

Research progress of Yinchenhao Decoction in the treatment of non-alcoholic fatty liver disease

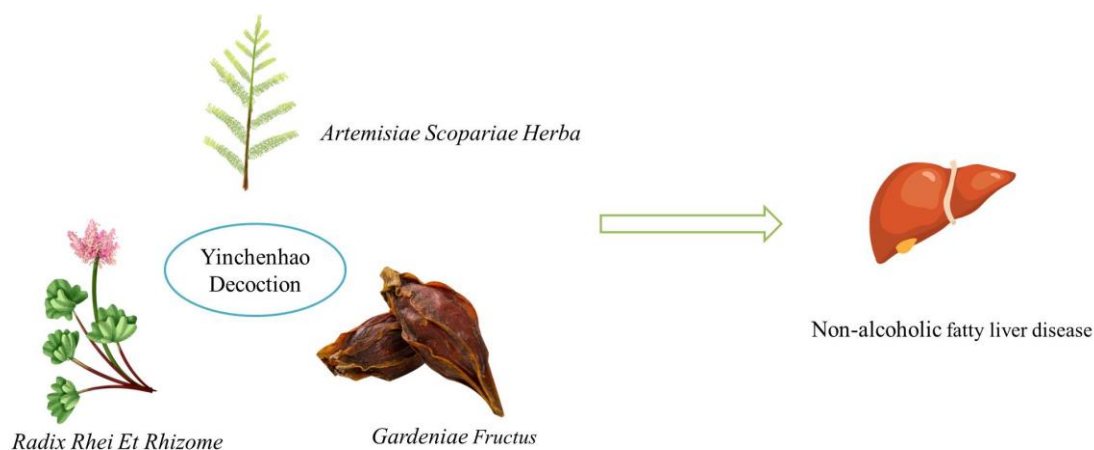
Xiao-Ting Ma¹, Jing-Na Zhou¹, Shou-Jing Sheng¹, Shao-Qin Ge^{1*}

1. College of Traditional Chinese Medicine, Hebei University, Baoding, Hebei, 071000, China.

***Correspondence to:** Shao-Qin Ge, College of Traditional Chinese Medicine, Hebei University, Baoding, Hebei, 071000, China. Email: gesq67@163.com.

Highlights

This article summarized that the clinical and basic research of Yinchenhao Decoction in the treatment of non-alcoholic fatty liver disease.



Abstract

Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases worldwide. Non-alcoholic steatohepatitis (NASH) is the most serious type and a turning point in the progression of NAFLD. If not treated actively, NASH will progress to irreversible liver damage such as cirrhosis and hepatocellular carcinoma. At present, there are no specific therapeutic drugs in western medicine. The treatment methods are mainly to improve lifestyle and exercise therapy, to alleviate the symptoms of discomfort, delay the progress of the disease, and improve the quality of life. However, the effect is often not ideal, prone to recurrence, and compliance is relatively poor. Dramatically, traditional Chinese medicine has certain advantages in the treatment of NAFLD. Modern research has confirmed that Yinchenhao Decoction has a good effect on liver-protective and choleric action and improving liver function. It has significant curative effect on various liver and gallbladder diseases such as acute liver injury and alcoholic liver disease. This article summarized the clinical and basic research of Yinchenhao Decoction in the treatment of NAFLD. We found that Yinchenhao Decoction can enhance the efficiency of NAFLD and improve symptoms such as dizziness, liver pain, hepatosplenomegaly and indigestion. The mechanisms may be related to that Yinchenhao decoction improves the disorder of glucose and lipid metabolism, inflammatory state and liver function.

Key Words: Yinchenhao Decoction, Non-alcoholic fatty liver disease, Non-alcoholic steatohepatitis

Citation: Ma XT, Zhou JN, Sheng SJ, Ge SQ. Research progress of Yinchenhao Decoction in the treatment of non-alcoholic fatty liver disease. *Drug Combination Therapy*. 2019, 1(4): 227-234.

Competing interests: The authors report no conflicts of interest in this work.

Funding: This study was funded by the Natural Science Foundation of Hebei Province (No. H2018201218).

DOI: 10.12032/DCT201904004

Submitted: 4 July 2019, **Accepted:** 18 August 2019, **Online:** 26 August 2019.

Background

Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases worldwide ^[1]. The prevalence of NAFLD is rising ^[2], affecting 20-40% of the population ^[3]. The Haikou survey in China showed that ^[4] the prevalence of NAFLD was 30.45%, of which the male prevalence rate was 41.74% and the female prevalence rate was 17.22%. NAFLD includes nonalcoholic simple fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). The most severe of these types is NASH ^[5], which is characterized by hepatocyte damage, liver inflammation, and progression of fibrosis. Chronic inflammation is the basis of the pathogenesis of NASH at various stages, and is also the basis for the development of cirrhosis and tumors ^[6]. At present, NASH has become an important cause of chronic liver disease and hepatocellular carcinoma (HCC) in the world ^[3].

With the increasing incidence of NAFLD in the world, people are paying more attention to the study of NAFLD. The related pathogenesis and the discovery of key factors for regulation provide a new target and theoretical basis for the treatment of NAFLD. Clinically, the treatment of NAFLD is mainly based on diet, exercise and weight control, but only a very small number of patients can lose weight by 10% to achieve the goal of effectively reversing the level of liver fibrosis. Therefore, there is an urgent need for specific NAFLD treatment drugs ^[7]. In addition, the study found that ^[8], ambient air particles with aerodynamic diameter less than 2.5 μm (PM_{2.5}) have a certain enhancement side-effect on NAFLD, so environmental management also has a positive effect on the prevention and control of NAFLD.

Western medicine has no specific treatment

drugs for NAFLD. At present, the commonly used drug is diammonium glycyrrhizinate enteric-coated capsule, which has the functions of improving liver function, protecting liver cells and anti-inflammatory. But the single treatment has poor efficacy and poor prognosis ^[9]. Long-term use of western medicine can lead to drug resistance and increase adverse reactions. Therefore, the treatment of NAFLD by Chinese medicine is particularly important.

Yinchenhao Decoction is derived from Zhang Zhongjing's "*Treatise on Febrile Diseases*". This formula consists of *Artemisiae Scopariae Herba*, *Gardeniae Fructus* and *Radix Rhei Et Rhizome*. *Artemisiae Scopariae Herba*, clearing away heat and dampness, is a sovereign drug in this formula. *Gardeniae Fructus*, Tongli Sanjiao and making the dampness-heat down, is a ministerial drug. *Radix Rhei Et Rhizome*, clearing heat and purging and Tongli stool, is an adjuvant. So this formula has the effect of removing dampness and yellowing, clearing heat and purging, and benefiting urination ^[10]. Modern pharmacological studies have shown that the chemical constituents in Yinchenhao Decoction include flavonoids, tannins, terpenoids, glucosides, organic acids, etc. ^[10] and the active ingredients include chlorogenic acid, geniposide, rhubarb acid, emodin, aloe-emodin, chrysophanol and emodin methyl ether ^[11]. Studies have confirmed that Yinchenhao Decoction has good functions of protecting liver and gallbladder, improving liver function, lowering blood fat and anti-inflammatory. So this formula has remarkable curative effect on various acute and chronic hepatobiliary diseases and it is widely used to treat various hepatobiliary diseases ^[12]. Recently, Jin-Yu Zhang ^[13] found that certain active ingredients in Yinchenhao Decoction

may play a role in the treatment of chronic hepatitis B through ABC transporter, bile secretion, TNF signaling pathways by network pharmacological analysis.

The etiology and pathogenesis of NAFLD

There are many causes of NAFLD, such as obesity, type 2 diabetes, hyperlipidemia, etc., which alone or together to become a susceptible factor for NAFLD ^[14]. However, its pathogenesis is not completely clear.

The pathogenesis of NAFLD is related to insulin resistance (IR), intrahepatic lipid accumulation, inflammatory factors, endoplasmic reticulum stress, abnormal expression of adipokines, oxidative stress, increased susceptibility to apoptosis, etc. ^[15]. Relevant drug interventions for different pathogenesis of NAFLD and different targets have become hotspots for the treatment of NAFLD ^[16]. NAFLD is mainly caused by the imbalance of absorption and metabolism of triglycerides in hepatocytes. The increase of triglyceride intake and synthesis or the decrease of metabolism can aggravate the occurrence and development of NAFLD ^[17]. The classic hypothesis of the onset of NAFLD is the “second strike” doctrine proposed in 1998 ^[18]. The “First hit” refers to the accumulation of intrahepatic triglycerides caused by IR and increased sensitivity to endogenous and exogenous damage factors. The “Second Strike” refers to the final inflammatory damage of hepatocytes caused by inflammatory cytokines, oxidative stress and endoplasmic reticulum stress after the accumulation of triglycerides in hepatocytes ^[19]. However, the “liver lipid toxicity” theory suggests that intrahepatic

triglyceride accumulation does not cause IR and hepatocyte damage, and the core mechanism of NASH is Reticulum stress and inflammatory response caused by abnormal metabolism of free fatty acids and their metabolites such as diglycerides and ceramides ^[20]. In addition, lipopolysaccharide secreted by intestinal bacterial translocation, especially highly immunological Gram-negative bacilli, can enter the systemic blood circulation, further activating the inflammatory process of the liver by activating macrophages and Kupffer cells ^[21].

The clinical manifestations and diagnosis of NAFLD

The definitive diagnosis of NAFLD should be based on the patient's clinical manifestations, blood tests, imageological examination, histopathological changes and the exclusion of alcoholic fatty liver and other specific liver diseases. Patients may have generalized fatigue, liver pain, right upper quadrant discomfort or fullness, loss of appetite, nausea and other non-specific symptoms ^[22]. Hepatomegaly is a common sign of NAFLD, followed by splenomegaly, and a small number of patients may have mild jaundice. Liver histology (referred to as liver biopsy) is the most reliable means for the diagnosis and classification of NAFLD, which can accurately determine the degree of fat accumulation, inflammation and fibrosis in liver tissue ^[23]. Imaging examination is the commonly used examination method for the diagnosis of NAFLD. Abdominal B-ultrasound has been the first choice for the diagnosis of fatty liver. Abdominal B-ultrasound can roughly determine the presence or absence of intrahepatic fat infiltration and its distribution

in the liver ^[24].

The treatment status

The symptomatic treatment

There is no specific drug for the treatment of NAFLD, and it is still based on symptomatic treatment. Simple fatty liver disease usually does not require medication. For steatohepatitis, polyene phosphatidylcholine, vitamin E, reduced glutathione, etc. may be used to reduce lipid peroxidation. Insulin receptor sensitizers such as metformin and thiazolidinediones can be used in patients with NAFLD who have type 2 diabetes. Hypolipidemic drugs can be used on the basis of comprehensive treatment for NAFLD with high blood lipids, but need to detect liver function, if necessary, combined with liver protection drugs ^[25].

Patient education

Controlling diet and increasing exercise are the best measures for the treatment of obesity-related NAFLD. Excessive weight loss may aggravate liver injury. Therefore, the body weight should be reduced steadily and we should pay attention to monitoring body weight and liver function ^[25].

Pay attention to correcting the imbalance of nutrition, prohibiting alcohol, and not taking drugs indiscriminately. During the period of taking hypolipidemic drugs, the liver function should be reviewed regularly according to the doctor's advice ^[25].

Yinchenhao Decoction for the treatment of NAFLD

Traditional Chinese medicine believes that

“damp heat and blood stasis and liver disorders” is the key to the pathogenesis of NAFLD ^[22,26,27]. At the same time, the phlegm, dampness, turbidity, stasis and heat accumulate in the liver caused by various causes, leading to the occurrence of NAFLD ^[22].

NASH is a rate-limiting step in the conversion of NAFLD to cirrhosis and is one of the important causes of cryptogenic cirrhosis. Therefore, the key to the treatment of NAFLD is to treat and delay the development of NASH ^[25]. Modern research has confirmed that Yinchenhao Decoction has a good effect of protecting liver and gallbladder, improving liver function, lowering blood fat and anti-inflammatory, and has significant curative effect on various acute and chronic liver diseases ^[12].

Some clinical studies have confirmed that Yinchenhao Decoction has a certain effect on the treatment of NAFLD. In a clinical trial of Yinchenhao Decoction for the treatment of NASH, Yinchenhao Decoction was the research group, and lifestyle improvement and exercise therapy were the control group. The improvement of symptoms such as dizziness, chest tightness, mouth pain and urine yellow was obvious in the study group compared with the control group and the difference was statistically significant ($P<0.05$). The total effective rate (90.00%) in the study group was significantly higher than that in the control group (50.00%), and the difference between the two groups was statistically significant ($P<0.05$) ^[28]. In addition, a meta-analysis of 12 RCT including 1214 patients with NAFLD found that Yinchenhao Decoction and its addition and subtraction treatment of NAFLD were effective and safe. Yinchenhao Decoction can reduce several serum maker abnormalities, including

ALT, AST, GGT, TG, TC, HDL, and LDL, reduce BMI, and reduce syndrome scores. Besides, B-ultrasound examination also shows the improvement of hepatosplenomegaly^[29].

At present, the research on the mechanism of Yinchenhao Decoction in the treatment of NAFLD is also being explored. Zhou Weiqing et al^[30] found that Yinchenhao Decoction can improve lipid metabolism and improve liver function in high fat-induced NAFLD rats, and its mechanism may be related to down-regulation of p38MAPK and Omentin expression in liver tissue. In addition, studies have shown that^[31], Yinchenhao Decoction can improve the glucose and lipid metabolism of NAFLD with IR rats in a dose-dependent manner, thereby reducing liver fat lesions and relieving liver fibrosis. The mechanism may be related to regulating adipokines levels, reducing IR, and improving glucose and lipid metabolism disorders, thereby reversing liver cell damage. Zhao Jiajing et al^[32] conducted experimental studies on model rats. The results showed that the levels of TAG, LDL-C and CH were significantly decreased and the level of HDL-C was increased in the serum of rats after administration of Yinchenhao Decoction. These results proved that Yinchenhao Decoction can effectively regulate the blood lipid level of rats with lipid metabolism disorder. At the same time, the expression levels of inflammatory factors such as TNF- α and IL-6 were significantly decreased, and the expression levels of C3, C5, ASP and FFA were significantly improved in the serum of rats in the Yinchenhao Decoction group. Therefore, Yinchenhao Decoction may play a role in the treatment of NAFLD by improving the disorders of glucose and lipid metabolism, inflammatory state and improving liver

function.

Conclusion and prospective

In summary, Yinchenhao Decoction for the treatment of NAFLD can improve the treatment efficiency, improve patients symptoms such as dizziness, liver pain, hepatosplenomegaly and indigestion, chest tightness, nausea, vomiting and other symptoms. The mechanisms may be related to that Yinchenhao Decoction improves the disorder of glucose and lipid metabolism, inflammatory state and liver function. However, traditional Chinese medicine has the characteristics of “multi-components and multi-targets”. The therapeutic advantages of traditional Chinese medicine need to be scientifically evaluated on the efficacy clear the targets of Chinese medicines, and develop precise formulas for the treatment of NAFLD.

References

- [1] Kitade H, Chen G, Ni Y, et al. Nonalcoholic fatty liver disease and insulin resistance: New insights and potential new treatments. *Nutrients* 2017, 9(4): 387.
- [2] Tacke F. Cenicriviroc for the treatment of non-alcoholic steatohepatitis and liver fibrosis. *Expert Opin Investig Drugs* 2018, 27(3): 301-311.
- [3] Ilan Y, Shailubhai K, Sanyal A. Immunotherapy with oral administration of humanized anti-CD3 monoclonal antibody: a novel gut-immune system-based therapy for metaflammation and NASH. *Clin Exp Immunol* 2018, 193(3): 275-283.
- [4] Ruan JW, Gao LJ, Liang XF, et al. An investigation of the prevalence rate of nonalcoholic fatty liver disease in the

- population undergoing physical examination in Haikou, China. *J Clin Hepatol (Chin)* 2018, 34(9): 1925-1928.
- [5] Ma ZZ, Lu LG. Cholesterol metabolism and non-alcoholic steatohepatitis. *Chin J Hepatol (Chin)* 2016, 24(8): 623-627.
- [6] Wang T, Yang W, Karakas S, et al. NASH in Nondiabetic Endocrine Disorders. *Metab Syndr Relat Disord* 2018, 16(7): 315-320.
- [7] Zhang WB, Zhang HY, Jiao FZ, et al. Progress in the treatment of nonalcoholic fatty liver disease. *J Med Res (Chin)* 2018, 47(3): 150-152.
- [8] Tarantino G, Capone D, Finelli C. Exposure to ambient air particulate matter and non-alcoholic fatty liver disease. *World J Gastroenterol* 2013, 19(25): 3951-3956.
- [9] Zhang B. Therapeutic effect of atorvastatin combined with diammonium glycyrrhizinate enteric-coated capsules on patients with nonalcoholic fatty liver disease. *Chin J Convalescent Med (Chin)* 2019, 28(6): 637-638.
- [10] Li FF, Deng X, Wen B. Clinical and Basic progress of research about Yinchenhao Decoction on viral hepatitis. *Liaoning J Tradit Chin Med (Chin)* 2015, 42(12): 2474-2476.
- [11] Li JY, Liu P, Sun MY. Research progress on the mechanism of Yinchenhao Decoction in the treatment of hepatobiliary diseases. *Pharmacol Clin Chin Mater Med (Chin)* 2015, 31(6): 241-244.
- [12] Liu Y. Experimental study on Yinchenhao Decoction and its decomposed prescriptions in the treatment of nonalcoholic steatohepatitis. *Beijing Univ Chin Med (Chin)* 2013.
- [13] Zhang JY, Cai XF. A network pharmacological study on the potential mechanism of Yinchenhao Decoction in treatment of chronic hepatitis B. *Drug Comb Ther* 2019, 1(3): 134-152.
- [14] Cobbina E, Akhlaghi F. Non-alcoholic fatty liver disease (NAFLD)-pathogenesis, classification, and effect on drug metabolizing enzymes and transporters. *Drug Metab Rev* 2017, 49(2): 197-211.
- [15] Guo Y, Li JX, Mao TY, et al. Effect of Combined prescription of Linggui Zhugan Tang and Yinchenhao Tang on Nrf2/ARE signaling pathway in rats with non-alcoholic steatohepatitis. *Chin Journal Exp Tradit Med Formulae (Chin)* 2017, 23(16): 108-113.
- [16] Connolly JJ, Ooka K, Lim JK. Future Pharmacotherapy for Non-alcoholic Steatohepatitis (NASH): Review of Phase 2 and 3 Trials. *J Clin Transl Hepatol* 2018, 6(3): 264-275.
- [17] Zhu X, Bian H, Gao X. The potential mechanisms of berberine in the treatment of nonalcoholic fatty liver disease. *Molecules* 2016, 21(10), 1336.
- [18] James OF, Day CP. Non-alcoholic steatohepatitis (NASH): a disease of emerging identity and importance. *J Hepatol* 1998, 29(3): 495-501.
- [19] Başaranoğlu M, Örmeci N. Nonalcoholic fatty liver disease: diagnosis, pathogenesis, and management. *Turk J Gastroenterol* 2014, 25(2): 127-132.
- [20] Brent A. Neuschwander-Tetri. Hepatic lipotoxicity and the pathogenesis of nonalcoholic steatohepatitis: The central role of nontriglyceride fatty acid metabolites. *Hepatology* 2010, 52(2): 774-788.
- [21] Chu H, Williams B, Schnabl B. Gut microbiota, fatty liver disease, and

- hepatocellular carcinoma. *Liver Res* 2018, 2(1): 43-51.
- [22] Zhang SS, Li JX. Consensus opinion of TCM diagnosis and treatment experts for nonalcoholic fatty liver disease (2017). *J Clinl Hepatol (Chin)* 2017, 33(12): 2270-2274.
- [23] Spengler EK, Loomba R. Recommendations for Diagnosis, Referral for Liver Biopsy, and Treatment of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis. *Mayo Clin Proc* 2015, 90(9): 1233-1246.
- [24] Arienti V, Aluigi L, Pretolani S, et al. Ultrasonography (US) and non-invasive diagnostic methods for non-alcoholic fatty liver disease (NAFLD) and early vascular damage. Possible application in a population study on the metabolic syndrome (MS). *Intern Emerg Med* 2012, Suppl 3: S283-S290.
- [25] Ge JB, Xu YJ. *Internal Medicine*. Beijing: People's Medical Publishing House (Chin) 2016: 409.
- [26] Qian Y. "Physical homology" is an important part of the treatment of chronic severe hepatitis. *Chin J Integrated Tradit West Med Liver Dis (Chin)* 2006, 16(4): 251-252.
- [27] Mao TY, Gao KL, Zhao WH, et al. Experimental study of "Wenyun Qingli" method on DAG-PKC ϵ signal pathway in liver tissue of NASH rats. *Global Tradit Chin Med (Chin)* 2016, 9(8): 908-913.
- [28] Jiang GY, Zhou WQ, Wang Z, et al. Efficacy of Yinchenhao Decoction in the treatment of non-alcoholic fatty hepatitis. *J Math Med (Chin)* 2018, 31(8): 1192-1193.
- [29] Zhang LD, Wei W, Sun XH, et al. Systematic and meta-analysis of randomized controlled trials of Yinchenhao Decoction in the treatment of nonalcoholic fatty liver disease. *World Chin J Digestol (Chin)* 2014, 22(16): 2327- 2337.
- [30] Zhou WQ, Wang XY, Lin J, et al. Study on the effect of Yinchenhao Decoction on P38MAPK pathway and reticulin in NAFLD rats. *Modern Diagn Treat (Chin)* 2018, 29(18): 2857-2859.
- [31] Zhou WQ, Wang XY, Liu DL, et al. Protective effect and mechanism of Yinchenhao decoction on liver of rats with non-alcoholic fatty liver disease with insulin resistance. *Shandong Med J (Chin)* 2019, 59(19): 18-22.
- [32] Zhao JJ, Yue YH, Shi YM, et al. Experimental study on the effects of Yinchenhao Decoction on CH, LDL-C and TAG in rats with Dyslipidaemia. *J Emerg Tradit Chin Med (Chin)* 2018, 27(8): 1387-1390+1395.