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Elucidation of the active ingredients of *Lamiophlomis herba* against hemorrhage based on network pharmacology and tail snipping model in mice

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This study aimed to elucidate the active ingredients of *Lamiophlomis herba* (LH), the overground part of *Lamiophlomis rotata* (Benth.) Kudo, against hemorrhage based on network pharmacology and tail snipping model in mice. A total of 118 hemorrhage-related target genes were identified by retrieving public databases, and 39 genes were identified as the hub genes of hemorrhage based on protein-protein interaction and module analyses. The interactions between 67 potentially active ingredients in LH and 7 genes in the 39 hub genes were established and analyzed through molecular docking and Cytoscape. A total of 21 ingredients were involved in the interactions, and were divided into three categories: iridoid (15 ingredients), flavonoid (2 ingredients) and other category (4 ingredients). Based on the "multi-ingredient, multi-target" characteristic of traditional Chinese medicines (TCMs), the results of network pharmacology indicated that iridoid might be the key active ingredient group of LH against hemorrhage. The contribution of iridoid to the hemostatic effect of LH was investigated by the tail snipping model in mice. The results showed that iridoid was the key active ingredient group of LH against hemorrhage, which confirmed the prediction in network pharmacology. Additionally, the previous reports also supported this prediction. In conclusion, the finding of the present study indicates that iridoid is the key hemostatic ingredient group of LH. This work provides valuable references for investigation of the hemostatic ingredients of LH based on the holistic theory of TCMs. Meanwhile, this work also provides further insight into the development of hemostatic drugs based on LH.

1. Introduction

Hemorrhage is a common and potentially life-threatening condition. The development of hemostatic drugs has been important since ancient times. Many ingredients from traditional Chinese medicines (TCMs) show considerable hemostatic effects such as dencichine and ergonovine (Yaju et al. 2013; Huang et al. 2014), and TCMs provides a huge ingredient library for the research and development of hemostatic drugs. Different from western medicine, the strategy of TCMs to treat diseases is to give patients a crude extract instead of a single ingredient. This indicates that monitoring the hemostatic active ingredients in TCMs is particularly important to ensure the effect of TCMs on hemorrhage. However, the premise of monitoring is to clarify the hemostatic active ingredients in TCMs, and the active ingredients of many hemostatic TCMs remain unknown at present. Therefore, studies need to be strengthened in this area.

Lamiophlomis herba (LH), the overground part of *Lamiophlomis rotata* (Benth.) Kudo, is a frequently-used TCM for treatment of hemorrhage (Li et al. 2008). Based on natural medicine research framework, experimental studies reported that iridoid from LH showed a considerable hemostatic effect (Li et al. 2009; Fan et al. 2016). However, natural medicine research does not reflect the "holistic theory" characteristic of TCMs in treating diseases (Li and Zhang 2013). Therefore, further research should be carried out to identify whether iridoid is the hemostatic ingredient of LH by some techniques that reflect the holistic theory of TCMs. Network pharmacology is a systematic analytical technology applied to investigate the interactions of multiple factors such as diseases, genes, protein targets and drugs (Hopkins 2007). Network pharmacology emphasizes the paradigm shift of drug discovery from "one target, one drug" to "network target, multi-ingredient therapeutics" (Hopkins 2008). The characteristic accords with the holistic theory of TCM. Hence, network pharmacology is a feasible method to elucidate the active ingredients of TCMs with holistic theory and has already been successfully applied (Huang et al. 2017; He et al. 2019; Xue et al. 2019).

In the present study, network pharmacology was used to predict the active ingredients of LH against hemorrhage. Network pharmacology-based prediction was carried out by identification of potentially active ingredients in LH, identification of hemorrhage-related hub genes and their protein structures, and establishment and network analysis of interactions between active ingredients in LH and hemorrhage-related hub genes. Tail snipping model in mice was applied to confirm the prediction.

2. Investigations and results

2.1. Hub genes of 118 hemorrhage-related target genes

A total of 118 hemorrhage-related target genes were identified by retrieving public databases. The protein-protein interactions (PPI) network of these genes with 105 nodes and 527 edges was established based on the STRING database. The result of module analysis indicated that the PPI network could be divided into 7 modules. The gene numbers of modules 1-7 were 39, 28, 19, 11,

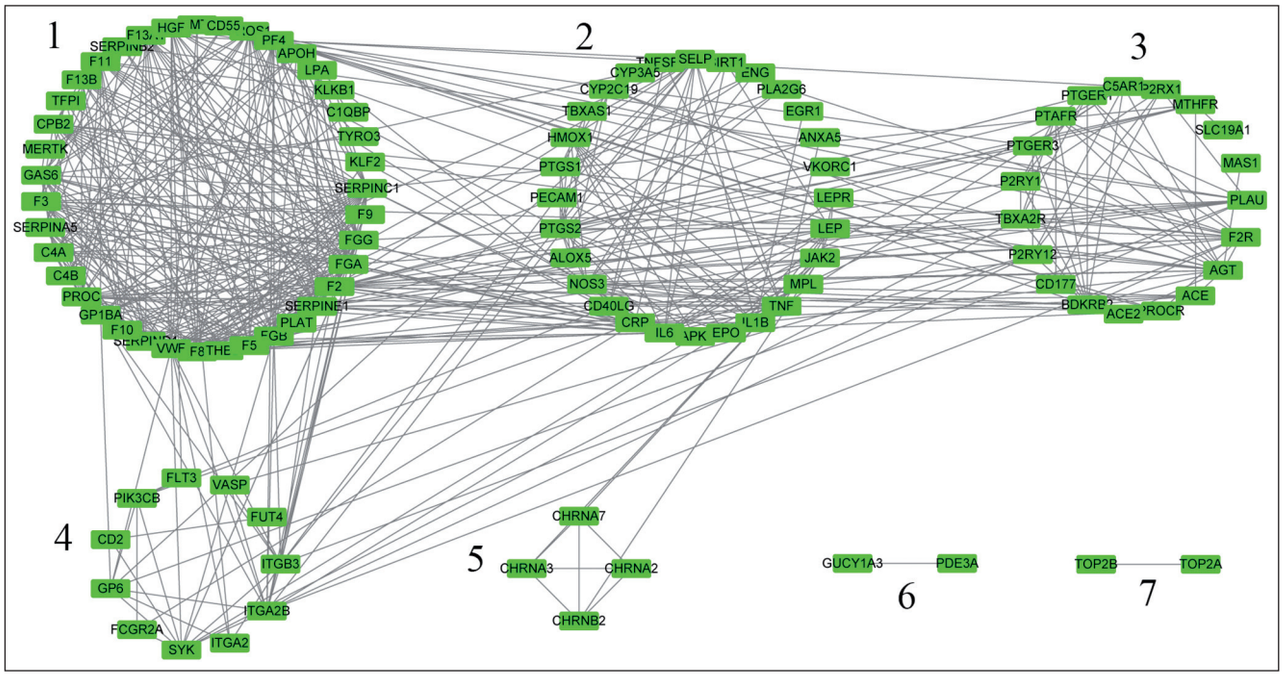

Fig. 1: Module analysis of PPI network of hemorrhage-related target genes.

Table 1: Information of 39 genes in the module 1

No.	Gene Symbol	UniProt ID	No.	Gene Symbol	UniProt ID
1	ADAMTS13	Q76LX8	21	GP1BA	P07359
2	APOH	P02749	22	HGF	P14210
3	C1QBP	Q07021	23	KLF2	Q9Y5W3
4	C4A	P0C0L4	24	KLKB1	P03952
5	C4B	P0C0L5	25	LPA	P08519
6	CD55	P08174	26	MERTK	Q12866
7	CPB2	Q96IY4	27	PF4	P02776
8	F10	P00742	28	PLAT	P00750
9	F11	P03951	29	PROC	P04070
10	F13A1	P00488	30	PROS1	P07225
11	F13B	P05160	31	SERPINA5	P05154
12	F2	P00734	32	SERPINB2	P05120
13	F3	P13726	33	SERPINC1	P01008
14	F5	P12259	34	SERPIND1	P05546
15	F8	P00451	35	SERPINE1	P05121
16	F9	P00740	36	TFPI	P10646
17	FGA	P02671	37	THBD	P07204
18	FGB	P02675	38	TYRO3	Q06418
19	FGG	P02679	39	VWF	P04275
20	GAS6	Q14393	–	–	–

4, 2 and 2, respectively. Based on the rule described in the experimental section, the 39 genes in the module 1 were identified as the hemorrhage-related hub genes. The results are shown in Fig. 1 and Table 1.

2.2. *Active ingredients of LH against hemorrhage*

Based on UniProt ID and gene symbol of the above-mentioned 39 hub genes, the protein structures of 9 hub genes that meet the requirements were obtained from the PDB website, and the protein structures of another 30 hub genes were unavailable. The results of docking method validation showed that root-mean-square deviation (RMSD) of the protein structures of 7 genes were ≤ 2.0 Å, and RMSD of the protein structure of PLAT was ≥ 2.0 Å. Moreover, the docking result of the protein structure of F8 was unavailable. The results are listed in Table 2. Therefore, the protein structures of the 7 genes (CPB2, F10, F11, F2, F9, MERTK and SERPINE1) were applied to molecular docking calculation.

As shown in Fig. 2, a network with 28 nodes and 70 edges linking 21 ingredients in LH and 7 proteins related to hemorrhage was established based on molecular docking, suggesting that the activity of LH against hemorrhage was related to the 21 ingredients. The degree values and categories of 21 ingredients are listed in Table 3. The 21 ingredients were divided into 3 categories: iridoid (15 ingredients), flavonoid (2 ingredients) and other category (4 ingredients). Based on the rule described in the experimental section, iridoid might be the key active ingredient group of LH against hemorrhage.

Table 2: PDB ID and RMSD of the protein structures of 9 hub genes related to hemorrhage

No.	Gene Symbol	PDB ID	RMSD (Å)
1	CPB2	4P10	0.8033
2	F10	2JKH	1.1687
3	F11	4X6P	0.8585
4	F2	3QX5	0.4194
5	F8	3HNB	\
6	F9	4Z0K	0.7988
7	MERTK	5U6C	0.4459
8	PLAT	1RTF	3.1447
9	SERPINE1	4AQH	1.1692

2.3. *Contribution of iridoid to the hemostatic effect of LH*

Shorter bleeding time was seen significantly in the positive, LH (0.5, 1 or 2 g/kg) and iridoid groups than that in the model group ($P < 0.01$), suggesting that Yunnan Baiyao, LH and iridoid showed well hemostatic effect. There was no difference between the bleeding time in 2 g/kg LH and iridoid groups, indicating that iridoid was the key active ingredient group of LH against hemorrhage. The results are listed in Table 4.

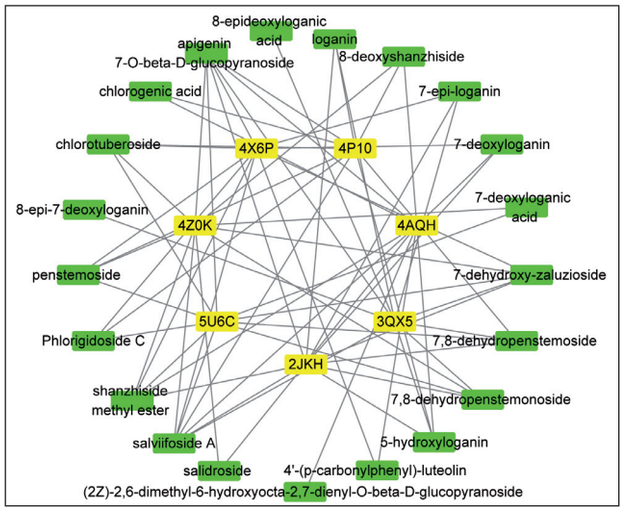

Fig. 2: Network with 28 nodes and 70 edges linking 21 ingredients in LH and 7 proteins related to hemorrhage.

Table 3: Degree values and categories of 21 ingredients

No.	Ingredient	Value	Category
1	Apigenin 7-O-beta-D-glucopyranoside	7	flavonoid
2	Salviifoside A	7	other
3	Shanzhiside methyl ester	5	iridoid
4	7-Dehydroxy-zaluzioside	5	iridoid
5	Penstemoside	4	iridoid
6	7,8-Dehydropenstemoside	4	iridoid
7	7,8-Dehydropenstemonoside	4	iridoid
8	Chlorotuberoside	4	iridoid
9	5-Hydroxyloganin	4	iridoid
10	Loganin	3	iridoid
11	7-Deoxyloganin	3	iridoid
12	7-Epi-loganin	3	iridoid
13	Phlorigidoside C	3	iridoid
14	8-Deoxyshanzhiside	3	iridoid
15	Salidroside	2	other
16	7-Deoxyloganic acid	2	iridoid
17	Chlorogenic acid	2	other
18	4'-(p-Carbonylphenyl)-luteolin	2	flavonoid
19	8-Epi-7-deoxyloganin	1	iridoid
20	8-Epideoxyloganic acid	1	iridoid
21	(2Z)-2,6-Dimethyl-6-hydroxyocta-2,7-dienyl-O-beta-D-glucopyranoside	1	other

Table 4: Effect of LH and iridoid on bleeding time in mice with tail snipping model

Group	Bleeding time (min)
Model	24.45 ± 3.76
Positive	12.60 ± 4.09**
0.5 g/kg LH	19.20 ± 3.26**
1 g/kg LH	17.70 ± 2.44**
2 g/kg LH	15.20 ± 3.09**
Iridoid	16.15 ± 2.30**

**$P < 0.01$, compared with that in the model group.

3. Discussion

Establishment of interactions between ingredients and disease-related target genes is the most important step in TCMs network pharmacology, and there are two methods to establish the interactions at present. First, the interactions between ingredients and disease-related target genes are identified by matching the ingredients-related target genes with disease-related target genes (Lee et al. 2018). Second, molecular docking is applied to establish the interactions when the overlapping genes are few or no between ingredients-related and disease-related target genes (Hong et al. 2017). In this work, we found that the overlapping genes were few between ingredients-related and hemorrhage-related target genes, so molecular docking was used to establish the interactions between ingredients in LH and genes related to hemorrhage.

Generally, a group of genes rather than a single gene is involved in the occurrence and development of disease. If all genes related to the disease are used to establish the interactions between ingredients and genes based on molecular docking, the operability and scientific character are poor due to huge workload and lack of attention to key genes of disease occurrence. Module analysis is a universally accepted method to identify the hub genes in disease-related target genes (Zhou et al. 2016). Therefore, module analysis was used to identify the hub genes of hemorrhage in the present study. A total of 39 genes in 118 hemorrhage-related target genes was identified as the hub genes of hemorrhage. However, the protein structures of only 7 hub genes were applied to molecular docking calculation because the protein structures of other hub genes were unavailable.

Degree values of ingredients are used to identify the active ingredients of TCMs in many extant literatures about TCMs network pharmacology (Huang et al. 2017; Jiang et al. 2020). The bigger degree values of ingredients are, the more important the ingredients are for the pharmacologic effect of TCMs. The universally accepted method only reflects the "multi-target" characteristic of TCMs, while ignoring the "multi-ingredient" characteristic. Therefore, the strategy of identifying the active ingredients of TCMs remains to be discussed based on the degree values of ingredients. In this work, the results showed that the degree values of 18 ingredients in the 21 ingredients related to the hemostatic effect of LH was ≥ 2, suggesting that most of the 21 ingredients can reflect the "multi-target" characteristic of TCMs. A total of 15 ingredients in the 21 ingredients were categorized as iridoid. Therefore, iridoid might be the key active ingredient group of LH against hemorrhage based on the "multi-ingredient, multi-target" characteristic of TCMs. The previous reports support this prediction (Li et al. 2009; Fan et al. 2016). Additionally, the contribution of iridoid to the hemostatic effect of LH was investigated by the tail snipping model in mice. The results showed that iridoid was the key active ingredient group of LH against hemorrhage, which confirmed the prediction in network pharmacology.

In conclusion, the active ingredients of LH against hemorrhage were elucidated by network pharmacology and tail snipping model in mice. The finding of the present study indicates that iridoid is the key hemostatic ingredient group of LH. This work provides valuable references for investigation of the hemostatic ingredients of LH based on the holistic theory of TCMs. Meanwhile, this work also provides further insight into the development of hemostatic drugs based on LH.

4. Experimental

4.1. Plant material, chemicals and reagents

LH was collected from Yushu, Qinghai, and identified as the overground part of *Lamiophlomis rotata* (Benth.) Kudo by Prof Ling Ma, a taxonomist in the College of Pharmacy, Chongqing Three Gorges Medical College. The voucher specimen of LH (voucher no. duyiwei2018.12) was deposited at the Herbarium of Southwest University for future reference. Yunnan Baiyao was purchased from Yunnan Baiyao Group Co., Ltd. (Kunming, China). Analytical grade ethanol, CMC-Na, polyamide and D101 macroporous adsorption resin were from Macklin (Shanghai, China).

4.2. Animals

Specific pathogen-free KM mice (20±2 g) were purchased from Ensiweier (Chongqing, China) and were housed in a temperature-controlled vivarium (25 °C) with 12 h light/12 h dark cycle. Moreover, water and feed were given *ad libitum*.

Animals experiment described has been carried out in accordance with the EU Directive 2010/63/EU for animal experiments. The study was approved by the Institutional Animal Care and Use Committee of Southwest University.

4.3. Identification of potentially active ingredients in LH

As the previous study from our team (Jiang et al. 2019), 148 ingredients in LH were identified through literatures retrieval, and the absorption, distribution, metabolism, excretion and toxicity virtual screening indicated that 67 ingredients showed good potential as active ingredients. The 3D structures of the 67 ingredients were obtained with the aids of SciFinder (https://scifinder.cas.org/), PubChem (https://pubchem.ncbi.nlm.nih.gov/), ChemSpider (http://www.chemspider.com/) and ChemDraw software.

4.4. Identification of hemorrhage-related hub genes and their protein structures

LH can be used for the treatment of different types of hemorrhage, and thrombosis is the shared and key step for different types of hemorrhage (Adams et al. 2007). Therefore, "thrombosis" was selected as the search term to identify hemorrhage-related target genes in Therapeutic Target Database (http://bidd.nus.edu.sg/group/cjttd/), Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (http://lsp.nwu.edu.cn/tcmsp.php) and DisGeNET (http://www.disgenet.org/). The PPI network of hemorrhage-related target genes was established by STRING (https://string-db.org/) with "Homo sapiens" setting. To obtain more credible PPI, PPI were filtered by setting "minimum required interaction score:" as "high confidence (0.700)" in STRING. The module analysis and visualization of PPI network were performed with "APPs-clusterMaker-Community cluster (Glay)" analysis on Cytoscape 3.7.1. The more gene numbers of module are, the more important these genes in this module are for the pathogenesis of hemorrhage (Zhou et al. 2016).
Based on the requirements in the previous report (Yang et al. 2016), the protein structures of hub genes were downloaded from the PDB website (https://www.rcsb.org/) with "Homo sapiens" setting.

4.5. Establishment and network analysis of interactions between potentially active ingredients in LH and hemorrhage-related hub genes

Molecular docking was applied to establish the interactions between the 67 ingredients and hemorrhage-related hub genes. Molecular docking was carried out with the following four steps on Discovery Studio (DS) software: ligand preparation (A), receptor preparation (B), docking method validation (C), docking calculation (D). The higher the docking score is, the stronger the affinity of ligand with receptor is. The interactions between all ingredients and one hub gene were retained following the requirements docking score (≥ 90), top 15%, and top 10. Network of all retained interactions was visualized and analyzed through Cytoscape. Then, the ingredients in the network were categorized based on their structures. The category including maximum ingredients was considered as the key active ingredient group of LH against hemorrhage based on the "multi-ingredient, multi-target" characteristic of TCMs.
(A) The 3D structures of the 67 ingredients were processed with adding hydrogens and CHARMm forcefield.
(B) The water in protein of hub gene was deleted, and then DS "Macromolecules|Prepare Protein|Clean Protein" function was used to remove multiple conformation, supplement non-intact amino acid residues and add hydrogens of protein. Subsequently, the protein was treated with CHARMm forcefield. Lastly, the position of original ligand of protein was defined as binding site, and the original ligand of protein was deleted.
(C) After separating the original ligand and receptor of protein, original ligand and receptor were processed according to (A) and (B), respectively. Then, the molecular docking calculation between original ligand and receptor was carried out on DS "Receptor-Ligand Interactions|Dock Ligands|Dock Ligands (LibDock)". Subsequently, the atom positional RMSD between original ligand and ligands produced by docking were calculated. Result differing by ≤ 2.0 Å in atom positional RMSD showed that the docking method of this protein was reliable (Song et al. 2015).
(D) The docking calculations between the 67 ingredients and hemorrhage-related hub proteins were performed with LibDock function on DS.

4.6. Samples preparation

Aqueous extract preparation of LH. LH (250 g) was cut into small pieces of 0.5-2 cm and extracted twice for 1.5 h through decoction with 3 L water. The extracts were combined and concentrated under reduced pressure to yield crude extract (500 mL).
Iridoid preparation of LH. Based on a previous report (Tao et al. 2016), the aqueous extract of LH (50 mL) was subjected to polyamide column chromatography, washed with water. Then, the combined water eluent was subjected to D101 macroporous adsorption resin column chromatography, washed with water. Subsequently, D101 macroporous adsorption resin column was eluted with 75% ethanol. The 75% ethanol eluents with characteristic absorption at 235 nm were combined and concentrated under reduced pressure to yield iridoid extract (50 mL).
Aqueous extract, iridoid extract, and Yunnan Baiyao were suspended in 0.5% CMC-Na to yield suitable concentration of pharmacodynamics samples, respectively.

4.7. Grouping and treatment of mice

Mice were randomly divided into 6 groups (n = 10): model, positive, 0.5 g/kg LH, 1 g/kg LH, 2 g/kg LH, and iridoid groups. The mice in the positive and LH (0.5, 1 or 2 g/kg) groups were orally administered Yunnan Baiyao at a dose of 2 g/kg and LH at doses of 0.5, 1 or 2 g/kg once a day for 7 days, respectively. The mice in the iridoid group received equivalent amount of iridoid once a day for 7 days, relative to that in the 2 g/kg LH group. The mice in the model group received equivalent amount of 0.5% CMC-Na once a day for 7 days, in place of Yunnan Baiyao, LH or iridoid.

4.8. Determination of bleeding time in mice

At 1 h after last administration, the tails of the mice were cut off at 3 mm from the tip of the tail to establish the tail snipping model. Blood was sucked away with neutral filter paper every 30 s. The bleeding time was from the start to the stop of blood extravasation. The contribution of iridoid to the hemostatic effect of LH was analyzed by comparing the difference between the bleeding time in 2 g/kg LH and iridoid groups.

4.9. Statistical analysis

All data are expressed as the mean±standard deviation. Data are subjected to ANOVA followed by LSD multiple comparison on SPSS 21.0. Differences were considered to be statistically significant at $P < 0.05$.

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Conflicts of interest: None declared.

References

Adams GL, Manson RJ, Turner I, Sindram D, Lawson JH (2007) The balance of thrombosis and hemorrhage in surgery. Hematol Oncol Clin North Am 21: 13–24.
Fan PC, Ma HP, Hao Y, He XR, Sun AJ, Jiang W, Li MX, Jing LL, He L, Ma J, Jia ZP (2016) A new anti-fibrinolytic hemostatic compound 8-O-acetyl shanzhiside methylester extracted from *Lamiophlomis rotata*. J Ethnopharmacol 187: 232–238.
He D, Huang JH, Zhang ZY, Du Q, Peng WJ, Yu R, Zhang SF, Zhang SH, Qin YH (2019) A network pharmacology-based strategy for predicting active ingredients and potential targets of LiuWei DiHuang pill in treating type 2 diabetes mellitus. Drug Des Devel Ther 13: 3989–4005.
Hong M, Zhang Y, Li S, Tan HY, Wang N, Mu S, Hao X, Feng Y (2017) A network pharmacology-based study on the hepatoprotective effect of *Fructus Schisandrae*. Molecules 22: 1617.
Hopkins AL (2007) Network pharmacology. Nat Biotechnol 25: 1110–1111.
Hopkins AL (2008) Network pharmacology: the next paradigm in drug discovery. Nat Chem Biol 4: 682–690.
Huang J, Cheung F, Tan HY, Hong M, Wang N, Yang J, Feng Y, Zheng Q (2017) Identification of the active compounds and significant pathways of yinchenhao decoction based on network pharmacology. Mol Med Rep 16: 4583–4592.
Huang LF, Shi HL, Gao B, Wu H, Yang L, Wu XJ, Wang ZT (2014) Decichine enhances hemostasis of activated platelets via AMPA receptors. Thromb Res 133: 848–854.
Jiang Y, Zhong M, Long F, Yang R, Zhang Y, Liu T (2019) Network pharmacology-based prediction of active ingredients and mechanisms of *Lamiophlomis rotata* (Benth.) Kudo against rheumatoid arthritis. Front Pharmacol 10: 1435.
Jiang Y, Zhong M, Long F, Yang R (2020) Deciphering the active ingredients and molecular mechanisms of *Tripterygium hypoglaucum* (Levl.) Hutch against rheumatoid arthritis based on network pharmacology. Evid Based Complement Alternat Med 2020: 2361865.
Lee AY, Park W, Kang TW, Cha MH, Chun JM (2018) Network pharmacology-based prediction of active compounds and molecular targets in Yijin-Tang acting on hyperlipidaemia and atherosclerosis. J Ethnopharmacol 221: 151–159.
Li M, Jia Z, Hu Z, Zhang R, Shen T (2008) Experimental study on the hemostatic activity of the Tibetan medicinal herb *Lamiophlomis rotata*. Phytother Res 22: 759–765.
Li M, Zhang R, Jia Z, Sheng J, Qiu J, Wang J (2009) Isolation and identification of hemostatic ingredients from *Lamiophlomis rotata* (Benth.) Kudo. Phytother Res 23: 816–822.
Li S, Zhang B (2013) Traditional Chinese medicine network pharmacology: theory, methodology and application. Chin J Nat Med 11: 110–120.
Song XG, Zhou W, Chen C, Wang SM, Liang SW (2015) Study on material base of Ligusticum wallichii for treating brain ischemia and its molecular mechanism based on molecular docking. Chin J Chin Mater Med 40: 2195–2198.
Tao R, Fu M, Cao X, Li M (2016) Optimization of the separation and purification process for iridoid glycosides from *Lamiophlomis rotata*. J Pharm Pract 34: 416–420, 449.
Xue J, Shi Y, Li C, Song H (2019) Network pharmacology-based prediction of the active ingredients, potential targets, and signaling pathways in compound Lian-Ge granules for treatment of diabetes. J Cell Biochem 120: 6431–6440.
Yaju Y, Kataoka Y, Eto H, Horiuchi S, Mori R (2013) Prophylactic interventions after delivery of placenta for reducing bleeding during the postnatal period. Cochrane Database Syst Rev 11: CD009328.
Yang X, Liu H, Liu J, Li F, Li X, Shi L, Chen J (2016) Rational selection of the 3D structure of biomacromolecules for molecular docking studies on the mechanism of endocrine disruptor action. Chem Res Toxicol 29: 1565–1570.
Zhou WX, Wang TX, Cheng XR, Han L, Zhang YX (2016) Techniques of molecular network analysis in study on network pharmacology. J Int Pharm Res 43: 399–409.