

The Mechanism of Niaoduqing Granules in Treating Diabetic Nephropathy Based on Network Pharmacology and Molecular Docking

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Abstract: Objective: It's to explore the mechanism of action of Niuduqing Granules in the treatment of diabetic nephropathy using network pharmacology methods and molecular docking. Methods: The active ingredients and targets of Uremiaqing granules were screened through the TCMSP database; targets related to diabetic nephropathy were screened in GeneCards and OMIM databases; Venn diagrams were drawn using Venny2.1 software to obtain common targets for drug treatment of diseases; Cytoscape software was used to construct "Uratoxicosis" "Qing granule-ingredient-target-DN" interaction network; build a PPI network on the STRING website to screen core targets for drug treatment of diseases; conduct GO and KEGG functional analysis of common targets through R language software; use AutoDock and PyMOL software to analyze Molecular docking of active pharmaceutical ingredients with core targets. Results: 138 potential active ingredients and 169 therapeutic targets of Niduqing Granules were screened out. The targets mainly involve the regulation of biological processes involve antioxidant stress, external response, etc., and are mainly enriched in lipids, atherosclerosis, and PI3K/AKT. and other signal pathways. Molecular docking shows that the core active ingredient and core target have good binding activity. Conclusion: The study reveal that Niaduqing Granules have the characteristics of multi-component, multi-target, and multi-pathway regulation. The mechanism of action of Niaduqing Granules in treating diabetic nephropathy may be related to anti-oxidative stress, regulation of cellular immunity, etc.

Keywords: diabetic nephropathy, Niaoduqing Granules, network pharmacology

1. Introduction

Diabetic nephropathy (DN) is a common and serious microvascular complication of diabetes, seriously endangering human life and health[1]. At present, there is no specific treatment method in modern medicine, and most patients will eventually develop ESRD.

Traditional Chinese medicine has remarkable effects in preventing and treating DN and is widely used clinically[2-4]. Niduqing Granules is a Chinese patent medicine that has the functions of clearing the fu-organs, and plays anti-inflammatory and immune-regulating functions[5]. It has been widely used clinically for the treatment of DN and chronic renal failure[6, 7]. However, the active ingredients and the mechanism of action of the medicine is still unclear. This study intends to use network pharmacology and molecular docking technology to explore the mechanism of action of Niuduqing Granules in the treatment of DN.

2. Materials and methods

2.1 Screening of active ingredients and targets of Niduqing Granules

Search all the chemical components of the single drug of Niduqing Granules in TCMSP, set the oral availability (OB) \geq 30%, drug-likeness (DL) \geq 0.18, and screen out the compounds that meet the requirements; obtain the active ingredient targets, and use the UniProt database to The target is converted into a gene symbol.

2.2 Screening of DN targets

Using "diabetic nephropathy" as the search term, search for disease-related targets in GeneCards and OMIM databases respectively, and integrate and remove duplications to obtain DN-related targets.

2.3 Screening of targets for the treatment of DN by Niduqing Granules

Import the drug action targets and disease action targets into the Venny2.1 software, and draw a Venn diagram of the

targets of DN treated by Niuduqing Granules.

2.4 Construction of PPI network for the target points of Niaduqing granules in the treatment of DN

Input the drug treatment disease targets obtained in 1.3 into the STRING database to construct a treatment target PPI network; draw an interaction frequency diagram between targets to obtain core target proteins.

2.5 Visualization of the network regulation of target points in the treatment of DN by Niduqing Granules

Import the drug action disease targets in 1.3 into the Cytoscape 3.10.0 software, draw a visual network control diagram, and construct a "Niaduqing granule-component-target-DN" visual control network. Sort according to the degree value to obtain the core active ingredients of the drug.

2.6 GO and KEGG enrichment analysis

Import the obtained drug action disease targets into R language software, conduct GO functional analysis and KEGG enrichment analysis, and display them in bubble charts.

2.7 Molecular docking

The 3D structure files of the components and target proteins were obtained through PubChem and PDB databases respectively. Autodock1.5.7 software was used to perform molecular docking on the components and core target proteins, and the molecular docking results were visualized through PyMOL2.5 software.

3. Results

3.1 Analysis of active ingredients and targets of Niaduqing Granules

A total of 206 active ingredients of Niduqing Granules were obtained, and some of the effective active ingredients are shown in Table 1; a total of 238 drug target genes were screened out.

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| Serial number | Active ingredients | OB (%) | DL | | | |
|---------------|--------------------|--------|------|--|--|--|
| MOL000098 | Quercetin | 46.43 | 0.28 | | | |
| MOL000006 | Luteolin | 36.16 | 0.25 | | | |
| MOL000422 | Kaempferol | 41.88 | 0.24 | | | |
| MOL002714 | Baicalein | 33.52 | 0.21 | | | |
| MOL007154 | tanshinone | 49.89 | 0.4 | | | |
| MOL000449 | Stigmasterol | 43.83 | 0.76 | | | |
| MOL002235 | EUPATIN | 50.8 | 0.41 | | | |
| MOL000471 | aloe-emodin | 83.38 | 0.24 | | | |
| MOL002651 | Dehydrotanshinone | 43.76 | 0.4 | | | |
| MOL007069 | przewaquinone c | 55.74 | 0.4 | | | |

3.2 Screening Targets for DN

A total of 4747 DN-related targets were screened through GeneCards and OMIM databases.

3.3 Target Screening for Niaduqing Granules in Treating DN

The results are displayed in a Venn diagram, as shown in Figure 1. The overlapping parts between the two are the potential targets of Niuduqing Granules in treating DN, with a total of 169.



Figure 1. Venn diagram of the targets of Niuduqing Granules in the treatment of diabetic nephropathy

3.4 Construction of PPI network for the target points of Niaduqing granules in the treatment of DN

The core target proteins of the PPI network are screened out, as shown in Figure 2; the interaction frequency diagram of the target proteins is drawn, as shown in Figure 3.



Figure 2. PPI network of targets for the treatment of DN by Niduqing Granules



Figure 3. Frequency chart of target-point interaction for the treatment of DN by Niduqing Granules

3.5 Visual analysis of target network regulation of Niaduqing granules in treating DN

The visual regulatory network of "Niaduqing Granules-Components-Target-DN" is shown in Figure 4. The core active ingredients in Niaduqing Granules that act as disease targets are screened out as quercetin, luteolin, kaempferol, baicalein, and tanshinone IIA.



Figure 4. "Niaduqing Granules-Components-Target-DN" network diagram

3.6 GO functional analysis and KEGG enrichment analysis

The GO functional analysis results are shown in Figure 5, and the KEGG functional analysis results are shown in Figure 6.



Figure 5. GO function analysis diagram of the target "Niaduqing Granules for the Treatment of DN"



Figure 6. KEGG pathway enrichment analysis chart of the target "Niaduqing Granules for the Treatment of DN"

3.7 Molecular docking results

The results of molecular docking are shown in Table 2, and the schematic diagram of molecular docking of some components and target points is shown in Figure 7.

| Table 2. Molecular docking scores | | | | | | | |
|-----------------------------------|-----------|---|------------|-----------|----------------|--|--|
| Target name q | | Docking energy /(kcal·mol ⁻¹) | | | | | |
| | quercetin | luteolin | kaempferol | baicalein | tanshinone IIA | | |
| STAT3 | -8.2 | -7.9 | -8 | -7.6 | -8.5 | | |
| AKT1 | -7 | -6.7 | -6.5 | -6.2 | -7.3 | | |
| HSP90AA1 | -8.3 | -7.9 | -7.9 | -8.5 | -9.1 | | |
| TP53 | -8.3 | -8.4 | -8.6 | -8.2 | -9.1 | | |
| TNF | -8.7 | -6.9 | -6.3 | -8.9 | -6.6 | | |



C.Kaempferol-TP53

Figure 7. Schematic diagram of molecular docking interaction

4. Discussion

This study used network pharmacology research methods to preliminarily explore the possible mechanism of the effectiveness of Niuduqing Granules in treating DN. Through the "Niaduqing Granules-Components-Action Targets-DN" interaction network, it is predicted that 138 ingredients in Niaduqing Granules may produce effects by acting on 169 common targets of drug diseases, and the main active ingredient of the drug is quercetin. quercetin, luteolin, kaempferol, baicalein, tanshinone IIA, and core target proteins STAT3, AKT1, HSP90AA1, TP53, and TNF. GO functional enrichment shows that the main biological processes involved include responses to oxidative stress and responses to reactive oxygen species. KEGG functional enrichment analysis suggested that signaling pathways such as lipids and atherosclerosis, PI3K/Akt, fluid shear stress, and atherosclerosis may be key pathways for the treatment of DN by Niduqing Granules. This shows that Niduqing Granules have the characteristics of multi-active ingredients, multi-targets, and multi-pathway interactions.

The molecular docking results of the core components and core targets show that the binding energies are both <-5kcal/ moL, indicating that the core components and core targets are well combined, indicating that Niaduqing Granules may pass through core components such as quercetin, luteolin, and kaempferol. The active ingredients play a therapeutic role in DN.

In summary, this study predicts the potential main active ingredients, action targets and signaling pathways of Niaduqing Granules in treating DN, and analyzes and verifies the possible molecular mechanism of action of Niaduqing Granules in the treatment of DN. Provide ideas and theoretical basis for the research on the mechanism of Niuduqing granules in treating diabetic nephropathy.

References

- [1] American Diabetes Association. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes-2021[J]. *Diabetes Care*, 2021,44(Suppl 1): S151-S167.
- [2] LIU X J, HU X K, YANG H, et al. A Review of Traditional Chinese Medicine on Treatment of Diabetic Nephropathy and the Involved Mechanisms[J]. *Am J Chin Med*, 2022,50(7): 1739-1779.
- [3] TANG G, LI S, ZHANG C, et al. Clinical efficacies, underlying mechanisms and molecular targets of Chinese medicines for diabetic nephropathy treatment and management[J]. *Acta Pharm Sin B*, 2021,11(9): 2749-2767.
- [4] BAI L, LI X, HE L, et al. Antidiabetic Potential of Flavonoids from Traditional Chinese Medicine: A Review[J]. Am J Chin Med, 2019,47(5): 933-957.
- [5] ZHOU P, HAO Z, XU W, et al. Effects of Niaoduqing granules on inflammatory response of diabetic kidney disease: A meta-analysis[J]. *Exp Ther Med*, 2023,26(4): 494.
- [6] SONG C, ZHU Z, LIU L, et al. The efficacy and safety of Niaoduqing granules in the treatment of diabetic kidney disease: a systematic review and meta-analysis[J]. *Front Pharmacol*, 2023,14: 1180751.
- [7] WANG X, YU S, JIA Q, et al. NiaoDuQing granules relieve chronic kidney disease symptoms by decreasing renal fibrosis and anemia[J]. *Oncotarget*, 2017,8(34): 55920-55937.