



Study on the mechanism of Ginseng-Gegen for mesenteric lymphadenitis based on network pharmacology

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Background: This study aimed to determine the main active ingredients of the Ginseng-Gegen (Panax Ginseng-Radix Puerariae) drug pair, to predict relevant action targets, and to establish a network of “drug-active ingredients-targets”, to ultimately explore the mechanism of Ginseng-Gegen in the treatment of mesenteric lymphadenitis.

Methods: The Traditional Chinese Medicine Systems Pharmacology (TCMSP) platform was used to screen the chemical constituents of Ginseng-Gegen, and the active ingredient targets were retrieved by UniProt database. The databases of GeneCards and the Online Mendelian Inheritance in Man (OMIM) were applied to search for mesenteric lymphadenitis-related targets. Cytoscape software was used to construct the network of active ingredient-action targets. The biological functions of the targets were analyzed in the Database for Annotation, Visualization, and Integrated Discovery (DAVID) database.

Results: A total of 26 potential active ingredients of the Ginseng-Gegen drug pair were screened, with 128 drug-related targets and 255 mesenteric lymphadenitis-related targets. After matching, 23 potential targets were obtained for treating mesenteric lymphadenitis. Among them, *MOL012297* (puerarin), *MOL005344* (ginsenoside Rh2), and *MOL000358* (beta-sitosterol) were linked to 3 or more key target genes. They were supposed to be important ingredients of Ginseng-Gegen in the treatment of mesenteric lymphadenitis.

Conclusions: Ginseng-Gegen is related to oxidative stress and inflammation, and it is a part of the nuclear factor κ B (NF- κ B) signaling pathway, tumor necrosis factor (TNF) signaling pathway, and the advanced glycation end products/receptor for advanced glycation end products (AGE-RAGE) signaling pathway. These biological processes and signaling pathways may be potential mechanisms of Ginseng-Gegen for treating mesenteric lymphadenitis.

Keywords: Ginseng; Gegen; mesenteric lymphadenitis; network pharmacology; traditional Chinese medicine drug pair (TCM drug pair)

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Introduction

Mesenteric lymphadenitis, also known as Brennemann syndrome, is one of the common causes of abdominal pain in children. The disease occurs in children with upper respiratory tract infections or intestinal infections, and the typical symptoms are abdominal pain in the form of dull or cramping pain, mostly in the right lower abdomen, with most children having fever and nausea, and a few children also experiencing discomforts such as diarrhea and constipation. Mesenteric lymphadenitis usually occurs in children under 7 years old and adversely affects their learning and life, even resulting in growth impairment. In modern medicine, it is common to use antibiotics and microecological therapy, together with symptomatic treatment such as antispasmodic infusion and pain relief. However, the use of antibiotics in the treatment of mesenteric lymphadenitis is often criticized due to the lack of pathogenetic evidence, and it may even cause dual infection and bacterial resistance. In 2021, Yan Jiajia from China to analyze the medication rules of Chinese medicine in the treatment of mesenteric lymphadenitis in children through the Ancient and Modern Consilia Cloud Platform (V2.1). It includes 10 core combination of Poria Cocos-Liquorice, Radix Paeoniae alba-Liquorice, Radix Paeoniae alba and Corydalis Tuber-Liquorice, Pericarpium citri reticulatae-Liquorice and so on. These data indicate that traditional Chinese medicine (TCM) has been effective in treating mesenteric lymphadenitis and has been intensively studied (1). From the TCM perspective, the abdominal pain in children is caused by Qi stagnation. To be specific, “if there is a blockage of Qi, there will be pain”, in which the Qi function is regulated by the lung, spleen, and liver. Treatment of recurrent mesenteric lymphadenitis with TCM has showed a great therapeutic effect. Professor Youjia Xu, a renowned pediatrician in Lingnan Traditional Chinese Medicine Center, found that mesenteric lymphadenitis in children is a deficiency-excess syndrome, making it hard to cure and prone to recurrence in most patients. Qiwei Baizhu powder (QWBZP) is often used by Professor Youjia Xu in the treatment of mesenteric lymphadenitis; it is used to transform dampness by strengthening the spleen, and to resolve stasis by moving the Qi. Based on the syndrome differentiation in mesenteric lymphadenitis, the usage of QWBZP (plus or minus certain ingredients) has shown a total effective rate of 97.2% (2). Therefore, network pharmacological analysis of TCM prescriptions for mesenteric lymphadenitis can lay a solid

foundation for subsequent research. Since 2019, Zhang *et al.* have summarized and evaluated the databases required for TCM network pharmacology, which has been cited 158 times (3). In 2020, Luo *et al.* reviewed the methods, applications and prospects of network pharmacology in TCM research (4). In 2021, the Guideline on the Evaluation Methods of Network Pharmacology formulated by Tsinghua University and the Network Pharmacology Professional Committee of World Federation of Traditional Chinese Medicine Societies was released, which stipulates the evaluation content and standards of network pharmacology research, and has important guiding significance for the standardized development of network pharmacology and the field of network pharmacology of TCM (5,6). TCM network pharmacology methods have also been used to explain the occurrence and development of diseases and syndromes from a holistic perspective. Some researchers have found through experimental studies that tonifying and replenishing medicine could enhance the intestinal microecological environment and the growth of beneficial micro-organisms in the intestine (7). Meanwhile, other researchers have found through experimental studies that using QWBZP for the treatment of mesenteric lymphadenitis could be very effective in inhibiting pathogens that cause gastrointestinal (GI) disorder, including *Staphylococcus aureus*, *Salmonella*, and so on (8,9). The main ingredients in QWBZP that have shown the ability to inhibit GI pathogens are Ginseng and Gegen (10). The first record of QWBZP was in the *Key to Therapeutics of Children's Diseases*, and the main ingredients were said to be Ginseng, Gegen, Poria, fried Atractylodes, Licorice, Patchouli leaf, and Costus root. It is used to strengthen the spleen and benefit the Qi, generating the fluid and nourishing the stomach, and treating spleen-stomach weakness and the syndrome of fluid-deficiency with internal heat. Ginseng-Gegen is a common drug pair in the treatment of spleen-stomach weakness. A pharmaceutical study showed Ginseng can tonify Qi and nourish yin and Gegen can upraise the middle Qi and engender fluid (11). These two herbs are the main and important ingredients of QWBZP. The syndrome of spleen-stomach Qi deficiency is often the impaired upraising of spleen and Qi deficiency with sagging performance. Ginseng (12) is an essential herb for invigorating the spleen and boosting vitality. Its flavor is sweet and slightly bitter. It has showed a good effect of invigorating Yuan and benefiting Qi, alongside calming the mind and improving mental health. Gegen has a slightly sweet flavor, cool nature, and exerts a very good

antipyretic muscle effect; at the same time, it also leads to very good secretion thirst, raising Yang Qi and deploying an antidiarrheal effect (13). The combination of Ginseng and Gegen can strengthen their propensity to uplift. Moreover, Gegen has the property of ascending and dispersing, which can promote the Yang energy of the spleen and stomach; and as “wind energy is better than dampness”, Gegen can dispel water dampness caused by the weakness of the spleen due to the inability to transport and transform (14). Therefore, the Ginseng-Gegen drug pair is the core of the QWBZP, thus playing a key role in the treatment of mesenteric lymphadenitis.

In general, abnormality of the lymph nodes has been associated with the occurrence of mesenteric lymphadenitis, which means, the chance of lymphadenitis was increased due to the abundance of lymph nodes in the mesentery. Specifically, the pathogen infects children through the digestive tract and upper respiratory tract. From there, the pathogen could invade the mesentery in the intestine, resulting in abnormal stimuli to the intestinal lymph and triggering an adverse immune response, from which abdominal pain could be one of the symptoms. The chemical composition of Ginseng, as a TCM drug, contains saponins, polysaccharides, proteins, and peptides (15), among which ginsenosides and Ginseng polysaccharides can enhance the phagocytic activity of macrophages and have the effect of promoting the production of interferon (IFN) and interleukin (IL)-2, thus enhancing immune function and the anti-inflammatory effect. Meanwhile, some researchers have also found that ginsenosides and Ginseng polysaccharides have a good health promoting effect on children’s intestinal microbiota (16), which can significantly improve the intestinal microbial environment and effectively inhibit the pathogen (17). Gegen (18) is rich in various chemical ingredients, which have papaverine-like antispasmodic effects on isolated intestinal tubes of mice and guinea pigs; it also has a certain antibacterial effect. Pueraria polysaccharide and Puerarin (19) exert an excellent inhibitory effect on various pathogenic bacteria of mesenteric lymphadenitis. However, there is an absence of in-depth investigation on the specific targets and pathways of “Ginseng-Gegen” in the treatment of pediatric mesenteric lymphadenitis.

In this study, the network pharmacology method was applied to construct the complex drug-biomolecule relationship of the interaction between “Ginseng-Gegen” and pediatric mesenteric lymphadenitis. The drug action target-endogenous protein-biological pathway relationship

was explored, to make proper predictions on the targets of the active ingredients and their regulated biological processes, which has laid a solid foundation for future research.

Methods

Materials

The Traditional Chinese Medicine Systems Pharmacology Database (TCMSP; <http://lsp.nwu.edu.cn/tcmsp.php>), UniProt Knowledgebase (<https://www.uniprot.org/>), Search Tool for the Retrieval of Interacting Genes/Proteins (<https://cn.string-db.org/>), Online Mendelian Inheritance in Man Database (<https://www.omim.org/>), GeneCards Database (<https://www.genecards.org/>), Database Visualization and Integrated Discovery system (<http://david.abcc.ncifcrf.gov/home.jsp>, version 6.8), Cytoscape 3.2.1 software (https://cytoscape.org/download_old_versions.html), and Venny 2.1.0 (<https://bioinfogp.cnb.csic.es/tools/venny/>) tools were used in this study.

Molecular information of the drug and screening of active ingredients

The molecular information of Ginseng-Gegen was obtained from the TCMSP database and carefully screened based on its oral bioavailability (OB), drug-likeness (DL), and half-life (HL). The specific screening conditions were OB $\geq 30\%$, DL ≥ 0.18 , and HL ≥ 4 hours. The active ingredients of Ginseng-Gegen were also located based on the literature review.

Prediction of action targets of Ginseng-Gegen

Based on the TCMSP database, the targets corresponding to the active ingredients of Ginseng and Gegen were screened by the UniProt database, to identify the targets of “human” species, which are the predicted targets of Ginseng-Gegen.

Construction of mesenteric lymphadenitis-related targets

In this study, the targets related to mesenteric lymphadenitis were constructed based on GeneCards and OMIM databases. The term “mesenteric lymphadenitis” was used for the search, and only one target from the duplicate targets was kept to complete the construction of mesenteric

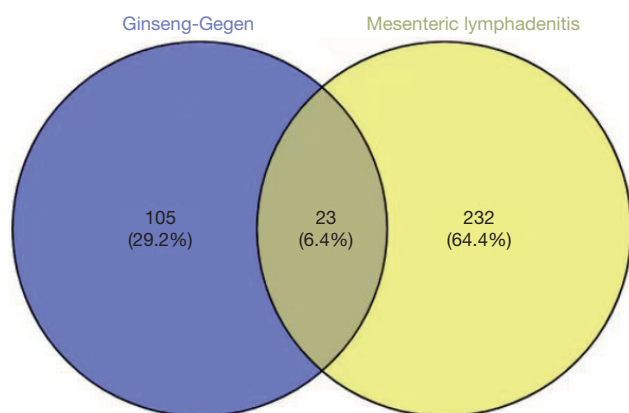


Figure 1 Venn diagram of overlapping targets of Ginseng-Gegen and mesenteric lymphadenitis.

lymphadenitis-related targets. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Network construction and analysis

Using the Venny 2.1.0 tool, the predicted targets of effective chemical ingredients were intersected with disease-related targets to obtain the predicted targets of the Ginseng-Gegen drug pair in mesenteric lymphadenitis. Cytoscape software was used to construct a network of active chemical ingredients of Ginseng-Gegen and their targets in mesenteric lymphadenitis. The mesenteric lymphadenitis-related targets and the potential targets of Ginseng-Gegen were imported into the STRING database, and protein-protein interaction (PPI) analysis was performed to construct a target-target PPI network using Cytoscape 3.2.1.

Analysis of biological processes and pathway enrichment of potential targets

The predicted targets of the action of Ginseng-Gegen in mesenteric lymphadenitis were imported into the DAVID 6.8 database for Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis.

Results

Screening of active ingredients from the Ginseng-Gegen drug pair

The TCMSP database was used to obtain the active

ingredients of Ginseng-Gegen, with the screening conditions being OB $\geq 30\%$, DL ≥ 0.18 , and HL ≥ 4 hours, and the information of confirmed active ingredients was added. A total of 26 active chemical ingredients and 128 action targets were obtained.

Disease targets results

A total of 269 mesenteric lymphadenitis-related targets were collected from the GeneCards and OMIM databases, and only one target was retained from duplicate targets, resulting in a total of 255 disease-related targets.

Network construction and analysis results

The Venny 2.1.0 tool was used to intersect and compare the potential targets of drug action with disease targets and to draw Venn diagrams (Figure 1), and a total of 23 common targets were obtained (Table 1). Cytoscape software was used to construct a chemical ingredient-target network with 37 nodes and 55 edges, as shown in Figure 2. To further investigate the mechanism of action of Ginseng-Gegen in the treatment of mesenteric lymphadenitis, protein interaction relationship data were imported into Cytoscape software to draw the PPI network, which involved 357 nodes and 2,875 edges, as shown in Figure 3. Furthermore, the key action targets were calculated according to CytoHubba, a plugin of Cytoscape. These key action targets include CXCL8, CXCL10, CCL5, CXCL2, CCL20, CCR5, CXCR4, CCL19, CCR7, and CXCR3 (Table 2). Many experiments have shown that the expression of CXCR3, CXCR4 (20), CCL20, CCR5, CCR7 (21), CXCL8, CXCL10 (22), CCL5, CXCL2 (23), and CCL19 (24) in this experiment is related to enteritis.

KEGG signal pathway analysis results

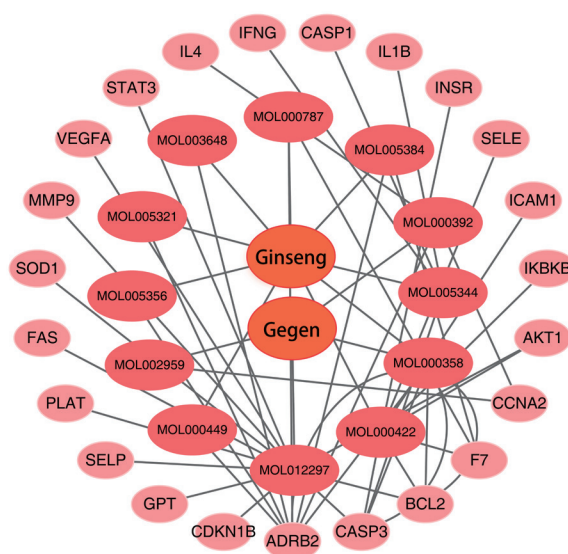
The KEGG pathway enrichment analysis was sorted according to the number of enriched genes in the pathway (Figure 4). The results showed that the effect mechanism of “Ginseng-Gegen” in the treatment of mesenteric lymphadenitis was mainly related to the advanced glycation end products/receptor for advanced glycation end products (AGE-RAGE) signaling pathway, tumor necrosis factor (TNF) signaling pathway, nuclear factor κ B (NF- κ B) signaling pathway, and so on, and may also be crossed with some pathways related to viral infections [influenza A, Epstein-Barr virus (EBV), etc.].

Table 1 List of common targets

No.	Targets
1	INSR
2	SELP
3	AKT1
4	STAT3
5	CASP1
6	PLAT
7	IKBKB
8	IL1B
9	SOD1
10	FAS
11	CDKN1B
12	IFNG
13	IL4
14	BCL2
15	ADRB2
16	VEGFA
17	F7
18	ICAM1
19	CCNA2
20	GPT
21	SELE
22	CASP3
23	MMP9

Discussion

Pediatric mesenteric lymphadenitis is a very common disease. The occurrence is always associated with infection of the respiratory tract and GI tract, and the symptoms include fever, vomiting, and diarrhea. Recurrent symptoms could affect the physical and mental health of affected children. The main incidence age of this disease in children is under 7 years old and the disease mainly occurs in spring and winter. As a recurrent inflammatory disease of the GI tract, it could affect the physical and mental health of the children (25), causing a great clinical concern. Although the cause of mesenteric lymphadenitis is not yet clear, the disease is characterized by repeated abdominal pain and

**Figure 2** Ginseng-Gegen-chemical ingredients-target network.

abdominal lymph node enlargement (26). Therefore, in the absence of a clear etiology, it is difficult to identify specific drugs, and therefore the treatment for mesenteric lymphadenitis has only provided symptomatic relief, not a cure. Under this circumstance, Chinese medicine has shown a significant advantage in the aspect of treating GI disorder, with good efficacy in both internal and external treatment. Furthermore, most studies (2,8,9,27) have shown that the clinical efficacy of the treatment of this disease with QWBZP is the most prominent among TCM treatments. The main functional herbs of QWBZP are Ginseng, Gegen, and so on (27). The combination of these two herbs comprises a drug pair that can be described as “mutually reinforcing, mutually assisting, mutually restraining, mutually inhibiting, antagonistic, mutually suppressive”, so that the cubic curative effect is more prominent.

Therefore, the drug pair is often considered the core of a prescription. Ginseng and Gegen were commonly used by ancient Chinese physicians as representative drugs for the method of benefiting Qi and raising Yang, as well as a first-choice for GI diseases with the spleen deficiency, often with good results in various relevant diseases. In this study, more than 20 active ingredients, such as daucosterol, β -sitosterol, kaempferol, ginsenoside, and Ginseng saponin, were found as functional in the Ginseng-Gegen drug pair. Among them, β -sitosterol, ginsenoside Rh2 (GRh2), and ginsenoside have very many predicted targets, which fully indicates that the above active ingredients or chemical

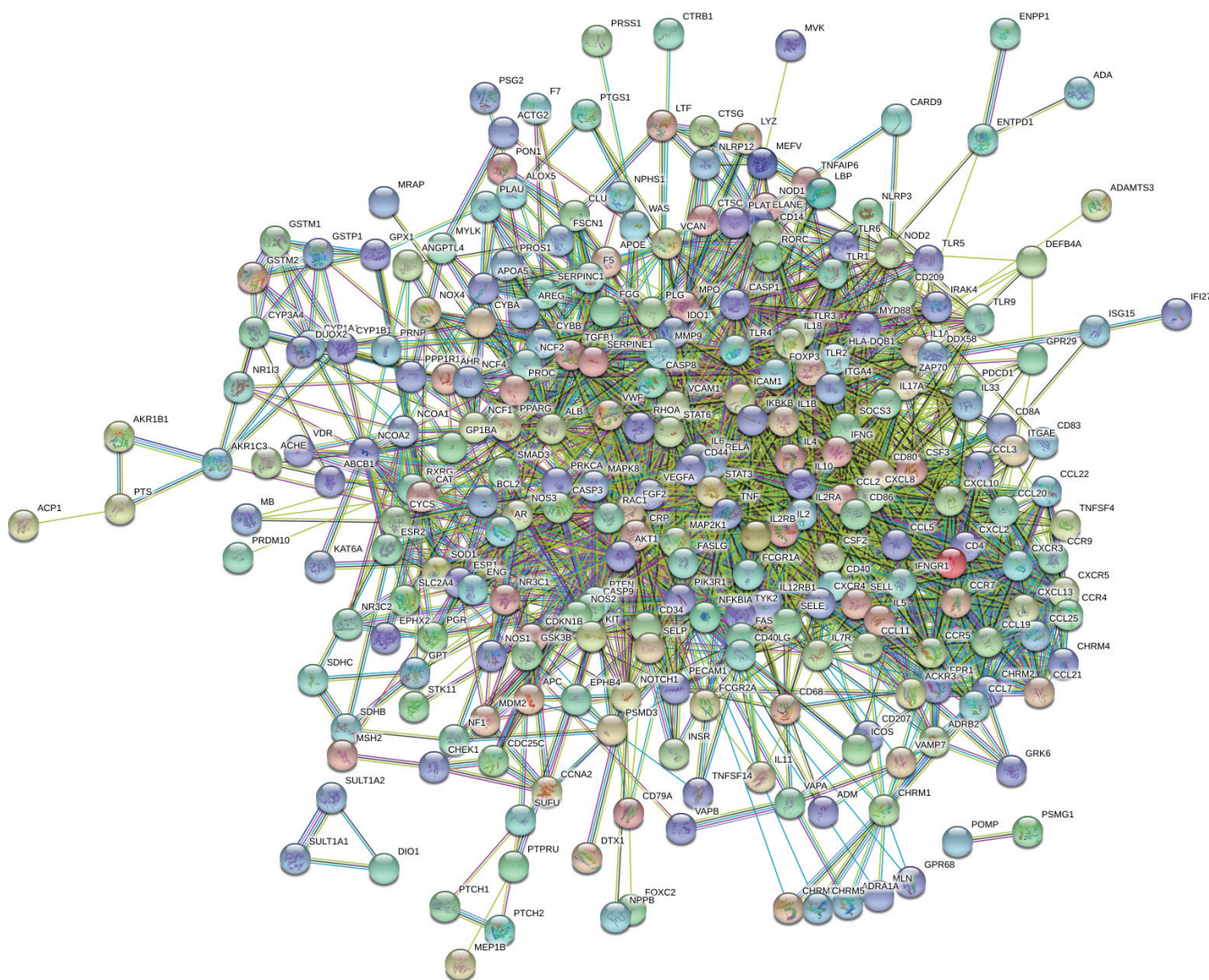


Figure 3 Ginsen-Gegen PPI network diagram. PPI, protein-protein interaction.

ingredients are the key to the pharmacological mechanism of the drug and are important for the treatment of pediatric mesenteric lymphadenitis when using Ginseng-Gegen.

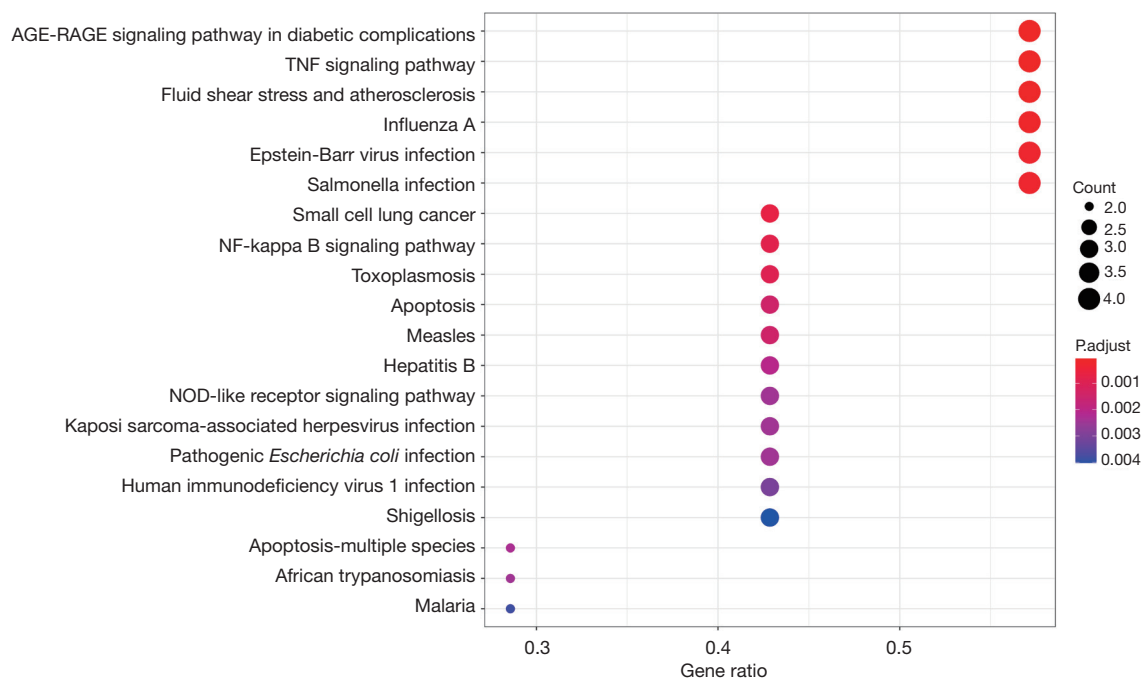
A type of plant sterol with the structure like cholesterol, β -sitosterol exists widely in human food. It has shown a significant anti-inflammatory effect (28). Male C57BL/6J mice induced with sodium dextran sulfate were observed to develop severe mucosal colitis with significant colonic surface epithelial distortion and crypt loss. In contrast, β -sitosterol was shown to significantly inhibit colonic shortening, decrease the numbers of hemoglobin content in feces, and reduced the severity of meso- and distal colitis. At the same time, significant decreases in colony-stimulating

factor-1 and NF- κ B were observed (29). For high-fat diet-induced colonic inflammation, the manifested symptoms such as increased expression of pro-inflammatory cytokines and activation of NF- κ B in the colon can be inhibited by β -sitosterol. As for endotoxin [lipopolysaccharide (LPS)]-stimulated intestinal macrophages, β -sitosterol inhibited the production of pro-inflammatory cytokines and the activation of inflammation-related enzymes and NF- κ B. In addition, β -sitosterol prevented the binding of LPS to intestinal and peritoneal macrophages. It also effectively inhibited the interaction of LPS with Toll-like receptor 4 in intestinal macrophages (30).

Ginsenosides in Ginseng are the main physiologically

Table 2 Topological property parameters of key targets in the treatment of mesenteric lymphadenitis by Ginseng-Gegen

Targets	Key action genes	Degrees	Betweenness centrality	CytoHubba-MCC score
Interleukin 8, chemokine CXCL8	<i>CXCL8</i>	80	0.51607445	1.12E+21
Chemokine CCL10	<i>CXCL10</i>	53	0.46564885	1.12E+21
Chemokine CCL5	<i>CCL5</i>	49	0.46423135	1.12E+21
Chemokine CXCL2	<i>CXCL2</i>	37	0.43696275	1.12E+21
Chemokine CCL20	<i>CCL20</i>	36	0.42776999	1.12E+21
CC chemokine receptor 5 (CCR5)	<i>CCR5</i>	44	0.44267054	1.12E+21
CC chemokine receptor 4	<i>CXCR4</i>	56	0.48644338	1.12E+21
Chemokine CCL19	<i>CCL19</i>	29	0.40131579	1.12E+21
CC chemokine receptor 7 (CCR7)	<i>CCR7</i>	46	0.43571429	1.12E+21
CC chemokine receptor 3 (CCR3)	<i>CXCR3</i>	37	0.41496599	1.12E+21

**Figure 4** KEGG pathway enrichment map of predicted targets of Ginseng-Gegen treatment for mesenteric lymphadenitis. AGE-RAGE, advanced glycation end products/receptor for advanced glycation end products; KEGG, Kyoto Encyclopedia of Genes and Genomes; NF, nuclear factor; NOD, nucleotide-binding oligomerization domain; TNF, tumor necrosis factor.

active and effective ingredients of the central nervous system, cardiovascular system, immune system, and endocrine system. GRh2 has been labeled one of the most important ginsenosides due to its anti-inflammatory effects; GRh2 reduces the production of LPS induced pro-inflammatory mediators nitric oxide (NO), TNF- α , IL-1 β ,

and anti-inflammatory cytokines (IL-4, IL-6, and IL-10) in lung tissue. It also blocks the inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), I κ B- α , ERK, JNK, p38, Raf-1, and MEK protein phosphorylation, suggesting that GRh2 intervenes in anti-inflammatory and anti-oxidative stress processes (31).

Puerarin has an antipyretic effect on LPS-induced rat fever by inhibiting pyrogens produced by macrophages (32). In LPS-induced RAW264.7 macrophages, puerarin inhibited the expression of iNOS, COX-2 and C-reactive protein by dose-dependently inhibiting phosphorylation and reducing p65 NF- κ B nuclear translocation (33). In addition, puerarin (34) regulates transcriptional levels through inhibition of the NF- κ B and MAPK signaling pathways and inhibits the production of IL-1 β , IL-6, TNF- α , prostaglandin E2 (PGE2), and NO in mouse thylakoid cells. Puerarin inhibited N-carboxymethyl lysine-induced inflammatory responses by inducing heme oxygenase-1 (HO-1) expression mediated by the PKC δ -Nrf-2/HO-1 pathway (35). The anti-inflammatory mechanism of puerarin (36) was mainly through inactivation of IKK α/β , inhibition of nuclear translocation of NF- κ B and prevention of degradation of iK β a cells, and inhibition of inflammatory mediator production by Danshen-Gegen drug pair on LPS-stimulated mouse mononuclear macrophage leukemia cells RAW264.7. Puerarin can achieve anti-inflammatory effects by down-regulating the secretion of NF- κ B and pro-inflammatory mediators, exhibit antioxidant effects by regulating the F-E2p45-related factor (Nrf2) pathway and the expression of antioxidant enzyme 11, and inhibit intestinal epithelial barrier dysfunction by increasing the expression of tight junction protein (claudin-2).

The core targets of the Ginseng-Gegen drug pair are also related to multiple signaling pathways, including the AGE-RAGE, NF- κ B, and TNF signaling pathways, among others. The NF- κ B pathway is an important signaling pathway mediating the inflammatory response, which can cause the expression of inflammatory factors such as TNF- α and IL-1 β , resulting in a series of non-specific inflammatory responses that cause recurrent abdominal pain and fever. The TNF signaling pathway is also an important pathway involved in the systemic inflammatory response. As one of the cytokines that make up the acute phase response, TNF is mainly produced by activated macrophages, which can trigger the activation of many pathways, with the NF- κ B pathway included. The AGE-RAGE signaling pathway is the binding product of AGE and its receptor RAGE, nicotinamide adenine dinucleotide phosphate hydrogen (NADPH), and enhances oxidative stress, activating the NF- κ B signaling pathway, which further stimulates the production of cytokines and growth factors. It can be hypothesized that the Ginseng-Gegen pair exerts its therapeutic effects largely by counteracting the

inflammatory response and oxidative stress damage.

In this study, the main active ingredients and their potential targets were identified through analysis of the Ginseng-Gegen drug pair by a network pharmacological approach. Their mechanisms for the treatment of mesenteric lymphadenitis were discussed through target and pathway analysis, but further experimental data are still needed. In addition, this study also revealed active ingredients in the Ginseng-Gegen drug pair, as well as the multiple targets and pathways of the characteristics of synergy, according to composition and efficacy of TCM prescription. It has provided important clues and laid a foundation for further in-depth study on the active ingredients and mechanism of the Ginseng-Gegen drug pair in the treatment of mesenteric lymphadenitis. Ginseng and Gegen, as part of QWBZP, have a wide range of pharmacological effects. Many experimental studies have shown that this pair can regulate the body in multiple pathways and targets, which is also a reflection of the “holistic view” of TCM in the microscopic world. Overall, this drug pair regulates the function of the spleen and stomach and the immune function, maintains the balance of the internal environment, and plays a therapeutic role in anti-inflammation and antioxidation in multiple targets.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tp.amegroups.com/article/view/10.21037/tp-22-386/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work, including ensuring that any questions related to the accuracy or integrity of any part of the work have been appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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