinese Medicine. 2024; 30(8): 1356-1361.
12. Li Q, Li F, Lang X, et al. Polygonum multiflorum glycoside antagonizes H2O2-induced oxidative damage in rat hippocampal neurons by activating the BDNF/TrkB signaling pathway. Natural Product Research and Development. 2019; 31(7): 1163-1169.
13. Liu W, Wang J, Wang S, et al. Effects of Polygonum multiflorum Thunb. Decoction on the Expression of Rb Cell Transduction Pathway-Related Proteins in the Brain Tissue of Aging Rats. Journal of Chengde Medical University. 2009; 26(4): 454-455.
14. Chen H, Zhou D. Study on the Effect of Polygonum multiflorum Thunb. Extract Stilbene Glycoside on Early Diabetic Nephropathy Rats Based on TLR4/NF-κB Signaling Pathway. China Medical Herald. 2020; 17(17): 21-25.
15. Li M, Wang H, Wang T, et al. Effects of Emodin in Prepared Polygonum multiflorum Thunb. on JAK2/STAT3 Pathway in Atherosclerosis Model of ApoE-/- Mice. Chinese Journal of Experimental Traditional Medical Formulae. 2018; 24(18): 101-106.
16. Erica HB, Deliang G, Paul M, et al. Targeting SREBP-1-driven lipid metabolism to treat cancer. Current Pharmaceutical Design. 2019; 20(15): 1887-1890.
17. Huang DW, Sherman BT, Lempicki RA. Lempicki. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nature Protocols erecipes for Researchers. 2020; 4(1): 44-57.
18. Huang DW, Sherman BT, Lempicki RA. Bioinformatics enrichment tools: paths toward the comprehensive functional analysis of large gene lists. Nucleic Acids Research. 2020; 37(1): 11-13.
19. Yang H, Cao Q, Xiong X, et al. Fluoxetine regulates glucose and lipid metabolism via the PI3K-AKT signaling pathway in diabetic rats. Molecular Medicine Reports. 2020; 22(4): 3073-3080.

20. Bhushan B, Banerjee S, Paranjpe S, et al. Pharmacologic Inhibition of Epidermal Growth Factor Receptor Suppresses Nonalcoholic Fatty Liver Disease in a Murine Fast-Food Diet Model. Hepatology: Official Journal of the American Association for the Study of Liver Diseases. 2019; 70(5): 1546-1563.
21. Antoine D, Olivier M, Vincent Z. SwissTargetPrediction: updated data and new features for efficient prediction of protein targets of small molecules. Nucleic Acids Research. 2019; 47(11): 357-364.
22. Uematsu S. Epidermal growth factor receptor inhibition attenuates non-alcoholic fatty liver disease in diet-induced obese mice. PLoS ONE. 2019; 14(2): 1-12.
23. Yee ST, Lee MK, Kang K, et al. Heshouwu (Polygonum multiflorum Thunb.) Ethanol Extract Suppresses Pre-adipocytes Differentiation in 3T3-L1 Cells and Adiposity in Obese Mice. Biomedicine & Pharmacotherapy. 2018; 10(15): 339-341.
24. Pan F, Yi B, Xu J, et al. Evaluation of the Effectiveness of Stewed Polygonum multiflorum Thunb. in Promoting Hair Blackening and Study on Its Network Pharmacological Mechanism. World Chinese Medicine. 2024; 19(15): 2222-2229.
25. Shin BK, Kang S, Kim DS, et al. Intermittent fasting protects against the deterioration of cognitive function, energy metabolism and dyslipidemia in Alzheimer's disease-induced estrogen deficient rats. Experimental Biology and Medicine: Journal of the Society for Experimental Biology and Medicine. 2018; 243(4): 334-343.