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ARTICLE

The functional components and mechanism of *Linderae Radix* in treating diabetic nephropathy based on the network pharmacology

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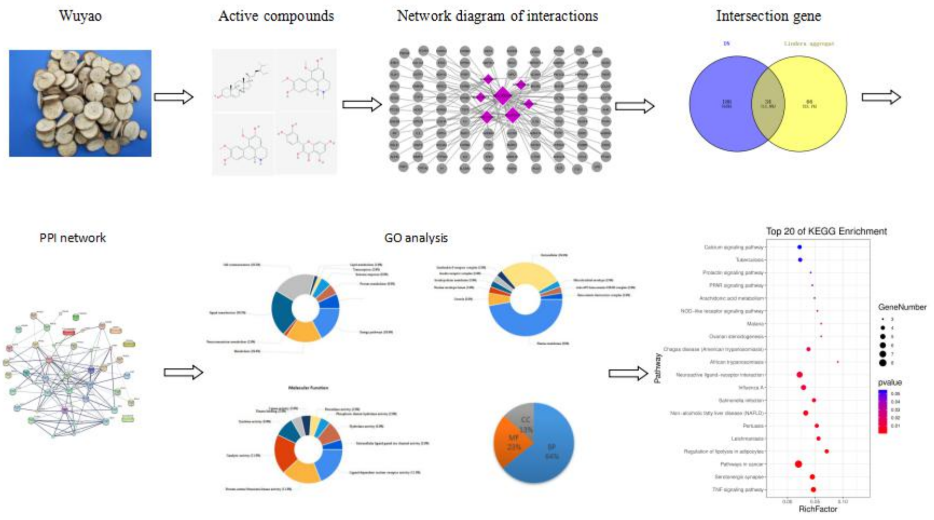
Highlights

This study applied the TCMSP, VBA, OMIM, DiGSeE, TDD, GEO, UniProt, DAVID, STRING a lot of online data and Cytoscape 3.2.1 analysis software to predict the drug's active ingredient, and the target of diabetic nephropathy (DN). The "drug-target-disease network" was constructed to analyze the components, targets and pathways of the herb and preliminarily reveal that the treatment of DN by Wuyao (*Linderae Radix*) is the result of the combined action of multiple components, targets and links, providing a basic research direction for the treatment of DN by *Linderae Radix.*

Traditionality

Linderae Radix, recorded in Supplement to Compendium of Materia Medica, is the root of the Lindera aggregata (Sims) Kosterm. *Linderae Radix* is a pungent-warm medicinal. In traditional Chinese medicine, the effect of *Linderae Radix* sinensis can enter the lung, spleen, kidney and bladder. It has the effect of activating Qi to relieve pain, warming the kidney and dispersing cold.



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Abstract

Objective: To analyze the components and mechanisms of Wuyao (*Linderae Radix*) in treating diabetic nephropathy (DN) based on network pharmacology.

Methods: Multiple online databases were used to search and screen out the active ingredients from *Linderae Radix*, the related targets of active components of *Linderae Radix* and the genes related to DN. Search the corresponding genes name of target through UniProt database. Cytoscape 3.2.1 was used to construct the corresponding target gene network of *Linderae Radix* compounds. Venn diagram was used to screen the intersection genes of the active components corresponding to the target and disease-related genes, and the intersection genes were constructed into the protein interaction relationship network. Finally, DAVID database was used to do GO function enrichment analysis and KEGG signaling pathway enrichment analysis for the intersection genes, and the results of GO and KEGG were visualized.

Results: 1. A total of 7 potential active ingredients and 100 target proteins were screened. 2. There are a total of 34 intersection genes between the potential active ingredient target in *Linderae Radix* in DN. 3. The top 10 of the interaction correlation between intersection proteins include:AR and NCOA2, NCOA2 and NR3C1, NCOA2 and PPARG, etc. 4. There were 16 entries of molecular function, 9 entries of cell component, 47 entries of biological process and 18 entries of signaling pathway (P <0.05).

Conclusion: DN was treated by *Linderae Radix* from multi-component, multi-target and multi-link synergies.

Keywords: *Linderae Radix*, Diabetic nephropathy, Network pharmacology

Abbreviations: DN, Diabetic nephropathy; BP, Biological process; MF, Molecular function; CC, Cellular component; ESRD, End stage renal disease; OB, Oral bioavailability; DL, Drug-likeness; PPI, protein protein interaction; PKC, protein kinase C; COX, cyclooxygenase; LOX, lipoxygenase; CYP450, cytochrome P450.

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Competing interests: The authors declare that there is no conflict of interests regarding the publication of this paper.

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Background

Diabetes is a serious chronic disease. In addition to the symptoms of hyperglycemia, it can also lead to a variety of microvascular and macrovascular complications. Diabetic nephropathy (DN) is one of the most serious complications of diabetes and one of the main causes of end-stage renal disease (ESRD). Early pathological changes of DN include glomerular ultrafiltration, hypertrophy, glomerular basement membrane thickening, fibrosis, endothelial dysfunction and glomerular mesangium matrix accumulation, which can lead to glomerular sclerosis and ESRD [1-4]. Currently, the main treatments include blood pressure control and blood glucose control as well as lifestyle changes, but these measures have only been able to delay the progression of diabetes to renal failure [5]. Therefore, it is urgent to find new treatment methods, such as traditional Chinese medicine (TCM), to treat DN and reduce the fatality rate.

Linderae Radix is often used to treat DN, *Linderae Radix* is a pungent-warm medicine. From the point of TCM, the effect of *Linderae Radix* can influence the lung, spleen, kidney and bladder. It is good for warming the kidney and activating Qi. *Linderae Radix* has the effect of activating Qi to relieving pain and dispersing cold. Indications of the herb are chest and abdomen pain, frequent urination and enuresis. The herb commonly used in asthenia cold enuresis, abdominal pain and other diseases. Because *Linderae Radix* treats DN clinical effect is good, so it always uses to mix with other medicines such as Yizhi (*Fructus Alpiniae oxyphyllae*).

Network pharmacology is an analysis method to use a variety of online databases and analytical techniques to analyze the relationship between drugs and diseases, to reveal the "drug-target-disease" interaction. Therefore, this study intends to analyze the action mechanism of *Linderae Radix* in the treatment of DN through network pharmacology, so as to provide more research programs for the application of *Linderae Radix* and the treatment of DN disease.

Methods

Screening of potential active ingredients and search of corresponding target proteins from *Linderae Radix*

Through TCMSP (http://ibts. hkbu. edu. hk/LSP/tcmsp. php) and the tool such as VBA, make *Linderae Radix* as keywords, search the chemical composition of *Linderae Radix*. Since the components of TCM are diverse and complex, and We considered the interaction between drugs and the human body.

Therefore, based on the oral bioavailability (OB) ≥30% and similarity (DL) ≥0.18 of the drug, the potential active ingredients and corresponding targets of the *Linderae Radix* were further screened (TCMSP and Swiss Target Prediction database were used).

Screening the related targets of DN

With "diabetic nephropathy" as the keyword, DN-related genes were retrieved through the OMIM database, DiGSeE text mining database, TTD database and GEO database.

Construction protein name transgenic gene name and potential active ingredient-corresponding target network.

UniProt database was used to convert target protein names into gene names. Cytoscape 3.2.1 was used to construct the potential active ingredient-corresponding target.

Screening of target genes at the intersection of *Linderae Radix* and DN, then the construction of the PPI network

Target genes of potential active ingredients of *Linderae Radix* and target genes related to DN were made Venn diagram to screen intersection genes, and constructed PPI network through STRING online database

GO analysis and KEGG signaling pathway analysis of intersection target genes.On the basis of the DAVID online database, the intersection target genes were analyzed by GO analysis and KEGG signaling pathway analysis, and the results were visualized by Omicshare online Drawing software.

Results

Screening of potential active ingredients of *Linderae Radix*

A total of 63 *Linderae Radix* compounds were retrieved from the database, with Oral availability (OB) ⩾ 30% and drug similarity (DL) ⩾ 0.18 were used as screening criteria, Screening 7 potential active ingredients of *Linderae Radix*. The basic information of the 7 potential active ingredients is shown in Table 1.

Prediction of potential active ingredient targets of *Linderae Radix* and construction of interaction network

The predicted targets of the potential active ingredients of the *Linderae Radix* are shown in Table 2. There are 100 targets of the active ingredients of the *Linderae Radix*. Analysis from the perspective of potential active ingredients, *Linderae Radix* has 2 active ingredients with more than 20 targets. There are four active ingredients in apples that target more than 10, respectively are MOL000098-quercetin, MOL000358 beta-sitosterol, MOL010917-Boldine, MOL010907-Norboldine, they interact respectively with 54, 15, 24, and 11 number targets. These four kinds of the compound structure as shown in Figure 1.

Table 1 basic information of the 7 active ingredients of *Linderae Radix*

Serial number	Chemical component name	OB(%)	DL Relative	molecular mass
MOL000358	β-sitosterol	36.91	0.75	414.79
MOL000359	sitosterol	36.91	0.75	414.79
MOL010917	Boldine	31.18	0.51	327.41
MOL010907	Norboldine	40.91	0.46	313.38
MOL000098	quercetin	46.43	0.28	302.25
MOL010913	*Linderae Radix* ether ester	77.08	0.25	260.31
MOL010916	2-hydroxyl-3-(4-Hydroxy phenyl)-1-(2, 4, 6-trihydroxyphenyl)-1-acetone	42.54	0.19	290.29

Table 2 The basic information of target of the 7 active components of the drug

Serial number	Chemical component	Targets
MOL000358	β-sitosterol	HTR2A, ADRA1A, PDE3A, DRD1, GABRA2, GABRA3, GABRA5, MAP2, CHRM2, CHRM3, OPRM1, CHRNA7, CHRNA2, PIK3CG, JUN
MOL000359	sitosterol	NR3C1, NR3C2 , NCOA2, PGR
MOL010917	Boldine	ADRA1B, ADRA1D, AR, ADRB2, CCNA2, OPRD1, DPP4, TOP2, ESR1, ESR2, GSK3B, HSP90AB1, MAPK14, CHRM1, CHRM4, CHRM5, NOS2, PPARG, PTGS2, PIM1, RXRA, CHEK1, SCN5A, SLC6A4,
MOL010907	Norboldine	ADRA1B, ADRA1D, AR, ADRB2, HSP90AB1, OPRM1, NOS3, PTGS1, PTGS2, RXRA, SCN5A
MOL000098	quercetin	MMP2, ACHE, ADH1C, MAOB, BCL2, ALOX5, AHR, CTSD, CCL2, TP53, F7, F10, COL1A1, COL2A1, CYP1A2, CYP3A4, TOP1, EGFR, SELE, SULT1E1, GJA1, GSTM1, GSTM2, GSTP1, HMOX1, INSR, IFNG, IL1B, IL2, IL6, MMP1, MGAM, MAPK1, MPO, NQO1, POR , ODC1, KCNH2, EGF, PTGER3, PTGS1, ACPP, PON1, MMP3, SOD1, THBD, F3, PLAT, PRSS1, TNFRSF1A, PLAU, VCAM1, VEGFA, XDH
MOL010913	*Linderae Radix* ether ester	GABRA1
MOL010916	2-hydroxyl-3-(4-Hydroxy phenyl)-1-(2, 4, 6-trihyd-roxyphenyl)-1-acetone	CA2

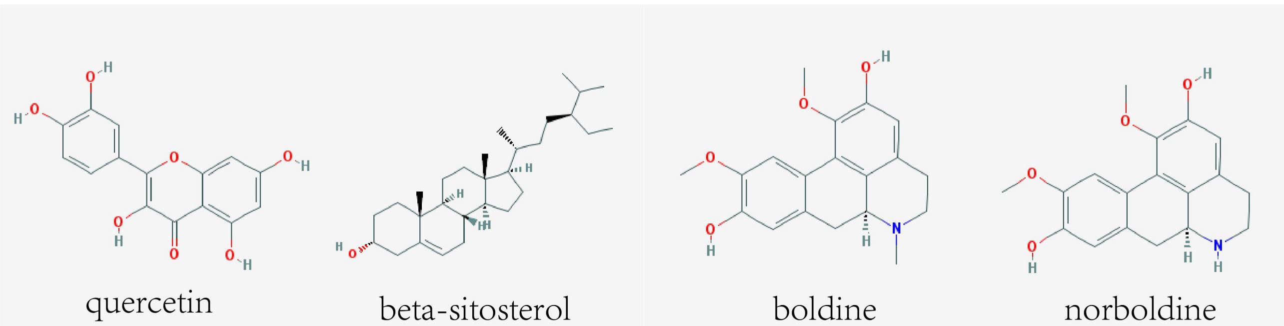

Figure 1 four potential structure diagram

The interaction network between potential active ingredients from *Linderae Radix* and predicted targets is shown in Figure 2, including 106 nodes and 109 edges. Green is the chemical composition of *Linderae Radix*. Blue is the target of the component.

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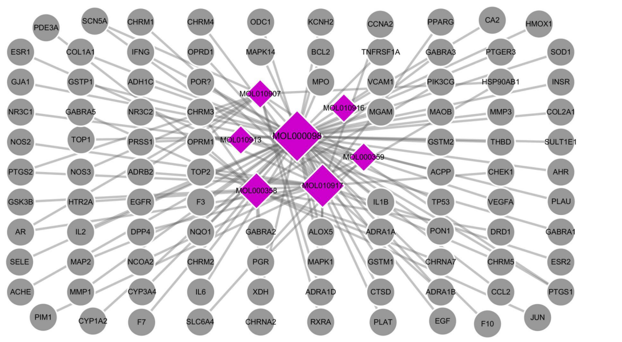

Figure 2 Network diagram of interactions between 7 potential active ingredients and 99 targets

Screening of crossover genes between *Linderae Radix* and DN and construction of PPI core network.

220 DN-related genes were screened through the database. As shown in Figure 3A, there are a total of 34 intersection genes between the target of potential active ingredient of *Linderae Radix* and DN, respectively:ACHE, ADH1C, MAOB, ALOX5, SELE, INSR, IL1B, IL6, MMP1, MGAM, PTGS1, PRSS1, HTR2A, PDE3A, NR3C1, NR3C2, NCOA2, PGR, AR, ADRB2, PTGS2, RXRA, GABRA1, CA2, CCNA2, DPP4, ESR2, GSK3B, MAPK14, CHRM1, NOS2, PPARG, PIM1 and CHEK1.

The 34 genes intersecting *Linderae Radix* and DN were brought into the STRING for analysis, and the results are shown in Figure 3B. PPI contains 40 nodes and 130 edges. The thicker line means the greater correlation degree. The top ten of the correlation degree of protein interaction include:AR and NCOA2, NCOA2 and NR3C1, and NCOA2 and PPARG, etc. as shown in Table 3.

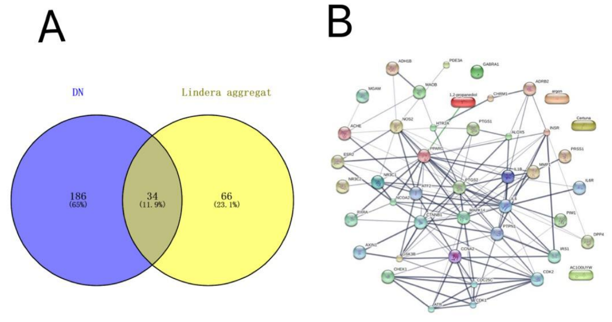

Figure 3 Composition of *Linderae Radix* potential targets associated with DN targets the intersection of genes and PI network diagram. (A)Venn diagram of the intersection of potential component action targets of *Linderae Radix* and DN-related targets; (B)PPI network relationship between *Linderae Radix* and DN.

Table 3 The top 10 interacting proteins

Node1	Node2	Score
AR	NCOA2	0.999
NCOA2	NR3C1	0.998
NCOA2	PPARG	0.998
NCOA2	RXRA	0.997
PPARG	RXRA	0.997
IL1B	IL6	0.984
IL1B	MAPK14	0.978
MAPK14	IL1B	0.978
ALOX5	PTGS2	0.975
IL1B	PTGS2	0.974

The visualization enrichment analysis of intersection targets in GO and KEGG

Based on the DAVID database, GO function enrichment analysis was performed on 34 key genes in the intersection. Among them, there were 16 entries with molecular function (MF) P < 0.05, and the top three in specificity were steroid hormone receptor activity, steroid binding and enzyme binding molecular function, as shown in Figure 4.

There were 9 items of cell components (CC) with P <0.05, and the top three were caveola, receptor complex andnucleus cells components, the result is as shown in Figure 4B. There were 47 entries of biological process (BP) with P < 0.05, the top three in specificity were transcription initiation of RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter and positive regulation of nitric oxide biosynthetic process by biological processes, as shown in Figure 4C; The parts where GO analysis plays a major role are biological processes, and the results are shown in Figure 4D.

A total of 31 signaling pathways were screened by KEGG enrichment analysis, among which 18 were P < 0.05, involving TNF signaling pathway, Arachidonic acid metabolism, PPAR signaling pathway and other pathways, as shown in Figure 5.

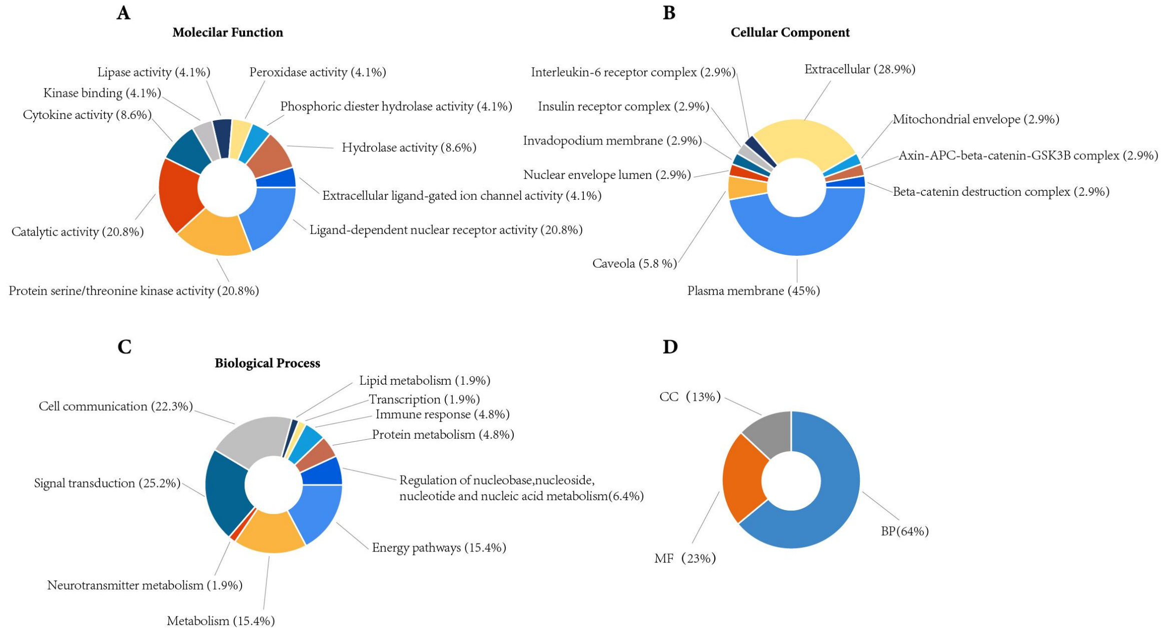

Figure 4 GO analysis diagram of target gene sat intersection of *Linderae Radix* and DN (A) molecular function (MF); (B) cell components (CC); (C) biological process (BP); (D) GO analysis pie chart.

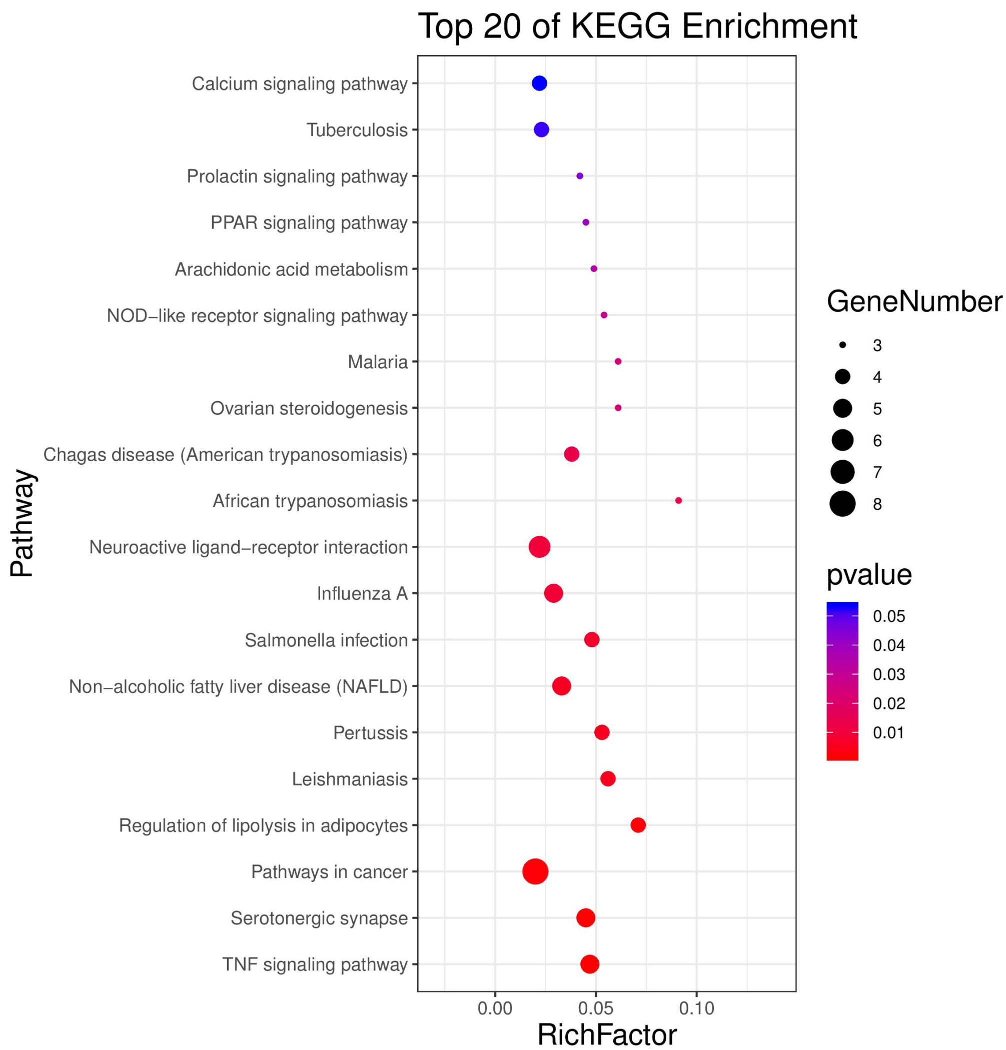

Figure 5 Bubble chart of the KEGG signaling pathway of target genes at the intersection of *Linderae Radix* and DN

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Discussion

Studies have shown that the pathogenesis of DN includes hemodynamic changes, inflammation, oxidative stress, micro-RNAs and intestinal microorganisms [6-11]. Hyperglycemia and compensatory hyperinsulinemia can promote the production of reactive oxygen species and activation of protein kinase C (PKC), leading to vascular endothelial dysfunction and age-mediated pro-inflammatory responses [12]. Clinically, the treatment programs for DN mainly include high-quality protein diet, moderate exercise, eating low sugar and low salt, avoiding infection and using nephrotoxic drugs. The overall treatment program of western medicine can only delay the progress of the disease course, and western medicine treatment can only play a role in the treatment of a certain symptom can not achieve the goal of a radical cure. As a natural medicine, Chinese herbal medicine can present multi-link and multi-target characteristics, such as anti-glucose, oxidative stress and inflammation. Therefore, Chinese herbal medicine therapy on DN has great advantages.

Linderae Radix is a pungent-warm medicine, it can affect the spleen, lung, kidney, bladder meridian and collateral channels. Because of its spicy and it is good at warming, *Linderae Radix* has the effect of activating Qi to relieve pain and warming the effectiveness of the kidney. The pharmacodynamic effect on the upper, middle and lower triple energizer, not only has the effect of treating Qi counterflow urgency asthma on the upper energizer but also has the effect on the abdominal distention pain of the middle energizer, in addition, the effect on the lower energizer is more prominent, for hernia, enuresis and other diseases also have the effect. The main chemical components of *Linderae Radix* include terpenes, lactones, volatile oils, alkaloids and flavonoids, etc. Itsmodern pharmacological effects are extensive, such as anti-inflammatory and analgesic, anti-tumor, anti-hypertension, liver protection and prevention and treatment of DN [13-17].

As it can be seen from the network diagram of the interaction between potential active components and targets, 7 potential active components of the *Linderae Radix* on 100 target proteins. Among them, quercetin, Boldine, beta-sitosterol and Norboldine, were the most targeted components. Quercetin is a natural flavonol with anti-diabetes and anti-fibrosis properties, and has strong anti-inflammatory, antioxidant and hypoglycemic effects in both animals and humans [18, 19]. In vitro studies have shown that quercetin can inhibit inflammation-induced cyclooxygenase (COX) and lipoxygenase (LOX) [20]. Similarly, in vivo studies have also demonstrated the anti-inflammatory activity of quercetin [21]. Beta-sitosterol is one of the phytosterol constituents. It is widely found in vegetable oils, nuts and other plant seeds, as well as in some plant drugs. beta-sitosterol has been widely used in pharmaceutical industry because of its special biological and physicochemical properties. Beta-sitosterol has cholesterol-lowering, anti-inflammatory, and tumor inhibition effects [22-25]. Studies have shown that beta-sitosterol can reduce blood glucose in T2DM rats [26]. Boldine and Norboldine belong to isoquinoline alkaloids. The results showed that Boldine had strong antioxidant activity. Norboldine has anti-inflammatory effects and can reduce the production of pro-inflammatory cytokines in cells [27, 28]. The study also proved that both Boldine and Norboldine can reduce the blood glucose of diabetic mice [29, 30].

According to the screening results of the intersection genes between the *Linderae Radix* and DN, there were 34 genes in total, including IL1B, IL6, PPARG, NCOA2 and NOS2 etc. Both IL1B and IL6 are interleukin-family cytokines. They play an important role in a series of the maturation, activation, proliferation and immune regulation of immune cells, and also participate in a variety of physiological and pathological reactions of the body. PPARG can control the peroxisome pathway of fatty acids and is a key regulator of adipocyte differentiation and glucose homeostasis. NCOA2, nucleus receptor co-activator 2 receptor, is a key regulator of transcription coactivator of Steroidal receptor and nucleus receptor and glucose metabolism regulation, which can specifically regulate the expression of G6P. NOS2, nitric oxide synthase, induces the production of nitric oxide (NO), a messenger molecule with multiple functions throughout the body. Studies have shown that NOS2 polymorphism is correlated with the occurrence and development of T2DM [31]. The results above indicate that the therapeutic effect of *Linderae Radix* on DN is the result of multi-target action.

GO enrichment analysis results show that the main steps of biological processes of DN therapy involved in *Linderae Radix*, such as the steroid hormone-mediated signaling pathway, positive regulation of MAPK cascade, inflammatory response, positive regulation of brown fat cell differentiation and regulation of cytokine production involved in the inflammatory response and oxidation-reduction process. According to the analysis of KEGG enrichment results, the main signaling pathways related to DN are TNF signaling pathway, Arachidonic acid metabolism and PPAR signaling pathway.

Arachidonic acid is the main component of lipids in cell membranes and is metabolized by three pathways, including cyclooxygenase, lipoxygenase and cytochrome P450. Based on these three metabolic pathways, arachidonic acid can be converted into a variety of metabolites from trigger different inflammatory responses. Studies have shown that arachidonic acid metabolism in DN patients is abnormal, which is of great significance for clinical observation of disease changes in DN patients [32, 33]. Inflammation releases large amounts of TNF, especially in diabetes, which activates sugar signaling pathways associated with cell survival and apoptosis. Studies have shown that mangiferin can inhibit the oxidative stress-mediated TNF-α related apoptosis pathway in the treatment of DN[34]. Peroxisomal proliferator-activated receptor (PPAR) is associated with insulin resistance and hyperglycemic-induced fibrosis of HK-2 cells in the human renal tubular epithelium, which can inhibit adipocyte differentiation and reduce cell migration and invasion.

Conclusion

The treatment of DN by *Linderae Radix* is the result of multiple components, targets and multiple links. Based on the selected active ingredients, targets and signaling pathways, it provides many directions for the subsequent basic research on the treatment of DN by *Linderae Radix*, and also provides more basis for the treatment of DN.

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