

Clinical effect of the extract of TCM *Fructus akebiae* combined with ursodeoxycholic acid on nonalcoholic fatty liver disease

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Abstract: *Fructus akebiae* extract (FAE) is a commonly used drug in the clinical treatment of liver cancer. FAE has many pharmacological activities, such as liver protection, anti-tumor, spasmolysis, pain relief and antifungal activity. Its clinical application is extensive, so far no toxic reports have been reported, and new drugs can be developed. This study was designed to investigate the therapeutic effect of predictor extract on non-alcoholic fatty liver disease (NAFLD). 180 patients with NAFLD were randomly divided into 2 groups. The control group was treated with ursodeoxycholic acid (UDCA), and the experimental group was treated with *Fructus akebiae* extract combined with ursodeoxycholic acid. The results showed that the comprehensive clinical efficacy of the treatment group was 95.56%, which was higher than that of the control group (93.33%), and $P < 0.01$. In the experimental group, 63 cases (70%) were improved after one course of treatment, main symptom score as (5.09 ± 3.98) , body mass index as (24.65 ± 3.86) , and liver CT value increased. It can be seen that the addition of FAE can significantly improve the clinical symptoms and serum biochemical indicators such as ALT, AST, TG and TC in patients with non-alcoholic fatty liver disease, which is supported by some histological evidence. These findings suggest that FAE combined with Ursodeoxycholic Acid is safe and effective in the treatment of fatty liver.

Keywords: Nonalcoholic fatty liver disease, *Fructus akebiae* extract (FAE), ursodeoxycholic acid, clinical observation.

INTRODUCTION

Epidemiological data show that the incidence of fatty liver is closely related to age, sex, blood lipid, hypertension, obesity, diabetes and so on. High-lipoprotein diet, bedtime meals and excessive sleep are the main risk factors of fatty liver (Chandrasekhar *et al.*, 2016). It can be predicted that with the improvement of people's living conditions, lifestyle changes and the increase of the aging population, the prevalence of fatty liver and related diseases will increase significantly (Carlo *et al.*, 2015). Non-alcoholic fatty liver disease (NAFLD) is the main type of fatty liver disease (FLD). The pathological types include simple fatty liver, non-alcoholic steatohepatitis (NASH) and NASH-related cirrhosis, which can develop into liver cancer (Fang *et al.*, 2017). NAFLD has become an intrahepatic clinical manifestation and pathological syndrome of metabolic insulin resistance syndrome. The prognosis of NAFLD is related to the occurrence of acute coronary artery events and stroke events (GU *et al.*, 2015).

Fructus Akebiae Extract (FAE) is a commonly used drug in the clinical treatment of liver cancer by promoting qi and blood circulation (Zhou *et al.*, 2010). Its fruit is sweet and edible, it can also make wine, and its seeds can press oil (Jin *et al.*, 2014). Triterpenoid saponins are the main components of the prognosticator (Liu *et al.*, 2017). These have a wide range of biological activities and effects, such

as anti-cancer, anti-depression and improving neurological function after stroke (Jin *et al.*, 2012; Kong *et al.*, 2015). So far, no toxicity reports have been found, so they have broad prospects in the research of new drugs.

The main component of FAE is Hederagenin (HG) (Wang *et al.*, 2014). HG and its derivatives have the functions of treating hyperlipidemia, anti-cancer, protecting liver, anti-fungi, etc (Kawamoto *et al.*, 2016). Their clinical application is more extensive, so far no toxicity reports have been found, and new drugs can be developed with broad prospects. Studies have confirmed that FAE has antidepressant effect, in which the purity of HG, the main component of FAE, is about 70% (Ling *et al.*, 2015). Saponins can play a role in reducing weight and lipid through various ways to improve lipid metabolism. Studies have found that soybean saponins can prevent the digestion and absorption of cholesterol in the digestive tract, reduce serum cholesterol (TC), triglyceride (TG), and reduce the risk of cardiovascular disease (Liu *et al.*, 2018). The effect of *Fructus foretti* extract combined with ursodeoxycholic acid on non-alcoholic fatty liver disease was studied (Liang *et al.*, 2015). As a natural source of traditional Chinese medicine, the extract of FAE has the characteristics of mild action and less side effects, and has good antioxidant activity as well as lipid-lowering. Therefore, it is of practical significance to study the prevention and treatment of NAFLD and related diseases by TCM.

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MATERIALS AND METHODS

General information

180 patients with clinically confirmed fatty liver were selected from the outpatient and inpatient departments of Hepatology of a third-class hospital in Jiangxi province from 2016 to 2017. They were randomly divided into two groups, 90 cases in each group. All patients were approved by ethics committee of our hospital, ethical approval number as 2016JUSPLD and all patients signed on the informed consent.

Diagnostic criteria

The diagnostic criteria were based on guidelines for diagnosis and treatment of fatty liver and alcoholic liver disease in the Chinese society of Hepatology. Inclusion criteria: total cholesterol (TC), serum triglyceride (TG), double or single elevation, ultrasound diagnosis of FLD, aspartate aminotransferase (AST), alanine aminotransferase (ALT), one or two of them increased. The active stage of chronic viral hepatitis, acute hepatitis, severe hepatitis, drug-induced liver disease and malnutrition were excluded by medical history, physical examination and supplementary examination. Diabetes mellitus, hyperuricemia, nephrotic syndrome and pregnant and lactating women were excluded.

Case grouping

180 patients were divided into experimental group and control group by stratified randomization. Symptoms and signs of the patients included swelling or dull pain of right hypochondria, swelling of abdomen under hypochondria, loss of appetite, fatigue and fatigue, uneasy stool and nausea. AST, ALT, TC and TG were abnormal. Liver ultrasound was diagnosed as FLD. There were 90 cases in the experimental group, 53 males and 37 females, with an average age of (45.8±7.9) years, with an average duration of (5.1±3.4) years. The control group consisted of 90 patients, 44 males and 46 females, with an average age of (45.4±8) years, with an average duration of (5.2±3.3) years.

Therapeutic method

Patients were given "exercise diet" treatment (low intensity, long-term aerobic exercise, about 40 minutes each time, 5-7 times a week; for abnormal TG, TC to give relevant treatment. The control group was treated with Ursodeoxycholic Acid (Ursofalk), 250mg/time, three times a day, and Keeping 24 weeks of treatment. On the basis of the experimental group, the experimental group was added with the extract of *Fructus foretti*, 12g every time, 3 times a day. 30d for 1 courses of treatment, after 3 courses of treatment, various indicators were detected.

Observation index

Clinical symptoms and signs: (1) Changes of right flank swelling or dull pain, subflank mass, epigastric fullness, loss of appetite, fatigue, feces discomfort, nausea and

belching. (2) New symptoms during treatment. Auxiliary examination: liver CT value.

Non-alcoholic fatty related indicators

According to the standard 191 of Guiding Principles for Clinical Research of New Traditional Chinese Medicine (Trial Implementation), the cure rate was 90% and the liver CT returned to normal 'TG, TC, ALT, AST'. Significant effect: the reduction rate of symptom integral score was 70% and < 90%. The liver CT value increased by more than 12 HU, while the TG, TC, ALT and AST decreased by more than 50%. Effective: the score of symptom score decreased by >30% and <70%, and the CT of liver increased by 8 to 12HU. Ineffective: the reduction of symptom integral score was more than 30%, the liver CT value did not change, and TG, TC, ALT and AST did not improve.

STATISTICAL ANALYSIS

The data were analyzed by t test and χ^2 test. All measurement data were expressed by mean (x+s) standard deviation, and the statistical software was processed by SPSS17.0.

RESULTS

Comparison of clinical efficacy

The comprehensive clinical efficacy of the experimental group was 95.56%, slightly higher than that of the control group (93.33%, $P < 0.01$), as shown in table 1.

Comparison of main symptom scores and body mass index

Fructus akebiae extract (FAE) and Ursofalk can effectively improve the symptoms and body mass index of the patients. The improvement of the main symptom score and body mass index of the experimental group is better than that of the control group. The experimental group improved 63 cases (70%) after one course of treatment, while the control group improved 50 cases (55.5%) after treatment. There was no significant difference between the two groups ($P > 0.05$), as shown in table 2.

CT value of liver

After treatment, the liver CT value of the experimental group and the control group increased slightly, but there was no significant difference between the two groups, as shown in table 3.

TG, TC

TG and TC decreased significantly in experimental group and control group, ALT and AST decreased significantly compared with control group, $P < 0.01$; the experimental group was lower than the control group, but there was no statistical difference.

Table 1: Comparison of clinical efficacy of patients

Group	Cases	Cure	Obvious effect	Partial validity	Invalid	Total effective rate (%)
Experimental group	45	15	17	11	2	95.56
Control group	45	16	14	12	3	93.33

Table 2: Comparison of main symptom scores and body mass index before and after treatment (*P<0.05)

Group	Cases	Time	Main symptom score	Body mass index
Experimental group	90	Before treatment	7.28±4.31	26.38±4.33
		After treatment	5.09±3.98	24.65±3.86
		difference	2.19±1.30*	1.73±0.84*
Control group	90	Before treatment	7.14±4.66	25.94±6.36
		After treatment	5.58±4.32	25.08±3.47
		difference	1.56±1.50	0.86±0.92

Table 3: Changes of liver CT, TG, TC, ALT and AST

Group	Time	CT value of liver (Hu)	TG (mmol/L)	TC(mmol/L)	ALT(U/L)	AST(U/L)
Experimental group	Before treatment	34.30±11.85	2.94±0.49	6.81±1.52	60.22±11.36	69.37±10.21
	After treatment	48.34±9.18	1.41±0.24	3.97±1.23	32.5±95.44	34.23±5.62
Control group	Before treatment	34.35±11.78	2.87±0.54	6.74±1.66	61.19±10.63	68.96±11.41
	After treatment	47.85±9.24	1.39±0.26	3.81±1.29	31.2±54.78	33.65±5.03

Table 4: Comparison of liver B ultrasound and CT improvement after treatment

Group	Project	No improvement	Improve +	Improve ++	Improve +++
Experimental group	B-mode ultrasonography	11	68	19	4
	CT	2	30	18	5
Control group	B-mode ultrasonography	5	22	6	0
	CT	2	10	6	0

Comparison of imaging improvement after two groups of treatment

Fructus akebiae extract (FAE) and Ursfolk can effectively improve the imaging performance of B-mode ultrasound and CT, there is no significant difference between the two groups (P>0.05), as shown in table 4.

DISCUSSION

With the increase of obesity, hyperlipidemia and diabetes mellitus, it leads to non-alcoholic fatty liver disease (NAFLD) and non-alcoholic fatty hepatitis (NASH). At present, B-ultrasound or CT is still an important method for the diagnosis of fatty liver, and has been widely used by scholars in the exploration and research of curative effect evaluation. *Fructus akebiae* extract is superior to ursodeoxycholic acid in improving major symptoms and body mass index, and has mild adverse reactions and low incidence, which patients can basically tolerate. *Fructus akebiae* extract has been used in clinic for 15 years, and no serious adverse reactions have been reported so far. Although it is impossible to exclude the influence of diet, exercise and other factors on the judgement of curative effect in this study, the results of this study can basically show that on the basis of lifestyle intervention.

Non-alcoholic fatty liver disease (NAFLD) is one of the most important public health problems in the world in the 21st century, and it is also a chronic liver disease that our country pays more and more attention (Martins *et al.*, 2018). NAFLD belongs to the category of "phlegm syndrome", "dampness obstruction", "swelling", "accumulation syndrome" and "hypochondriac pain" in traditional Chinese medicine (Park *et al.*, 2018). Its pathogenesis is related to phlegm, dampness, blood stasis and accumulation, which are mainly responsible for the liver and spleen (Paccez *et al.*, 2014). The drugs in the compatibility components of the extract of *Fructus foretunii* can play a direct role in the pathogenesis of NAFLD.

Previous studies have shown that the traditional Chinese medicine treatment of primary hepatocellular carcinoma, activating blood circulation, has a significant inhibitory effect on malignant proliferation of hepatocellular carcinoma cells (Savonitto *et al.*, 2012). Follow-up studies found that the inhibitory effect of Predictor on the malignant proliferation of hepatocellular carcinoma cells was significantly stronger than that of other Chinese medicines in the treatment of 5 mg/mL, and also stronger than that of cytotoxic antibiotic G418 0.6 mg/mL, which

constituted the basis for further observation and prediction of seeds and other parts of non-seeds in this experiment (Solinas *et al.*, 2015). The results showed that, under the same conditions, compared with the whole fruits of the predicted seeds and their non-seed coats and sacs, the predicted seeds had the most significant inhibitory effect on the malignant proliferation of hepatocellular carcinoma cells (Sheng *et al.*, 2015). At the dose of 2.5 mg/mL, the inhibition of HCC cells was stronger than that of the positive control drug G418, suggesting that the FAE was the main site of inhibiting the malignant proliferation of HCC cells.

Fructus akebiae extract (FAE) can treat fatty liver on a high-fat diet or delay the progression of the disease. In this study, the extract of predictors was used as a control drug for the treatment of fatty liver (Wang *et al.*, 2014). Observation of efficacy in NAFLD treatment has always been the bottleneck of clinical prevention and treatment research. Liver biopsy has been regarded as the gold standard, but it is difficult for patients to accept. Ultrasonography is non-invasive, inexpensive, but does not energize the degree of fatty liver. Previous studies have shown that liver CT can quantify NAFLD level (Zhang *et al.*, 2016). Previous studies have found that CT is superior to B-mode ultrasonography in the diagnosis and efficacy evaluation of fatty liver. The accuracy rate of NAFLD diagnosis is 97.9% (Paccez *et al.*, 2014). In this study, liver CT was used to quantify efficacy. Fatty liver currently lacks the authoritative criteria for syndrome differentiation and typing, and some scholars have certain curative effect from the treatment of spleen deficiency, phlegm and dampness (Savonitto *et al.*, 2012). Clinical practice shows that most patients with fatty liver often have abnormal liver function. The main clinical manifestations are bilateral flank pain, loose stool and yellow greasy tongue coating, which should be treated with "damp-heat". *Fructus akebiae* extract (FAE) has the effect of soothing liver and gallbladder, clearing away heat and turbidity, and is the main drug for the treatment of chronic cholecystitis and cholelithiasis (Ling *et al.*, 2015). Animal experiments showed that the FAE had the effects of anti hepatic steatosis and scavenging free radicals. *Fructus akebiae* extract (FAE) has a certain therapeutic effect on fatty liver, suggesting that *Fructus akebiae* extract (FAE) can be used in combination with ursodeoxycholic acid in the treatment of chronic hepatobiliary diseases (Kawamoto *et al.*, 2016).

According to the above theory, the patients in the experimental group took the extract of Prophet orally, one dose a day, 30 days as a course of treatment. After three courses of treatment, the symptoms improved significantly, the CT value of liver increased, the degree of FLD decreased significantly, TC, TG, ALT and AST decreased significantly (Carlo *et al.*, 2015). It is indicated that the extract of *Fructus foretti* has good curative effect

on NAFID and has synergistic effect on lowering blood fat. Triterpenoid saponins from the extract of Predictor have been used in clinical treatment of hyperlipidemia, which has obvious therapeutic effect on experimental hyperlipidemia in rats (Paccez *et al.*, 2014). After administration, the contents of TC, TG, LDL-C in serum can be significantly reduced, and the contents of HDL-C in serum can be increased. Therefore, from the perspective of pharmacology of traditional Chinese medicine, the *Fructus akebiae* extract (FAE) has the effect of regulating blood lipid.

In summary, the three terpenoid saponins from the *Fructus akebiae* extract (FAE) can show excellent weight loss effect (Park *et al.*, 2018). The mechanism of saponins improving lipid metabolism is significantly different from that of non-thermal degradable saponins, which do not inhibit the digestion and absorption of exogenous fat. However, triterpenoid saponins can increase the levels of hormones related to metabolism, promote calorie consumption, inhibit the activity of enzymes related to fatty acid synthesis and promote the activity of fatty acid beta-oxidase CPT, which hinders the endogenous synthesis of fat.

CONCLUSION

This study found that *Fructus akebiae* extract can significantly improve the symptoms of liver discomfort, fatigue, loss of appetite in patients with non-alcoholic fatty liver disease, reduce body mass index, effectively improve liver function, reduce TG and TC, and improve the imaging manifestations of fatty liver. The use of the extract of prophets can significantly improve the clinical symptoms and serum biochemical indicators such as ALT, AST, GGT, TG, TC in patients with non-alcoholic fatty liver disease. It was supported by some histological evidence. These results suggest that *Fructus akebiae* extract combined with Ursosulfate is safe and effective in the treatment of fatty liver.

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