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Research Progress of Hawthorn in the Treatment of Non-alcoholic Fatty Liver Disease

Minna Wu[1], Feng Huang[2,*]

[1]Shaanxi University of Chinese Medicine, Xianyang, Shaanxi 712046, China
[2]Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang, Shaanxi 712000, China
**Correspondence Author, 1162438446@qq.com*

Abstract: ***Non-alcoholic fatty liver disease refers to a metabolic disease of the liver caused by long-term heavy drinking and other clear liver damage factors, with triglyceride-dominated lipids accumulating in liver cells for pathological changes. In traditional Chinese medicine, it is often classified as "accumulation", "liver puffiness", "liver", "fat qi" and other categories. Hawthorn is the most commonly used Chinese medicine for the treatment of non-alcoholic fatty liver disease. This review is to summarize the latest research progress of hawthorn effective components in the treatment of this disease, and summarize and explain the understanding and application of traditional Chinese medicine, pharmacological effects and mechanism progress, in order to provide more basis for the clinical treatment of NAFLD with traditional Chinese medicine.***

Keywords: Non-alcoholic fatty liver disease, Hawthorn, Research progress**.**

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) refers to a metabolic disease of the liver in which triglyceride-dominated lipids accumulate as pathological changes in liver cells in addition to long-term heavy drinking and other definite liver damage factors. According to statistics, the global prevalence rate of NAFLD is about 25%, and the total number of people with NAFLD is expected to increase by 18.3% in the next 10 years. The global incidence of NASH will also increase by approximately 56%, with the highest relative growth rate in our country [1]. At present, no specific drugs for NAFLD/NASH have been approved in Western medicine. The existing treatment and prevention methods are mainly reasonable diet and exercise. Drugs that target lipid metabolic pathways, including FXR receptor agonists (such as 4 obecholic acid), PPAR agonists (such as pioglitazone), statins, and inhibitors of key enzymes in lipid metabolism (ACC inhibitors, SCD1 inhibitors); GLP-1 receptor agonists for IR (such as exenatide, semalutide, liraglutide, etc.), SGLT-2 inhibitors (such as dagaglizin, NGI001, etc.) and insulin sensitizers; In addition, there are intestinal biologics, adipokine inhibitors, inflammation and immune signaling inhibitors. However, these drugs have not been widely used in the clinic for this disease, and there are large side effects, so patients mostly choose traditional Chinese medicine and weight loss treatment. Therefore, this review summarizes the latest research progress related to the effective ingredients of hawthorn in the treatment of this disease, and summarizes and elaborates on the understanding and application of traditional Chinese medicine, pharmacological effects and mechanism progress.

2. Understanding of NAFLD in TCM

Fatty liver has no clear disease name in traditional Chinese medicine, and it is classified as "accumulation", "liver fullness", "fat qi" and other categories according to symptoms. There are many causes of fatty liver, currently believed to be mainly caused by improper diet, patients with excessive eating fat, thick and greasy, resulting in endogenous damp and heat, concentrated in the middle jiao, damage to the spleen and stomach, long-term body obesity, lipid, sputum turbidity attached to the liver, the main disease of the disease in the liver and spleen, long-term and kidney. The pathological products were dampness, phlegm and stasis. Therefore, in the treatment of the main use of strengthening the spleen, soothing the liver, diuresis, turbidification, blood circulation, and so on, while adjusting the diet structure, enhance physical exercise to reduce weight. The advantage of traditional Chinese medicine in treating fatty liver is that it can reverse the progression of fatty liver and improve clinical symptoms. "Danxi's Experiential Therapy" cloud: "Lumps in the middle for phlegm drink, on the right for food accumulation, on the left for blood clots. Qi can not be made into blocks, blocks are tangible things. Phlegm and food accumulation of dead blood also... Treat block when lowering fire and eliminating food accumulation, food accumulation is phlegm also." Yang Xiling believed that the pathological factors of NAFLD, such as dampness, phlegm and blood stasis, were all negative. The basis of NAFLD was insufficient production of Yang in the human body, weakened warming function, insufficient vaporization, excessive Yin and liquid phase, and the formation of tangible objects in the liver. It was necessary to strengthen the spleen to keep qi flowing without stagnation, and warm the spleen to transform Qi, so that the disease could heal and the body could achieve the state of Yin and Yang. Yang Lexuan [2] summarized Professor Huang Labing's many years of clinical experience and believed that the fundamental pathogenesis of NAFLD lies in the disorder of fire, which was divided into six syndrome types according to clinical manifestations, namely the syndrome of qi stagnation and fire with absolute excess excess fire, the syndrome of dampness-heat, the syndrome of stasis and heat, and the syndrome of Yin deficiency and fire with relative excess deficiency fire, Yang deficiency and qi deficiency and fire. And on the basis of Professor Yang Zhen's three major treatment methods of fire syndrome, namely: the real fire can be reduced, the weak fire can be replenishment, and the fire depression should be emitted. Professor Zhou Zhongying believes that the mechanism of dampness-heat stasis toxin is universal in liver disease, and phlegm is the characteristic mechanism of fatty liver, so treating fatty liver from phlegm is easier to grasp the essence of the disease, so as to achieve

good results.

3. Understanding and Application of Hawthorn in the Treatment of NAFLD

Hawthorn is mild, sour and sweet taste, spleen, stomach, liver meridian, can digest spleen, qi dispersing stasis, turbidification and lipid reduction. "Along with the rest of the diet spectrum", hawthorn "wake up temper, eliminate meat, break blood stasis, dissipate swelling, cure alcohol and phlegm, eliminate malnutrition, stop diarrhea." In recent years, it has often been used in the treatment of hyperlipidemia, fatty liver, hypertension and coronary heart disease [3-5]. "Compendium of Materia Medica" said: "the diet, the elimination of meat accumulation, syndrome, phlegm drink fullness of swallowing acid, stagnant blood distension pain." Hawthorn on the diet caused by greasy stagnation effect is better, and hawthorn can be solid kidney essence, "drug theory" cloud: "the main kidney deficiency essence from the treatment of five drenching, bladder heat, propaganda water", hawthorn can through the drenching, fatty liver patients with wet turbidness with urine discharge. And the use of hawthorn treatment to remove blood stasis without hurting the right, "pearl bag" said its "eating accumulation without hurting in the engraved, qi and blood without hurting in the shaking", it can be seen that hawthorn also has the effect of Qi activating blood, for the treatment of fatty liver patients safe and effective, as Zhang Xichun discusses: "bitter with sweet drugs, blood stasis without hurting new blood, open qi without hurting the right qi, its nature especially peace also", It can be seen that hawthorn can ease the liver and regulate the qi, remove stasis and produce new, remove turbidity. Tao Zhenhui believed that in the process of treating fatty liver with hawthorn, it must be cooked hawthorn, and a large amount of raw hawthorn would lead to gas consumption, damage to the spleen, stomach and teeth of patients, and increased diet. Because raw hawthorn has a higher organic acid content, patients will have stomach pain if taken on an empty stomach, so it must be cooked when using hawthorn to treat fatty liver [6]. Nie Chunxia [7] studied the effects of different hawthorn products on hyperlipidemia rats based on H-NMR metabolomics, and found that net hawthorn, stir-fried Hawthorn and burnt Hawthorn could all regulate the metabolic state of endogenous substances in serum of rats, but the regulation differences were obvious among them, and net hawthorn had the strongest effect on reducing blood lipids. Based on the data mining and network pharmacology analysis of 83 literatures in recent years, Wu Yuan found that hawthorn, salvia miltiorrhiza, purpura and Baizhu were the most commonly used drugs, and hawthorn was the most frequently used drug [8]. Thus, the role of hawthorn in the treatment of fatty liver by traditional Chinese medicine was widely recognized.

3.1 Hawthorn Active Components Improve the Pharmacological Effects of NAFLD

Lin Daobin analyzed the main active ingredients and potential targets of hawthorn in the treatment of nonalcoholic fatty liver disease based on network pharmacology, and obtained the 6 main active ingredients and 148 targets found in hawthorn at present. Among the 4 main ingredients with the highest Degree, Quercetin can treat NAFLD by inhibiting the expression of inflammatory factors [9], improving insulin resistance, antioxidant stress response [10] and lipid metabolism disorder [11], etc. Kaempferol also has similar anti-inflammatory [12] and antioxidant effects [13]. Isorhamnin can inhibit the formation of collagen [14], prevent liver fibrosis, inhibit the expression of PPARγ, and prevent liver steatosis [15]. Stigmosterol can increase the expression of catalase, superoxide dismutase and glutathione [16], reduce the generation rate of peroxyradical ions, remove oxygen free radicals in the liver, and reduce hepatic fat peroxidation [17].

3.2 Hawthorn Active Components Improve the Mechanism of NAFLD

3.2.1 Anti-steatogenic

Hepatic steatosis is a hallmark of the development of nonalcoholic fatty liver disease, which is characterized by the accumulation of triglycerides in the cytoplasm of hepatocytes. Therefore, anti-hepatic steatosis is one of the important strategies to treat NAFLD and prevent it from developing into NASH. prostaglandin G/H synthase 1(PTGS1) and prostaglandin G/H synthase 2(PTGS2), also known as cyclocoxidase (COX1/2), are key rate-limiting enzymes that convert arachidonic acid into prostaglandin [18]. The role of COX1 in the disease process of NAFLD remains unclear. At present, the research mainly focuses on COX2. COX2 is sharply upregulated under the action of stimulating factors such as inflammatory mediators and endotoxins, which further increases prostaglandin synthesis and exacerbates the inflammatory response of the body [19]. COX2 and NAFLD promote each other. In the early stage of NAFLD, steatosis of hepatocytes can induce high expression of COX2, while COX2 and its mediated production of interleukin-6, tumor necrosis factor-α, and prostaglandin interfere with normal lipid metabolism of hepatocytes, thus forming a vicious cycle. Therefore, hawthorn may reduce inflammation and restore normal lipid metabolism in liver by acting on the target of cycoperoxidase. Peroxisome proliferator activated receptor (PPARG) is a class of transcription factors activated by ligands, and three subtypes of PPARα, PPARβ, and PPARγ have been found so far [20]. If PPARγ is over-expressed, it can inhibit the binding of cyclic adenosine phosphate reaction elements to proteins and induce liver adipocyte degeneration [21], but if PPARγ gene is knocked in mice, it will promote the formation of NASH [22]. Studies have also shown [23] that PPARγ can regulate the expression of adiponectin, control the secretion of inflammatory factors, and delay the process of liver fibrosis; in addition, PPARγ can also increase the expression of carnitine fatty acyltransferase and acetyl-CoA and reduce liver fat deposition [24]. In general, PPARγ has a bidirectional regulatory effect, which can accelerate the evolution of NAFLD disease and alleviate steatosis and liver fibrosis. The mechanism is not yet clear, and may be related to other subtypes of PPARγ.

3.2.2 Antioxidant

Oxidative stress is a part of the pathological transformation from simple hepatic steatosis to steatohepatitis and liver fibrosis. Therefore, antioxidant is a positive means to treat NAFLD.NOS3, also known as endothelial nitric oxide synthase (eNOS), is one of the key synthases for the synthesis

of nitric oxide (NO) in human body [25]. Excessive synthesis of NO will destroy the balance between NO and O2- and generate nitrous peroxide anion, which will then cause the oxidation of unsaturated fatty acids, cholesterol and superoxide dismutase [26], which will aggravate the degree of oxidative stress and cause serious consequences. Kuang Rong et al. [27] found that total flavonoids from hawthorn leaves can reduce the levels of NO, C-reactive protein and tumor necrosis factor in rabbit serum, and increase the content of superoxide dismutase and glutathione peroxidase to resist oxidation, so as to antagonize atherosclerosis. In addition, studies [28] pointed out that medium-high doses of hawthorn acid (100 and 200mg/kg) can significantly enhance the expression of glutathione and superoxide dismutase in liver tissue, so as to enhance the antioxidant effect of liver tissue, remove oxygen free radicals, reduce the degree of free radical attack on liver, and thus play a liver protective effect. Therefore, hawthorn action on eNOS targets can reduce the oxidative stress response of NAFLD.

3.2.3 Anti-inflammatory and anti-fibrotic

Inflammation and fibrosis are closely associated with the progression of simple steatosis of the liver to steatohepatitis and cirrhosis close. coagulation factor VII(F7) During liver injury caused by NAFLD, hepatic stellate cells will be recruited at the injured site, and this process will induce the activation of coagulation factor, convert circulating fibrinogen into fibrin, promote platelet aggregation [29], and participate in the formation of liver fibrosis and the reconstruction of intrahepatic structures. This is also one of the mechanisms by which anticoagulants or antiplatelet drugs can treat liver fibrosis [30]. MAOB belongs to a subtype of the flavin-binding protein (MAO). In the course of NAFLD disease, MAO can improve the binding rate of collagen and elastin under the action of stimulating factors, forming a large number of collagen fibers, which then leads to the occurrence of liver fibrosis. RELA, also known as transcription factor P65, is one of the important heterodimers of NF-κB [31]. The NF-κB pathway promotes the proliferation of hepatic stellate cells and releases inflammatory factors in the body, thus accelerating the development of liver fibrosis [32]. Hypericin is based on MAPK/Sirt6/NF-κB signaling axis to down-regulate the expression of pro-inflammatory factors, while antagonizing lipopolysaccharids-induced apoptosis in the treatment of NASH patients.

3.2.4 Hyperlipidemic

Hypercholesterolemia leads to liver cholesterol overload, and the cholesterol burden in the liver leads to fatty liver. In addition, cholesterol deposition activates resident macrophages, Kupffer cells, and subsequently leads to NASH. androgen receptor (AR) can enhance the regulation of several key lipid metabolism enzymes such as stearyl CoA desaturase 1, lipoprotein esterase, fatty acid synthetase and acetyl-CoA carboxylase in the liver by increasing the release of androgens, and maintain the homeostasis of fat synthesis and decomposition [33]. It can also reduce the expression levels of tumor necrosis factor α, interleukin-6 and interleukin-1β [34], and reduce the damage of inflammatory factors to liver cells. Hawthorn acts on AR targets and can produce therapeutic effects by regulating lipid metabolism and inflammatory response. Studies have confirmed that flavonoids and lipolytic enzymes contained in hawthorn can not only significantly inhibit the activity of light methylpentoyl coenzyme A reductase, the rate-limiting enzyme of cholesterol biosynthesis, reduce the generation of endogenous cholesterol, but also promote the decomposition and removal of fat, so as to achieve lipid-lowering effects.

3.2.5 The mechanism of regulating insulin resistance

Studies have shown that insulin resistance is not only an important risk factor for the progression of non-alcoholic fatty liver disease, but also a major feature of the disease. Adipose ectopic deposition can lead to IR, which in turn induces liver inflammation and promotes its development, which in turn aggravates IR, forming a vicious cycle. The continuous inflammatory response will make the simple accumulation of fat develop into liver fibrosis, cirrhosis, and even liver cancer. Therefore, active regulation of insulin resistance is of great significance in the treatment of non-alcoholic fatty liver disease. dipeptidyl peptide IV(DPP4) participating in NAFLD is related to its promotion of glucagon-like peptide-1 (GLP-1) degradation [35]. GLP-1 can improve the body's sensitivity to insulin, reduce liver fat deposition and regulate liver fatty acid metabolism. Hawthorn acts on this target and may also act as a DPP-4 inhibitor. When stimulated by inflammatory factors, PRSS1 will be phosphorylated secondary [36], and the phosphorylation process will prevent the normal tyrosine phosphorylation of insulin receptor substrate [37], thus blocking the binding of insulin receptor substrate to SH2 domain signal molecules [38], interfering with insulin signal transduction and inducing insulin resistance. Studies have shown that [39] hawthorn fruit extract can promote the phosphorylation of adenylate activated protein kinase in liver of type 2 diabetic mice, reduce the expression of phosphoenolpyruvate carboxykinase and glucose generation to achieve the purpose of hypoglycemia. Li Xidong et al. found that the combination of hawthorn proanthocyanidins and VC can improve insulin sensitivity and reactivity, thereby improving the liver oxidative stress caused by IR. However, flavonoids from Hawthorn leaves can increase GLUT4 by activating AMPK phosphorylation, and improve leptin resistance associated with IR, thus playing a role in insulin sensitization.

4. Smmary and Prospect

The occurrence and development of NAFLD is caused by a variety of factors, among which the pathogenesis involved, such as glycolipidism, oxidative stress, endoplasmic reticulum stress, mitochondrial dysfunction, hepato-intestinal axis disorder, inflammation and immunity interact with each other, thereby jointly causing the occurrence and development of the disease. This review summarizes the current research status of hawthorn treatment of NAFLD in recent years. It is concluded that hawthorn has therapeutic effects on NAFLD mainly through the regulation of insulin resistance, anti-inflammatory, anti-fibrosis and other aspects, but there are still some mechanisms and pathways that have not been clearly explained. Therefore, it is still a long way to go to explore the pathogenesis and treatment pathways of NAFLD.

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References

[1] Estes C, Anstee Q M, Arias-Loste M T, et al. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030[J]. J Hepatol, 2018, 69(4): 896-904.

[2] YANG Lexuan, HUANG Laping. Discussion on Treating Non-Alcoholic Fatty Liver Disease Based on Theory of Ministerial Fire[J]. New Chinese Medicine, 2024,56(14):184-190.

[3] Peng Danyang, Wang Lin, Zhu Dezeng. Clinical study of hawthorn pure extract tablet in treatment of metabolic syndrome[J]. Journal of Changchun University of Chinese Medicine, 2011,27(05):723-724.

[4] Li Guangshan, Zhang Hong. Effect of hawthorn and wolfberry tea on blood lipids in patients with type 2 diabetes mellitus and hyperlipidemia[J]. Jilin Journal of Chinese Medicine, 2008(07):495.

[5] Zheng Shuwei, Cao Anmin, Huang Junmin, et al. Ultrasonic evaluation of Shanzhajiangzhi prescription combined with ear pressure in the treatment of nonalcoholic fatty liver[J]. Modern Journal of Integrated Traditional Chinese and Western Medicine, 2015, 24(31):3494-3496.

[6] TAO Zhenghui. Pharmacologic Analysis of Long-term High Dose Single Herb Hawthorn on Blood Lipids in Patients with Nonalcoholic Fatty Liver Disease Caused by High Fat Diet[J]. GUANGMING JOURNAL OF CHINESE MEDICINE, 2021,36(12):1991-1993.

[7] NIE Chun-xia, HE Pan, HAO Yan-yan, LIU Cong, NI Yan, HAO Xu-liang. Effects of different processed products of Crataegi Fructus on hyperlipidemia rat model by ~1H-NMR metabolomics[J]. Chinese Traditional and Herbal Drugs, 2019,50(10):2362-2370.

[8] Wu Yuan. Based on data mining and network pharmacology, the rule and mechanism of Chinese medicine in improving insulin resistance in non-alcoholic fatty liver disease were studied[D]. Heilongjiang University of Chinese Medicine, 2023.

[9] Marcolin E, San-Miguel B, Vallejo D, et al. Quercetin treatment ameliorates inflammation and fibrosis in mice with nonalcoholic steatohepatitis[J]. J Nutr, 2012, 142(10):1821-1828.

[10] Panchal S K, Poudyal H, Brown L. Quercetin ameliorates cardiovascular, hepatic, and metabolic changes in diet-induced metabolic syndrome in rats[J]. J Nutr, 2012,142(6):1026-1032.

[11] Zhang Jie, Chen Jiebin. Effects of quercetin on the expression of ATP-bindingcassette transporter A1 in nonalcoholic fatty liver cells[J]. Journal of Jiangsu University: Medicine Edition, 2009,19(05):398-400.

[12] Liu Z K, Xiao H B, Fang J. Anti-inflammatory properties of kaempferol via its inhibition of aldosterone signaling and aldosterone-induced gene expression[J]. Can J Physiol Pharmacol, 2014,92(2):117-123.

[13] Huang Y B, Lin M W, Chao Y, et al. Anti-oxidant activity and attenuation of bladder hyperactivity by the flavonoid compound kaempferol[J]. Int J Urol, 2014, 21(1):94-98.

[14] Hubbard G P, Wolffram S, de Vos R, et al. Ingestion of onion soup high in quercetin inhibits platelet aggregation and essential components of the collagen-stimulated platelet activation pathway in man: a pilot study[J]. Br J Nutr, 2006,96(3):482-488.

[15] Zhang Y, Gu M, Cai W, et al. Dietary component isorhamnetin is a PPARgamma antagonist and ameliorates metabolic disorders induced by diet or leptin deficiency[J]. Sci Rep, 2016,6:19288.

[16] Yoshida Y, Niki E. Antioxidant effects of phytosterol and its components[J]. J Nutr Sci Vitaminol (Tokyo), 2003,49(4):277-280.

[17] Huang Jianchun, Qing Lijuan, Xuan Feifei, et al. Study on Antioxidant Activity of Stigmaserol from Yulangsan in vitro[J]. Chinese Journal of Experimental Traditional Medical Formulae, 2014,20(05):154-156.

[18] Saliba S W, Marcotegui A R, Fortwangler E, et al. Correction to: AM404, paracetamol metabolite, prevents prostaglandin synthesis in activated microglia by inhibiting COX activity[J]. J Neuroinflammation, 2018, 15(1):34.

[19] Ribeiro D, Freitas M, Tome S M, et al. Flavonoids inhibit COX-1 and COX-2 enzymes and cytokine / chemokine production in human whole blood[J]. Inflammation, 2015,38(2):858-870.

[20] Yao L, Liu F, Sun L, et al. Upregulation of PPARgamma in tissue with gastric carcinoma[J]. Hybridoma (Larchmt), 2010,29(4):341-343.

[21] Ohkubo Y, Sekido T, Nishio S I, et al. Loss of mu-crystallin causes PPARgamma activation and obesity in high-fat diet-fed mice[J]. Biochem Biophys Res Commun, 2019,508(3):914-920.

[22] Moran-Salvador E, Lopez-Parra M, Garcia-Alonso V, et al. Role for PPARgamma in obesity-induced hepatic steatosis as determined by hepatocyte- and macrophage-specific conditional knockouts[J]. FASEB J, 2011,25(8):2538-2550.

[23] Nan Y M, Fu N, Wu W J, et al. Rosiglitazone prevents nutritional fibrosis and steatohepatitis in mice[J]. Scand J Gastroenterol, 2009,44(3):358-365.

[24] Elshorbagy A K, Valdivia-Garcia M, Mattocks D A, et al. Cysteine supplementation reverses methionine restriction effects on rat adiposity: significance of stearoyl-coenzyme A desaturase[J]. J Lipid Res, 2011, 52(1):104-112.

[25] Janaszak-Jasiecka A, Siekierzycka A, Bartoszewska S, et al. eNOS expression and NO release during hypoxia is inhibited by miR-200b in human endothelial cells[J]. Angiogenesis, 2018,21(4):711-724.

[26] Wu Xinyi. To study the prevention and treatment effect of panax notoginseng saponins on nonalcoholic fatty liver based on the changes of NO and iNOS[D]. Yunnan University of Traditional Chinese Medicine, 2018.

[27] Kuang Rong, Chen Nan, Kang Hua, et al. Mechanisms of Total Flavones of Crataegus Leaves on Experimental Atherosclerosis in Rabbits[J]. Chinese Journal of Modern Applied Pharmacy, 2013,30(04):372-375.

[28] Chang lulin. Effect of Total Flavone of Hawthorn on Ethanol Induced Alcoholic Liver Disease in Mice[J]. Chinese Medicine Modern Distance Education of China, 2014,12(07):152-153.
[29] Calvaruso V, Maimone S, Gatt A, et al. Coagulation and fibrosis in chronic liver disease[J]. Gut, 2008, 57(12): 1722-1727.
[30] SUN Yuanpei, GUO Xiaoxia. Clinical effect of probiotics in treatment of liver cirrhosis: a Meta-analysis[J]. Journal of Clinical Hepatology, 2018, 34(01):73-79.
[31] Pradere J P, Hernandez C, Koppe C, et al. Negative regulation of NF-kappaB p65 activity by serine 536 phosphorylation[J]. Sci Signal, 2016,9(442):ra85.
[32] Garcia-Compean D, Gonzalez-Gonzalez J A, Lavalle-Gonzalez F J, et al. Current Concepts in Diabetes Mellitus and Chronic Liver Disease: Clinical Outcomes, Hepatitis C Virus Association, and Therapy [J]. Dig Dis Sci, 2016,61(2):371-380.
[33] Yu I C, Lin H Y, Sparks J D, et al. Androgen receptor roles in insulin resistance and obesity in males: the linkage of androgen-deprivation therapy to metabolic syndrome[J]. Diabetes, 2014,63(10):3180-3188.
[34] Chin K Y, Ima-Nirwana S. The Effects of Testosterone Deficiency and Its Replacement on Inflammatory Markers in Rats: A Pilot Study[J]. Int J Endocrinol Metab, 2017,15(1):e43053.
[35] Pipatpiboon N, Pintana H, Pratchayasakul W, et al. DPP4-inhibitor improves neuronal insulin receptor function, brain mitochondrial function and cognitive function in rats with insulin resistance induced by high-fat diet consumption[J]. Eur J Neurosci, 2013, 37(5):839-849.
[36] Lagathu C, Bastard J P, Auclair M, et al. Chronic interleukin-6 (IL-6) treatment increased IL-6 secretion and induced insulin resistance in adipocyte: prevention by rosiglitazone[J]. Biochem Biophys Res Commun, 2003,311(2):372-379.
[37] Zhou Ying, Zhang Lijuan. Insulin resistance and inflammatory factors and their related signaling pathways[J]. Chinese Journal of Cardiovascular Rehabilitation Medicine, 2010,19(01):107-109.
[38] Yuan Y, Wang X, Lu X, et al. Effect of Coptidis Rhizoma extracts in a water-based solution on insulin resistance in 3T3-L1 adipocytes[J]. Biomed Res, 2014, 35(5):321-327.
[39] Shih C C, Lin C H, Lin Y J, et al. Validation of the Antidiabetic and Hypolipidemic Effects of Hawthorn by Assessment of Gluconeogenesis and Lipogenesis Related Genes and AMP-Activated Protein Kinase Phosphorylation[J]. Evid Based Complement Alternat Med, 2013, 2013:597067.