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Research Article

A Multi-target Mechanism Study of Paeoniflorin in the Treatment of Depression Based on Network Pharmacology

Jing Zhang[1, 2], Keming Li[2, 3], Xinjing Xie[4], Hailing Ding[2], Xuehui Wang[2], Yihui Li[2], Xing Gao[2, *], Jinlong Han[5, *]

[1]Department of Traditional Chinese Medicine, Shandong Mental Health Center, Shandong University, Jinan, China

[2]Department of Medicine, Qilu Institute of Technology, Jinan City, China

[3]Department of Medicine, Shandong Xiehe University, Jinan City, China

[4]Shandong Jie's Traditional Chinese Medicine Decoction Co., Ltd, Shunwangcheng Traditional Chinese Medicine Market, Heze City, China

[5]Shandong Academy of Agricultural Sciences, Jinan City, China

Abstract

Objective: To investigate the potential targets and molecular mechanisms of paeoniflorin in treating depression using network pharmacology. Methods: Targets of paeoniflorin were predicted via the Swiss Target Prediction database. Depression-related targets were obtained from the GeneCards database, and an intersection of "drug-disease" targets was constructed. A protein-protein interaction (PPI) network was built using the STRING platform, followed by Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses ($P < 0.05$) via DAVID. Results: Twenty-four paeoniflorin targets and 5,443 depression-related targets were identified, yielding 15 intersection targets. The PPI network contained 11 nodes and 18 edges, with core targets including FGF2, HSP90AA1, and others. GO enrichment analysis revealed: biological processes (BP) involving wound healing, cell chemotaxis, and regulation of body fluid levels; cellular components (CC) enriched in cytoplasmic vesicle lumen and platelet alpha granule; molecular functions (MF) associated with heparin binding and glycosaminoglycan binding. KEGG pathway analysis highlighted significant enrichment in PI3K-Akt signaling pathway, Rap1 signaling pathway, and Ras signaling pathway. Conclusion: Paeoniflorin exerts antidepressant effects through multitargets and multipathways, providing a theoretical basis for its therapeutic application in depression.

Keywords

Paeoniflorin, Depression, Network Pharmacology, Enrichment Analysis, Mechanism Study

1. Introduction

Depression is a mental disorder characterized by significant and lasting depression and loss of interest, with a global prevalence rate of 4.4%, which has become one of the main causes of disability worldwide [1, 2]. At present, sin-

*Corresponding author: gaoxing620@126.com (Xing Gao) goldendragonh@163.com (Jinlong Han)

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gle-target drugs such as serotonin reuptake inhibitors (SSRIs) are mainly used in clinical treatment, but there are limitations such as slow onset of effect, many side effects (such as sexual dysfunction and withdrawal reaction) and low response rate (about 30% of patients have no response) [3, 4]. Traditional Chinese medicine provides a new idea for the treatment of depression due to its overall regulatory advantages of multiple components and multiple targets [5]. Paeoniflorin, the main active ingredient of Paeonia lactiflora Pall., may ameliorate depressive symptoms, but its molecular mechanism remains unclear [6].

As an interdisciplinary subject of systems biology and pharmacology, network pharmacology has successfully revealed the antidepressant mechanism of many active ingredients of traditional Chinese medicine by analyzing the multi-target mode of action of complex drugs through the "drug-target-disease" network [7-9]. The aim of this study was to: (1) predict potential targets of paeoniflorin in the treatment of depression; (2) Construct the "drug-disease" interaction network, analyze the core targets and key pathways; (3) To reveal the molecular mechanism of paeoniflorin's intervention in depression through multi-target and multi-pathway, and to provide theoretical basis for its clinical application.

2. Materials and Methods

2.1. Prediction of Active Ingredient Targets of Paeoniflorin

Will SMILE of paeoniflorin, "C/C @ 12 C/C @ @ 3 (@ @ H [C] 4 C/C @ 1 (@ @ [C] 4 (@ H [C] (O2) O3) COC (= O) C5 = CC = CC = C5) O @ H [C] 6 @ @ H [C] (@ H [C] (@ @ H [C] (@ H [C] (O6) CO) O) O O O "upload to Swiss Target Prediction database (HTTP: / / swisstargetprediction. Ch /), set the species to homosapiens, selection probability greater than 0 targets, paeoniflorin Target database is established.

2.2. Collection of Potential Targets for the Treatment of Prostatic Hyperplasia by Salvia Miltiorrhiza

"'depression" as keywords, Gene in the human genome database Cards (https://www.genecards.org/), the retrieval depression related genes, and established paeoniflorin targets intersection, obtain paeoniflorin set targets for the treatment of depression.

2.3. Construction of Protein-Protein Interaction Network

The targets collected in section 1.2 were imported into the STRING platform (https://string-db.org/) for protein-protein interaction (PPI) analysis, and the species human was specified. The minimum interaction threshold is set to 0.4 for screening, hiding discrete nodes, and constructing PPI network relationship. The download results are saved in *.tsv format, imported into Cytoscape3.7.2 for visualization, and analyzed with Network analyzer plug-in for network feature targets.

2.4. Gene Ontology and Signaling Pathway Analysis

Use DAVID 2021 (https://davidbioinformatics.nih.gov/) for the treatment of paeoniflorin depression core targets of potential targets for gene ontology (GO), Kyoto encyclopedia (KEGG) gene and genome pathway enrichment analysis. The data obtained from the enrichment analysis tool is sorted according to the -lgP value. GO Biological processes (BP), Celular components (Cc), and Molecular functions (MF) Select the top 10 items. KEGG path enrichment analysis results The top 10 items were selected and enrichment maps were drawn respectively.

3. Results

3.1. Prediction Results of Paeoniflorin Targets

A total of 24 targets for predicting paeoniflorin were obtained through Swiss Target Prediction (Table 1). With "depression" as the key word, Gene Cards database was used to search for disease targets, and 5443 targets related to depression were screened with "Relevance score>1". After intersection with paeoniflorin action targets, 15 potential targets for the treatment of depression were obtained (Figure 1).

Table 1. *Paeoniflorin predicted targets.*

NO.	Target	Common name	Uniprot ID	Probability*
1	Galectin-3	LGALS3	P17931	0.136844681
2	Galectin-9	LGALS9	O00182	0.136844681
3	Heat shock protein HSP 90-alpha	HSP90AA1	P07900	0.128531578
4	Norepinephrine transporter	SLC6A2	P23975	0.120225751

NO.	Target	Common name	Uniprot ID	Probability*
5	Somatostatin receptor 5	SSTR5	P35346	0.120225751
6	Somatostatin receptor 2	SSTR2	P30874	0.120225751
7	Somatostatin receptor 4	SSTR4	P31391	0.120225751
8	Somatostatin receptor 1	SSTR1	P30872	0.120225751
9	Somatostatin receptor 3	SSTR3	P32745	0.120225751
10	P-glycoprotein 1	ABCB1	P08183	0.120225751
11	Vascular endothelial growth factor A	VEGFA	P15692	0.120225751
12	Acidic fibroblast growth factor	FGF1	P05230	0.120225751
13	Basic fibroblast growth factor	FGF2	P09038	0.120225751
14	Heparanase	HPSE	Q9Y251	0.120225751
15	Thrombin and coagulation factor X	F10	P00742	0.120225751
16	AMY1C	AMY1A	P04745	0.120225751
17	Protein-tyrosine phosphatase 1B	PTPN1	P18031	0.120225751
18	Plasminogen activator inhibitor-1	SERPINE1	P05121	0.120225751
19	T-cell protein-tyrosine phosphatase	PTPN2	P17706	0.120225751
20	Beta-secretase 1	BACE1	P56817	0.120225751
21	Squalene monooxygenase (by homology)	SQLE	Q14534	0.120225751
22	Platelet activating factor receptor (by homology)	PTAFR	P25105	0.120225751
23	P-selectin	SELP	P16109	0.120225751
24	Aldose reductase	AKR1B1	P15121	0.120225751

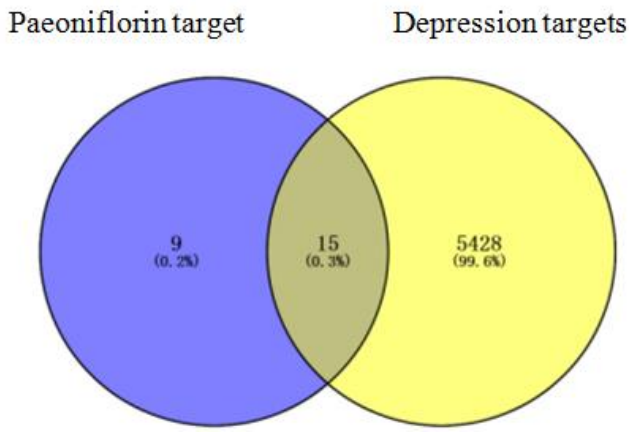

Figure 1. *VENN diagram of paeoniflorin drug-depression disease target.*

3.2. PPI Network Results

The PPI relationship of the target of paeoniflorin in the treatment of depression obtained by STRING platform was imported into Cytoscape3.7.2 software for visual analysis, and the PPI network was generated, as shown in Figure 2. There are 11 nodes and 18 edges in the network, among which the edges represent the PPI relationship, the circular nodes represent the target protein, and the node color represents the degree value. It can be seen that targets such as FGF2 and HSP90AA1 play a core role in the network, with degree values of 6 and 5, respectively, which are valuable for further research.

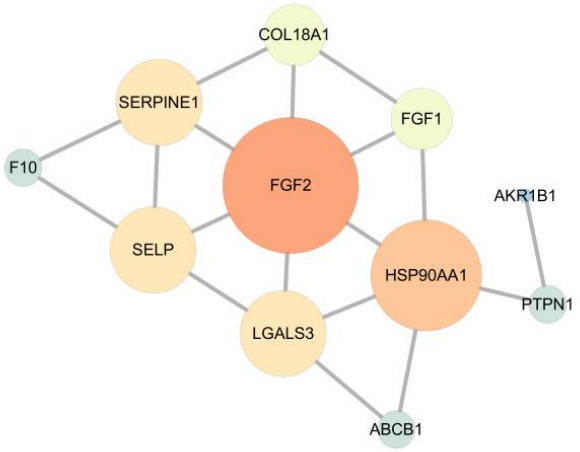

Figure 2. *Target PPI network.*

Note: Color range, From left to right the degree value decreases.

3.3. Enrichment Results of GO and KEGG

GO analysis consists of three branches, namely molecular function (MF), cell component (CC) and biological process (BP). Processes with P≤0.05 are screened and the top ten processes with enrichment number are listed (Figure 3). Among them, at the BP level, the predicted targets were mainly related to wound healing, cell chemotaxis, regulation of body fluid levels, etc. At CC level, cytoplasmic vesicle lumen, vesicle lumen and platelet alpha granule accounted for a large proportion. At MF level, it is closely related to heparin binding, glycosaminoglycan binding, sulfur compound binding and so on. KEGG enrichment was used to analyze the pathways that paeoniflorin may be involved in antidepressant depression, and 12 signaling pathways with P≤0.05 were obtained. Figure 4 lists the relevant pathways with the top 10 enrichment numbers. Among them, PI3K-Akt signaling pathway, Rap1 signaling pathway, and Ras signaling pathway are closely related to depression, indicating that paeonipeony may act on these pathways and thus play a role in the treatment of depression.

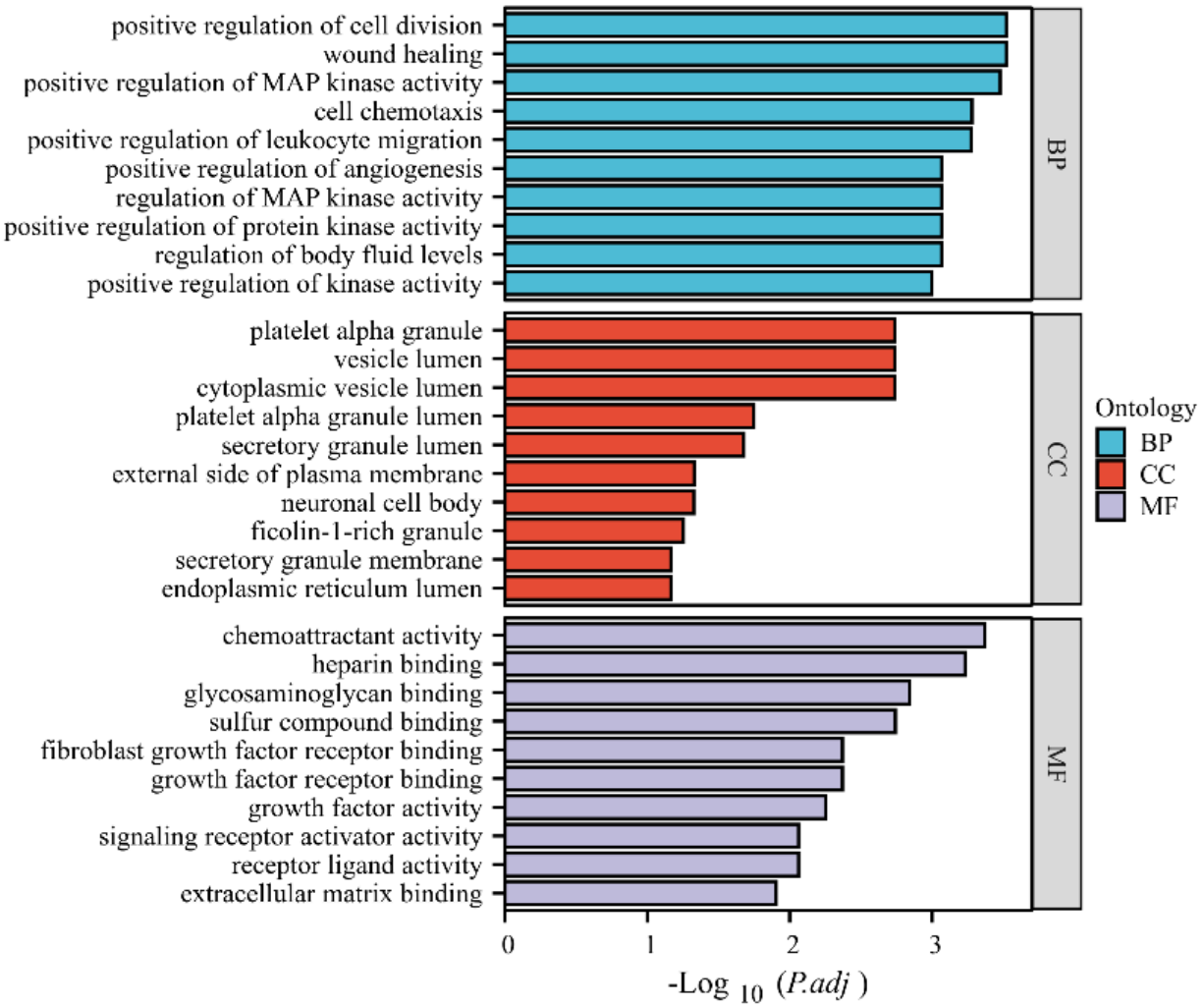

Figure 3. *GO enrichment analysis results.*

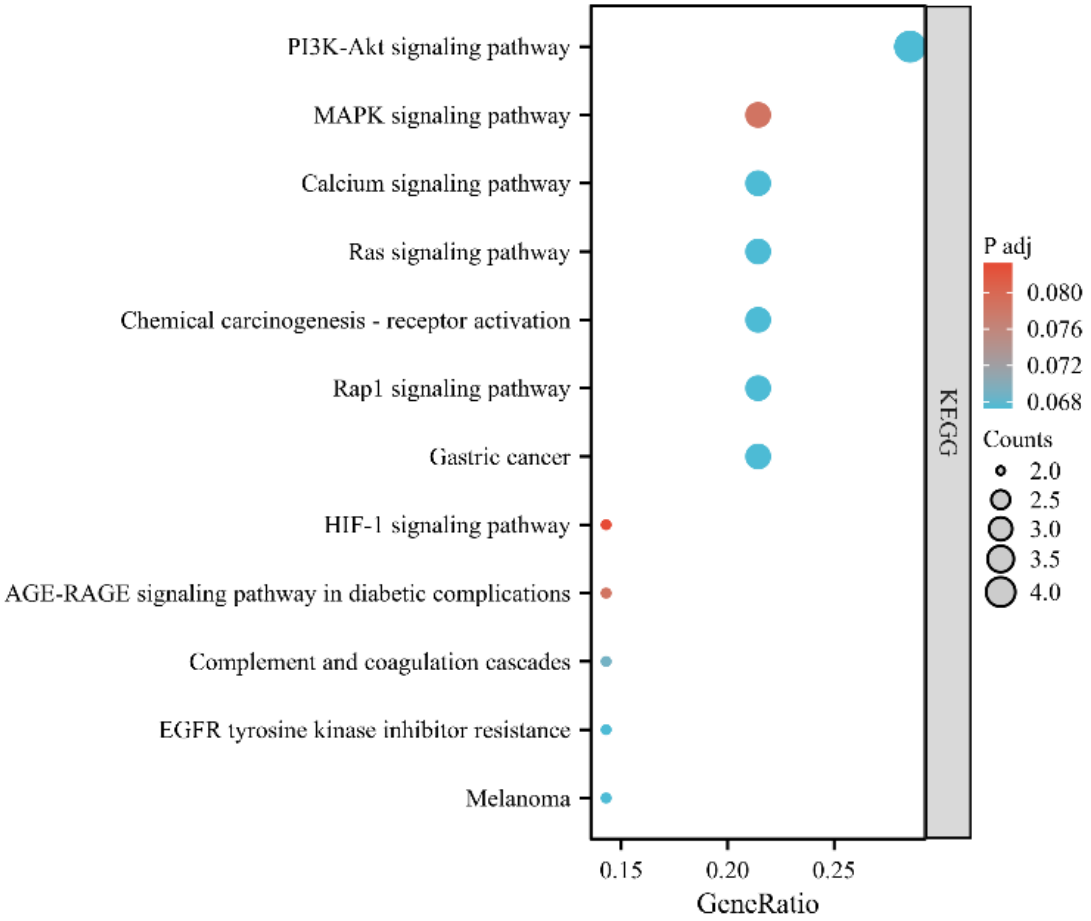

Figure 4. *KEGG enrichment analysis results.*

4. Discussion

The complex pathological mechanisms of depression and the limitations of single-target drugs highlight the importance of multi-target treatment strategies. This study reveals the potential molecular mechanism of paeoniflorin's intervention in depression through a "multi-target-multi-pathway" model through network pharmacology. Fifteen "drug-disease" intersection targets were selected, and the constructed PPI network showed that FGF2 (degree value 6) and HSP90AA1 (degree value 5) were the core nodes. FGF2 (Basic fibroblast growth factor), a member of the family of neurotrophic factors, can promote hippocampal neuron regeneration and synaptic plasticity, and improve depression-like behavior induced by chronic stress [10]. Studies have found that the serum level of FGF2 in depressive models is significantly reduced, and its expression is higher after antidepressant treatment [11]. HSP90AA1 (heat shock protein 90α), as a molecular chaperone, participates in the activation and nuclear translocation of glucocorticoid receptor (GR) and regulates the abnormal activation of HPA axis - the core pathological mechanism of depression [12]. Paeoniflorin may restore GR function and relieve neuroendocrine disorders caused by chronic stress by targeting HSP90AA1.

KEGG enrichment revealed that paeoniflorin is mainly involved in the PI3K-Akt, Rap1 and Ras signaling pathways. PI3K-Akt pathway is the core regulatory axis of nerve survival and apoptosis, and its abnormal inhibition is closely related to neuronal loss in depression [13]. Paeoniflora may inhibit apoptosis and promote neurogenesis by activating Akt, phosphorylating Bad, GSK-3β and other downstream targets [14]. The Rap1/Ras pathway is involved in neuron migration, axon orientation and synaptic formation, and its dysfunction is closely related to depression-related cognitive impairment [15]. The synergistic effect of these pathways reflects the advantage of "multi-pathway integrated regulation" of paeoniflorin.

This study systematically analyzed the multi-target network of Paeoniflorin in the treatment of depression for the first time, revealing its synergistic effect through multi-target-multi-pathway, and providing a theoretical framework for the desvelopment of novel antidepressant drugs based on Paeoniflorin. The research results also fit the characteristics of the "whole concept" of traditional Chinese medicine, and provide a methodological reference for the mechanism research of the active ingredients of traditional Chinese medicine.

Abbreviations

SSRIs	Serotonin Reuptake Inhibitors
PPI	Protein-Protein Interaction
GO	Gene Ontology
KEGG	Kyoto Encyclopedia
BP	Biological Processes
CC	Celular Components
MF	Molecular Functions
GR	Glucocorticoid Receptor

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Conflicts of Interest

The authors declare no competing financial interests or personal relationships that could bias this work. All contributions to the research, writing, and review were made independently and objectively.

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