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Exploration on the Mechanisms of Chinese Herbal Medicine (Golden Thread) for Tuberculosis based on the Focused Network Pharmacology

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Abstract: In order to explore the active ingredient, potential targets, and the tuberculosis-related molecular mechanism of Golden thread along with the scientific explanations based on the method of network pharmacology. We retrieved the active components and the targets of the Golden thread from the TCMSP database. The target genes corresponding to tuberculosis were screened and obtained from GeneCards and OMIM, and the disease-drug protein target genes were obtained after the intersection of the two. The target network of Golden thread's active ingredient for tuberculosis was constructed using Cytoscape. String database was used for the protein-protein interaction analysis.Resultly, a total of 48 corresponding components of Golden thread were searched in the TCMSP database and screened, which revealed 14 active components having good interactions with 75 TB-related target proteins. The network pharmacology analysis revealed that the biological functions of the Golden thread–TB intersection target genes mainly included immune response, signal transduction, metabolism, and the regulation of the tumor necrosis factor signaling pathways, IL-17 and Toll-like receptors signaling pathways, HIF-1 signaling pathway, and tuberculosis-related pathways to play a role in the intervention of TB. To sum up, the present work explored the different active ingredients of Golden thread playing a role in the intervention of TB and the role of multiple pathway characteristics, and performed a preliminary validation of the basic pharmacological effects of Golden thread and their underlying mechanism, providing novel insights into the mechanism of action of Golden thread intervention in TB.

1. Introduction

Tuberculosis has been recognized as an extremely serious chronic infectious disease by the ancient medical scientists of China [1]. In traditional Chinese medicine, the development of tuberculosis caused by infection with the tuberculosis bacteria is known as pulmonary tuberculosis, while tuberculosis related to the disorder of immune function is considered to occur due to the deficiency

of vital qi. Moreover, certain studies have demonstrated that the pathogenesis of pulmonary tuberculosis involves immune regulation, inflammatory response, and multiple regulatory sites rather than a single-pathway regulation. Therefore, it is crucial to study tuberculosis in relation to multiple pathways.

The first documented record of Golden thread is found in an herbal monograph titled 'Shennong's Classic of Materia Medica' written during the Han dynasty, which states it as a "Top grade" herb. The golden thread is a medicinally important perennial herb from the genus Coptis and family Ranunculaceae. According to the concept of TCM, Golden thread exerts the effects of removing heat, drying the dampness, purging fire, and detoxification, along with antibacterial and anti-inflammatory functions.Modern pharmacological studies have demonstrated that Golden thread exhibits anti-inflammatory, antibacterial, and other pharmacological effects. However, since Golden thread contains several complex and diverse components, it is difficult to explain their real scientific connotations without studying the effect of each component on tuberculosis to unravel the mechanism underlying its pharmacodynamics. Therefore, it is of great significance to explore the effective targets and pathways of Golden thread involved in tuberculosis to scientifically demonstrate the mechanism of Golden thread intervention in tuberculosis from a molecular perspective.

Network pharmacology involves elucidating the process of disease occurrence and development from the perspective of systems biology and balance of the biological networks, to understand the interaction between drug and organism and guide the research and development of novel drugs from the holistic perspective of improving or restoring the network balance. The network of "drug-target-disease-pathway" interactions is particularly suitable for studying the mechanism and the material basis of multi-component, multi-target, and multi-pathway-based traditional Chinese medicine, as it provides novel insights and methods for the study of the holistic mechanisms of TCMs [2]. In this context, the present study used network pharmacology to summarize and arrange the components and targets of Golden thread intervention in tuberculosis, and through a systematic biological analysis, reveal the synergy among the components, targets, and pathways of Golden thread, in order to have novel insights into the mechanism of Golden thread intervention in tuberculosis.

2. Materials and Methods

2.1. Screening of Golden thread ingredients

The ingredients of the Golden thread were searched in the traditional pharmacology database of the TCM system and the analysis platform TCMSP [3] using "Golden thread" as the keyword. Quantitative analysis of multiple components is becoming increasingly important for the quality evaluation of TCM. The criteria for selecting the active ingredients were: oral bioavailability (OB) ≥30% and drug-like (DL) ≥ 0.18 [4].

2.2. Screening of targets and collection of related information

The TCMSP database was used to query the drug target genes corresponding to a particular ingredient of Golden thread and for the subsequent summarizing and sorting. The keyword Tuberculosis (TB) was entered into the GeneCards (Version 4.5.0) and OMIM databases to retrieve the target genes related to Tuberculosis (TB). The target genes of the Golden thread were constructed with the target genes of Tuberculosis (TB) to generate the target genes of the disease-drug protein.

2.3. The network construct of the active ingredient–drug targets

The results of the target genes of disease, i.e., drug-protein, from the databases were imported into

the Cytoscape software version 3.7.1, in which the relative target network of the active ingredient of Golden thread was constructed.

2.4. Analysis of the contribution and interactions of proteins

The String software (version 10.5) comprises a database of known and predicted protein-protein interactions and can automatically score the interactions of proteins, with the higher scores implying higher credibility of protein-protein interaction. In order to ensure the reliability of the database, the PPI network comprising the products of gene expression was constructed by selecting a high confidence score of over 0.7, followed by visualization and analysis of the network using the Cytoscape software [5].

2.5. Genes function and pathway analysis

In order to further explore the function of the pathways [6], GO classified enrichment analysis of the obtained 75 targets was performed, and the top 10 pathways in the analysis results were noted. The GO classified enrichment analysis included the molecular function (MF), cellular component (CC), and biological process (BP) analyses.

2.6. Classification of the target types

The DisGeNET database (version 5.0) contains the genes and variants associated with human diseases. In order to select the genes in the DisGeNET database for retrieval, the interaction target of coptis was input into the database to obtain the tape information of the target (Protein Class) [7].

3. Results

3.1. Screening of the active ingredients of Golden thread

The search for the chemical ingredients of Golden thread in the TCMSP database revealed a total of 48 chemical ingredients. After applying >30% and >0.18 percent as the screening conditions and simultaneously screening out the components without corresponding targets, 14 potentially effective components were finally obtained (Table 1).

Table 1: Potential effective ingredients of Golden thread

Molld	MolName	OB	DL
MOL001454	Berberine	36.86	0.78
MOL013352	Obacunone	43.29	0.77
MOL002894	Berberrubine	35.74	0.73
MOL002897	Epiberberine	43.09	0.78
MOL002903	(R)-Canadine	55.37	0.77
MOL002904	Berlambine	36.68	0.82
MOL002907	Corchoroside A-qt	104.95	0.78

3.2. Screening of the targets corresponding to the active components

The drug targets corresponding to the effective components of the Golden thread were obtained after the deletion of duplicate and false-positive results. A total of 148 targets were identified for the 14 active components of Golden thread, which are listed in Table 2.

Table 2: Collection and screening of target information of the potential effective ingredients of Golden thread

Molld	MolName	Target	Symbol
MOL001454	berberine	Nitric oxide synthase, inducible	NOS2
MOL001454	berberine	Prostaglandin G/H synthase 1	PTGS1
MOL001454	berberine	Potassium voltage-gated channel subfamily H member2	KCNH2
MOL001454	berberine	Estrogen receptor	ESR1
MOL001454	berberine	Androgen receptor	AR
MOL001454	berberine	Sodium channel protein type 5 subunit alpha	SCN5A
MOL001454	berberine	Prostaglandin G/H synthase 2	PTGS2
MOL001454	berberine	Retinoic acid receptor RXR-alpha	RXRA
MOL001454	berberine	Beta-2 adrenergic receptor	ADRB2
MOL001454	berberine	Berberine Trypsin-1	PRSS1

3.3. Screening of the disease targets

The genes related to Tuberculosis were retrieved from the GeneCards and OMIM databases, and the duplicate targets were merged, providing a total of 2173 Tuberculosis-related targets (Table 3).

Table 3: Collection and screening of tuberculosis-related targets

Gene symbol	Description	GC ID	Relevance score
IFNG	Interferon Gamma	GC12M068064	47.60
SLC11A1	Solute Carrier Family 11 Member 1	GC02P218382	47.20
IFNGR1	Interferon Gamma Receptor 1	GC06M137197	44.61
IL12RB1	Interleukin 12 Receptor Subunit Beta 1	GC19M018030	41.39
TNF	Tumor Necrosis Factor	GC06P032499	39.25
TLR2	Toll Like Receptor 2	GC04P153684	38.10
IL12B	Interleukin 12B	GC05M159314	37.14
IL10	Interleukin 10	GC01M206767	33.86
VDR	Vitamin D Receptor	GC12M047841	28.42
ADA	Adenosine Deaminase	GC20M044620	28.07

3.4. Prediction of the active components of the Golden thread intervention–Tuberculosis (TB) targets

Figure 1: Venn diagram of the active ingredients-intervention tuberculosis targets of Golden thread

As visible in the Venn diagram (Figure 1), the intersection of the targets corresponding to the active ingredient of Golden thread and the tuberculous-related targets generated 75 active ingredient-disease targets.

3.5. Construction of the network of active components-interaction targets

The active components–disease target results were input into the Cytoscape 3.7.1 software, and the Bisogenet plug-in was used to construct the disease-protein interaction network. Finally, the target network of the main active ingredients of Rhizoma coptiae for tuberculosis intervention was obtained (Figure 2). As depicted in Figure 2, the network had 227 nodes and 265 edges. The purple color represents the active components of coptis chinensis, the yellow color represents the tuberculosis-related targets corresponding to these active components, and the side represents the interaction between the active components and the intervention target of TB. The results demonstrated that the three gene targets, namely, NOS2, PTGS2, and ADRB2, in the outer ring were highly correlated with the chemical components and, respectively associated with 8, 8, and 6 active components, indicating that these three might be the core targets of Golden thread intervention in tuberculosis. Each active ingredient could act on multiple targets, and each target is related to multiple compounds, implying that different compounds may share a common role in the pharmacodynamics action of Rhizoma coptiae. It was observed that all the 14 active components of coptis obtained after screening had multiple targets (Figure 2); the same target could correspond to different active components, while different targets could correspond to the same active component. Each target connected to multiple components reflected the characteristics of coptis of having multiple components and multiple targets.

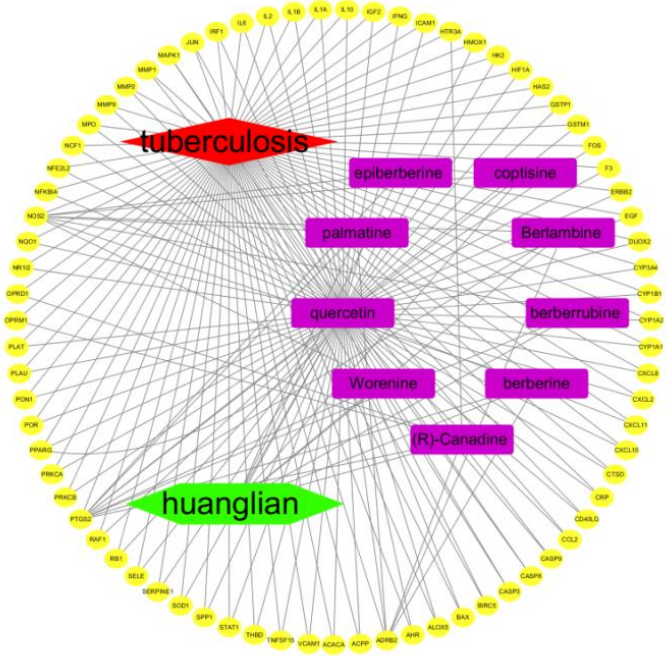

Figure 2: The network of active components-interaction targets

3.6. Network construction and analysis of protein interactions

In order to further explore the mechanism of Golden thread intervention in tuberculosis in relation to PPI, the present study employed the Cytoscape software to analyze the topological characteristics of the network, and a PPI network of the potential targets of Golden thread was constructed (Figure

3). The PPI network contained 75 nodes and 397 interaction relations. In the figure, the nodes represent the proteins and the edges represent the relationship among the proteins. The size and color of the nodes represent the degree value of the size; the bigger spots or deeper color correspond to a higher degree value. Bigger spot implies more effectiveness in TB. The thickness of the side represents the Combine score; the thicker the side, the higher the score. A higher score implies a larger node and a larger position in the whole network. The topological properties of each node were calculated, revealing the key targets of Rhizoma coptiae's effect on tuberculosis intervention. The target proteins with the highest degree value in the protein interaction network were selected and were expected to play an important role in the process of Rhizoma coptiae's intervention in tuberculosis. There were 19 key nodes between the betweenness centrality and the betweenness greater than the mean (betweenness = 10.6 and betweenness = 0.0189), which accounted for 25.3% of the total number of nodes. Finally, the key nodes with a degree value of 15 or greater than 17 degrees, the betweenness centrality acuity of 0.020479, and the closeness (center close to the degree of nodes) of 0.5 or more were selected as the main ones. These selected key nodes included the target proteins of IL6, JUN, MMP9, HMOX1, MAPK1, IL1B, FOS, CASP3, EGF, CXCL8, IL10, PTGS2, CCL2, STAT1, MMP2, NFE2L2, AHR, and ICAM1, which had among the highest degree of value for interleukin 6 (IL - 6) and could interact with 35 proteins, suggesting that this target protein plays an important role in the whole network. In the ranking of its network, the nodes with JUN and MMP9 were the key nodes in the network, indicating that they might be the core targets of Golden thread intervention in tuberculosis. The key targets were subsequently imported into the DisGeNET database to obtain the corresponding target types [8]. The main information is presented in Table 4. The results revealed that signal molecules, pro-inflammatory cytokines, tumor necrosis factors ligands, transcriptional activators, chemokines, receptors (peroxisome proliferator-activated receptor, serotonin receptors), proteins (regulatory proteins, heat shock proteins), enzymes (hydrolase, catalase, transferase, protein kinase), among others, participated in the intervention process of Golden thread.

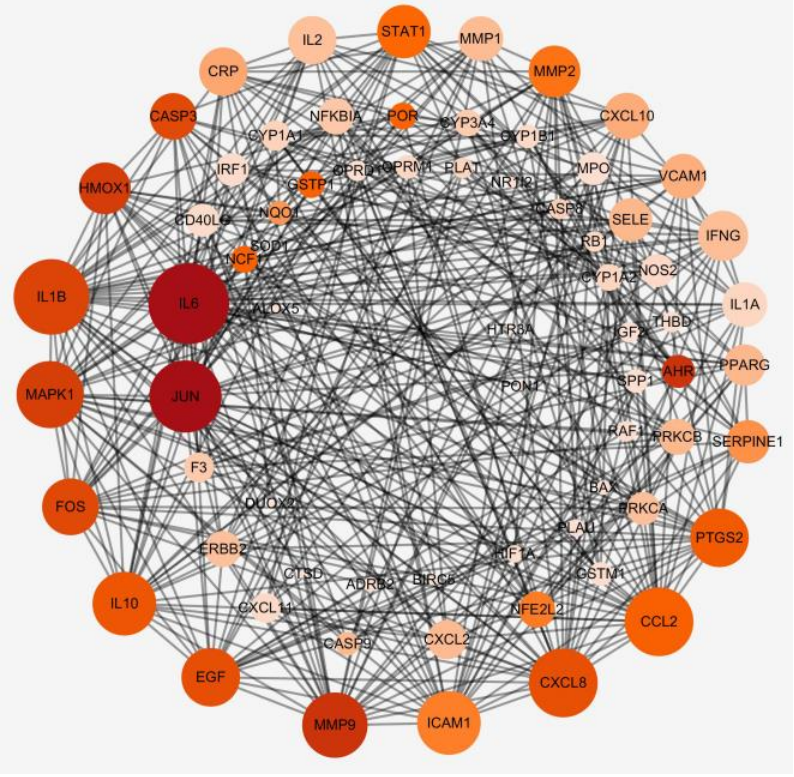

Figure 3: Network construction and analysis of protein interactions

Table 4: Key targets of tuberculosis intervention effect of Golden thread and their topological properties

Gene	Protein	Protein classification	Betweenness	Closeness	Degree
IL6	Interleukin-6	Null	0.12651797	0.65714286	35
JUN	Transcription factor AP-1	Nucleic acid binding; Transcription factor	0.12521004	0.62162162	30
IL1B	Interleukin-1 beta	Null	0.06441885	0.61061947	32
IL10	Interleukin-10	Null	0.04448691	0.58974359	25
MAPK1	Mitogen-activated protein kinase 1	Kinase; transferase	0.07063447	0.58474576	27
MMP9	Matrix metalloproteinase-9	Hydrolase; protease	0.08266563	0.57983193	26
CXCL8	Interleukin-8	Signaling molecule	0.05134135	0.57983193	28
CCL2	C-C motif chemokine 2	Signaling molecule	0.03278853	0.57983193	28
HMOX1	Heme oxygenase 1	Oxidoreductase	0.07318182	0.55645161	18
FOS	Proto-oncogene c-Fos	Transcription factor	0.05986419	0.55200000	21
STAT1	Signal transducer and activator of Transcription 1-alpha/beta	Nucleic acid binding; transcription factor	0.02582693	0.55200000	19
ICAM1	Intercellular adhesion molecule 1	Null	0.0209095	0.55200000	25
PTGS2	Prostaglandin G/H synthase 2	Oxidoreductase	0.03903318	0.54761905	22
EGF	Pro-epidermal growth factor	Null	0.05233476	0.54330709	22
MMP2	72 kDa type IV collagenase	Hydrolase; protease	0.02314096	0.51111111	18
CASP3	Caspase-3	Enzyme modulator; hydrolase; protease	0.05793456	0.50364964	15

3.7. Gene functions and pathway analysis

In order to explore the functions of its pathways, GO classified enrichment analysis was performed, and 75 targets were obtained. Subsequently, the top 10 pathways corresponding to the analysis results were listed. The GO classified enrichment analysis included the molecular function (MF), the cellular component (CC), and the biological process (BP) analyses.

It may be observed in Figure 4 that, on the level of molecular function, coptis chinensis exerted a great influence on the receptor-binding activity, superoxide dismutase activity, metalloproteinase activity, catalytic activity, REDOX enzyme activity, cofactor-binding activity, glutathione transferase activity, cysteine peptidase activity, chemokine activity, and cytokine activity. It was also inferred that the main targets involved exhibited protein-binding, heme-binding, cytokine-binding, and other functions at the molecular level. IL10 belongs to the IL-10 family and inhibits the synthesis of several cytokines, including IFN-gamma, IL-2, IL-3, TNF, and GM-CSF produced by activated macrophages and helper T cells. As an inducible rate-limiting enzyme belonging to the IL-10 family, IL-10 assists in inhibiting the production of inflammatory cytokines, such as interferons, tumor necrosis factors, interleukin-2 (IL-2), and IL-3, and is a key molecule in the regulation of the inflammatory response

and oxidative stress in various diseases. The targets mainly included cytoplasm, nucleus, membrane, and extracellular secretions. Nitric oxide synthase (NOS2) is usually present in the cytoplasm and is a messenger molecule with various functions, including the production of nitric oxide. Studies have reported that in macrophages, NO mediates the effective killing of tumor cell, serves as an antiseptic, and is also a part of the trans tyrosine enzyme complexes involved in the regulation of inflammatory activity [9]. The anti-TB drugs might also have NOS2-mediated inflammatory response. After six reexaminations of the doses, the following changes were observed: the appetite increased, staple food intake increased to 2 steamed buns per meal, symptoms such as nausea, vomiting, belching, stomach distension, and chest tightness disappeared, daily or twice a day stool, patency, insomnia and night sweat improved, red tongue, moss-white slightly thick. After half a month, the patient's body weight increased to 60 kg. MPO regulates the defense system of the host cell responsible for the active killing of a variety of microorganisms, thereby playing an anti-tuberculosis role in humans [10].

4. Discussion

The Golden thread is known to exhibit antibacterial and anti-inflammatory effects, although the underlying mechanism is unclear. The concept of network pharmacology is consistent with the holistic view of traditional Chinese medicine and helps explain the mechanism of Golden thread's intervention in tuberculosis in a systematic and comprehensive manner. In the present study, 48 candidate constituents of Golden thread with OB $\geq$ 30% and DL $\geq$ 0.18 were screened-out from the TCMSP database, among which 14 active chemical constituents, including berberine, golden thread, berberine, berberine, and methyl were screened-out through docking with TB disease targets. Among the previously reported ones were berberine and coptis. In addition, a few unreported biological processes and active components exhibiting efficacy were identified, which may provide a direction for future research on Golden thread intervention in tuberculosis. However, the pharmacodynamics and the mechanism of action of these compounds require further verification. These compounds also improved medication compliance, reduce adverse drug reactions, strengthen resistance, and improve the overall therapeutic effect, thereby playing an indispensable role in TB intervention. The pathogenesis of tuberculosis is related to immune regulation, inflammatory responses, and multiple regulatory sites. Therefore, the present study predicted 75 key targets for intervention in tuberculosis, including IL2, IL6, IFNG, IRF1, IL1A, IL1B, CD40LG, and TNFSF15. Among these, IL2 was involved in the inflammatory pathway commonly used in the T cell response to antigens or to promote/stimulate mitosis. The protein is also involved in T cell proliferation and other activities crucial to the immune response regulation, such as stimulation of B cells, monocytes, lymphatic factor-activated killer cells, and natural killer cells. IL6 plays an important role in the differentiation of lymphocytes and monocytes. It is a gene necessary for the production of Th17 cells and closely related to the other predicted targets. In addition to antiviral activity, the IFNG gene has several important immunomodulatory functions [11]. IRF1 is involved in the regulation of IFN and IFN-inducible genes, host response to viral and bacterial infections, mediated immune response, and regulation of cell proliferation and differentiation. IL1A and IL1B are involved in inflammation, promotion of the activation of T cells, B cells, and cytokines, the production of antibodies, and the promotion of T cells for Th17 differentiation. CD40LG stimulates T cell proliferation and cytokine production, and its cross-linking on T cells produces co-stimulation signals. CD40LG, together with TCR/CD3 and CD28, enhances the production of IL4 and IL10 and induces the activation of NF-κB and kinases MAPK8 and PAK2 in T cells [12]. TNFSF15 mediates the activation of NF-κB, which is a multi-effect transcription factor present in almost all cell types. It is the endpoint of a series of signal transduction events, and several biological processes, such as inflammation, immunity, differentiation, cell growth, and apoptosis, are closely related to it [13]. Therefore, these targets play

a vital role in several biological processes, such as immune regulation, inflammatory response, signal transduction, protein metabolism, metabolism, and energy pathways, and are also important targets in tuberculosis treatment [14]. Tuberculosis involves the deficiency of spleen and stomach elements mostly. The anti-tuberculosis drugs attack fiercely, further damaging the spleen and stomach, resulting in weak spleen and stomach, disordered transport of water and body fluids, dampness, block qi, heat, and phlegm, easy to appear stool, and tongue that is sticky and greasy. Greasy coating on the tongue is a common feature in such patients. The main locations of this disease are medium coke, spleen, and stomach, with the side involvement of the liver and gall bladder. The pathogenesis of the disease is based on the weakness of the spleen and stomach and marked by the appearance of dampness (phlegm) and heat.

The active component–action target network revealed the multi-component and multi-target characteristics of Golden thread in the intervention of tuberculosis. The protein interaction network indicated that the target proteins of astragalus were interrelated; it was a complex and interleaved network and did not play a role alone. The results of this study demonstrated that all the 14 active components exerted effects in TB intervention, among which berberine and coptidine appeared to have more connected targets. The degree values of IL6, JUN, IL1B, IL10, MAPK1, MMP9, and CXCL8, which were the main targets of golden thread intervention in tuberculosis, were large and predicted their central role in Golden thread's intervention in tuberculosis [15]. The results of the enrichment and targets for attribution analyses revealed that Golden thread intervention tuberculosis process, involving various cells, metabolic processes, and the biological process in response to stress, including cell membranes, extracellular matrix, cytosol cell components, small molecules such as cationic molecules, metal ions, and signaling molecules, transcription factors, receptors, proteins, and enzymes, among other substances, is a complex process. After clearing the heat and dampness (phlegm), the coating on the tongue turns thin and white, which may then be reduced with the use of bitter cold products such as coptis chinensis and bitter orange [16]. If the coating on the tongue is not reduced, the mouth becomes sticky and greasy due to moisture retention, for which patchouli, perlin, and other aromatic wet products may be used or the temperature of the Yang medicine may be increased slightly to remove the Yin evil.

The results of the present study indicate that Golden thread intervention in tuberculosis has the characteristics of multiple components, multiple targets, and multiple pathways. The next step in this research would involve the scientific verification of the predicted target pathways. In summary, the present study applied network pharmacology to study the mechanism of Golden thread intervention in tuberculosis, and the results revealed that 14 active components of Golden thread acted on 75 targets, involving multiple processes, molecules, and pathways, reflecting a multi-component–multi-target–multi-pathway action of Golden thread. The multiple targets were expounded with a further complex network interaction relationship among the components of Golden thread predicted using the protein interaction network. The important target proteins, the key target function, and the map path were explored through the literature review to validate the various pathways, although further investigation of the related targets is required.

The present study provided a theoretical basis for the systematic research and clinical application of Golden thread in tuberculosis intervention. "Slow cure of its origin" to invigorate the spleen and stomach is the approach to prevent wet heat and for the fundamental regeneration of these organs. The Golden thread wendan decoction contains the essence of the erchen decoction, which has the effect of drying the dampness and reducing phlegm. Moreover, warm Yang also has the effect of strengthening the spleen and stomach.

Fourteen among the 48 active compounds were selected by using a DL strategy, and their potential targets were identified using TCMSP and then analyzed using network-related tools [17]. The results revealed that the 14 active compounds exerted their antitumor effects via 75 targets from several

pathways. This was consistent with the TCM concept of "multiple compounds, multiple targets, and multiple effects." Although further experiments are required to support our findings, the present study provided a systematic view of the potential tuberculosis intervention mechanisms of Huang Lian from a network-based perspective.

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