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Researching Prospect of Correspondence between Prescription and Syndromes on the Pathologic Basis of Yin Deficiency Syndrome of Liver and Kidney and Effective Mechanism of Decoction of Yiguan Jian

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Abstract

The theory of correspondence between prescription and syndrome is an important starting point for studying modern TCM. Yin deficiency syndrome of liver and kidney is a common clinical syndrome found in many chronic diseases, and modern researches had found its pathobiological basis involving synthetic and metabolic disorders of the body material, chronic inflammation, and damage and apoptosis of cells, etc. Decoction of Yiguan Jian is an effective prescription for Yin deficiency syndrome of liver and kidney, commonly used in clinical treatment of a variety of chronic diseases. Based on summarizing studies on pathobiological basis of Yin deficiency syndrome of liver and kidney and clinical effects of Decoction of Yiguan Jian, this article has discussed the meaning of correspondence between prescription and syndrome in the treatment of Yin deficiency syndrome of liver and kidney with decoction of Yiguan Jian, demonstrated the practical values and developing prospects, and provided new ideas for the study of correlation of syndrome and treatment.

Keywords: Syndrome of liver and kidney; Chronic diseases; Prescription and syndrome; Pathobiological basis

Introduction

Correspondence between prescription and syndrome refers to the efficacy of the prescription corresponds to the pathogenesis of the syndromes of its indications, which is an important clinical basis of syndrome differentiation and same treatment for different diseases. Yin deficiency syndrome of liver and kidney is the pathogenesis generalization of a group of Yin deficiency syndrome of liver and kidney characterized by a series of manifestations like dizziness, eyes dryness, tinnitus, dry mouth and throat, insomnia, weak waist, flank pain, numbness, red tongue, thin pulse, and so on. Modern studies found that there existed a biological basis of pathological synthesis and metabolism of the body material, chronic inflammation, damage and apoptosis of cells in Yin deficiency syndrome of liver and kidney.

Decoction of Yiguan Jian, originated from "Continued famous doctor's category case Heart and stomach pain" written by Wei yuhuang in Qing dynasty, is the representative prescription of nourishing yin and soothing liver, commonly used in a variety of chronic diseases with Yin deficiency syndrome of liver and kidney. Experimental studies have shown that it has the effects of inhibiting cell damage, anti-liver fibrosis, and anti-chronic inflammatory, anti-tumor, regulating immune function and cell differentiation, and so on.

This article summarized and reviewed the pathologic and biological basis of Yin deficiency syndrome of liver and kidney and the mechanism of decoction of Yiguan Jian, and demonstrated the theoretical basis of correspondence between prescription and syndrome for boosting the development of TCM theory of syndrome and treatment.

Pathobiological Basis of Yin Deficiency Syndrome of Liver and Kidney

Synthetic and metabolic disorders of the body material

Liu et al. [1], by using two-dimensional electrophoresis combined with mass spectrometry to comparatively analyze plasma proteome of chronic hepatitis B with yin deficiency syndrome of liver and kidney group and normal control group. Six protein points of 2 times or more differences in the total standardized gray value among groups are obtained. 4 proteins with differentially expressed plasma proteome were identified by matrix-assisted laser desorption ionization - time of flight mass spectrometry (MALDI-TOF-MS) in chronic hepatitis B with yin deficiency syndrome of liver and kidney, which are Apolipoprotein A (ApoA), apolipoprotein A (Apo A), haptoglobin (HPT), retinol binding protein (RBP). Compared to the healthy control group, the expression of those 4 proteins is significantly decreased. By analyzing different types of syndromes and laboratory indexes of hepatitis-related cirrhosis, Zhang et al. [2] found synthesis of hepatocytes in patients with yin deficiency syndrome of liver and kidney was declining, manifested as significantly reduced serum apolipoprotein a-1 (ApoA-1), and significantly lower platelet (PLT) levels. Li et al. [3] demonstrated that serum triacylglycerol (TG), total cholesterol (TC), cholinesterase (ChE), blood fibronectin (FN), blood coagulation factors (F), plasma coagulation factor (F), albumin (Alb) were significantly reduced in hepatitis -related cirrhosis patients with

yin deficiency syndrome of liver and kidney, suggesting liver damage, liver cell dysfunction might be one of the pathologic basis of hepatitis - related cirrhosis patients with yin deficiency syndrome of liver and kidney [4].

Chronic inflammation and tissue damage

Monocyte chemoattractant protein-1 (MCP-1) is mainly generated by monocytes/macrophages, MCP-1 and its receptor (human CC chemokine receptor -2, CCR2) are the important inflammatory mediators of the pathophysiological process of hypertension.

In elderly hypertensive research, Zhigang et al. [5] found that MCP-1/CCR2 inflammatory factors in hypertension patients with yin deficiency syndrome of liver and kidney were not only significantly higher than those in the healthy control group, and higher than flaring-up of liver fire group and excessive rising of liver-yang group; with the progression of the disease, inflammatory cytokines like MCP-1/CCR2 in peripheral blood were more significantly increased, suggesting that MCP-1/CCR2 played an important pathological role in hypertension with yin deficiency syndrome of liver and kidney.

In the study of metabolic syndrome, Li [6] found that the expressions of a variety of inflammatory cytokines like liver and kidney tumor necrosis factor group (tumor necrosis factor, TNF)-α, high-sensitivity C-reactive protein, endothelin (enduthelin, eT)-1 were significantly higher than those in the groups of turbid sputum and blood stasis, and with the severity progression of yin deficiency syndrome of liver and kidney, the levels of inflammatory cytokines were further increased; in IgA nephropathy, renal interstitial inflammatory cell infiltration and tubular atrophy are higher than those in the qi deficiency syndrome of spleen and kidney; the vascular disease scores were significantly higher than those in deficiency syndrome of both Qi and Yin, and those scores were significantly related to the degree of the interstitial inflammatory cell infiltration and vascular wall thickening.

That is to say, inflammatory cell infiltration, interstitial fibrosis, tubular atrophy, thickening of the vascular wall were worse in yin deficiency syndrome of liver and kidney, suggesting that pathological changes in yin deficiency syndrome of liver and kidney were related to the interstitial inflammatory cell infiltration and wall thickening of blood vessels [7]; in addition, some studies [8] found that serum C-reactive protein and insulin resistance level in hemodialysis patients with yin deficiency syndrome of liver and kidney were more changeful than those in the other syndromes.

The tendency of axonal damage in multiple sclerosis with yang deficiency syndrome of spleen and kidney was more obvious. choline/creatine ratio (CHO/CR) is higher than that in the yang deficiency syndrome of spleen and kidney, suggesting that the tendency of demyelination and tissue lesions were worse than that in yang deficiency syndrome of spleen and kidney yang [9].

Hypoxia and oxidative stress injury

Fan et al. [10] found that hyroxia-inducible factor (HIF)-1α expression could be observed in tubulointerstitial and glomerular of the primary mesangial proliferative glomerulonephritis (MsPGN) patients with yin deficiency syndrome of liver and kidney patients, and the expression of HIF-1α was positively correlated with the degree of mesangial proliferation.

And there was no HIF-1α expression in the normal control group, suggesting glomerular and tubular of MsPGN with yin deficiency syndrome of liver and kidney were in chronic hypoxia state. and HIF-1α expression of glomerular and tubular in MsPGN patients with glomerulosclerosis and interstitial fibrosis were increased with aggravation of extracellular matrix and mesangial cell damage, suggesting that MsPGN with yin deficiency syndrome of liver and kidney was associated with mesangial cells and extracellular matrix lesions due chronic hypoxia; in the study between yin deficiency syndrome of liver and kidney (diseases involving cerebral infarction, hypertension and dementia) and vascular endothelial function disorder, Tan et al. [11] showed that ET-1 level was significantly higher than that in non yin deficiency syndrome of liver and kidney group, and SOD, NO levels were significantly lower. Quantitative score of yin deficiency syndrome of liver and kidney were significantly positively correlated with ET-1 level, and were negatively correlated with NO and SOD levels.

Free radical scavenging capacity was decreased significantly in yin deficiency syndrome of liver and kidney leading to the increased free radical and endothelial cell damage, suggesting that oxidative stress and endothelial damage might be the pathological basis of yin deficiency syndrome of liver and kidney; by using gene chips to detect changes in leukocyte gene expression profiles of chronic hepatitis B, Yan et al. [12], found there were obvious differences of gene expression profiles between chronic hepatitis B with yin deficiency syndrome of liver and kidney and syndrome of damp-heat accumulation, specific modulation of gene of yin deficiency syndrome of liver and kidney was correlated to the activity of peroxidase and maintenance of stem cell.

Immune dysfunction

In the study on patients with vitiligo, Mai et al. [13] found that serum prolactin (PRL) levels in yin deficiency syndrome of liver and kidney were significantly increased by comparing to blood stasis group, dual directional effect of PRL on the immune system might be one of the causes of declination of NK cells, T lymphocytes and their subsets, suggesting vitiligo patients with yin deficiency syndrome of liver and kidney might be associated with immune factors; by observation the peripheral blood CD4+T cell subsets changes in yin deficiency syndrome of liver and kidney patients with multiple sclerosis, Yang et al. [14] found CD4+T cells in hormone therapy were significantly higher than the duration of early stage of hormone therapy, the effecting stage of hormone therapy and stable stage. CD3+CD19 T cell subsets were significantly higher than those in the stable stage, and declined after hormone therapy, significantly lower than the level in the hormone therapy, suggesting the pathology of yin deficiency syndrome of liver and kidney were closely related to immune responses and inflammation in multiple sclerosis.

Cell metabolism dysfunction

By using whole genome chip on gene expression profiles of leukocytes, Weng et al. [15] analyzed the gene expression changes of primary liver cancer with yin deficiency syndrome of liver and kidney. Compared with patients with non-yin deficiency syndrome of liver and kidney, the functions of upregulating genes with yin deficiency syndrome of liver and kidney were involved in transmembrane transportation, regulation of cytoplasmic calcium ion release, cell cycle arrest, cellular transcription, apoptosis, and regulation of phosphorylation and so on. Downregulating functions were related to gene transcription, anti-apoptosis, cell cycle regulation, and

phospholipids transportation, synthesis of adenosine triphosphate (ATP), regulating mitosis, and immune response and so on, demonstrating the presence of cell metabolism dysfunction in yin deficiency syndrome of liver and kidney from the angle of gene; and further tests of significant differences of the mRNA and protein levels in two groups were verified, and found that mRNA expression of SEC62, CCNB1, BIRC3 protein in yin deficiency syndrome of liver and kidney were lower than those in yin deficiency syndrome of liver and kidney, suggesting further study on the changes in cell metabolism in yin deficiency syndrome of liver and kidney had good applying prospects on elucidating the pathobiological basis.

The Effective Mechanisms of Decoction of Yiguanjian

Decoction of Yiguanjian is composed of north adenophora stricta, radix ophiopogonis, Angelica sinensis, rehmannia, wolfberry fruit, Toosendan fruit, possessing therapeutic features of nourishing yin and stomach, soothing liver and regulating qi. Clinical Study had reported Yiguanjian was effective in the treatment of chronic atrophic gastritis, reflux esophagitis, acute and chronic cholecystitis, chronic hepatitis B and liver cirrhosis and refractory ascites, and other diseases all differentiated as yin deficiency syndrome of liver and kidney [16-21].

Yiguanjian in combination with radiotherapy, chemotherapy and intervention could effectively improve immunity of the body, accelerate tumor regression in radiotherapy and shorten the course of treatment.

It also can effectively improve the clinical symptoms, reduce and prevent the incidence of adverse reactions of radiotherapy, significantly improve survival time of patients with advanced liver cancer and improve their quality of life [22-25]. In addition, Yiguanjian is also effective in the treatment of liver damage caused by anti-tuberculosis drugs as reduced glutathione [26].

It showed good prospects on clinical application, and some related basic research showed its relevance with the pathological changes of yin deficiency syndrome of liver and kidney.

Suppressing chronic inflammatory response

In the conventional therapy (clarithromycin, omeprazole, troxipide combined therapy) Zhi et al. [27] added Yiguanjian into the treatment of 43 cases of chronic atrophic gastritis, and the content of serum interleukin-12 (IL-12) and TNF-α were significantly lower than those in the conventional therapy group. It showed Yiguanjian could effectively downregulate the expression of serum IL-12 and TNF-α, suppress chronic inflammatory immune response, and thus played a clinical effect of treatment of chronic atrophic gastritis.

Deng [28] treated type 2 diabetic rat model by Yiguanjian intervention, found that nuclear transcription factor (NF-κB), TNF-α, serum free fatty acid (FFA) levels were significantly decreased, and insulin body substrate-2 (IRS-2) levels significantly increased, suggesting that Yiguanjian played a role in the treatment of type 2 diabetes by regulating the NF-κB signaling pathway; Wen et al. [29] treated mouse hepatitis model induced by TNF-α and D-galactos amine (GaIN) to study mouse TNF-α signaling pathway with Yiguanjian intervention, found Yiguanjian could reduce liver tissue inflammation by regulating the expression of TNF-α protein signaling pathway; Yu et al. [30] treated primary biliary cirrhosis (PBC) model mice with ursodeoxycholic acid (UDCA), Yiguanjian, and the two drugs in combination.

Results were shown that there was a significant decrease of ALP, γ-GT level in the different treatment groups compared to those in the model group. The Yiguanjia group or combination group could reduce the rate of mononuclear cell infiltration in the portal area of liver tissue, and SPMNC BCMAmRNA, suggesting that Yiguanjian suppressed inflammatory immune response and played an important role in the anti-experimental PBC effect; Feng et al. [31] observed the treatment of chronic urinary tract infection of mice model by Yiguanjian Modified description.

β2-MG and urine NAG, serum IL-10 and MCP-1 levels in the urine of rats with treatment were lower than those in the model control group, suggesting Yiguanjian could reduce levels of inflammatory cytokines; Hui et al. [32] took the experimental allergic encephalomyelitis (EAE) as a rat model of multiple sclerosis, and found Yiguanjian had significant therapeutic effect on EAE, and significantly inhibited Th1 type cell activity, enhanced the activity of Th2 cells, reduce d Inflammatory plaque, and decreased serum interferon-γ (IFN-γ) and TNF-α concentrations.

Anti-oxidative stress

Studies showed that Yiguanjian could inhibit the progression of liver fibrosis in rats CC14 development. The results of proteomics and immunohistochemistry, western blot of liver tissue consistently indicated that the expression of the liver tissue copper/zinc superoxide dismutase (Cu/Zn SOD), DJ-1, glutathione S-transferase Yb-1 subunit, AKR 7, A2 in Yiguanjian treatment group had a significant increase in comparison with the model group, and the expression of glutathione synthetase decreased, suggesting Yiguanjian could improve the anti-oxidative stress of cirrhosis rat induced by CC14 [33].

In the study of mice model induced by CC14 with Yiguanjian intervention, it was found that Yiguanjian could reduce MDA levels, improved content of SOD and HSH's, reduced the levels HSP-70 and HO-1, thereby reducing lipid peroxidation [34]. In addition, Yiguanjian also could treat and prevent liver cell injury induced anti-tuberculosis drugs by inhibiting lipid peroxidation in hepatocytes [35].

Regulating apoptosis

Yiguanjian inhibited apoptosis of liver cells by promoting the expression of apoptosis inhibiting protein (IAP), and played a role in the treatment of hepatitis [29]. In the CC14 rat model, Yiguanjian could significantly inhibit the expression of Fas, Bax, Caspase-12, Caspase-3 protein, reduce hepatocyte apoptosis index, suggesting that Yiguanjian might play protecting role to liver cells and anti-fibrosis by inhibiting liver cells apoptosis [36-38]. The tests *in vitro* showed that Yiguanjian also could induce apoptosis of hepatic stellate cells and anoikis of Bel-7402 hepatoma cells [39,40], showing Yiguanjian's positive regulation to different cells.

Regulating cell differentiation orientation

Wang et al. [41] conduced the transplantation of bone marrow from EGFP transgenic ICR mice to the whole body irradiated ICR mice. After the reconstruction of bone marrow system in 4 weeks, the model group and Yiguanjian mice were injected subcutaneously with CCl4 respectively for 13 weeks. At the 8th week, Yiguanjian group was administered orally with Yiguanjian, and continued to the 13th week.

The results showed that:

In the CCl4 liver injury mouse model. Bone marrow cells differentiated to myofibroblast and and participated in repairing damaged liver (fibrosis). And hepatocytes from bone marrow could differentiated to kupffer cells, but did not differentiate into parenchymal hepatic cells;

Yiguanjian might improve the liver function of CCl4 liver fibrosis mice with bone marrow transplantation, reduce liver fibrosis and collagen deposition, and Inhibit bone marrow cells returned to liver differentiating into myofibroblast, thereby remitting the degree of liver fibrosis;

Bone marrow cells returning to liver might be associated with chemotaxis between hemokine MCP-1 and CCR2, suggesting Yiguanjian could influence the bone marrow cells returning to the liver to affect the development of hepatic fibrosis, by intervention the expression of MCP-1 and CCR2 gene and protein.

Inducting bone marrow mesenchymal stem cells BMSCs differentiated to myofibroblast *in vitro* also showed that Yiguanjian could prevent differentiating BMSCs into myofibroblast. With isolating and culturing BMSCs, the 3rd generation cells were added TGF-β1 to induce directional differentiation. After induction, immunofluorescence and real-time quantitative PCR showed that TGF-β1 induced mesenchymal stem cells to express α-SMA, and α-SMA expression of the cells intervened by Yiguanjian was significantly reduced [42].

Regulating extracellular matrix formation and tissue remodeling

Yiguanjian could significantly inhibit the formation and development of rat liver cirrhosis models induced by CC14. Wang et al. [43] found that Yiguanjian could inhibit the expression of metalloproteinase -1 (TIMP-1), TIMP-2, matrix metalloproteinase (MMP) -14 protein in model's liver tissue, and inhibit MMP-2 activity, decrease the expression of α-smooth muscle actin (α- SMA) and type I collagen.

Gene chip analysis revealed it could reduce the expression of α-SMA and AP1γ subunit binding protein 1 (AP1GBP1), growth hormone releasing hormone receptor (GHRHR) in liver tissues, and expression thrombospondin 2 (Thrombospondin 2, TSP2) showed an increasing trend in the dynamic process of change, this change was consistent with the activity of MMP-2 in liver tissue.

TSP2 is an extracellular matrix protein and an important regulator of extracellular of MMP-2; MMP-2 and TSP2 interacting into each other formed TSP2/MMP2 complexes, which involved in tissue repair during angiogenesis and matrix remodeling. Yiguanjian could significantly reduce the expression liver tissue RNA binding motif protein 3 (RBM3) involved in the body's adaptive response to hypoxia, suggesting that its mechanism of inhibition liver cirrhosis and might be related with improving liver tissue hypoxia, inhibiting angiogenesis and tissue remodeling [44]; in the further studies of experimental CC14 hepatic fibrosis in mice, it was demonstrated that Yiguanjian could significantly reduce the protein expression of l CD31, HIF-1α, vascular endothelial growth factor receptor (VEGFR) 2, in liver tissue, and increase the expression of dimethylarginine dimethyl amino hydrolytic enzyme 1 to degrade the asymmetric dimethyl arginine (DMDA), and increase the activity of eNOS.

It suggested that liver cirrhosis inhibiting mechanism of Yiguanjian might be related to the improving tissue hypoxia, protecting sinusoidal endothelial cells, inhibiting angiogenesis and tissue remodeling mediated by HIF-1α.

Bin et al. [45,46] conducted the study of using Yiguanjian associated with cyclophosphamide to treat H22 mice with liver cancer, and found exclusively using Yiguanjian and chemotherapy or the combination of the two all had anti-tumor effect. Comparing to the model group, the spleen index could be increased in three groups, and NF-κB protein expression could be reduce.

Yiguanjian group could improve the expression of vascular endothelial growth factor (VEGF); chemotherapy could reduce the expression of vascular endothelial growth factor receptor (VEGFR) 2. The combination group could improve the expression of VEGF, VEGFR2 protein, and decrease and reduce the expression of MMP9 protein.

In combination with chemotherapy drugs, it showed a good synergistic effect. NF-κB is one of the incentive factors leading to tumor development by regulating the transcription of corresponding gene to promote tumorigenesis, tumor cell proliferation, invasion and metastasis. In recent research, MMP9 is considered to be an important molecular marker of tumor invasion and metastasis, and to inhibit its expression might be effective in inhibiting tumor invasion and metastasis.

And the central role of angiogenesis in tumor growth had also been confirmed in many of the studies, VEGF is one of the strongest positive regulators of angiogenesis. Therefore, on the above findings, it revealed that the antitumor mechanism of Yiguanjian was to inhibit tumor angiogenesis, reduce metastasis of liver cancer cells.

New discoveries based on metabolomics

As a powerful analytical tool, metabolomics could be used as a new tool to evaluate the efficacy of Chinese herbal compound and find potential associated biological makers related to the therapeutic effects. Gou et al. [47] used metabolomics method to evaluate the pharmacodynamic effect of Yiguanjian CCL4 in treatment in induced hepatic fibrosis in rats.

The results showed that: Compared to the normal group, the urine-derived metabolites malonic acid, benzoic acid, diethyl pimelic acid, leucine, acid, phenol, glycine, indole, oleic acid, lysine content in model group had all significantly decreased, but there were different degrees of increase in Yiguanjian treatment group, suggesting Yiguanjian could effectively reverse metabolic disorders of CCL4 induced liver fibrosis rats.

And the above metabolites could be studied as the relevant potential biological markers and provide the basis for further study of the formation mechanism of liver fibrosis and the active mechanism of Yiguanjian in liver fibrosis.

Researching and Developing Prospects of Correlation between Disease and Syndrome, and Correspondence between Prescription and Syndrome

Combining disease and syndrome, clarifying the different methods and prescriptions are the scientific basis for obtaining the therapeutic effect, and the important means of communication between traditional Chinese medicine and modern science.

In this paper, on the basis of pathological findings of yin deficiency syndrome of liver and kidney in different diseases, the data were collated and analyzed to extract the common pathological features of yin deficiency syndrome of liver and kidney.

Confined to current research stage, the studies still were preliminary inducted and refined, but to a certain extent, showing the importance of pathological changes of yin deficiency syndrome of liver and kidney in the progression of many chronic diseases such as synthetic and metabolic disorders, chronic inflammation, cell injury and tissue repair.

The Yiguanjian possessed the functions of anti-peroxidation damage, inhibition of chronic inflammation, regulation of apoptosis and differentiation, improving tissue hypoxia, promoting the repair of damaged tissue, which had a certain correspondence with yin deficiency syndrome of liver and kidney.

Thus, taking Yiguanjian as an example, it could reveal the good developing prospects of the research of correlation between disease and syndrome, correspondence between prescription and syndrome from the other side. Meanwhile, focusing on the effective prescription, depth research of pharmacological effects and mechanism of the effective material basis could be carried out for analyzing effective traditional Chinese medicine prescriptions and their effective component, which would help promote further research on the pathophysiological mechanism of the related disease.

On this basis, we could carry out the process of re-combination of components or ingredients of traditional Chinese medicine to create new Chinese herbal medicine with clear composition and mechanism, and improve the therapeutic effect.

Epilogue

Analyzing pathobiological basis of TCM syndrome is a long and arduous task that requires the researching accumulation, collaboration and repeated verification of many researching teams, and gradually forms a consensus. And the theory of correlation between disease and syndrome, correspondence between prescription and syndrome are important ideas to form the consensus.

Focusing on correspondence between prescription and syndrome, intensive studies on mechanisms of effective prescription, and fully introduced modern research results of diseases related to certain syndrome, correlation analysis should be carry out in the modern research of the pathogenesis of chronic diseases and effective mechanisms of the Prescription, which might both find pathological aspect of correspondence between prescription and syndrome, but also provide a reference for biological research and application of innovative prescription. It might also provide new ideas for the prevention and treatment of chronic diseases in Chinese medicine.

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