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Short Communication

Research on the Mechanism of Shenghua Decoction in the Treatment of Common Postpartum Diseases of Women Based on Network Pharmacology

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Abstract

This paper mainly studies the mechanism of action of Shenghua Decoction base on network pharmacology. Additionally, it aims to verify the accuracy of the results of network pharmacology through related experiments. The results show that Shenghua Decoction may reduce the level of CRP, PTGS2, IL6 and TNF when used in common postpartum diseases of women. It is found that Shenghua decoction can treat gynecological diseases with blood stasis and blood deficiency syndrome mainly by influencing response to external stimulus, regulating multicellular organismal process, promoting wound healing, affecting inflammatory reaction, affecting coagulation and anticoagulation system, so as to play the role of nourishing blood, removing blood stasis and relieving pain. This paper provides a theoretical basis for further study of the components and mechanism of action of Shenghua Decoction in the treatment of common postpartum diseases of women.

Introduction

Shenghua Decoction (SHD) is a classic prescription for the clinical treatment of postpartum diseases of women. It was first derived from Fu Qingzhu's Obstetrics and Gynecology. It is composed of Angelica sinensis, Ligusticum chuanxiong, Peach kernel and dried ginger and roasted licorice. After childbirth, blood deficiency and Qi are weak. Cold evil is very easy to take advantage of the deficiency and coagulate blood stasis, which resulted in lochiorrhea. Blood stasis blocks the uterus, and obstruction leads to pain, which lead to abdominal pain in postpartum women [1]. Therefore, blood stasis, abdominal pain and continuous lochia are common symptoms of postpartum women. SHD is commonly used to treat postpartum or post pregnancy bleeding, postpartum abdominal pain, dysmenorrhea or irregular menstruation and other diseases [2-5].

Network pharmacology is to understand the interaction between drugs and the body from the perspective of improving or restoring the balance of biological network [6]. The core of network pharmacology is the network target. It refers to the key links in the biological network that can mechanically associate drugs and diseases and quantitatively represent the overall regulatory mechanism of drugs, including key molecules, key pathways or key modules [7]. This paper will analyze the key network target of SHD by using the method of network pharmacology, and elaborate the mechanism of SHD in treating women's postpartum diseases, and use animal experiments to verify the results.

Results and Discussion

We searched MalaCards (https://www.malacards.org/), China Knowledge Network (https://www.cnki.net/) and PubMed (https://www.ncbi.nlm.nih.gov/) for the targets related to dysmenorrhea, postpartum lochia, blood stasis and abdominal pain. Bioinformatics Analysis Tool for Molecular Mechanism of TCM (http://bionet.ncpsb.org.cn/batman-tcm/index.php) and Traditional Chinese Medicine Integrative Database (http://119.3.41.228:8000/tcmid/) were used to analyze and predict the targets of all molecules of TCM in SHD. The intersection of disease target and SHD prediction target is highly relevant targets for the treatment of common postpartum diseases in women, which were named SHD-GD (Table 1).

SHD-GD targets					
G6PD	EPO	CRP	IL6	TNF	HIF1A
XDH	CYGB	CAT	FGF23	SELP	CD34
ACO1	ACE	INS	GSR	SOD1	BMP2
KIT	GSTM1	ENPP3	GHRL	IREB2	ALAD
GGT1	IGF1	HMOX1	CYP1A1	NPPA	BMP6
ESR1	HSD11B1	HSD17B1	F2	PPARG	NR3C1
BCL2	EGFR	PTGS2	MTOR	CA2	PLAT
THBD	PROC	F9	F3	PROS1	TFPI
MTHFR	F10	PF4	F7	VKORC1	

Table 1: SHD-GD targets.

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Go and KEGG enrichment analysis of 53 high correlation targets in table 1 was carried out on Webgestalt platform (http://www.webgestalt.org/). Ten GO categories and seven KEGG channels were enriched, as shown in the figures 1&2 and shown in the tables 2&3. Through GO and KEGG enrichment analysis, it is found that Shenghua decoction can treat gynecological diseases with blood stasis and blood deficiency syndrome mainly by influencing response to external stimulus, regulating multicellular organismal process, promoting wound healing, affecting inflammatory reaction, affecting coagulation and anticoagulation system, so as to play the role of nourishing blood, removing blood stasis and relieving pain.

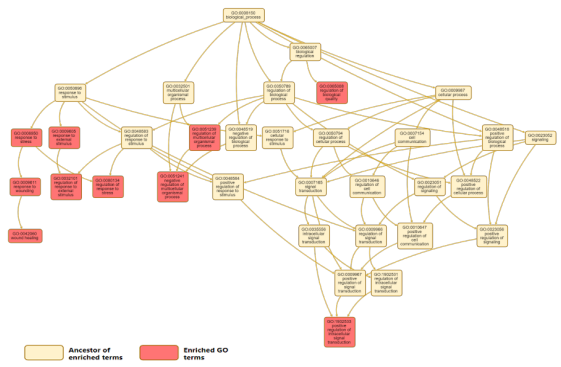

Figure 1: Go enrichment analysis of 53 high correlation targets.

Enriched GO categories (Top 10 categories)	
GO:0006950	response to stress
GO:0009605	response to external stimulus
GO:0009611	response to wounding
GO:0032101	regulation of response to external stimulus
GO:0051239	regulation of multicellular organismal process
GO:0051241	negative regulation of multicellular organismal process
GO:0065008	regulation of biological quality
GO:0080134	regulation of response to stress
GO:1902533	positive regulation of intracellular signal transduction
GO:0042060	wound healing

Table 2: Enriched GO categories of 53 high correlation targets.

The 53 determined composite targets are input into STRING to plot the PPI (Required score=0.4,FDR stringency=5%) network without unconnected targets. According to the characteristics of the network topology, Eigenvector Centrality (EC) selects the target with twice the median value, and Closeness Centrality (CC) and Betweenness Centrality (BC) select the target with the median value. The average EC of the network is 0.2145, and the averages of BC and CC are 48 and 0.65. Then, we inputted them into Cytoscape 3.6.1 software. After the network analysis with NetworkAnalyzer, seven core targets were selected as CAT, CRP, PTGS2, TNF, IL6, INS, IGF1 (Figure 3).

Next, we made female rat model with postpartum blood stasis symptoms. After the rats were given Shenghua Decoction by gavage

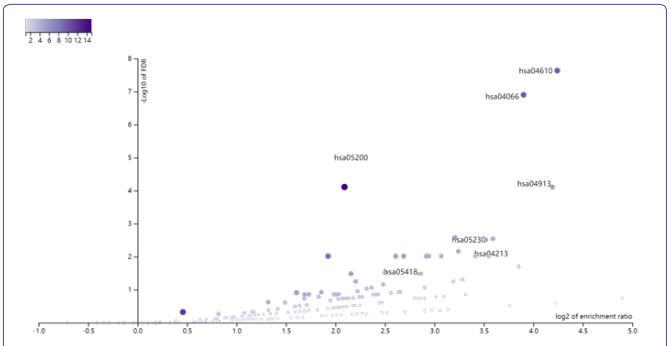

Figure 2: The volcano plot of KEGG enrichment analysis.

Pathway	Description
hsa04610	Complement and coagulation cascades
hsa04066	HIF-1 signaling pathway
hsa04913	Ovarian steroidogenesis
hsa05200	Pathways in cancer
hsa04213	Longevity regulating pathway
hsa05230	Central carbon metabolism in cancer
hsa05418	Fluid shear stress and atherosclerosis

Table 3: Enriched KEGG pathway of 53 high correlation targets.

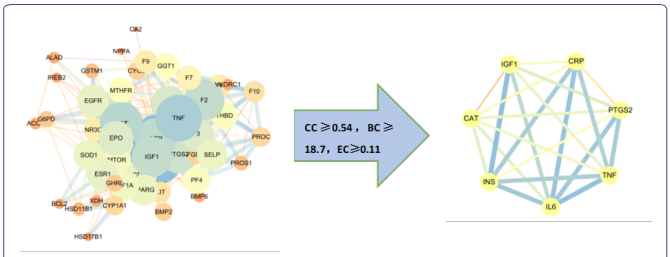

Figure 3: The PPI network diagram of 7 core targets was obtained by screening 53 SHD-GD targets through EC,BC,CC.

for one week, the contents of seven core target proteins in serum were measured to figure out whether Shenghua decoction has a regulatory effect on the core target predicted by network pharmacology.

The concentration of seven core target proteins (CRP, PTGS2, TNF, IL6, INS, CAT and IGF1) in rat serum was detected with an ELISA kit. The expressions of CRP, PTGS2, IL6 and TNF in the model group were significantly higher than those in the Normal group. This indicates that the target proteins of CRP, PTGS2, IL6 and TNF are highly expressed after delivery in rats. After using SHD, the levels of CRP, PTGS2, IL6, and TNF were significantly lower than those in the model group ($P<0.05$). In addition, the protein concentration was negatively correlated with the drug dose. This indicates that SHD has a significant regulatory effect on CRP and other proteins in postpartum rats, as shown in figure 4. The results of CAT and IGF1 target protein concentrations were not statistically significant, as shown in figure 5. The INS concentration was undetectable or lower than the detection limit.

By querying the target gene annotations, it was found that the targets of PTGS2 [8], CRP [9], IL6 [10], and TNF [11] down-regulated by SHD in rats were related targets of inflammatory response. This indicates that SHD may exert anti-inflammatory and analgesic effects

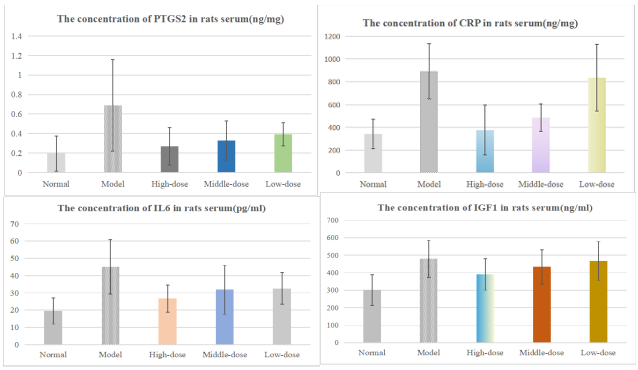

Figure 4: The concentration of PTGS2,CRP,IL6 and TNF in rats serum.

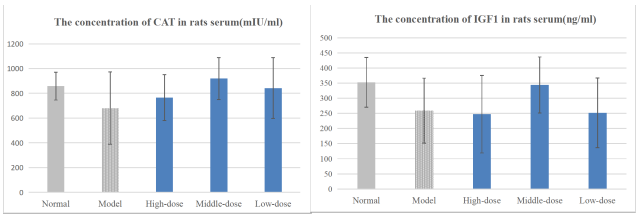

Figure 5: The concentration of CAT and IGF1 in rats serum.

by down-regulating inflammation-related targets, which is its main mechanism for the treatment of common gynecological diseases. Likewise, the activation of inflammatory biological network is closely related to the occurrence of gynecological diseases with blood deficiency and blood stasis syndrome. Although the protein determination results of CAT [12], IGF1 [13] and INS [14] were not significant, the expression of CAT and IGF1 in the model group were lower than those in the blank control group. Since IGF1, CAT and INS are all anemia-related targets; postpartum hemorrhage in rats is the reason for the lower expression of CAT and IGF1 proteins. The up-regulation effect of Shenghua Decoction on these three targets has not been sufficiently confirmed from the experimental data. This may be related to the method of model building in rats. The short time of postpartum hemorrhage in rats resulted in the symptoms of "blood stasis" and "blood deficiency" not significant enough. This cannot demonstrate the efficacy of Shenghua Decoction for nourishing blood and removing blood stasis. We will further optimize the rat blood deficiency model and validate the three targets.

Materials and Methods

Sexually mature Sprague-Dawley rats (6-8 weeks old; weighing 200-220 g were purchased from the Experimental Animal Center of Jiangxi University of Traditional Chinese Medicine (Jiangxi, China, approval No. SYXK (Gan) 2017-004). According to the ratio of angelica, chuanxiong, peach kernel, licorice and ginger (25:9:6:2:2) in the Fu Qingzhu's Obstetrics and Gynecology [15], the five medicinal materials were purchased from the Affiliated Hospital of Jiangxi University of Traditional Chinese Medicine. The five drugs were boiled together to prepare an aqueous solution SHD (drug concentration entration: 0.5g/ml).

Sixty 8-week-old sexually mature SD female rats and 25 male rats were selected, weighing 200-220 g. After 7 days of adaptive feeding, 10 female mice were randomly selected as blank control. The other 50 female mice and 25 male mice were caged together, and each cage was placed with 2 female mice and 1 male mouse. We checked the vaginal suppository or vaginal secretion smear of female mice on the morning of the second day after cage closure (within no more than 12 hours from the cage closure). Those who are positive are regarded as pregnant rats and are raised separately, and those who are negative are kept in cages until the number of pregnant female rats reaches more than 40. After conception, the female mice were raised as usual until they gave birth to pups, and were immediately divided into groups (model group, Shenghua Decoction high-dose group, Shenghua Decoction medium-dose group, Shenghua Decoction low-dose group). Ten mice in each group. In order to make the rats reach the disease state of blood stasis and blood deficiency, the rats in the model group and the medication group were placed in 0-2°C water for 20 minutes every morning, and then administered by gavage in the afternoon.

The rats in the sample group were intragastrically administered with high, medium and low doses (2.26g/d, 1.13g/d, 0.57g/d) of Shenghua Decoction in the morning for 7 days. Meanwhile, the rats in the blank control group were given normal saline for 7 days. The model group rats were given normal saline for 7 days after delivery as well. Anatomy was performed the next day, about 3-5ml of abdominal aortic blood was taken, and it was allowed to stand for 10-20 minutes. Serum was obtained after centrifugation at 3000 r·min-1 for 15 min.

We used the ELISA method to detect the concentration of the target protein. The kit used was produced by CUSABIO Company (CUSABIO, Wuhan, Hubei, China), and was implemented in accordance with the kit operating specifications. The experiment adopts double antibody sandwich ABC-ELISA method, the standard is diluted to 7 concentrations, and the standard curve is plotted. The sample dilution was used as a blank control. We added different concentrations of standards, standard dilutions, and samples to be tested into 96-well plates coated with CRP, PTGS2, TNF, IL6, INS, CAT and IGF1 monoclonal antibodies. Then, we added biotinylated secondary antibody and TMB substrate for color development. Finally, we measured the absorbance (OD value) with a microplate reader at 450nm wavelength to calculate the sample concentration.

Competing Interest's Statement

There is no conflict of interest.

Foundation

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