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Drug Combination Therapy 2022;4(3):15. https://doi.org/10.53388/DCT2022015

Clinical efficacy of Qingre Quzhuo capsule in the treatment of non-alcoholic fatty liver disease

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Competing interests
The authors declare no conflicts of interest.
Acknowledgments
Project source: Hebei Provincial Planning Commission (No. 20171185); Hebei Provincial Administration of Traditional Chinese Medicine (No. 2018479, No. 2021308); Yuan-Song Wang Heritage Studio of Famous Traditional Chinese Medicine in Hebei.
Abbreviations
NAFLD, non-alcoholic fatty liver disease; CAP, controlled attenuation index; ALT, alanine aminotransferase; r-GT, r-glutamyltransferase; TC, cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; MDA, malonaldehyde; LPO, lipide peroxide; TAC, total antioxidant capacity; SOD, superoxide dismutase; CAT, catalase; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; AST, aspartate transaminase.
Peer review information
Drug Combination Therapy thanks all anonymous reviewers for their contribution to the peer review of this paper.
Citation
Qi YY, Zhang ZY, Liu C, et al. Clinical efficacy of Qingre Quzhuo capsule in the treatment of non-alcoholic fatty liver disease. *Drug Comb Ther*. 2022;4(3):15. doi: 10.53388/DCT2022015.

Executive editor: Guang-Ze Ma.
Received: 31 July 2022; **Accepted:** 01 August 2022; **Available online:** 01 August 2022.

Abstract
Background: To observe the clinical effect of Qingre Quzhuo capsule in the treatment of non-alcoholic fatty liver disease. **Methods:** 90 patients with non-alcoholic fatty liver disease in our hospital from January 2021 to January 2022 were randomly divided into observation group and control group, 45 cases in each group. All patients received routine lifestyle intervention and the control group received oral polyene phosphatidylcholine capsules 2 capsules/time (456 mg), three times daily; 45 cases in the observation group were given Qingre Quzhuo capsule (Jiyao Z2017040, 0.5 g/grain) 2.5 g/time, 3 times/day, for 12 weeks. The clinical efficacy, liver function, liver transient elastography controlled attenuation index value, lipid metabolism, oxidation and antioxidant indexes were compared between the two groups after treatment. **Results:** The observation indexes of the two groups after treatment were better than those before treatment ($P < 0.05$). After treatment, the total effective rate of the observation group was higher than that of the control group. Lipid metabolism indexes and oxidation indexes were lower than those in the control group. All antioxidant indexes were higher than control group. The decrease of liver transient elastography controlled attenuation index value was better than that of the control group and the difference was statistically significant ($P < 0.05$). There was no significant difference in the decrease of alanine aminotransferase between the observation group and the control group after treatment. The decrease of r-glutamyltransferase was statistically significant ($P < 0.05$). **Conclusion:** Qingre Quzhuo capsule in the treatment of non-alcoholic fatty liver disease can improve liver function, regulate lipid metabolism indexes of patients, improve the antioxidant capacity of liver cells and improve the controlled attenuation index value of liver transient elastography. In addition, it is superior to polyene phosphatidylcholine in regulating lipid metabolism, antioxidant capacity and controlled attenuation index value of patients with non-alcoholic fatty liver disease which is safe and worthy of promotion.

Keywords: Qingre Quzhuo capsule; polyene phosphatidylcholine capsules; non-alcoholic fatty liver disease; curative effect

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Highlights

This work mainly discussed the clinical efficacy of Qingre Quzhuo capsule in the treatment of non-alcoholic fatty liver disease and the mechanism of its role. Combined with liver function, liver transient elastography controlled attenuation index value, lipid metabolism, oxidation and antioxidant, the main indicators reflect the degree of liver function recovery from the perspective of serum biochemistry, which is very representative. In-depth analysis of the molecular role of traditional Chinese medicine provides ideas for multi-target therapy.

Background

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver injury induced by overnutrition, insulin resistance and related metabolic disorders, which includes the development of non-alcoholic steatohepatitis, non-alcoholic steatohepatitis, liver cirrhosis and hepatocellular carcinoma [1]. NAFLD is the most common liver disease in the world, accounting for about a quarter of the population [2]. Its high prevalence is closely related to the rapid increase in the prevalence of metabolic syndromes, such as poor lifestyle, overweight and dyslipidemia. Among them, developing a good lifestyle is an effective treatment for NAFLD. Reducing the degree of fatty liver change is the cornerstone for the treatment of NAFLD by reducing the intake of high fat and high calories and promoting glucose and lipid metabolism. Silymarin, dicyclol, polyene phosphorylcholine, diammonium glycyrrhizinate, reduced glutathione, adenosine methionine and ursodeoxycholic acid, which are widely used in China, have good safety in the treatment of liver injury. Some drugs have achieved relatively accurate curative effects in patients with drug-induced liver injury and cholestasis liver disease [3, 4], but the therapeutic impact of these drugs on non-alcoholic steatohepatitis and liver fibrosis still needs further clinical trials to confirm. In view of this disease, our hospital has developed a hospital preparation of Qingre Quzhuo capsule. After years of clinical application, it has achieved good clinical efficacy and is now clinically studied.

Clinical data

General information

90 patients with NAFLD who were treated in our hospital from January 2021 to January 2022 were collected. All patients signed informed consents and were in line with the guidelines for the prevention and treatment of NAFLD (2018 updated version) and excluded: 1) serum ammonia transferase of liver function > 5 times the normal upper limit; 2) non-alcoholic fatty liver disease progress to cirrhosis, liver cancer stage; 3) patients with renal disease, cardiovascular disease and hypertension control instability (blood pressure ≥ 160/100mmHg); 4) women during pregnancy or lactation; 5) test drug allergy history; 6) in recent 1 month to participate in other drug clinical researchers; 7) patients who used drugs for non-alcoholic fatty liver disease in recent one week. The patients were randomly divided into observation group and control group, with 45 cases in each group. There were 23 males and 22 females in the control group. Body weight 62–81 kg, average (71.53 ± 3.47) kg; 24 males and 21 females in the observation group; body weight 65–82 kg, average (71.62 ± 3.39) kg; there was no significant difference in the general data between the two groups (P > 0.05), indicating comparability.

Method

Both groups were given routine lifestyle guidance. On this basis, the observation group was given Qingre Quzhuo capsules (Ji medicine Z2017040 0.5 g/granule; drug composition: *Rhizoma coptidis*, Rhizoma anemarrhenae, Fructus aurantii immaturus, *Rhizoma alismatis, Poria*, *Radix et rhizoma rhei*, *Cortex mori*, etc.) 2.5 g/time, 3 times/day. The control group was given polyene phosphatidylcholine capsules (Sanofi Pharmaceutical Co., Beijing, China, Ltd., H20059010) 2 grains/time (456 mg), three times daily. The liver function, controlled attenuation index (CAP) value, lipid metabolism, oxidation and antioxidant indexes of the two groups after 12 weeks of treatment were observed. Patients voluntarily participated in the research and signed the informed consent. Ethical approval was approved by the Ethics Committee of Cangzhou Hospital of Integrated Traditional Chinese and Western Medicine (Ethics No. : 2018-KY-009).

Observation indicators

liver function: alanine aminotransferase (ALT) and r-glutamyltransferase (r-GT); lipid metabolism indexes: cholesterol (TC), triglyceride (TG) and low-density lipoprotein cholesterol (LDL-C); oxidation index: malonaldehyde (MDA), lipide peroxide (LPO); the antioxidant indexes were total antioxidant capacity (TAC), superoxide dismutase (SOD) and catalase (CAT). The above indexes were quantitatively detected by the corresponding enzyme-linked immunosorbent assay kit.

Evaluation standard of curative effect

Clinical recovery: clinical signs, symptoms disappeared or basically disappeared, the indicators returned to normal; significantly: the clinical symptoms and signs were significantly improved and the examination indexes basically returned to normal. Effective: clinical symptoms and signs have been improved, the inspection indicators have improved. Ineffective: the above standards were not met.

Statistical method

SPSS 24.0 statistical software was used for data processing. Measurement data were expressed as ($\bar{x}$ ± s) and t test was used. Count data are expressed in relative numbers and tested. $P < 0.05$ indicated that the difference was statistically significant.

Results

Comparison of clinical efficacy between the two groups after treatment

Comparison of overall curative effect between the two groups after 12 weeks of treatment. The curative effect of the treatment group was better than that of the control group ($P < 0.05$) (Table 1).

Comparison of lipid metabolism indexes between the two groups before and after treatment

Before treatment, there was no significant difference in lipid metabolism indexes between the two groups ($P > 0.05$). After treatment, the lipid metabolism indexes(TC/TG/LDL-c) in the observation group were lower than those in the control group and the difference was statistically significant ($P < 0.05$) (Table 2).

Comparison of oxidation indexes between the two groups before and after treatment

Before treatment, there was no significant difference in each oxidation index between the two groups ($P > 0.05$). After treatment, the oxidation indexes in the observation group were lower than those in the control group and the differences were statistically significant ($P < 0.05$) (Table 3).

Comparison of antioxidant indexes between the two groups before and after treatment

Before treatment, there was no significant difference in antioxidant indexes between the two groups ($P > 0.05$). After treatment, the antioxidant indexes in the observation group were higher than those in the control group and the differences were statistically significant ($P < 0.05$) (Table 4).

Comparison of ALT before and after treatment between the two groups

The intra-group comparison before and after treatment showed that P values were less than 0.01 and the difference was statistically significant. There was no significant difference in ALT level between the two groups after treatment ($P = 0.684 > 0.05$) (Table 5).

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Comparison of r-GT levels between the two groups before and after treatment

Comparison before and after treatment, $P < 0.05$, significant difference between the two groups before and after treatment. Comparison of r-GT between the two groups after treatment, by rank sum test, $P < 0.05$, the difference was statistically significant (Table 6).

Comparison of CAP values between the two groups before and after treatment

Before and after treatment, the paired t test P-values were less than 0.01, the difference was statistically significant. The CAP value of the two groups after treatment was compared, $P = 0.037 < 0.05$, the difference was statistically significant (Table 7).

Table 1 Comparison of clinical efficacy between the two groups after treatment (%)

Group	Time	Significantly	Effective	Ineffective	Total efficacy
Control group (n = 45)	Post treatment	12 (26.50)	12 (26.50)	21 (46.50)	24 (53.50)
Observer group (n = 45)	Post treatment	19 (42.50)	12 (26.50)	14 (31.50)	31 (68.50)

Table 2 Comparison of lipid metabolism indexes between the two groups before and after treatment (mmol/L, ($\bar{x} \pm s$))

Group	TG		TC		LDL-c	
	Before treatment	Post treatment	Before treatment	Post treatment	Before treatment	Post treatment
control group (n = 45)	2.7 ± 0.21	2.61 ± 0.13	5.57 ± 0.21	5.27 ± 0.13	3.12 ± 0.23	2.86 ± 0.19
observer group (n = 45)	2.90 ± 0.13	2.24 ± 0.16	5.64 ± 0.23	4.98 ± 0.15	3.07 ± 0.12	2.23 ± 0.15
t	0.837	12.172	0.868	10.515	0.623	16.905
P	0.215	0	0.187	0	0.267	0

TG, triglyceride; TC, cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 3 Comparison of oxidation indexes between the two groups before and after treatment (μmol/L, ($\bar{x} \pm s$))

Group	MDA		LPO	
	Before treatment	Post treatment	Before treatment	Post treatment
Control group (n = 45)	31.13 ± 3.17	25.45 ± 2.79	15.31 ± 1.47	13.25 ± 1.45
Observer group (n = 45)	29.87 ± 3.12	22.48 ± 2.61	15.72 ± 1.75	10.73 ± 1.43
t	0.27	5.231	0.252	7.592
P	0.391	0	0.42	0

MDA, malonaldehyde; LPO, lipide peroxide.

Table 4 Comparison of antioxidant indexes between the two groups before and after treatment ($\bar{x} \pm s$)

Group	TAC (U/mL)		SOD (nU/mL)		CAT (U/mL)	
	Befor treatment	Post treatment	before treatment	Post treatment	before treatment	Post treatment
Control group (n = 45)	5.04 ± 0.63	7.14 ± 1.3	73.19 ± 6.66	76.81 ± 6.84	16.45 ± 1.67	18.62 ± 1.23
Observer group (n = 45)	4.87 ± 0.50	9.20 ± 1.10	72.31 ± 6.54	81.23 ± 7.31	15.10 ± 1.87	21.31 ± 2.53
t	0.362	8.865	0.504	2.84	0.324	6.457
P	0.361	0	0.306	0.004	0.365	0

TAC, total antioxidant capacity; SOD, superoxide dismutase; CAT, catalase.

Table 5 Comparison of ALT before and after treatment between the two groups (U/L)

Group	Before treatment	Post treatment	t	*P*
Control group (n = 45)	85.00 (68.25, 120.75)	37.40 (28.00, 46.75)	7.73	$P < 0.01$
Observe group (n = 45)	90.00 (71.75, 118.25)	36.90 (30.00, 55.50)	9.02	$P < 0.01$

ALT, alanine aminotransferase.

Table 6 Comparison of r-GT levels between the two groups before and after treatment (U/L)

Group	Before treatment	Post treatment	t	*P*
Control group (n = 45)	67.50 (64.75, 83.25)	42.50 (24.4, 53.25)	2.81	0.05
Observe group (n = 45)	66.50 (67.75, 855.50)	33.00 (26.50, 39.75)	1.94	0.05

r-GT, r-glutamyltransferase.

Table 7 Comparison of CAP values between the two groups before and after treatment

Group	Before treatment	Post treatment	t	*P*
Control group	299.40 (283.50, 324.75)	248.00 (237.00,261.25)	15.78	$P < 0.01$
Observe group	298.00 (268.00, 340.25)	273.00 (243.75,309.00)	9.913	$P < 0.01$

CAP, controlled attenuation index.

Discussion

The prevalence of non-alcoholic fatty liver disease is still increasing. In addition to liver function indicators and abnormal lipid metabolism, the imbalance of oxidation and antioxidant cannot be ignored. Oxidative index MDA, LPO expression increased, TAC, SOD, CAT antioxidant index decreased, will further aggravate liver oxidative stress injury, increase the adverse effects on the liver. Therefore, in the treatment of non-alcoholic fatty liver disease, the balance between oxidation and antioxidation is also one of the criteria for evaluating the therapeutic effect [5]. Transient elastography is based on the principle of ultrasound, which generates shear waves and propagates to deep tissues by probe vibration control technology. The degree of liver steatosis is measured by liver controlled attenuation index (CAP). In addition, the degree of liver fibrosis was evaluated by measuring liver hardness (LSM value). Polyene phosphatidylcholine enters the liver cells and combines with the liver cell membrane and organelle membrane by a complete molecule. It directly affects the membrane structure to restore the damaged liver function and enzyme activity, regulates the energy balance of the liver, promotes liver tissue regeneration, converts neutral fat and cholesterol into a form of easy metabolism, and stabilizes bile.

The main components of Qingre Quzhuo capsule are Huanglian, Zhimu, Zhishi, Zexie, Fuling, Dahuang, Sangbaipi, etc. Modern pharmacological studies have shown that emodin and rhein, the main components of rhubarb, can improve liver function, prevent and treat hepatocyte necrosis and promote hepatocyte regeneration [6]. Safflower yellow is the main pigment component in safflower. Studies have shown that Safflower yellow can significantly reduce serum TC, TG, LDL-C levels and LDL-C/HDL-C ratio in hyperlipidemia mice and prevent fatty liver by inhibiting intracellular cholesterol biosynthesis [7]. Total saponins of yam can promote the oxidation of fatty acids by up-regulating the expression of ACADM and ACADS genes, down-regulated the expression of SREBP-1C. FAS and ACC1 and inhibited the synthesis of triglyceride and cholesterol; it can prevent lipid deposition and thus treat non-alcoholic fatty liver disease [8]. Flavonoids extracted from *Cortex Mori* can reduce FPG, TC, TG, LDL-C in serum of NAFLD rats, improve insulin sensitivity and reduce the mRNA expression of vascular endothelial growth factor and platelet derived factor in liver, so as to protect the liver [9]. Achyranthes bidentata decoction, 20% ethanol elution fraction and steroid ketone fraction could reduce the serum TC, TG, LDL-C, ALT and AST values of hyperlipidemia rats and increase HDL-C values. Decrease MDA level and increase SOD level in liver tissue; it shows that Achyranthes bidentata has certain preventive effects on hyperlipidemia and hepatic steatosis [10].

Conclusion

The improvement of lipid metabolism index and CAP value in the observation group were significantly better than those in the corresponding control group. From the perspective of serum biochemistry, it was confirmed that Qingre Quzhuo capsule could further improve the blocking state of liver blood circulation, reduce fatty liver and reverse and restore liver function in patients with non-alcoholic fatty liver disease.

In summary, Qingre Quzhuo capsule can treat different degrees of non-alcoholic fatty liver disease, effectively improve the imbalance of oxidation and antioxidants, promote cholesterol metabolism, and also has a positive role in promoting liver tissue regeneration, which provides a new idea and direction for non-alcoholic fatty liver disease.

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