Study on Mechanism of Tripterygium Wilfordii in Treatment of Henoch-Schonlein Purpura Nephritis Based on Network Pharmacology and Molecular Docking Technology

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Research

Keywords: Tripterygium wilfordii, Henoch-Schonlein purpura nephritis, network pharmacology, molecular docking, mechanisms

Posted Date: February 1st, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1264964/v1>

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Abstract

Objective.

Predict the main active ingredients, potential targets, and critical pathways of *Tripterygium wilfordii* treatment in Henoch-Schonlein purpura nephritis, and explore possible mechanisms by network pharmacology and molecular docking technology.

Methods.

The active ingredients and their corresponding targets of *Tripterygium Wilfordii* were screened based on the Traditional Chinese Medicine Systematic Pharmacology Database and Analysis Platform. Access to Henoch-Schonlein purpura nephritis targets by searching the GeneCards database, the online human Mendelian genetic database, and the DisGeNET database. The intersection targets of *Tripterygium Wilfordii* and Henoch-Schonlein purpura nephritis were obtained by Venn software. Construction of dynamic ingredient-target networks and protein-protein interaction networks using Cytoscape 3.7.2 software. PPI network analysis using the STRING database. Gene ontology enrichment analysis and Kyoto Encyclopedia of Genes and Genomes enrichment analysis of intersecting genes using the R cluster Profiler. Select key targets and core active ingredients, and use AutoDock software for molecular docking.

Result.

Network pharmacology predictions show 42 active ingredients in *Tripterygium Wilfordii* for the treatment of Henoch-Schonlein purpura nephritis, with the core active ingredients being triptolide, kaempferol, Isoxanthohumol. The key targets are tumor necrosis factor, interleukin 8 and matrix metalloproteinase-9, vascular endothelial growth factor A, etc. The biological processes in GO analysis are mainly concerned with response to lipopolysaccharide, response to molecule of bacterial origin, extrinsic apoptotic signaling pathway, positive regulation of peptidyl-tyrosine phosphorylation. The molecular function includes cytokine activity, cytokine receptor binding, receptor ligand activity, and signal receptor activator activity. The cell composition provides membrane rafts, membrane microdomain, external side of plasma membrane, and collagen-containing extracellular matrix. KEGG analysis obtains relevant signaling pathways as a nuclear transcription factor NF- κ B, tumor necrosis factor signaling pathway, interleukin 17 signaling pathway. The molecular docking results showed that triptolide, kaempferol, and Isoxanthohumol had suitable binding activities with TGFB1, MMP9, and TNF.

Conclusion.

The mechanism of action of *Tripterygium wilfordii* in the treatment of Henoch-Schonlein purpura nephritis lies in applying active ingredients such as triptolide, kaempferol, and Isoxanthohumol, with TNF, CXCL8, MMP-9, and VEGFA as crucial targets, through NF- κ B, TNF, and IL-17 signaling pathways inhibit the inflammatory response, thus play a role in the treatment of Henoch-Schonlein purpura nephritis.

1. Introduction

Henoch-Schonlein purpura nephritis (HSPN) is common secondary glomerulonephritis caused by the deposition of immune complexes containing immunoglobulin A1 (IgA1) in mesangial, subepithelial, and subendothelial spaces in children ^[1,2]. The incidence of this disease is about 30% ~ 50%, about 1% ~ 7% can develop into end-stage renal disease ^[3,4]. Currently, hormones and immunosuppressive drugs are the primary treatment for HSPN. Although these drugs have made some progress, they have more side effects and a single therapeutic target.

There is no specific name of HSPN in ancient literature. According to the different clinical manifestations of patients, the disease belongs to the 'purpura,' 'rash,' 'hematuria 'categories. Traditional Chinese medicine believes that HSPN is mainly caused by wind, dampness, toxicity, heat, and other pathogens based on weakness. Heat evil invades the human body, long-term stagnation of dampness heat, blood heat junction, forcing blood flow, blood spill outside the veins for muscle bleeding, urine blood.

Tripterygium Wilfordii(TW) belongs to the vine of Euonymusaceae. It has a bitter taste, heart entry, liver meridian, twelve meridians, and collaterals. It has the effects of clearing heat and detoxicating, dispelling wind and dredging collaterals, soothing tendons and promoting blood circulation, detumescence and pain relief, and insecticidal hemostasis. Modern pharmacological studies have shown that TW has anti-inflammatory, immunosuppressive, and other effects ^[5,6]. Several studies have shown that TW has achieved an excellent curative effect or synergistic effect in treating HSPN. It inhibits the glomerular mesangial proliferation process by inhibiting the autoimmune response and can also reduce the damage to the kidney caused by proteinuria and hematuria ^[7, 8]. Although many studies have shown that TW treatment of HSPN is more explicit, its specific molecular mechanism still needs further exploration. Based on the characteristics of multi-component, multi-target, and multi-pathway of traditional Chinese medicine, this study used the method of network pharmacology to construct the network of the active components of TW and its targets and the targets of TW-HSPN. It analyzed the potential effect of TW in the treatment of HSPN from multiple levels to provide a basis for further pharmacological research and clinical application.

2. Materials And Method

2.1 Acquisition of active ingredients and targets of TW

With the keywords of TW and the screening conditions of oral bioavailability $\geq$ 30%, drug likeness $\geq$ 0.18, hydrogen bond donor $\leq$ 5, and hydrogen bond acceptors $\leq$ 10, the active ingredients and corresponding target proteins of TW were obtained in the TCMSP database^[9]. Use the Uniprot database (<https://www.uniprot.org/>) to correct the obtained target proteins to common target gene names. Building drug-component-target networks with Cytoscape 3.8.2 software.

2.2 Acquisition of disease targets

Using ' Henoch-Schonlein purpura nephritis ' as the keyword. Access to HSPN-related disease targets in GeenCards database (<https://www.genecards.org/>), Online Mendelian Inheritance in Man(<https://www.omim.org/>) and DisGeNET database (<https://www.disgenet.org/>). Combine the results of three databases and delete duplicate targets. Finally, the target is the related target of HSPN.

2.3 Interaction network between active components of TW and HSPN targets

The intersection genes of TW and HSPN were obtained by Venn 2.1 online mapping software. Constructing the TW-component-target-HSPN network by using Cytoscape 3.7.1 software. Using network analyzer function to analyze the degree of freedom and predict the critical nodes in the treatment of HSPN by TW.

2.4 Construction of Protein-Protein Interaction (PPI) Network

Network data of PPI interactions were predicted by introducing intersection genes in the String database (<https://stringdb.org/>) with a confidence level of 0.4000 as a filtering condition. The network analyzer in Cytoscape 3.7.1 software was used to analyze the CSV files of PPI, where the larger the degree value, the relatively larger and darker the nodes presented. The larger the Combine score value, the thicker the edges and the darker the color^[10].

2.5 GO and KEGG enrichment analysis

Using R cluster Profiler made GO and KEGG enrichment analyses. According to $P < 0.05$, screening the first ten biological processes, molecular functions, cellular components, and the top 20 KEGG pathways. Then draw the bar chart and bubble chart. Utilizing the Cytoscape 3.7.1 software to construct the 'TW-HSPN-component-target-pathway' network.

2.6 Molecular docking verification

The 3D structures of the core targets were downloaded from the RSCB PDB database (<https://www.pdbus.org/>), and the 2D structures of the active components were downloaded from the TCMSP database. Then the HSPN target proteins were pre-treated with PyMOL 2.4.0 software for dehydration and hydrogenation. The molecular docking was performed by AutoDock Vina software. Finally, the docking results were visualized and analyzed in 3D by PyMOL software.

3. Results

3.1 Collection of active ingredients and targets of TW

The TCMSP database retrieved a total of 144 components of TW. After setting the ADME parameters for screening, 42 active ingredients were obtained. Among them, 26 compounds were obtained after excluding the active components without corresponding target proteins and non-human target proteins

as potential active compounds. For the convenience of subsequent research, these components were numbered as TW1 - TW26, as shown in Table 1. The target proteins of TW were transformed into standard gene names by the Uniprot database, and 130 target proteins were obtained by removing repetitive items. Construct TW - active ingredients - target protein network, as shown in Figure 1. The rhombic, octagonal, and circular shapes represent drugs, active ingredients, and target proteins, respectively, and the edges represent their interactions.

Table 1
TW active ingredients that meet the criteria

No.	Name	Hdon	Hacc	OB	DL
TW1	Hederagenin	1	1	36.91	0.75
TW2	(+)-Medioresinoldi-O-beta-D-glucopyranoside_qt	2	7	60.69	0.62
TW3	81827-74-9	1	4	45.42	0.53
TW4	(1R,4aR,10aS)-5-hydroxy-1-(hydroxymethyl)-7-isopropyl-8-methoxy-1,4a-dimethyl-4,9,10,10a-tetrahydro-3H-phenanthren-2-one	2	4	48.84	0.38
TW5	Triptolide	1	6	51.29	0.68
TW6	Tryptophenolide	1	3	48.5	0.44
TW7	5,8-Dihydroxy-7-(4-hydroxy-5-methyl-coumarin-3)-coumarin	3	7	61.85	0.54
TW8	Triptidolnide	2	6	56.4	0.67
TW9	Triptinin B	2	3	34.73	0.32
TW10	Triptonoterpene	1	2	48.57	0.28
TW11	beta-sitosterol	1	1	36.91	0.75
TW12	Kaempferol	4	6	41.88	0.24
TW13	Stigmasterol	1	1	43.83	0.76
TW14	(2R,3R,4S)-4-(4-hydroxy-3-methoxy-phenyl)-7-methoxy-2,3-dimethylol-tetralin-6-ol	4	6	66.51	0.39
TW15	Nobiletin	0	8	61.67	0.52
TW16	Celallocinnine	2	6	72.94	0.44
TW17	Isoxanthohumol	2	5	56.81	0.39
TW18	Hypodiolide A	1	3	76.13	0.49
TW19	Triptoditerpenic acid B	1	3	40.02	0.36
TW20	Triptonoditerpenic acid	2	4	42.56	0.39
TW21	21-Hydroxy-30-norhopan-22-one	1	2	34.11	0.77
TW22	Mairin	2	3	55.38	0.78
TW23	40957-99-1	2	7	57.2	0.62
TW24	Zhebeiresinol	1	6	58.72	0.19

No.	Name	Hdon	Hacc	OB	DL
TW25	(5S,8S,9S,10R,13R,14S,17R)-17-[(1R,4R)-4-ethyl-1,5-dimethylhexyl]-10,13-dimethyl-2,4,5,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthrene-3,6-dione	0	2	33.12	0.79
TW26	3,3'-bis-(3,4-dihydro-4-hydroxy-6-methoxy)-2H-1-benzopyran	2	6	52.11	0.54

3.2 Collection of HSPN potential targets

Received 118, 29, and 14 marks after querying the GeenCards, OMIM, and DisGeNET databases, respectively. Retrieved 134 known targets related to the pathogenesis of HSPN after removing duplicate items.

3.3 TW active ingredient-HSPN target network

Eighteen intersecting genes were obtained by inputting the active ingredient target protein genes of TW and HSPN genes into VENNY 2.1, and the Venn diagram is shown in Figure 2. Construct the network of TW - active ingredients - target gene - HSPN according to 13 active ingredients corresponding to 18 genes, as shown in Figure 3. The network suggests that TW may play a therapeutic role in HSPN by responding to 18 target protein genes through these 13 active components. Through the analysis of topological properties in the network diagram, the top five compounds were TW5 (triptolide), TW12 (kaempferol), TW17 (isoxanthohumol), TW7 (5,8-dihydroxy-7- (4-hydroxy-5-methyl-coumarin-3) -coumarin), and TW18 (hypodiploid A), and their degrees were 9, 5, 4, 3 and 2. The top five targets were NR3C1 (degree 4), ESR1 (degree 4), NOS3 (degree 4), NOS2 (degree 3), and PRSS1 (degree 3), respectively.

3.4 Construction of PPI Network

Importing intersection gene into String database to get PPI network map of the core target, as shown in Fig. 4. The larger the degree value in the graph, the larger the point presented, and the deeper the color, indicating that the role of the target is more critical. The higher the Combine score, the thicker the connection, the deeper the color, implying a more vital interaction between the two marks. The target degree values are shown in Table 2, indicating that TNF, CXCL8, MMP9, VEGFA, and NOS3 are more prominent, darker in color, and higher in degree, suggesting that they play a crucial role in the treatment of HSPN by TW.

Table 2
Information of 18 potential targets

Gene	Uniprot ID	target	Degree
TNF	P01375	Tumor necrosis factor	15
CXCL8	P10145	Interleukin-8	14
MMP9	P14780	Matrix metalloproteinase-9	14
VEGFA	P15692	Vascular endothelial growth factor A	14
IL2	P60568	Interleukin-2	12
IL4	P05112	Interleukin-4	12
ICAM1	P05362	Intercellular adhesion molecule 1	12
VCAM1	P19320	Vascular cell adhesion protein 1	12
NOS2	P35228	Nitric oxide synthase, inducible	12
NOS3	P29474	Nitric-oxide synthase, endothelial	12
SELE	P16581	E-selectin	11
TGFB1	P01137	Transforming growth factor beta-1	11
CD40	P25942	Tumor necrosis factor receptor superfamily member 5	10
ESR1	P03372	Estrogen receptor	8
NR3C1	P04150	Glucocorticoid receptor	7
PON1	P27169	Serum paraoxonase/arylesterase 1	2
BCL2	P10415	Apoptosis regulator Bcl-2	1
PRSS1	P07477	Trypsin-1	1

3.5 GO and KEGG enrichment analysis results

18 common targets of TW and HSPN using cluster profile and enrichplot in R software Bioconductor database performed go and kegg enrichment analysis. The results obtained 1411 Go enrichment analysis results ($p < 0.05$). In terms of 1317 biological processes, TW treatment of HSPN mainly involves response to lipopolysaccharide (GO : 0032496, $n = 9$), response to molecule of bacterial origin (GO : 0002237, $n = 9$), extrinsic apoptotic signaling pathway (GO : 0097191, $n = 7$), positive regulation of peptidyl-tyrosine phosphorylation (GO : 0050731, $n = 7$), regulation of leukocyte mediated immunity (GO : 0002703, $n = 7$); the 64 molecular functions mainly involve cytokine activity (GO : 0005125, $n = 6$), cytokine receptor binding (GO : 0005126, $n = 6$), receptor ligand activity (GO : 0048018, $n = 6$), signal receptor activator activity (GO : 0030546, $n = 6$) and growth factor activity (GO : 0008083, $n = 4$); the 30 cell components mainly involve membrane rafts (GO : 0045121, $n = 4$), membrane microdomain (GO :

0098857, n = 4), external side of plasma membrane (GO : 0009897, n = 4), collagen-containing extracellular matrix (GO : 0062023, n = 4) and blood microparticle (GO : 0072562, n = 3), as shown in Fig. 5.

The results obtained a total of 86 Go enrichment analysis results ($p < 0.05$). TW treatment of HSPN mainly involves NF- κ B signaling pathway (hsa04064, n = 6), TNF signaling pathway (hsa04668, n = 5), IL-17 signaling pathway (hsa04657, n = 4), intestinal immune network for IgA production (hsa04672, n = 4), rheumatoid arthritis (hsa05323, n = 4), as shown in Fig. 6.

Cytoscape software imports the active ingredients of TW, TW, HSPN, and the top 20 KEGG signaling pathways to construct the ' TW-HSPN-component-pathway ' network. The network has 53 nodes, including TW(purple oval), HSPN (yellow round), 13 active components of TW (pink diamond), 18 common targets of TW and HSPN (green oval), and the top 20 pathways and 166 edges. TW5 (triptolide) is the core component of TW in the treatment of HSPN, as shown in Fig. 7.

3.6 Molecular docking verification results

According to the literature query results, refer to whether there is direct medical evidence and new research hotspots of TW, docking targets are Eight related protein receptors TNF, TGFB1, MMP9, VEGFA, IL2, IL4, ICAM1, and VCAM1^[11–17]. Molecular docking of the pdbqt files of the three active ingredients in TW met the screening criteria and the pdbqt files of the protein receptors mentioned above. The results extracted and sorted the docking binding energy score. The lower the binding energy score was, the better the binding was. It can be concluded from Table 3 that triptolide, kaempferol, and Isoxanthohumol have suitable binding activities with TGFB, MMP9, and TNF, respectively. Finally, the docking of triptolide, kaempferol, and Isoxanthohumol with TGFB, MMP9, and TNF was selected for visual display, as shown in Fig. 8.

Table 3
The binding free energy of 3 small molecules with 8 genes

Molecule Name	Affinity (kcal/mol)							
	TNF	TGFB	VCAM1	VEGFA	ICAM1	MMP9	IL4	IL2
kamepferol	-8.8	-10.0	-7.1	-8.1	-6.6	-9.8	-6.5	-6.4
triptolide	-9.5	-6.9	-8.0	-8.7	-6.9	-9.6	-6.7	-8.1
isoxanthohumol	-9.3	-8.8	-6.9	-7.5	-6.9	-9.3	-6.2	-6.5

4. Discussion

Deposition of abnormal glycosylated IgA1 in the glomerular region is the pathogenesis of HSPN, and its pathogenesis is mainly related to food, drugs, infection, genetics, and intestinal microecological imbalance^[18, 19]. At present, many studies have confirmed that TW has an immunosuppressive effect by

inhibiting T cell activity and reducing cell proliferation, improving capillary permeability treatment HSPN^[20]. TW mainly contains triptolide, beta-sitosterol, triptonoditerpenic acid, and other biologically active ingredients^[21]. The results of this study showed that epoxy diterpene lactone (triptolide), flavonoids (kaempferol, nobiletin), sterols (β -sitosterol), coumarin derivatives (5,8-dihydroxy-7- (4-hydroxy-5-methyl-coumarin-3) -coumarin), and other compounds in TW have potential activity in the treatment of HSPN. The above components have specific anti-inflammatory effects and sound curative impacts on rheumatoid arthritis, nephrotic syndrome, systemic lupus erythematosus, lupus nephritis, and other diseases^[22–28].

In this study, network pharmacology of traditional Chinese medicine research methods, with the help of relevant databases and software to explore the mechanism of TW treatment of HSPN. There were 13 potential active components and 18 therapeutic targets in the treatment of HSPN. According to these targets, the biological processes and enrichment pathways of TW in the treatment of HSPN were further collected to explore its therapeutic mechanism, provide evidence support for the treatment of HSPN, and also provide a new way of thinking for the experimental study of TW as a treatment of HSPN.

The main active ingredients of TW in the treatment of HSPN obtained in this study include triptolide, kaempferol, isoxanthohumol, etc. One study found that serum IL-1 β and TNF- α levels were significantly lower in rats in all dose groups of triptolide relative to the model group, suggesting a significant anti-inflammatory effect of triptolide^[24].

According to PPI and literature analysis, TW treatment of HSPN may be through TNF, MMP9, VEGFA, IL-2, IL-4, ICAM1 VCAM1, and TGF- β 1. TNF- α is secreted by monocytes-macrophages and is a multi-biologically active peptide regulator involved in the body's immune defense function and is an essential mediator in the pathogenesis of inflammation, injury, and even shock in the body^[29]. Some studies have reported that high expression of TNF- α leads to the production of inflammatory factors such as interleukins and leukocyte adhesion molecules by endothelial cells and their deposition in the lining of small blood vessels, resulting in microvascular damage, which leads to skin purpura and kidney damage^[30]. VCAM1 is a cell adhesion molecule that covers the surface of endothelial cells, is mainly produced by activated endothelial cells, mediates leukocyte adhesion and extravasation, is primarily driven by the pro-inflammatory transcription factor NF- κ B, and plays a crucial role in the inflammatory response^[31]. It has been suggested that its increased expression in HSPN can lead to increased infiltration of inflammatory cells, thus reflecting the severity of the disease^[32]. MMP9 is one of the critical enzymes in glomerular basement membrane degradation, which can specifically degrade type IV collagen^[33]. It is reported that the serum level of MMP-9 in children with HSPN is significantly increased, and it is related to the occurrence and development of renal damage^[34, 35]. TGF β 1, an immunomodulatory factor secreted by CD4-positive helper T cells, is an inflammatory polypeptide factor with multiple biological functions. And some studies have shown that increased TGF β 1 expression is associated with the thickened tubular basement membrane, glomerular and tubular hypertrophy, and proteinuria formation. That inhibition of TGF β 1 expression is beneficial for protecting renal function^[36]. IL4 is an essential factor in allergic

diseases, promoting the conversion of immunoglobulin Ig to IgE and promoting the development of eosinophils, mast cells, etc., and inducing the activation of B cells^[37].

In the predicted pathway analysis, TNF signaling pathway, Toll-like receptor signaling pathway, PI3K-Akt signaling pathway, IL-17 signaling pathway, etc. The TNF signaling pathway can intervene in various signaling, mainly by regulating cell apoptosis or controlling the inflammatory response to release inflammatory mediators such as NO and pro-inflammatory factors such as IL-4 and IL-2, resulting in an inflammatory response that further activates more inflammatory genes, leading to kidney damage in children with HSP^[38–40]. The PI3K-Akt signaling pathway is one of the critical intracellular signaling pathways that play an essential role in inhibiting apoptosis and promoting proliferation in cells by directly or indirectly affecting a family of transcription factors (e.g., Forkhead, NF- κ B, p53, etc.)^[41]. Fu Yun-Yun^[42] et al. increased the anti-apoptotic effect of the PI3K-Akt signaling pathway by drug-promoted Akt phosphorylation expression and activity so that the non-phosphorylated form of Akt protein could not play a signaling response and finally exerted a therapeutic effect on HSPN in rats. The toll-like receptor is a relatively essential protein in the human body. It is a type I transmembrane protein. This protein can effectively activate intracellular signaling mechanisms by recognizing relevant molecules in pathogens, leading to inflammation^[43]. TLR2 signaling is involved in various autoimmune diseases, such as apoptosis and hypersensitivity reactions^[44]. TLR4 is expressed in multiple epithelial and endothelial cells, glomerular thylakoid cells, and tubular epithelial cells. Some studies have found that the TLR4 signaling pathway is activated when severely injured kidneys^[45].

In conclusion, by analyzing the interactions between the key targets and pathways of TW for the treatment of HSPN, the potential action targets and pathways of TW for the treatment of HSPN were revealed, providing a basis for subsequent related studies.

5. Conclusions

In this study, the active components of TW and the potential targets and key pathways acting on HSPN were predicted by network pharmacology. The active ingredients such as triptolide, kaempferol, isoxanthohumol in TW may inhibit the inflammatory response by acting on TNF, MMP9, VEGFA, IL-2, IL-4, ICAM1 VCAM1, and other targets, thus playing a role in the treatment of HSPN. Due to the limitations of the database and the software itself, the above results need to be further verified by experiments.

Declarations

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this article.

Acknowledgments

This work is supported by China's National Natural Science Foundation (81873339).

Authors' contributions

ZMM and ZWS: study design; acquisition of data; analysis of data; drafting of the manuscript. NJY, LB, and LG: acquisition of data; critical revision of the manuscript. HGL and LPF: revision of the manuscript and study supervision. All the author(s) read and approved the final manuscript.

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Figures

Figure 1

TW-active ingredient-target protein gene network

Figure 2

Veen diagram of drug target protein gene-disease gene

Figure 3

TW-Ingredients-HSPN-Targets network

Figure 4

Interaction network diagram of core targets

Figure 5

GO terms of TW against HSPN disease

Figure 6

Enrichment analysis of KEGG metabolic pathway Advanced bubble chart

Figure 7

TW-HSPN-Ingredients-Pathway network

Figure 8

Diagram of docking