ISSN 2706-6819 Vol.4, Issue 11: 7-13, DOI: 10.25236/IJFM.2022.041102

Advances in network pharmacology-based Chinese medicine for the treatment of IgA nephropathy

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Abstract: *IgA nephropathy is the most common autoimmune nephropathy which have high incidence rate and even appear renal failure. With the continuous development of network pharmacology, the characteristic with"Drug-active ingredient-disease" has been used in the treatment of IgA nephropathy. Making the characteristic which use TCM, the combination of TCM, medicine made of two or more ingredients to treatment IgA nephropathy in multi-component, multi-target, multi-pathway therapy and network pharmacology together. We found biological activity ingredient which can treat IgA nephropathy, that is quercetin, luteolin and kaempferol. They restrain producing inflammation cytokine which mainly inhibit PI3K/Akt and Akt through the synergistic action of the drug. They decrease immune complex's sedimentation on lomerulus mesangial cell to reduce inflammation. The combine of TCM and network pharmacology open up a new idea which can remedy IgA nephropathy.*

Keywords: *Network pharmacology; IgA nephropathy; Single herbal medicine; Herbal compounding*

1. Introduction

IgA nephropathy(IgAN) is a primary glomerular inflammation by the deposition of IgA and antibody complex in glomerular mesangial area, accounting for 30%-40% of primary glomerular disease[1]. Studies have shown, 15%-20% of IgAN will become end-stage renal disease(ESRD) within 10 years after onset if patients left untreated[2]. It will become the needed solveing public health issues and will make Greatly increase the medical burden.

IgAN's pathogenesis is complicated right now, the sick is resulted from the galactose deficient-IgA1(Gd-IgA1) and antibody complex deposited on glomerular mesangial area. This contribute to lomerulus mesangial cell unduly proliferation, living nephron progressively reduce and have glomerulosclerosis[3]. Traditional western medicine uses glucocorticoid medicine, Angiotensin medicine and immunosuppressor to therapy but the side effects of long-term treatment in western medicine are large. IgAN belongs to"hematuria", "lumbago" and "edema" in TCM. TCM's treatment always remember the pathomechanism which is"xu, yu, shi, re", and the remedy has the advantage of multitarget and multipathway, and Chinese medicine treatment is safe and effective, which is easily accepted by patients. We will use network pharmacology to explore the possible mechanisms of Chinese medicine in the treatment of IgAN, exploit the advantages of Chinese medicine and develop new approaches in treatment.

Network pharmacology is a spring up subject nearly years, it can build the interaction network of "medicine-active ingredients-disease", filtrate the active ingredients of medicine and discover targets and key pathways for drug treatment. This has the advantage of this is to explore the mechanism of how TCM treats the disease. The main applied databases are the Traditional Chinese Medicine Integrated Database (TCMSP), GeneCards and other gene databases. The combination of network pharmacology and treatment of disease will adequately give play to the integrity and systematism of TCM, has guiding significance in the field of biomolecular mechanisms of TCM treats this disease. Therefore, this paper provide reference in the use of network pharmacology treatment IgAN and modernization development of TCM.

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2. A medicinal herb research

2.1. Dioscoreae Nipponicae Rhizoma

The researches show that the increase of galactose-deficient IgA1(Gd-IgA1) is critical factor which due to patients with IgAN[4]. Scholars[5]have show that a large number of mature B cells activation can produce Gd-IgA1. Shen Jiachen et al used network pharmacology techniques, screen 12 active ingredients from dioscoreae, including dioscin, desgalactotigonin, and paclitaxel[6]. Interaction network reveal that the key targets included albumin (ALB) and caspase-3(CASP3), molecular docking show that the active ingredients of dioscoreae which is dioscin, desgalactotigonin and paclitaxel are combine well with ALB and CASP3. In vitro experiments showed that CASP3, a key target protein, can be regulated up by dioscin, play a role in restrain B lymphocytes to inhibit the abnormal activation thus treat IgAN. CASP3 is also closely related to cell apoptosis. The studies has confirmed that dioscin can regulate the signal path of phosphatidylinositol 3-kinase/protein kinase B(PI3K/Akt), influence lomerulus mesangial cell 's deposition.

2.2. Astragalus membranaceus

Pang Shuang et al obtain filtrate twenty-five actives ingredients and forty-nine drug targets of medicine such as astragaloside[7]. Kyoto Encyclopedia of Genes and Genomes(KEGG)'s pathway enrichment analysis is mainly related to the PI3K/Akt signaling pathway. In vitro experiments showed that PI3K/Akt signaling pathway is mainly related to autophagy and apoptosis, when it was suppressed that can reduce abnormal proliferation of glomerular thylakoid cells, thus inhibiting renal fibrosis and alleviating glomerulosclerosis[8-10]. Studies have confirmed that astragaloside inhibits glomerular thylakoid cell proliferation by regulating the PI3K/AKt/p53 signaling pathway, thereby treating IgAN[7].

2.3. Red peony root

Pang Xinxin et al filtrated eleven effective activities which is related to IgAN from Paeonia lactiflora, refer to total paeony glycoside(TPG), catechin, etc, thirty-five drug targets[11]. KEGG signaling pathway enrichment analysis refers to hepatitis B pathway, kaposi sarcoma-associated herpes-virus infection pathway, tumor necrosis factor signaling pathway, inflammatory factor-17(IL-17)signaling pathway. Research finding, TPG could block Toll-like receptor activation in vivo, restrain macrophage infiltration, reduce proteinuria levels, improve kidney function and treat IgAN nephropathy[12]. Catechin is the other active ingredient screened from Paeonia lactiflora which can inhibit kidney mesangial cell value-added, reduce proteinuria levels and improve kidney function[13]. IL-17 is a regulator of the inflammatory response which is plays an important role in the development of the renal inflammatory response[14]. Li Jiaru et al found that IL-17 promotes the secretion of galactose-deficient IgA (GD-IgA)and the deposition of immune complexes, which triggers IgAN in turn[15].

2.4. Hedyotis diffusa Willd

Li Hongyan et al obtained twenty-two hedyotis diffusa willd's key targets which can treat IgAN nephropathy, obtained signals including cancer pathway, diabetic myocardial pathway and human papillomavirus infection pathway by KEGG analysis[16]. The nucleoside component from hedyotis diffusa willd can inhibits the human erythroleukemia cell line K562[17]. Mitogen activated protein kinase(MAPK) signaling pathway is a key pathway inhedyotis diffusa willd for the treatment of IgAN, give play to exerting anti-inflammatory effects by inhibiting the MAPK pathway and the nuclear transcription factor pathway[18]. Its flavonoid component regulates T-cell immune function, inhibits the occurrence of immune response and reduces the occurrence of proteinuria and haematuria[19]. It follows that hedyotis diffusa Willd give play in protect kidney by anti-inflammatory, antitumour and anti-immune effects.

2.5. Honeysuckle

Wang Rumeng et al think respiratory infections can cause IgAN such as pharynx and tonsils, which can be treated from the pharynx[20]. Studies have shown that honeysuckle can restrain the active ingredients from nuclear transcriptional factor Kappa B(NF-κB), improve inflammatory pathological

ISSN 2706-6819 Vol.4, Issue 11: 7-13, DOI: 10.25236/IJFM.2022.041102

damage in the kidney[21]. The targets of treat IgAN include interleukin-6 (IL-6), albumin (ALB), vascular endothelial growth factor (VEGF), serine/threonine protein kinase (serine/AKT1), and prostaglandin G/H synthase 2 (PTGS2). Quercetin, luteolin and kaempferol is the active ingredient that can treat IgAN. Quercetin can resist inflammation and regulate immune activity, improve kidney function, reduce oxidative stress factors, fibroblast growth factor and tissue growth factor, thus inhibit kidney fibrosis, and reduce the renal inflammatory response and tubular damage[22-23]. Luteolin has antioxidant activity and inhibits the activation of NF-κB and the expression of cyclooxygenase-2, thus reduce the production of inflammatory factors such as IL-6 and IL-12. And it also participates in immune regulation and is able to inhibit Toll-like receptor signaling pathways[24-25]. Kaempferol exerts antibacterial, anti-inflammatory and anticancer effects by inducing apoptosis, reducing cell viability, reduce phosphatidylinositol 3 kinase and protein kinase B[26].

3. Traditional Chinese Medicine Pair

3.1. Honeysuckle-forsythia

Bai Yawen et al found that the active ingredients of honeysuckle-forsythia in the intervention of IgAN include quercetin, digitalis flavone and kaempferol[27]. Effect target have PKB, IL-6, NF-κB, VEGF, MAP2K1, MAP2K8, IL-1β, MMP-9. Which were enriched by KEGG. The analysis showed that honeysuckle-forsythia is through the inhibition of advanced glycosylation end products(AGEs)-receptor of AGE (RAGE), IL-17, TNF signaling pathway, etc, to meddle the intervention of IgA. AGEs/RAGEs is related to the proliferation and hypertrophy of IgA kidney mesangial cell and renal fibrosis[28]. IL-17, TNF signaling pathways are related to IgA nephropathy immune inflammatory activity with the progression of disease and are positively correlated with proteinuria, renal function, and blood uric acid[29].

3.2. Chinese Foxglove-Rhizoma Imperatae

Liu Huaxi et al filtrated twenty-seven targets related to IgAN from Chinese Foxglove-Rhizoma Imperatae and filtrated pathways include VEGF pathways, leishmaniasis pathways, calcium signaling pathways and other pathways[30]. PTGS2 is a key enzyme for prostaglandin synthesis. COX-2 derives prostaglandins, it can involved in podocyte injury, renal interstitial fibrosis and thus get IgAN[31-32]. Blocking the MAPK signaling pathwaycan inhibit glomerular IL-6 secretion, thylakoid cell value-added, inflammatory factor secretion, and delay the development of IgAN[33].

The JAK-STAT signaling pathway is elevated in patients with early-stage IgAN which is contained in the VEGF signaling pathway, lomerular filtration function is destroyed[34]. β-sitosterol also has a good renal protective effect, cholesterol lowering effects, anti-inflammatory, antitumour which is found in Chinese Foxglove-Rhizoma Imperatae. Research also find that β-sitosterol has also been proven in protective kidney effect. β-sitosterol has also been proven to have a variety of pharmacological effects, such as antioxidant, anti-inflammatory, antitumour, and cholesterol lowering effects, on the improvement of learning and memory et al.

4. Research on herbal compound formulas

4.1. Kidney-strengthening and sperm-fixing formula

Wang Ailin et al investigated the mechanism of action of kidney-strengthening and sperm-fixing formula for the treatment of IgAN based on network pharmacology and found that it was mainly related to inflammatory response and oxidative stress[35]. Active ingredients such as quercetin, luteolin, kaempferol, baicalein and formononetin were obtained by screening, and KEGG enrichment showed that MAPK signaling pathway, NF-κB signaling pathway, PI3K-Akt signaling pathway, TNF signaling pathway, and IL-17 signaling pathway were closely related to the mechanism of this formula for the treatment of IgAN. Kaempferol is the active ingredient shared by several drugs in the formula, which mediates the inflammatory response by inhibiting NF-κB. Studies have shown that estrogen receptors can inhibit the TGF-β1/Smad signaling pathway, thereby improving renal tubular interstitial fibrosis and protecting renal function. Luteolin with its anti-inflammatory response, can in turn modulate the polarization of macrophages, protect podocytes and improve renal injury. It mainly mediates inflammatory responses by inhibiting NF-κB, p65, and Toll-like receptor 2 protein expression, reducing

ISSN 2706-6819 Vol.4, Issue 11: 7-13, DOI: 10.25236/IJFM.2022.041102

oxidative stress and delaying renal failure. Nuclear factor E2-related factor2(Nrf) in the Kidney Strengthening Formula plays a key role in protecting the body from oxidative stress as a key transcription factor regulating the inflammatory response of the body. Thus, it is evident that the treatment of IgAN with Strong Kidney and Essence Formula is associated with oxidative stress and inflammatory response.

4.2. Ginseng-Qi Dihuang Decoction

Li Ming et al screened 2038 IgA nephropathy disease targets from Ginseng-Qi Dihuang Tang, of which the key targets were MAPK1, Akt1, IL-6, VEGFA[36]. KEGG enrichment analysis results involved in the signaling pathway of pathogenic microbial infection. The main active ingredient in Ginseng Dihuang Tang is Diosgenin ligand, which has been shown to play an important role in apoptosis and autophagy of cells in renal tissues. MAPK1 is also known as extracellular signal-regulated kinase. IgA1 immune complexes were found to induce activation of MAPK/ERK kinase pathway in glomerular mesangial cells, secrete pro-inflammatory cytokines, damage the kidney, and promote proteinuria and hematuria. When the Akt1 signaling pathway is activated it causes the deposition of immune complexes in the mesangial region of the glomeruli. IL-6 cytokines secreted by immune cells cause damage to the podocytes, which in turn leads to glomerular fibrosis. It has been shown that VEGFA gene can lead to kidney injury by inducing podocyte lesions. MMP9 plays an important role in glomerular fibrosis[36]. Li Ming et al suggested that infection is an important factor in the pathogenesis of IgAN, After pathogen infection, the body expresses chemokines in large amounts, promoting the recruitment of inflammatory cells which in turn leads to kidney injury[36]. In addition the low glycosylated structure of the bacterial surface allows immune reactions of abnormally glycosylated IgA1 with autoantibodies. The study of Ginseng-Dihuang Tang for the treatment of IgAN by network pharmacology revealed that it acts through anti-pathogenic microbial infection.

4.3. Modified Shengjiang powder

Zhang Yuanyuan et al obtained 59 core therapeutic targets through screening, and the targets closely related to IgAN are neurotrophic tyrosine kinase receptor type 1 (NTRK1), Ubiquitinated ligase E3 protein(CUL3), tumor protein p53 (TP53), epidermal growth factor receptor (EGFR) ect[37]. The results of KEGG analysis showed that the treatment of IgAN with Modified Shengjiang powder mainly involved PI3K/Akt signaling pathway, NF-κB signaling pathway, cytokine-cytokine receptor interaction and other pathways.

Interestingly, both platycodin and Centella asiatica inhibited inflammatory response, apoptosis and fibrosis by activating PI3K/AKt signaling pathway. The molecular docking results further confirmed that target proteins such as NTRK1, TP53, and EGFR protect the kidney by reducing inflammatory mediator production through PI3K/AKt signaling pathway to mitigate pathological damage in the kidney. It plays a role in delaying IgAN. Thus, it can be seen that the treatment of IgAN by Modified Shengjiang powder exerts its therapeutic effect by affecting the expression of target proteins and the regulation of signaling pathways.

4.4. Addition of Huangqi Chi Feng Decoction

Ma Sijia et al used the network pharmacology technique to screen the key targets for the treatment of IgAN in Addition of Huangqi Chi Feng Decoction, including ALB, IL-6, AKT1, and VEGFA, and the pathways including AGE-RAGE signaling pathway, IL-17 signaling pathway, and TNF signaling pathway[38]. The main active ingredients in Addition of Huangqi Chi Feng Decoction are quercetin, paeoniflorin, baicalin and kaempferol. It can be seen that this formula mainly exerts the effect of the active ingredients of the drug through inhibiting IL-17 signaling pathway, TNF signaling pathway and VEGF signaling pathway, and then treats IgAN.

4.5. Tao Hong Si Wu Decoction

Ma Jin et al obtained active ingredients such as luteolin and quercetin through their research on the network pharmacology study of Taohong Siwu Decoction (THSWD), a representative formula for activating blood circulation and resolving siltation, and the systemic pharmacology technology platform of traditional Chinese medicine[39]. The results of KEGG pathway analysis showed that THSWD treats IgAN mainly through TGF-β1/Smad3, TGF-β1/JNK, MAPK signaling pathway, HIF-1

ISSN 2706-6819 Vol.4, Issue 11: 7-13, DOI: 10.25236/IJFM.2022.041102

signaling pathway and PI3K-Akt signaling pathway. Studies have shown that blocking the ERK signaling pathway can delay glomerulosclerosis and thus alleviate the process of IgAN fibrosis, and Tao Hong Si Wu Tang can treat IgAN by inhibiting ERK factors.

5. Conclusion

In conclusion, the treatment of IgAN with Chinese herbs and compound formulas such as Huang Qi, Red Peony Root, and Kidney-strengthening and sperm-fixing formula mainly includes biological components such as quercetin, kaempferol, and luteolin. These bioactive components can down-regulate the expression of IL-6, IL-17 and TNF, inhibit PI3K/AKt pathway, MAPK pathway and NF-κB pathway to regulate the immune response of the mechanism, reduce the deposition of immune complexes in glomerular mesangial cells, and inhibit glomerulosclerosis. This suggests that traditional Chinese medicine mostly inhibits glomerular mesangial cells proliferation and renal interstitial fibrosis by reducing oxidative stress and inflammatory response to protect the kidney and thus delay the development of IgAN.

The essential theory of network pharmacology is largely connected with the treatment based on syndrome differentiation and concept of wholism of TCM. The use of network pharmacology can explore the bioactive components and signaling pathways of Chinese herbs and compound formulas to treat diseases, providing ideas for multi-component and multi-target therapy of Chinese herbs and promoting the modernization of TCM. However, network pharmacology is still in the stage of gradual development, and further experimental studies are needed for validation due to the limitations of its own data and analysis methods. Moreover, the component system of Chinese herbs is relatively complex, and the concept of wholism of TCM and in vivo metabolism should be taken into consideration.

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