Network Pharmacology Identifies the Mechanisms of Action of TaohongSiwu Decoction Against Essential Hypertension

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF   Tian-hao Liu*
CDE   Wei-hao Chen*
DEF   Xu-dong Chen*
BC   Qiu-er Liang
DE   Wen-cong Tao
DF   Zhen Jin
EFG   Ya Xiao
ADEFG   Li-guo Chen

Chinese Medicine College, Jinan University, Guangzhou, Guangdong, P.R. China

Corresponding Authors:
Source of support:

* Tian-hao Liu, Wei-hao Chen, Xu-dong Chen contributed to this study equally
Li-guo Chen, e-mail: tchenly@jnu.edu.cn, Ya Xiao, e-mail: 404271426@qq.com

Background: TaohongSiwu decoction (THSWT), a traditional herbal formula, has been used to treat cardiovascular and cerebrovascular diseases such as essential hypertension (EH) in China. However, the pharmacological mechanism is not clear. To investigate the mechanisms of THSWT in the treatment of EH, we performed compounds, targets prediction and network analysis using a network pharmacology method.

Material/Methods: We selected chemical constituents and targets of THSWT according to TCMSP and UniProtKB databases and collected therapeutic targets on EH from Online Mendelian Inheritance in Man (OMIM), Drugbank and DisGeNET databases. The protein-protein interaction (PPI) was analyzed by using String database. Then network was constructed by using Cytoscape_v3.7.1, and the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment was performed by using Database for Annotation, Visualization and Integrated Discovery (DAVID) software.

Results: The results of our network pharmacology research showed that the THSWT, composed of 6 Chinese herbs, contained 15 compounds, and 23 genes regulated the main signaling pathways related to EH. Moreover, the PPI network based on targets of THSWT on EH revealed the interaction relationship between targets. These core compounds were 6 of the 15 disease-related compounds in the network, kaempferol, quercetin, luteolin, Myricanone, beta-sitosterol, baicalein, and the core genes contained *ADRB2*, *CALM1*, *HMOX1*, *JUN*, *PPARG*, and *VEGFA*, which were regulated by more than 3 compounds and significantly associated with Calcium signaling pathway, cGMP-PKG signaling pathway, cAMP signaling pathway, PI3K-Akt signaling pathway, Rap1 signaling pathway, and Ras signaling pathway.

Conclusions: This network pharmacological study can reveal potential mechanisms of multi-target and multi-component THSWT in the treatment of EH, provide a scientific basis for studying the mechanism.

MeSH Keywords: Computer Communication Networks • Hypertension • Phenylephrine

Abbreviation: THSWT – TaohongSiwu decoction; EH – essential hypertension; TCM – Traditional Chinese medicine; OB – oral bioavailability; DL – drug-likeness; OMIM – Online Mendelian Inheritance in Man; DAVID – Database for Annotation, Visualization and Integrated Discovery; KEGG – Kyoto Encyclopedia of Genes and Genomes

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/920682

📄 2803   ▦ 1   📊 6   📚 54

Background

Essential hypertension (EH) is a cardiovascular syndrome characterized by elevated systemic circulatory arterial pressure and caused by the combination of genetic and environmental factors. The survey showed that 30% of adults between the ages of 30 and 45 years old suffered from high blood pressure, 13.5% of the world's 7.6 million premature deaths are caused by high blood pressure, about 54% of stroke patients and 47% of ischemic heart disease is caused by high blood pressure [1]. The incidence of EH accounts for more than 90% of the hypertension population. Wang et al. found that the prevalence rate of hypertension in adults over 18 years old in China was 23.2%, the number of hypertension patients was 245 million, and the prevalence rate of normal high blood pressure was 41.3%, and the number of patients was 435 million [2]. High blood pressure has become the leading risk factor of stroke, coronary heart disease, and other cardiovascular, and cerebrovascular diseases in China.

The harm of EH is not only the increase of arterial pressure. More dangerous is that high blood pressure can also harm the corresponding target organs, resulting in a series of functional and organic complex lesions. Therefore, the American Society of Hypertension (ASH) pointed out that lowering blood pressure was no longer the only goal, whereas as a cardiovascular syndrome, EH was closely related to other cardiovascular-related diseases and can be treated by combination therapy [3,4]. Traditional Chinese medicine (TCM) has the advantages of integrity, multi-target, multi-channel and so on [5]. Furthermore, it is widely used in the treatment of EH and is mainly based on the method of promoting blood circulation and removing blood stasis.

TaohongSiwu decoction (TaohongSiwu Tang, THSWT) was first reported in Wuqian'sbook named "Yizhongjinjian" in the Qing Dynasty and is often used to treat cardiovascular and cerebrovascular diseases such as EH in China. "If the blood has more blood clots, the color purple sticky, is the internal blood stasis, with Siwu Tang and *Persicae Semen*, *CarthamiFlos* broke blood stasis, named THSWT". Studies have shown that THSWT has a variety of effects on cardiovascular diseases, and through a variety of mechanisms. For instance, THSWT could treat acute blood stasis model rats through regulating amino acid and lipid metabolism [6] and could decrease infarct volume and improve neurological function in the rat of a stroke model [7]. THSWT is composed of 6 traditional Chinese medicines, which contains *Persicae Semen* (Taoren), *CarthamiFlos* (Honghua), *AngelicaeSinensis Radix* (Danggui), *Rehmanniae Radix Praeparata* (Shudihuang), *ChuanxiongRhizoma* (Chuanxiong), and *Paeoniae Radix Alba* (Baishao).

Network pharmacology is one of the most popular research methods in the field of Chinese medicine. The results of network analysis showed that different proteins or genes could regulate the same diseases, and some proteins could also regulate a variety of diseases [8]. Moreover, network pharmacology can analyze the mechanisms of multi-component action of Chinese herbal compounds as a whole [9,10]. In addition, it can also independently present the "component-target-pathway" related to a particular disease, and its systematic and holistic characteristics are consistent with the principle of holistic view and syndrome differentiation and treatment of Chinese medicines, which can effectively promote the in-depth study of Chinese herbal compound prescription [11,12]. It is a new way to reveal the material basis and molecular mechanisms of the efficacy of TCM by network pharmacology. Network pharmacological herb targets are found through Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP), which is a unique systems pharmacology platform of Chinese herbal medicines. It captures the relationships between drugs, targets, and diseases and the disease-related targets through Online Mendelian Inheritance in Man (OMIM) database, Drugbank and DisGeNET, then the common targets are selected and the protein-protein interaction (PPI) data were integrated and derived from String database. After that, enriched-related signal pathways marked by Database for Annotation, Visualization and Integrated Discovery (DAVID), meanwhile, network are constructed using Cytoscape software.

Although the chemical constituents of THSWT have been shown, the main active components and target-level signaling pathways of THSWT in the treatment of EH have not been elucidated. Therefore, this study used the method of network pharmacology to explore the mechanisms of THSWT in the treatment of EH, in order to provide a theoretical basis for further experimental research. The research was conducted in 3 steps: 1) THSWT and EH related targets were predicted by databases; 2) the related network relationships were constructed using the software of Cytoscape_v3.7.1; and 3) network analysis and target verification were completed. The flowchart is shown in Figure 1.

Material and Methods

The chemical database construction

The herbs and chemical ingredients were searched from Traditional Chinese Medicine Systems Pharmacology database (TCMSP, *http://lsp.nwu.edu.cn/tcmsp.php*, updated on December 25, 2018), which is considered as an herbal encyclopedia can supply herbal ingredients information [13,14]. TCMSP is famous for its unique pharmacology platform for Chinese herbs containing the herbal ingredients chemical structural
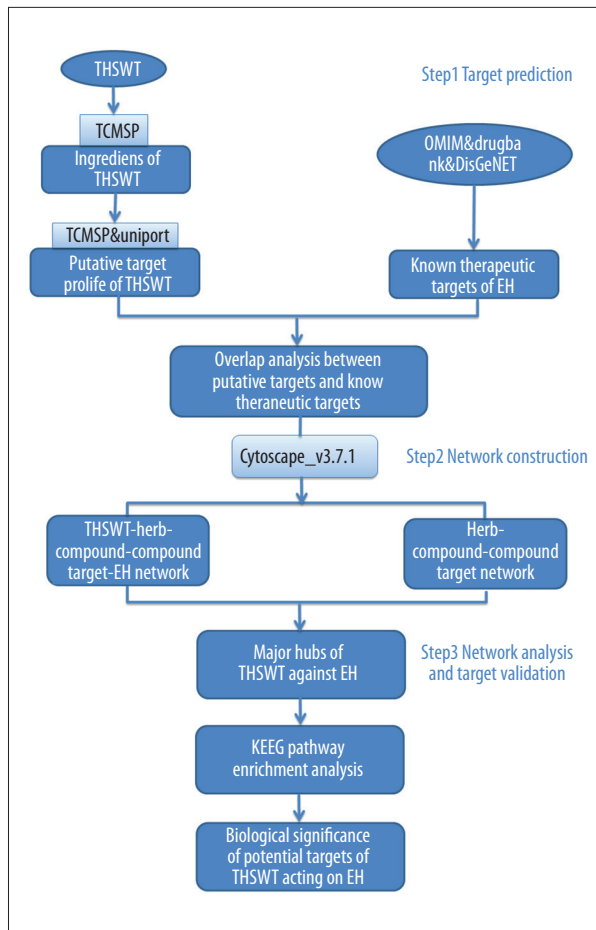
Figure 1. The flowchart for the treatment of EH (essential hypertension) by network pharmacology.

data, oral bioavailability, drug targets, as well as their relationships with diseases [14].

Constituents and targets of THSWT

Herbal medicines formula often contains even up to thousands of chemical compounds, and only a part of them exhibit favorable pharmacokinetics (the absorption, distribution, metabolism, and excretion (ADME) properties of a drug) with the potential of a biological effect. All compounds were selected using TCMSP and screened using the ADME system in this research [15,16]. The evaluation of oral bioavailability (OB) and drug-likeness (DL) included in the ADME system were used to screen compounds of THSWT with OB ≥30% and DL ≥0.18 according to the suggested drug screening criteria of TCMSP [17,18].

The putative target of the ingredients within THSWT

The compound targets of each herb found in THSWT were collected from TCMSP and UniProtKB [19,20] (*http://www.uniprot.org/*,

updated on December 27, 2018) was employed to identify the standard compound targets. UniProtKB is regarded as a scientific community which always provides a high-quality and accessible resource of detailed protein information [19,20]. The collected protein names were entered into UniProtKB with the organism selected as "Homo sapiens." The compound targets having no satisfaction with the selection were deleted. Therefore, we obtained the compound targets for each herb in THSWT.

The prediction of known therapeutic targets on EH

The 3 databases from which we collected therapeutic targets on EH are as follows: 1) Online Mendelian Inheritance in Man (OMIM) database [21,22] (*https://omim.org/*, updated on December 29, 2018), which was famous for its knowledge related genes with diseases. 2) Drugbank [23,24] (*https://www.drugbank.ca/*, updated on December 30, 2018), which was used to find specific drug information with drug targets. 3) DisGeNET [25,26] (*http://www.disgenet.org/*, updated on December 30, 2018), which contained detailed genes with diseases. We searched the data from the three databases using the same keyword "Essential Hypertension".

Target protein interaction analysis

After the putative targets of the ingredients within THSWT and the known therapeutic targets on EH combined and connected, the protein-protein interaction (PPI) data were integrated and derived from String (*https://string-db.org*, updated on December 13, 2019) which is an update online database, known as revealing target protein interaction analysis.

Network construction and pathway enrichment analysis

Herb-Compound-Compound Target Network and THSWT-Herb-Compound-Compound Target-EH Network were then constructed by using Cytoscape_v3.7.1. Besides, functional annotation of genes-related EH in THSWT was carried out by using Database for Annotation, Visualization and Integrated Discovery (DAVID) ver. 6.8 (*https://david.ncifcrf.gov/*, updated on December 31, 2018), and enrichment analysis of Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway was performed. KEGG (updated on December 31, 2018) was established in 1995 by the bioinformatics center of Kyoto University, Japan, and could be used to predict gene enrichment pathways [27,28]. The Advanced Bubble Diagram was performed by using the OmicShare tools [29,30], a free online platform for data analysis (*http://www.omicshare.com/tools*).
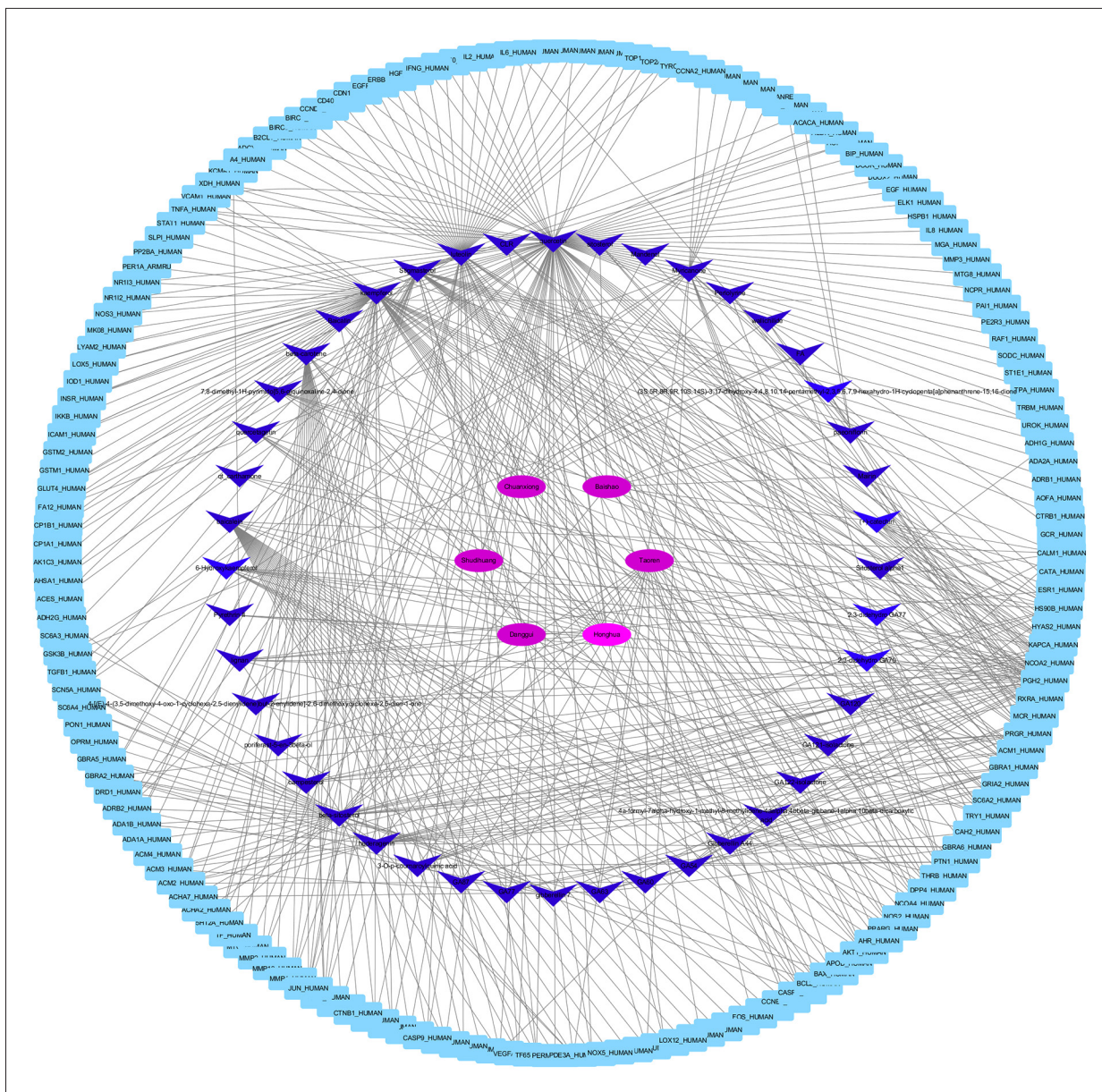
Figure 2. Interaction network to indicate herb-compound-compound target composited of 6 Chinese medicines (purple), 61 compounds (green) and 170 targets (blue).

Results

Compounds in THSWT

All compounds of Chinese herbs in THSWT were screened by TCMSP database according to OB ≥30% and DL ≥0.18. Finally, we found 23 compounds in Taoren, 22 compounds in Honghua, 2 compounds in Danggui, 2 compounds in Shudihuang, 7 compounds in Chuanxiong, and 13 compounds in Baishao. There was a total of 61 compounds identified in 6 kinds of Chinese herbs in THSWT (Supplementary Table 1).

Target compounds and target genes

According to the target screening of the compounds, we found that there were 170 target genes in 6 Chinese herbs in THSWT. There were 45 targets in Taoren, 159 targets in Honghua, 46 targets in Danggui, 29 targets in Shudihuang, 23 targets in Chuanxiong, and 78 targets in Baishao, respectively. The network relationship between 6 Chinese herbs, 61 compounds, and 170 compound-related targets are shown in Figure 2, which showed the interaction of targets contained 221 nodes and 531 edges. The interaction of targets is vital in herbal interaction. Therefore, the interaction network indicated the
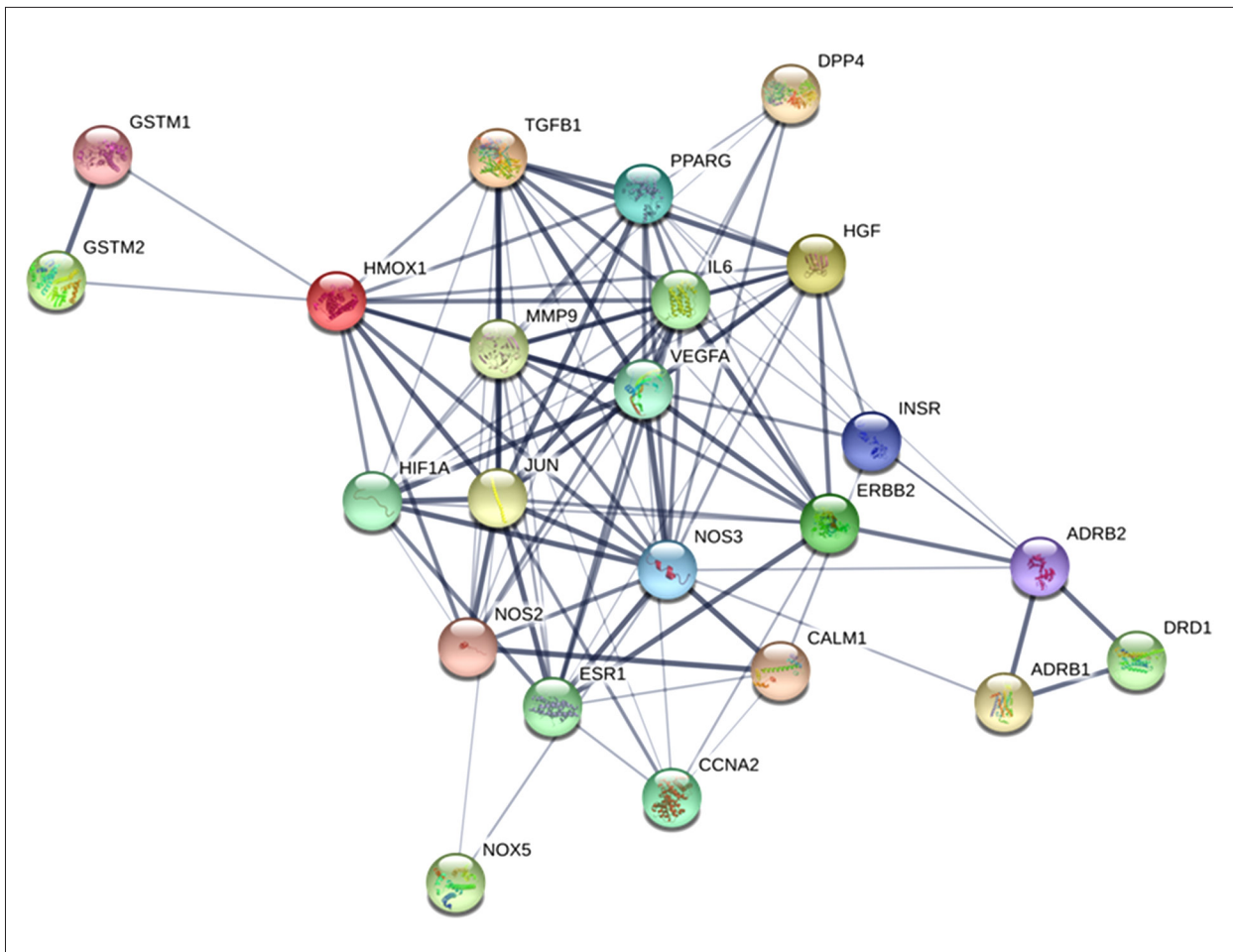
Figure 3. The PPI network based on targets of THSWT on EH. Network nodes represent different proteins. Edges represent protein-protein associations, the line thickness indicates the strength of data support. PPI – protein–protein interaction; THSWT – TaohongSiwu decoction; EH – essential hypertension.

relationship of the herb-compound-compound target of THSWT. Also, the predicted targets for herbs in THSWT are shown in Supplementary Table 2.

Linkage of compounds targets and target genes related to EH

Through the prediction of EH targets in the databases, we found 690 gene targets related to EH (Supplementary Table 3). Furthermore, a total of 23 targets related to EH were screened in 6 herbs of THSWT (Supplementary Table 4). Moreover, we used string to illustrate the interaction between these 23 targets. As show in Figure 3, there were 23 nodes and 103 edges, and the average node degree was 8.96, meanwhile, the avg. local clustering coefficient was 0.742. In addition, the P-value <0.001 showed that the PPI enrichment was of great significance. There was the greatest correlation between VEGFA and HIF1A, many other correlations are shown in the Supplementary Table 5. The network of "THSWT-Compounds-Targets-EH,"

including 46 nodes and 185 edges, as established in Figure 4, which exhibited 1 formula, 15 compounds, and 23 targets related to EH. We found that 6 of the 15 compounds, such as kaempferol, quercetin, luteolin, Myricanone, beta-sitosterol and baicalein, regulated more than 3 genes. At last, 6 of the 23 genes (*ADRB2*, *CALM1*, *HMOX1*, *JUN*, *PPARG*, and *VEGFA*), were regulated by more than 3 herbal compounds at the same time in this network pharmacological study. Therefore, these 6 compounds and 6 genes may be the core nodes.

Pathway Enrichment analysis of potential target genes

Based on the pathway enrichment results of 23 target genes, we found the top 20 pathways, as shown in Figure 5. The enrichment pathways were mainly concentrated in Calcium signaling pathway, hepatitis B, cGMP-PKG signaling pathway, and other pathways. According to the results of KEGG analysis, the main pathways with $P<0.05$, which were considered as significant enrichment effects of the representative pathway, more than
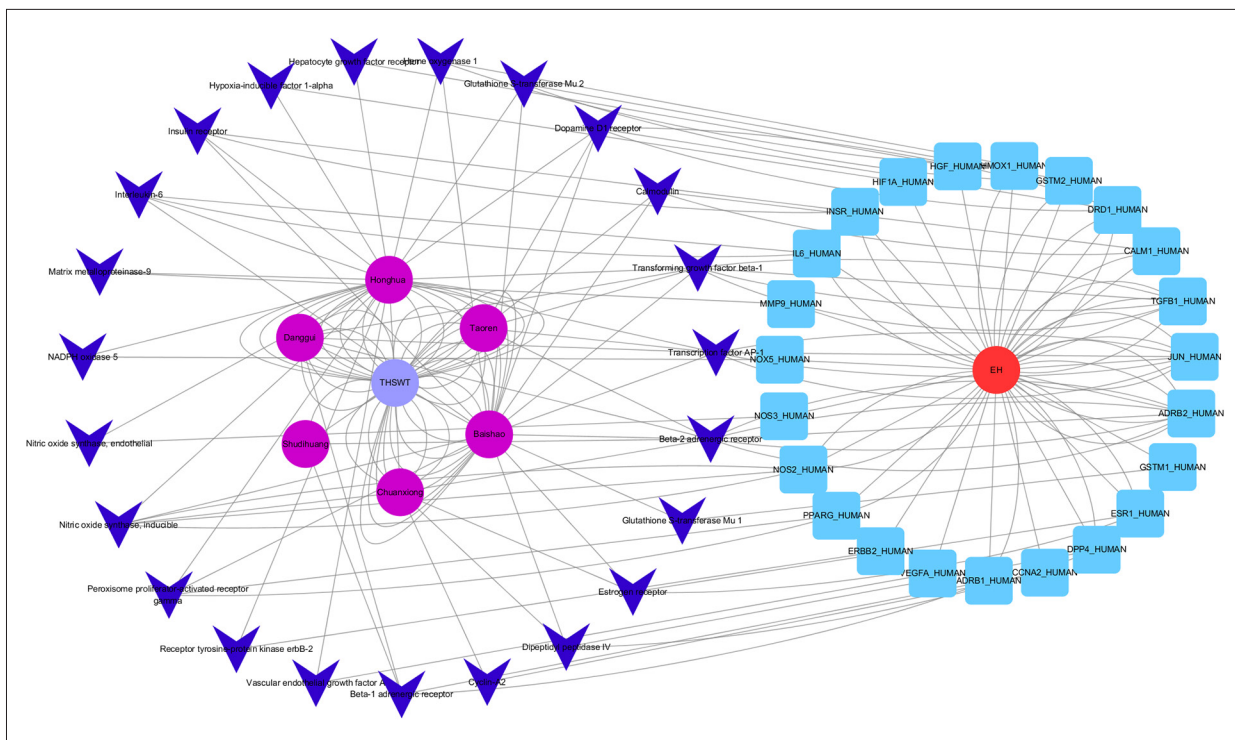
Figure 4. THSWT-herb-compound-compound target-EH Network with 1 formula (brown), 6 Chinese medicines (purple), 15 compounds (green), 23 targets (blue) and 1 kind of disease (red). THSWT – TaohongSiwu decoction; EH – essential hypertension.
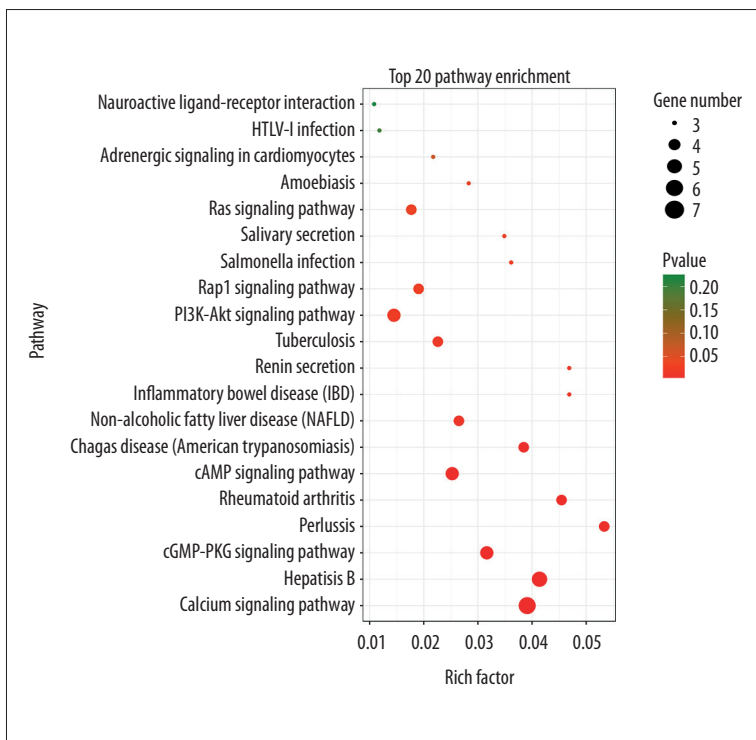

Figure 5. Top 20 pathways enriched based on target genes (the abscissa is the rich factor, the ordinate is pathway name, the number of genes is represented by the size of the dot and the color represents the *P* value).

Table 1. Functions of potential target genes based on Kyoto Encyclopedia of Genes and Genomes pathway analysis.

ID	Term	P value	Genes
hsa04020	Calcium signaling pathway	1.51E-05	CALM1, ADRB2, NOS3, ERBB2, NOS2, DRD1, ADRB1
hsa04022	cGMP-PKG signaling pathway	1.42E-03	CALM1, ADRB2, NOS3, INSR, ADRB1
hsa04024	cAMP signaling pathway	3.24E-03	CALM1, JUN, ADRB2, DRD1, ADRB1
hsa04151	PI3K-Akt signaling pathway	2.22E-02	HGF, NOS3, VEGFA, INSR, IL6
hsa04015	Rap1 signaling pathway	2.82E-02	CALM1, HGF, VEGFA, INSR
hsa04014	Ras signaling pathway	3.40E-02	CALM1, HGF, VEGFA, INSR
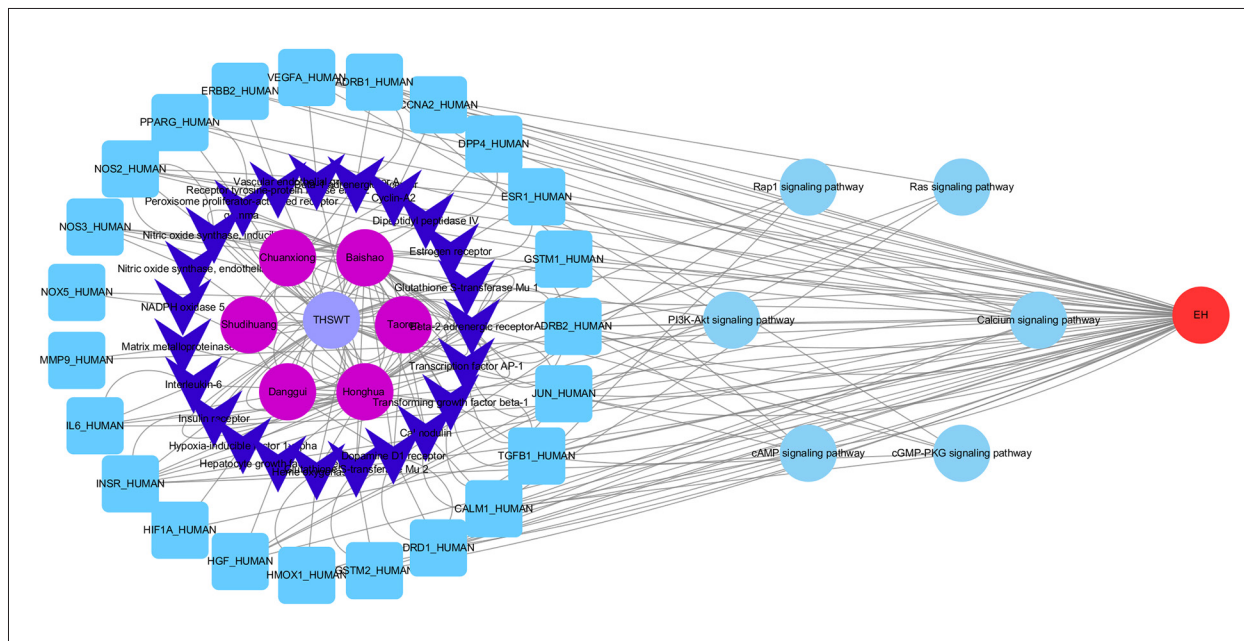
Figure 6. The THSWT-herb-compound-compound target-EH Network and main pathways with 1 formula (brown), 6 Chinese medicines (purple), 15 compounds (green), 23 targets (blue square) 5 pathways (blue circle), and 1 kind of disease (red). THSWT – TaohongSiwu decoction; EH – essential hypertension.

3 enriched genes listed in Table 1. Therefore, the mechanisms of THSWT against EH may be mainly related to Calcium signaling pathway, cGMP-PKG signaling pathway, cAMP signaling pathway, PI3K-Akt signaling pathway, and Rap1 signaling pathway. At last, the merged network was constructed, indicated the possible mechanisms by which THSWT against EH as shown in Figure 6.

Discussion

Network pharmacological analysis of Chinese medicines is becoming a research method to study the effect of Chinese medicines on diseases, in order to reveal the complex components and unknown targets [8,9,11]. Although THSWT is often used in the treatment of EH in China, the mechanism is not clear.

Therefore, this study was used to study the components and targets of the effect of THSWT on EH through the method of network pharmacology.

The results of our network pharmacology showed that the THSWT, composed of 6 Chinese herbal medicines, contained 15 compounds, and 23 genes regulated the main signaling pathways related to EH. Moreover, the PPI network based on targets of THSWT on EH revealed the interaction relationship between targets. These core genes were *ADRB2, CALM1, HMOX1, JUN, PPARG, VEGFA*, which were regulated by more than 3 compounds and significantly associated with Calcium signaling pathway, cGMP-PKG signaling pathway, cAMP signaling pathway, PI3K-Akt signaling pathway, Rap1 signaling pathway, and Ras signaling pathway.

Six of the 15 disease-related compounds in the network, kaempferol, quercetin, luteolin, Myricanone, beta-sitosterol, baicalein, were thought to be associated with cardiovascular diseases. Kaempferol was the main component of Honghua and Baishao, which has the functions of reducing lipid, anti-oxidation, and anti-inflammation, and considered to be related to cardiovascular diseases [31]. Quercetin in the formula was mainly in Honghua, considered to exist mainly in Chinese herbal medicines, fruits and vegetables, is a natural flavonoid active substance, in anti-inflammatory, antioxidant, and anti-cancer effects were significant [32,33]. Luteolin mainly existed in Honghua, which has many functions, such as anti-inflammation, anti-allergy, anti-tumor, anti-fibrosis, and so on [13,34,35]. Myricanone mainly existed in Chuanxiong and has an obvious anti-tumor effect [36,37]. Beta-sitosterol mainly existed in Taoren, Honghua, Danggui, and Baishao, which is considered to have the function of lowering blood lipids and has a protective effect on cardiovascular and cerebrovascular diseases [38,39]. Baicalein exists in Honghua and has many pharmacological effects, such as anti-tumor, anti-bacterial, anti-obesity, anti-oxidation etc. [40,41] In general, our research shows that the main components of THSWT play an important role in regulating EH.

In addition, these 6 significant target genes were associated with EH and other diseases. The *ADRB2* gene can increase the risk of hypertension, and the systolic blood pressure level of its carriers is high [42]. *CALMI* gene plays an important role in the intracellular Calcium signaling pathway [43]. As a marker of adipose tissue dysfunction induced by iron excess, *HMOX1* gene can affect the glucose uptake and respiratory ability of human adipocytes [44]. The *JUN* gene plays an important role in immune anti-inflammation [45,46]. The *PPARG* gene is considered to regulate fatty acid metabolism gene networks [47]. The *VEGFA* gene mainly mediates angiogenesis and metabolism [48]. Besides, there were the interaction correlations between these targets, which is very important in drug interaction.

The results of KEGG revealed that 5 signaling pathways (Calcium signaling pathway, cGMP-PKG signaling pathway, cAMP signaling pathway, PI3K-Akt signaling pathway, Rap1 signaling pathway, and Ras signaling pathway) might be the main signaling pathways related to EH in this network study. The Calcium signaling pathway can increase calcium load and cause cardiovascular diseases such as arrhythmia [49]. The cGMP-PKG signaling pathway regulates vascular circulation and induces arterial relaxation [50].The cAMP signaling pathway is one of the signals activate G-protein in intracellular information transmission and activator by binding to specific receptors on the cell membrane, and then promote the transformation of adenosine triphosphate into cAMP [51]. The PI3K-Akt signaling pathway promotes the expression of PI3K, Akt proteins and activates thrombopoietin receptor-2, thus promoting

neovascularization [52]. The Rap1 signaling pathway promotes apoptosis and protects myocardial ischemia-reperfusion injury [53]. The Ras signaling pathway induced the increase of intracellular reactive oxygen species (Ros) and apoptosis of vascular smooth muscle cells (VSMCs) [54]. Therefore, our results suggest that these 5 signaling pathways might be the mechanisms of THSWT affecting EH.

Network pharmacology is indeed considered to be a new method to study the relationship between Chinese herbal compounds and diseases. The network pharmacology revealed the composition and targets of THSWT, as well as EH-related genes and targets, and bioinformatics was used to study the main enrichment pathways. Our study predicted the potential therapeutic targets of THSWT on EH, revealed its action on the main pathways through core compounds and genes, which explained the mechanisms of THSWT on EH, and provided scientific evidence for THSWT to EH. According to our findings from the present study, further studies should be undertaken to research the relationship between agents used about THSWT in EH. Moreover, the validation of molecular levels of our findings is necessary for the future. However, the main limitation of this study is the lack of experimental verification. In the future, it is of great significance to conduct a further systematic study of THSWT, to investigate the detailed mechanisms.

Conclusions

This study aimed to investigate the mechanisms of THSWT in the treatment of EH, we performed compounds, targets prediction and network analysis by using a network pharmacology method. We analyzed the composition and targets of THSWT by network pharmacology, screened 61 compounds and 170 genes, and finally found 15 compounds and 23 genes related to EH through further screening. THSWT resisted EH mainly by 6 key compounds, such as kaempferol, quercetin, luteolin, Myricanone, beta-sitosterol and baicalein, and the 6 key target genes (*ADRB2*, *CALM1*, *HMOX1*, *JUN*, *PPARG*, and *VEGFA*), which might be through 5 main signaling pathways (Calcium signaling pathway, cGMP-PKG signaling pathway, cAMP signaling pathway, PI3K-Akt signaling pathway, Rap1 signaling pathway, and Ras signaling pathway) related to EH in this network study. This network pharmacological study can reveal potential mechanisms of multi-target and multi-component THSWT in the treatment of EH, provide a scientific basis for studying the mechanism.

Data availability

The data used to support the study are included within the article and can be made freely available. Any questions of data will be considered to be answered by the corresponding author.

Acknowledgements

Conflicts of interest

Supplementary Data

Supplementary Table 1. Predicted compounds for herbs in THSWT.

Supplementary Table 2. Predicted targets for herbs in THSWT.

Supplementary Table 3. Known therapeutic targets for essential hypertension.

Supplementary Table 4. Total target genes in THSWT for EH.

Supplementary Table 5. String interactions of total in targets.

Supplementary/raw data available from the corresponding author on request.

References:

1. Mancia G, Fagard R, Narkiewicz K et al: 2013 ESH/ESC Guidelines for the management of arterial hypertension. Blood Pressure, 2013; 22(4): 193–278

2. Wang Z, Chen Z, Zhang L et al: Status of hypertension in China results from the China Hypertension Survey, 2012–2015. Circulation, 2018; 137(22): 22: 2344–56

3. Aalbers J: Combination therapy in hypertension: new recommendations. Cardiovasc J Afr, 2010; 21(2): 120

4. Mancusi C, Losi MA, Izzo R et al: Higher pulse pressure and risk for cardiovascular events in patients with essential hypertension: The Campania Salute Network. Eur J Prev Cardiol, 2018; 25(3): 235–43

5. Liu R, Runyon RS, Wang Y et al: Deciphering ancient combinatorial formulas: The Shexiang Baoxin pill. Science, 2015; 347(6219): S40–42

6. Zhang X, Li P, Hua Y et al: Urinary metabolomics study the mechanism of Taohong Siwu Decoction intervention in acute blood stasis model rats based on liquid chromatography coupled to quadrupole time-of-flight mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci, 2018; 1074: 51–60

7. Li L, Yang N, Nin L et al: Chinese herbal medicine formula Tao Hong Si Wu decoction protects against cerebral ischemia-reperfusion injury via PI3K/Akt and the Nrf2 signaling pathway. J Nat Med, 2015; 69(1): 76–85

8. Liang X, Li H, Li S: A novel network pharmacology approach to analyse traditional herbal formulae: The Liu-Wei-Di-Huang pill as a case study. Mol BioSyst, 2014; 10(5)5: 1014–22

9. Huang T, Ning Z, Hu D et al: Uncovering the mechanisms of Chinese herbal medicine (MaZiRenWan) for functional constipation by focused network pharmacology approach. Front Pharmacol, 2018; 9: 270

10. Wang YY, Bai H, Zhang RZ et al: Predicting new indications of compounds with a network pharmacology approach: Liuwei Dihuang Wan as a case study. Oncotarget, 2017; 8(55): 93957–68

11. Zhao M, Chen Y, Wang C et al: Systems pharmacology dissection of multi-scale mechanisms of action of *Huo-Xiang-Zheng-Qi* formula for the treatment of gastrointestinal diseases. Front Pharmacol, 2019; 9: 1448

12. Lyu M, Zhou Z, Wang X et al: Network pharmacology-guided development of a novel integrative regimen to prevent acute graft-*vs.*-host disease. Front Pharmacol, 2018; 9: 1440

13. Ru J, Li, P Wang J et al: TCMSP: A database of systems pharmacology for drug discovery from herbal medicines. J Cheminform, 2014; 6: 13

14. Zhong Y, Luo J, Tang T et al: Exploring pharmacological mechanisms of Xuefu Zhuyu decoction in the treatment of traumatic brain injury via a network pharmacology approach. Evid Based Complement Alternat Med, 2018; 2018: 8916938

15. Yamashita F, Hashida M: In silico approaches for predicting ADME properties of drugs. Drug Metab Pharmacokinet, 2004; 19(5): 327–38

16. Tao W, Xu X, Wang X et al: Network pharmacology-based prediction of the active ingredients and potential targets of Chinese herbal Radix Curcumae formula for application to cardiovascular disease. J Ethnopharmacol, 2013; 145(1): 1–10

17. Wang N, Zheng Y, Gu J et al: Network-pharmacology-based validation of TAMS/CXCL-1 as key mediator of XIAOPI formula preventing breast cancer development and metastasis. Sci Rep, 2017; 7(1): 14513

18. Xu X, Zhang W, Huang C et al: A novel chemometric method for the prediction of human oral bioavailability. Int J Mol Sci, 2012; 13(6): 6964–82

19. Southan C, Sharman JL, Benson HE et al: The APHRA/BPS Guide to Pharmacology in 2016: Towards curated quantitative interactions between 1300 protein targets and 6000 ligands. Nucleic Acids Res, 2016; 44(D1): D1054–68

20. Breuza L, Poux S, Estreicher A et al: The UniProtKB guide to the human proteome. Database (Oxford), 2016; 2016: pii: bav120

21. Lee-Barber J, Kulo V, Lehmann H et al: Bioinformatics for medical students: A 5-year experience using OMIM(R) in medical student education. Genet Med, 2019; 21: 493–97

22. Hartley T, Balci TB, Rojas SK et al: The unsolved rare genetic disease atlas? An analysis of the unexplained phenotypic descriptions in OMIM(R). Am J Med Genet C Semin Med Genet, 2018; 178(4): 458–63

23. Wishart DS, Wu A: Using DrugBank for in silico drug exploration and discovery. Curr Protoc Bioinformatics, 2016; 54: 14

24. Van Den Driessche G, Fourches D: Adverse drug reactions triggered by the common HLA-B*57: 01 variant: Virtual screening of DrugBank using 3D molecular docking. J Cheminform, 2018; 10(1): 3

25. Piñero J, Queralt-Rosinach N, Bravo À et al: DisGeNET: A discovery platform for the dynamical exploration of human diseases and their genes. Database (Oxford), 2015; 2015: bav028

26. Piñero J, Bravo À, Queralt-Rosinach N et al: DisGeNET: A comprehensive platform integrating information on human disease-associated genes and variants. Nucleic Acids Res, 2017; 45(D1): D833–39

27. Zhang Y, Wu Z, Shu Y et al: A novel bioactive vaterite-containing tricalcium silicate bone cement by self hydration synthesis and its biological properties. Mater Sci Eng C Mater Biol Appl, 2017; 79: 23–29

28. Di S, Han L, Wang Q et al: A network pharmacology approach to uncover the mechanisms of Shen-Qi-Di-Huang decoction against diabetic nephropathy. Evid Based Complement Alternat Med, 2018; 2018: 7043402

29. You J, Sun L, Yang X et al: Regulatory protein SrpA controls phage infection and core cellular processes in *Pseudomonas aeruginosa*. Nat Commun, 2018; 9(1): 1846

30. Qin Y, Wei H, Sun H et al: Proteomic analysis of differences in fiber development between wild and cultivated *Gossypium hirsutum* L. J Proteome Res, 2017; 16(8): 2811–24

31. Xiao Y, Xin L, Li L et al: Quercetin and kaempferol increase the intestinal absorption of isorhamnetin coexisting in *Elaeagnus rhamnoides* (L.) A. Nelson (Elaeagnaceae) extracts via regulating multidrug resistance-associated protein 2. Phytomedicine, 2019; 53: 154–62

32. Karimian M, Zandi M, Sanjabi MR et al: Effects of grape seed extract, quercetin and vitamin C on ovine oocyte maturation and subsequent embryonic development. Cell Mol Biol, 2018; 64(4): 98

33. Huang Z, Chen P, Su W et al: Antioxidant activity and hepatoprotective potential of quercetin 7-rhamnoside *in vitro* and *in vivo*. Molecules, 2018; 23: 11885

34. Zhang X, Du Q, Yang Y et al: The protective effect of Luteolin on myocardial ischemia/reperfusion (I/R) injury through TLR4/NF-kappa B/NLRP3 inflammasome pathway. Biomed Pharmacother, 2017; 91: 1042–52

This work is licensed under Creative Common Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

e920682-9

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

35. Chen G, Shen H, Zang L et al: Protective effect of luteolin on skin ischemia-reperfusion injury through an AKT-dependent mechanism. Int J Mol Med, 2018; 42(6): 3073–82

36. Paul A, Das S, Das J et al: Diarylheptanoid-myricanone isolated from ethanolic extract of Myrica cerifera shows anticancer effects on HeLa and PC3 cell lines: signalling pathway and drug-DNA interaction. J Integr Med, 2013; 11(6): 405–15

37. Paul A, Das J, Das S et al: Anticancer potential of myricanone, a major bioactive component of *Myrica cerifera*: Novel signaling cascade for accomplishing apoptosis. J Acupunct Meridian Stud, 2013; 6(4): 188–98

38. Loizou S, Lekakis I, Chrousos GP, Moutsatsou P: Beta-Sitosterol exhibits anti-inflammatory activity in human aortic endothelial cells. Mol Nutr Food Res, 2010; 54(4): 551–58

39. Sikder K, Das N, Kesh SB, Dey S: Quercetin and beta-sitosterol prevent high fat diet induced dyslipidemia and hepatotoxicity in Swiss albino mice. Indian J Exp Biol, 2014; 52(1): 60–66

40. Kuang L, Cao X, Lu Z: Baicalein protects against rotenone-induced neurotoxicity through induction of autophagy. Biol Pharm Bull, 2017; 40(9): 1537–43

41. Shi R, Wei Z, Zhu D et al: Baicalein attenuates monocrotaline-induced pulmonary arterial hypertension by inhibiting vascular remodeling in rats. Pulm Pharmacol Ther, 2018; 48: 124–35

42. Gu W, Liu J, Wang Z et al: ADRB2 polymorphisms and dyslipidemia risk in Chinese hypertensive patients. Clin Exp Hypertens, 2017; 39(2): 139–44

43. Yuenyong W, Chinpongpanich A, Comai L et al: Downstream components of the calmodulin signaling pathway in the rice salt stress response revealed by transcriptome profiling and target identification. BMC Plant Biol, 2018; 18(1): 335

44. Kim G, Piao C, Oh J, Lee M: Combined delivery of curcumin and the heme oxygenase-1 gene using cholesterol-conjugated polyamidoamine for anti-inflammatory therapy in acute lung injury. Phytomedicine, 2018; 56: 165–74

45. Suh S, Hong J, Kim EJ et al: Anti-inflammation and anti-cancer activity of ethanol extract of antarctic freshwater microalga, *Micractinium* sp. Int J Med Sci, 2018; 15(9): 929–36

46. Monmai C, Go SH, Shin I et al: Anti-inflammatory effect of *Asterias amurensis* fatty acids through NF-kappa B and MAPK pathways against LPS-stimulated RAWzb4.7 cells. J Microbiol Biotechnol, 2018; 28(10): 1635–44

47. Nedvedova I, Kolar D, Neckar J et al: Cardioprotective regimen of adaptation to chronic hypoxia diversely alters myocardial gene expression in SHR and SHR-mt(BN) conplastic rat strains. Front Endocrinol, 2019; 9: 809

48. Best B, Moran P, Ren B: VEGF/PKD-1 signaling mediates arteriogenic gene expression and angiogenic responses in reversible human microvascular endothelial cells with extended lifespan. Mol Cell Biochem, 2018; 446(1–2): 199–207

49. Berridge MJ: The inositol trisphosphate/calcium signaling pathway in health and disease. Physiol Rev, 2016; 96(4): 1261–96

50. Persoon S, Paulus M, Hirt S et al: Cardiac unloading by LVAD support differentially influences components of the cGMP-PKG signaling pathway in ischemic and dilated cardiomyopathy. Heart Vessels, 2018; 33: 948–57

51. Ravnskjaer K, Madiraju A, Montminy M: Role of the cAMP pathway in glucose and lipid metabolism. Handb Exp Pharmacol, 2016; 233: 29–49

52. Sun H, Chen D, Han Y et al: Relaxin in paraventricular nucleus contributes to sympathetic overdrive and hypertension via PI3K-Akt pathway. Neuropharmacology, 2016; 103: 247–56

53. Aoyama M, Kawase H, Bando YK et al: Dipeptidyl peptidase 4 inhibition alleviates shortage of circulating glucagon-like peptide-1 in heart failure and mitigates myocardial remodeling and apoptosis via the exchange protein directly activated by cyclic AMP 1/Ras-related protein 1 axis. Circ Heart Fail, 2016; 9: e0020811

54. Han J, Jiang DM, Ye Y et al: Farnesyl pyrophosphate synthase inhibitor, ibandronate, improves endothelial function in spontaneously hypertensive rats. Mol Med Rep, 2016; 13(5): 3787–96