MEDS Chinese Medicine (2023)
Clausius Scientific Press, Canada

DOI: 10.23977/medcm.2023.050105
ISSN 2616-1753 Vol. 5 Num. 1

Research Progress on the Mechanism of Traditional Chinese Medicine in the Treatment of Non-Alcoholic Fatty Liver Disease Based on Oxidative Stress

Xinyi Li[1], Jianping Xi[2,*], Haitao Liu[2], Lingna Jia[1], Huayi Zhang[1]

[1]Shaanxi University of Chinese Medicine, Xianyang, 712046, China
[2]Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang, 712046, China
**Corresponding author*

Keywords: Nonalcoholic fatty liver disease, Traditional Chinese medicine, Chinese medicine compound, Chinese patent medicine, Oxidative stress, Research progress

Abstract: Nonalcoholic fatty liver disease (NAFLD) accounts for an increasing proportion of liver diseases, but its pathogenesis is more complex, and there is no more effective clinical treatment. Oxidative stress is considered to be an important factor leading to the progression of NAFLD. Therefore, improving the oxidative stress status of NAFLD patients is of great significance for the prevention and treatment of the disease. In recent years, a number of experimental studies have shown that traditional Chinese medicine has unique advantages in the treatment of various clinical diseases, and domestic and foreign researches on the treatment of NAFLD with traditional Chinese medicine are also emerging one after another. Based on this, this paper summarizes the mechanism of some traditional Chinese medicine, traditional Chinese medicine compound and Chinese patent medicine on oxidative stress in the development of NAFLD, in order to provide new ideas for clinical treatment of NAFLD.

1. Introduction

With the development of society and the improvement of living standards, great changes have taken place in people's diet, and the proportion of fat in food is increasing. However, long-term high-fat diet and lack of exercise can easily lead to abnormal biochemical indexes such as blood sugar and blood lipids, which leads to a variety of diseases. Non-alcoholic fatty liver disease (NAFLD) is a clinicopathological syndrome characterized by diffuse hepatic cell bullous steatosis and fat storage, except for excessive drinking and other clear liver damage factors [1].Including non-alcoholic fatty liver (NAFL),non-alcoholic steatohepatitis (NASH), fatty liver fibrosis, cirrhosis and liver cancer[2].According to relevant statistics, NAFLD has developed into the most common chronic liver disease in the world, and 25% of the world's population is considered to have NAFLD[3].Currently, clinical treatment of NAFLD is mostly based on diet and lifestyle changes, but the compliance is poor; and there is no ideal plan for drug treatment of the disease[4].Numerous studies have shown that traditional Chinese medicine plays a unique role in alleviating chronic liver disease, improving liver function and protecting hepatocytes. In this paper, the research progress of

some Chinese medicine, Chinese medicine compound and Chinese patent medicine against NAFLD in recent years was elaborated based on oxidative stress, which was expected to provide new ideas for the clinical treatment of NAFLD.

2. Oxidative stress and NAFLD

Oxidative stress is a state of imbalance between the oxidative system and antioxidant system. Oxidative stress will occur when the degree of oxidation of the body exceeds the removal ability of oxides for a variety of reasons. It generally exists in various pathophysiological processes of the body, and is closely related to aging, tissue damage and disease occurrence. Reactive oxygen species (ROS) is the main active substance of oxidative stress, which are natural by-products of intracellular metabolic reaction and can regulate the specific biochemical pathway of normal cell function and survival. However, the imbalance of ROS signal or the excessive non-specific generation of ROS can cause serious harm to human body[5].

The most classic pathogenesis of NAFLD is the "two-hit" hypothesis proposed by Day and James in 1998[6].In the "two-hit" hypothesis, the first strike is mainly insulin resistance associated with obesity, type 2 diabetes mellitus, hyperlipidemia, etc. Insulin resistance can lead to abnormal lipid metabolism and lipid accumulation in hepatocytes. The second blow mainly refers to oxidative stress and mitochondrial dysfunction. After being taken up by the liver, free fatty acids (FFA) mainly generates excessive ROS in the mitochondria through β-oxidation, resulting in the imbalance between the oxidation system and the antioxidant system, oxidative stress occurs. ROS can also activate Kupffer cells, leading to the production of TGF-β,TNF-α,IL-6 and other inflammatory factors. In addition to further aggravating hepatic inflammatory responses, inflammatory factors can also activate hepatic stellate cells (HSCs) to switch on liver repair, which in turn leads to liver fibrosis and cirrhosis, and even hepatocellular carcinoma. Persistent oxidative stress causes mitochondrial dysfunction and even rupture leading to ROS leakage. The leaked ROS and unsaturated fatty acids can produce lipid peroxide, which has strong cytotoxicity, can damage mitochondria and cells, further promoting ROS and peroxide production, forming a vicious circle[7].

However, in recent years, it has been found that the pathogenesis of NAFLD is relatively complex. The "two-hit" hypothesis is no longer enough to explain the mechanism, so it gradually tends to "multiple strikes", including insulin resistance, hormones secreted by adipose tissues, nutritional factors, intestinal microflora, and genetic and epigenetic factors, etc[8].However, oxidative stress is still an important link in the pathogenesis of NAFLD. Therefore, inhibiting oxidative stress is of great significance to slow down NAFLD progression.

3. Effects of traditional Chinese medicine on oxidative stress during the progression of NAFLD

3.1 Monomer of traditional Chinese medicine

3.1.1 Scutellaria baicalensis (Baicalin)

Baicalin, a flavonoid compound, is a natural product with antioxidant and anti-inflammatory effects extracted from the traditional Chinese medicine Scutellaria baicalensis, and its efficacy on NAFLD has been confirmed by various studies[9].Zhong et al[10] found that compared with a high-fat and high-cholesterol diet alone, administration of baicalin to mice significantly increased the levels of antioxidant factors such as glutathione (GSH) and superoxide dismutase (SOD), while it also decreased the levels of malondialdehyde (MDA),4-hydroxynonenoic acid (4-HNE) and

8-hydroxydeoxyguanosine (8-OhdG) which are products of lipid peroxidation in the liver. The mechanism may be related to the down-regulation of cytochrome P450 enzyme 2E1(CYP2E1). CYP2E1 is an oxidoreductase that, when increased in the NASH liver, promotes the oxidation of a variety of substances, including fatty acids, leading to the progression of NASH[11].Gao et al[12] also further confirmed that baicalin could significantly increase the content of GSH and SOD and decrease the content of MDA after establishing a 3D model of NAFLD, and speculated that the enhancement of SOD and GSH by baicalin was more likely due to the decreased consumption rather than the increased synthesis. The experiment also found that baicalin could reverse the expression of mitochondrial membrane matrix metalloproteinase (MMP) and ATP5A to improve mitochondrial function and then inhibit cell apoptosis.

3.1.2 Polygonum cuspidatum (Resveratrol)

The traditional Chinese medicine Polygonum cuspidatum is derived from the dried rhizomes of the plant Polygonum cuspidatum, which in traditional Chinese medicine is considered to return to the liver, biliary, and lung meridians. Resveratrol is a non-flavonoid polyphenolic organic compound that can be extracted from Polygonum cuspidatum. Modern pharmacological research has found that it has the characteristics of anti-tumor, cardiac protection, antiviral, anti-inflammatory, antibacterial, antioxidant, regulating body lipid metabolism and regulating blood glucose[13].Cheng et al[14] established a NAFLD model by feeding mice a high-fat diet and found that resveratrol could significantly reduce the MDA content in the liver of mice, which may be related to the increase of total superoxide dismutase (T-SOD) and glutathione peroxidase (GSH-PX) activities in liver tissue. The experiment also confirmed that resveratrol could reduce liver lipid accumulation by reducing the mRNA expression of fatty acid transporter CD36 in mouse liver, which was also of important significance in reducing liver oxidative stress and inflammation. Hajighasem et al[15] found that after treatment with resveratrol, NAFLD model rats had significantly reduced liver damage. This effect was associated with a significant increase in SOD and catalase (CAT) activity, interleukin 10 (IL-10) content, and a decrease in tumor necrosis actor-α(TNF-α), lipid peroxidation and apoptotic cell death amounts.

3.1.3 Coptis chinensis (Berberine)

Modern research has found that Coptis chinensis, a heat-clearing and dampness-drying medicine, contains various chemical components including alkaloids, lignans, coumarins, flavonoids, terpenoids, steroids, organic acids, volatile oils, polysaccharides and so on[16].Berberine is the most abundant chemical component in coptis chinensis, up to 5%~8%[17].Sun et al[18] found that berberine reduced lipid accumulation in the liver of high-fat diet fed mice, inhibited NADPH oxidase 2(NOX2) expression and in turn reduced ROS formation, and also inhibited mitochondrial ROS production by down-regulating the expression of complex I, a major leakage site of electrons in the mitochondrial electron transport chain, and reducing oxygen species required for ROS formation. Methylenetetrahydroberberine (DMTHB) is a novel derivative of berberine. Zhang et al[19] found through experimental research that DMTHB can inhibit the synthesis of pro-inflammatory factors by inhibiting TLR4/NF-αB signaling pathway, regulate the expression of genes related to lipid metabolism in mouse liver tissue, and reduce the oxidative stress and endoplasmic reticulum stress of mouse liver fed by MCD and L02 cells induced by palmitic acid.

3.1.4 Other

In addition to the above several traditional Chinese medicines, a large number of traditional Chinese medicines have been proved to have inhibitory effects on oxidative stress. Ming et al[20]

found through network pharmacology analysis that Salvia extract could increase the activities of SOD,GSH Px, and CAT and reduce the levels of ROS and MDA to exert antioxidant effects in a NAFLD model. Tanshinone IIA, salvianolic acid B, and tanshinol can also activate peroxisome proliferator-activated receptor α(PPARα) and related signal pathways, thus further alleviating oxidative damage in the liver. Zhou et al[21] confirmed through experiments that the main active components of *Psoralea corylifolia L*, such as psoralen, isopsoralen, neopsoralen isoflavones, psoralen B and psoralen, can reduce the superoxide anion level of hepatocytes and alleviate the oxidative stress in the liver of NASH juvenile mice, which is related to the inhibition of protein kinase C-α(PKC-α)/nicotinamide-adenine dinucleotide phosphate oxidase (NOX) signaling pathway. Experimental results reported by He et al have shown that cultivation of Calculus bovis in vitro can increase SOD activity and reduce MDA and ROS levels in high fructose-induced NAFLD animals, and also protect hepatocytes from oxidative damage. The mechanism may be related to the activation of Nrf2 pathway[22].Nrf2-ARE pathway is the most important endogenous antioxidant stress pathway found at present[23].When oxidative stress occurred in hepatocytes,Nrf2 was uncoupled from Keapl and transferred to the nucleus where it combined with antioxidant response elements (ARE) to activate downstream antioxidant proteins and phase II detoxification enzymes, such as heme oxygenase -1(HO-1), NADPH quinone oxidoreductase (NQO1), etc. This helps to improve the synthesis of antioxidant stress factors and the ability of hepatocyte injury repair[24-25].In addition, the components taurine and ursodeoxycholic acid present in cultured Calculus bovis in vitro have been shown to exert antioxidant effects in NAFLD by increasing liver GSH levels and inhibiting hydrophobic bile salt-induced Kupffer cell activation[26-27]. Yang et al[28] found that high-fat diet feeding increased hepatic mitochondrial MDA and decreased SOD and GSH-Px levels in rats, which could be recovered by treatment with Polygonati Rhizoma.

3.2 Chinese medicine compound

3.2.1 Alisma Decoction

It is recorded in Synopsis of the Golden Chamber that Alisma Decoction is composed of Alisma orientalis and Atractylodis Macrocephalae, which has the functions of eliminating dampness, eliminating phlegm and strengthening spleen and stomach. Through experimental research, Xu et al[29] found that, in addition to inhibiting lipogenesis and anti-inflammatory activity, Alisma Decoction could also reduce NASH-induced liver injury by inhibiting oxidative stress and autophagy in hepatocytes. This experiment showed that Alisma Decoction gavage could increase SOD activity and decrease MDA content in hepatocytes of NAFLD mouse model, down-regulate the expression of LC3-II in liver tissue and reduce the number of autophagosomes.LC3 is a marker of autophagy, and LC3-II reflects the activity of autophagy[30]. In the later stage of NAFLD, autophagy can activate HSCs by decomposing lipid droplets in HSC and promote the progress of liver fibrosis[31].This experiment also confirmed that Alisma Decoction could down-regulate the expression of α-SMA, a marker of HSC activation, in liver tissue to inhibit HSC activation.

3.2.2 Soothing-liver and Invigorating-spleen formulas

Liver stagnation and spleen deficiency as well as soothing liver and invigorating spleen are the important pathogenesis and treatment of NAFLD[32].Tu et al[33] selected Soothing-liver formulas (Chai-hu-shu-gan-San) and Invigorating-spleen formulas (Seng-ling-bai-zhu-San) divided into normal group, model group, soothing-liver formula group (SLG),invigorating-spleen formula group (ISG) and integrated formulas group (Chai-hu-shu-gan-San:Seng-ling-bai-zhu-San =1:1, IG) and found that the levels of MDA,SOD and GSH PX in SLG group were not significantly different from

those in model group, while the levels of MDA were significantly decreased and the levels of SOD and GSH PX were significantly increased in ISG and Ig groups. In addition, the expression of Nrf2, Keap-1,HO-1,NQO-1 mRNA and protein in each treatment group increased, and the IG group had the best effect. Therefore, it can be seen that Shugan Jianpi Decoction has a good effect on NAFLD model mice, and Nrf2-ARE pathway may be an effective target of its extract.

3.2.3 Lizhong Decoction

Lizhong Decoction capable of warming middle energizer and removing cold can be used for treating various diseases caused by deficiency of middle yang. Xiaoling Zhou et al[34] found that after treatment with Lizhong Decoction for NASH model rats, the liver lipid deposition, inflammatory cell infiltration degree, endoplasmic reticulum damage and mitochondrial damage were significantly improved, and the corresponding indicators serum liver function (ALT, AST),blood lipids (TG, TC),IKB inhibitory protein kinase α(IKK-α),nuclear transcription factor p65(NF-κBp65), IL-1β,IL-6,and TNF-α were all significantly decreased. The IKK/NF-κB signaling pathway is associated with ROS activation in Kupffer cells that further leads to the production of a large number of inflammatory factors[35-36].Therefore, this experiment concluded that Lizhong Decoction could reduce ROS production and relieve oxidative stress by reducing mitochondrial damage. It can also inhibit the activation of IKK/IKB/NF-κB signaling pathway and the production of inflammatory factors, thereby improving hepatocyte injury.

3.3 Chinese patent medicine

3.3.1 Yinzhihuang Oral Liquid

Yinzhihuang oral liquid is prepare from Artemisia capillaris, Cape jasmine, Baikal Skullcap, and honeysuckle. It has the effect of remove dampness, eliminate jaundice, and detoxify the human body. It is now used clinically to treat neonatal jaundice. Zeng et al [37] found through the establishment of NASH rat model that Yinzhihuang Oral Liquid could inhibit lipogenesis and accelerate lipid β-oxidation, down-regulate chemokines and other inflammation-related factors to reduce intrahepatic inflammation by regulating fatty acid metabolism and PPAR signaling pathway, and alleviate oxidative stress by increasing the expression of mitochondrial respiratory chain complex. Mitochondrial oxidative phosphorylation damage results in a decrease in ATP production and affects lipid β-oxidation, leading to hepatocellular steatosis, oxidative stress, and subsequent necrotic inflammation[38-39].After administration of Yinzhihuang Oral Liquid, the number of mitochondrial respiratory chain complexes in the liver of NASH rats was significantly increased, mitochondrial function was restored, lipid β-oxidation was increased, and oxidative stress was alleviated.

3.3.2 Dangfeiliganning Capsule

Dangfeiliganning capsule, a Chinese patent medicine, has the effect of clearing away dampness and heat, benefiting liver and eliminating jaundice, and can be used to treat a variety of acute and chronic hepatitis. Its main ingredients are milk thistle and swertia. Many studies have shown that Dangfeiliganning capsule can effectively improve blood lipids, serum liver function and other biochemical indicators in patients with NAFLD[40]-[41].Zhao et al[42] found through clinical observation experiments that Dangfeiliganning capsule can significantly increase the activity of serum SOD and GSH-PX enzymes in patients with hepatitis B, reduce the content of MDA, thereby improving the anti-oxidation ability of patients and reducing their liver cell damage. Based on the above experiments, Zhao et al[43] established a NAFLD mouse model, and gavage the mice in the

experimental group with Dangfeiliganning capsule to intervene and measure the corresponding indicators. The results showed that compared with the mice in the model group, the SOD activity of the liver of the mice in the experimental group was increased, the MDA content was decreased, and the expression of Nrf2 and its downstream related molecules glutathione S-transferase P1 (GSTP1) and NQO1 was enhanced. Therefore, it can be concluded that Dangfeiliganning capsule may play a therapeutic role in NAFLD by regulating the Nrf2 pathway.

4. Conclusions

According to the results of the experimental studies mentioned above, a variety of Chinese medicines, Chinese medicine compound and Chinese patent medicines all improved the oxidative stress of NAFLD, and they could be promoted as effective therapies for NAFLD. However, the current research in this area is not mature enough, and the following problems remain to be solved:① A variety of Chinese medicine, compound and Chinese patent medicine components are relatively complex, in addition to the therapeutic effect, is likely to cause other toxic and side effects on the liver, but few studies at the same time observe the toxic and side effect.② Chinese medicine compound and Chinese patent medicine are derived from the compatibility of multiple drugs, and the interaction relationship between each drug has not yet been elucidated. In the future, we should carry out more and more extensive high-quality experimental research to provide a more reliable basis for the treatment of NAFLD with traditional Chinese medicine and further expand the advantages of traditional Chinese medicine.

References

[1] Li J, Chen J, Wang Y. Consensus opinion on the diagnosis and treatment of non-alcoholic fatty liver disease in the integrative medicine (2017) [J]. chinese journal of integrated traditional and western medicine on digestion, 2017, 25(11): 805-811.

[2] Anstee Q M,Reeves H L，Kotsiliti E , et al. From NASH to HCC: current concepts and future challenges [J]. Nature Reviews Gastroenterology & Hepatology, 2019, 16(7): 411-428.

[3] Younossi Z, Tacke F, Arrese M, et al. Global Perspectives on Nonalcoholic Fatty Liver Disease and Nonalc- oholic Steatohepatitis [J]. Hepatology, 2019, 69(6): 2672-2682.

[4] XU Y, Fan J. Research progress of therapeutic drugs for non-alcoholic fatty liver disease [J]. Shanghai Medicine, 2020, 41(19): 3-11.

[5] Forrester S J, Kikuchi D S, Hernandes M S, et al. Reactive Oxygen Species in Metabolic and Inflammatory Signaling [J]. Circulation Research, 2018, 122(6): 877-902.

[6] James O, Day C P. Non-alcoholic steatohepatitis (NASH): a disease of emerging identity and importance [J]. Journal of Hepatology, 1998, 29(3): 495-501.

[7] Oyewole A O, Mark A. Birch-Machin. Mitochondria-targeted antioxidants [J]. The FASEB Journal, 2015, 29(12): 4766-4771.

[8] Buzzetti E, Pinzani M, Tsochatzis E A. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD) [J]. Metabolism-clinical & Experimental, 2016; 65(8): 1038-1048.

[9] Hu Q, Zhang W, Wu Z, et al. Baicalin and the liver-gut system: Pharmacological bases explaining its therapeutic effects [J]. Pharmacological Research, 2021, 165(1): 105444.

[10] Zhong X, Liu H. Baicalin attenuates diet induced nonalcoholic steatohepatitis by inhibiting inflammation and oxidative stress via suppressing JNK signaling pathways [J]. Biomedicine & Pharmacotherapy, 2018, 98: 111-117.

[11] Caro A A, Cederbaum A I. Oxidative Stress, Toxicology, and Pharmacology of CYP2E1 [J]. Annual Review of Pharmacology, 2004, 44(1): 27-42.

[12] Gao W, Xu B, Zhang Y, et al. Baicalin Attenuates Oxidative Stress in a Tissue-Engineered Liver Model of NAFLD by Scavenging Reactive Oxygen Species [J]. Nutrients, 2022, 14(3): 541.

[13] Kong T, Ma Y, Yang Z,et al. Biological function and action mechanism of resveratrol [J]. China Journal of Clinical Pharmacology, 2022, 38(06): 59 2-596.

[14] Cheng K, Song Z, Zhang H, et al. The therapeutic effects of resveratrol on hepatic steatosis in high-fat diet-induced obese mice by improving oxidative stress, inflammation and lipid-related gene transcriptional expression [J]. Medical electron microscopy, 2019, 52(4): 187-197.

[15] Hajighasem A, Farzanegi P, Mazaheri Z. Effects of combined therapy with resveratrol, continuous and interval exercises on apoptosis, oxidative stress, and inflammatory biomarkers in the liver of old rats with non-alcoholic fatty liver disease [J]. Archives of Physiology and Biochemistry, 2019, 125(2): 142-149.
[16] GAI X, Liu S, Ren T, et al. Research progress on chemical constituents and pharmacological action of Rhizoma Coptidis [J]. Chinese Herbal Medicine, 2018, 49(20): 4919- 4927.
[17] FU L, FU Q, LI J, et al. Research progress on chemical constituents and pharmacological action of Rhizoma Coptidis [J]. Journal of Traditional Chinese Medicine, 2021, 49(02): 87-92.
[18] Sun Y, Yuan X, Zhang F, et al. Berberine ameliorates fatty acid-induced oxidative stress in human hepatoma cells [J]. Scientific Reports, 2017, 7(1):11340.
[19] Zhang Y, Wen J, Liu D, et al. Demethylenetetrahydroberberine alleviates nonalcoholic fatty liver disease by inhibiting the NLRP3 inflammasome and oxidative stress in mice [J]. Life Sciences, 2021, (16): 119778.
[20] Ming H, Sha L, Ning W, et al. A Biomedical Investigation of the Hepatoprotective Effect of Radix salviae miltiorrhizae and Network Pharmacology-Based Prediction of the Active Compounds and Molecular Targets [J]. International Journal of Molecular Sciences, 2017, 18(3): 620.
[21] Zhou L, Tang J, Yang X, et al. Five Constituents in Psoralea corylifolia L. Attenuate Palmitic Acid-Induced Hepatocyte Injury via Inhibiting the Protein Kinase C-α/Nicotinamide-Adenine Dinucleotide Phosphate Oxidase Pathway [J]. Frontiers in pharmacology, 2019, 10: 1589-1589.
[22] He W, Xu Y, Zhang C, et al. Hepatoprotective effect of calculus bovis sativus on nonalcoholic fatty liver disease in mice by inhibiting oxidative stress and apoptosis of hepatocytes [J]. Drug Design, Development and Therapy, 2017, 11: 3449-3460.
[23] Ahmed SM, Luo L, Namani A, et al. Nrf2 signaling pathway: Pivotal roles in inflammation [J]. Biochim Biophys Acta Mol Basis Dis, 2017, 1863(2): 585-597.
[24] Copple I M, Goldring C E, Kitteringham N R, et al. The Nrf2-Keap1 defence pathway: role in protection against drug-induced toxicity [J]. Toxicology, 2008, 246(1): 24-33.
[25] Gupte AA, Lyon CJ, Hsueh WA. Nuclear factor (erythroid-derived 2)-like-2 factor (Nrf2), a key regulator of the antioxidant response to protect against atherosclerosis and nonalcoholic steatohepatitis [J]. Curr Diab Rep. 2013; 13(3): 362-371.
[26] Sokolovic D, Nikolic J, Kocic G, et al. The effect of ursodeoxycholic acid on oxidative stress level and DNase activity in rat liver after bile duct ligation [J]. Drug & Chemical Toxicology, 2013, 36(2): 141-148.
[27] Gentile C L, Nivala A M, Gonzales J C, et al. Experimental evidence for therapeutic potential of taurine in the treatment of non-alcoholic fatty liver disease [J]. Ajp Regulatory Integrative & Comparative Physiology, 2011, 301(6): R1710-R1722.
[28] Yang XX, Wang X, Shi TT, et al. Mitochondrial dysfunction in high-fat diet-induced nonalcoholic fatty liver disease: The alleviating effect and its mechanism of Polygonatum kingianum [J]. *Biomed Pharmacother. 2019; 117: 109083.*
[29] Xu L, Jing M, Yang L, et al. The Alisma and Rhizoma decoction abates nonalcoholic steatohepatitisassociated liver injuries in mice by modulating oxidative stress and autophagy [J]. BMC Complement Altern Med, 2019, 19(1): 92.
[30] Li K, Wu D, Chen X, et al. Current and emerging biomarkers of cell death in human disease [J]. Biomed Res Int. 2014; 2014: 690103.
[31] Zhou F, Peng J, Fan F, et al. The relationship between autophagy and oxidative stress in the pathogenesis of non-alcoholic fatty liver disease [J]. Journal of Clinical Hepatobiliary Disease, 2018, 34(08): 1805-1808.
[32] Zhang S, Li J. Expert consensus on diagnosis and treatment of non-alcoholic fatty liver disease in traditional Chinese medicine (2017) [J]. Journal of Clinical Hepatobiliary Disease, 2017, 33(12): 2270-2274.
[33] Tu G, Gong X, Yang Q, et al. Effects of extracts from soothing-liver and invigorating-spleen formulas on the injury induced by oxidative stress in the hepatocytes of rats with non-alcoholic fatty liver disease induced by high-fat diet [J]. Journal of Traditional Chinese Medicine, 2018.
[34] Zhou X, Tang N, Zack Z, et al. Exploration of the mechanism of Lizhong Decoction in the treatment of non-alcoholic steatohepatitis based on IKK/IKB/NF-κB signaling pathway [J]. Chinese Journal of Traditional Chinese Medicine, 2020, 35(06): 2771-2777.
[35] Liu J, Kan D, Liu L. Blocking of IKK/IκB/NF-κB signaling pathway and its clinical application [J]. Journal of Practical Medicine, 2008, 24(23): 4147-4149.
[36] Sun K, Xu L, Jing Y, et al. Autophagy-deficient Kupffer cells promote tumorigenesis by enhancing mtROS-NF-κB-IL1α/β-dependent inflammation and fibrosis during the preneoplastic stage of hepatocarcinogenesis [J]. Cancer Letters, 2017, 388: 198-207.
[37] Zeng J, Liu XL, Xin FZ, et al. Effects and therapeutic mechanism of Yinzhihuang on steatohepatitis in rats induced by a high-fat, high-cholesterol diet [J]. J Dig Dis, 2020, 21(3): 179-188.
[38] Mansouri A, Gattolliat CH, Asselah T. Mitochondrial dysfunction and signaling in chronic liver diseases [J]. Gastroenterology, 2018, 155(3): 629-647.

[39] Begriche K, Massart J, Robin MA,,et al. Mitochondrial adaptations and dysfunctions in nonalcoholic fatty liver disease [J]. Hepatology, 2013, 58(4): 1497-1507.
[40] Wang X, Li J, Miao Y. Effect observation of Dangfeiliganning capsule combined with life intervention in the treatment of non-alcoholic fatty liver [J]. Journal of Chengdu University of Chinese Medicine, 2013, 36(03): 69-70+78.
[41] Hong H, Zhao X, Zhang S, et al. Clinical observation on 37 cases of non-alcoholic fatty liver with syndrome of liver stagnation and spleen deficiency and damp heat accumulation treated with Dangfeiliganning capsule and Chinese medicine tea [J]. journal of traditional chinese medicine, 2018, 59(03): 227-230.
[42] Zhao H, Chen W, Jiang L. Effect of Dangfeiliganning capsule on antioxidant system in patients with chronic hepatitis B [J]. journal of traditional chinese medicine, 2007(05): 466.
[43] Zhao Y, Shu X, Yang Z, et al. Study on the mechanism of Dangfeiliganning capsule in regulating liver oxidative stress and improving non-alcoholic fatty liver disease in mice [J]. Journal of Shanghai University of Traditional Chinese Medicine, 2021, 35(05): 37-43+74.