Review Article
The therapeutic effect of Chaihu-Shugan-San in fatty liver disease: a meta-analysis randomized controlled trials

Yong-Yong Zhang1, San-Qiang Li1, Ying Song1, Wei-Qiang Qiao2, Ping Wang1, Xin-Juan Pan1, Dong-Mei Wang1, Rui-Fang Li1, Yi-Xiang Chen1

1The Molecular Medicine Key Laboratory of Liver Injury and Repair, Medical College, Henan University of Science and Technology, Luoyang 471003, Henan, China; 2Department of Breast Surgery, The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, Henan, China

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Abstract: Subject: To assess the effect of Chaihu-Shugan-San (CSS) in the treatment of fatty liver disease. Method: A meta-analysis was conducted to examine the effect of CSS treating on fatty liver. Comprehensive literature searches were performed to search for randomized controlled trials up to August 2017. Result: 12 randomized controlled trials involving 1,049 patients were included in this study. The results showed that CSS had significant effect for the treatment of fatty liver patients in comparison with control groups (Cure OR = 2.47, 95% CI 1.77 to 3.45, P < 0.00001; Significant effect OR = 1.57, 95% CI 1.16 to 2.12, P = 0.004; Effective OR = 0.65, 95% CI 0.47 to 0.89, P = 0.008; Invalid OR = 0.23, 95% CI 0.15 to 0.36, P < 0.00001), and also revealed that CSS could significantly reduce the levels of TG, TC, AST and ALT in fatty liver patients group (TG mmol/L MD = -0.88, 95% CI -1.23 to -0.54: P < 0.00001; TC mmol/L MD = -1.29, 95% CI -1.92 to -0.66: P < 0.00001; AST U/L MD = -10.89, 95% CI -12.70 to -9.09: P < 0.00001; ALT U/L MD = -13.46, 95% CI -18.25 to -8.67: P < 0.00001), but no significant effect on HDL and LDL (HDL mmol/L MD = 0.07, 95% CI -0.12 to 0.27: P = 0.46; LDL mmol/L MD = -0.48, 95% CI -1.02 to -0.06: P = 0.08). Conclusion: CSS has positive effect on blood lipids, liver function and fatty liver condition of fatty liver patients. However, due to the limitation of number and quality of trials included, more clinical randomized controlled trials with high quality are needed for further verification.

Keywords: Chaihu-Shugan-San, meta-analysis, fatty liver

Introduction

Liver, as a vital organ of the human body, plays important roles in digestive and excretory functions, nutrient storage, metabolic functions, synthesis of new molecules, and purification of toxic chemicals [1]. The fatty liver disease is currently one of the world’s major public health problems, and its pathologic processes include fatty liver, steatohepatitis and cirrhosis. Fatty liver is a clinical syndrome caused by various factors such as environmental, genetic and metabolic stress [2], and it contains alcoholic and nonalcoholic liver diseases. Around the world, the morbidity of nonalcoholic fatty liver disease (NAFLD) is 6.3%-33%, but in Europe and other western countries, the average prevalence rate in adults ranging from 20-33% [3], and a previous study showed a trend toward a gradual increase in the younger generations [4]. In particular, it should be considered that simple NAFLD can progress to non-alcoholic steatohepatitis (NASH) in about 20-25% of cases and nearly 20% of patients with NASH can develop fibrosis and cirrhosis [9]. However, its pathogenesis is not clear, and hepatic fibrosis may be a pathological pathway through which steatohepatitis develops toward cirrhosis [5, 6].

At present, there was no particularly effective Western medicine in the treatment of fatty liver through liver protection, anti-inflammatory, and lipid-lowering. Traditional Chinese medicine (TCM) has been clinically used in China for thousands of years for the treatment of...
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many diseases. Chaihu-Shugan-San (CSS), an ancient classical formula from “Jingyue Quanshu”, is composed of seven Chinese herbs: Bupleurum Chinese DC (also known as Chaihu in Chinese), Pericarpium Citri Reticulatae, Ligusticum chuanxiong Hort, Rhizoma Cyperi, Fructus Aurantii, Radix Paeonia Alba, and Glycyrrhiza uralensis Fisch with a traditional dose ratio of 6:6:5:5:5:5:3 [7]. Many studies have demonstrated that CSS protected against lipid peroxidation [8], liver fibrosis [9, 10] and insulin resistance. The major compounds from CSS such as saikosaponins [11] and total glucosides of peony have been demonstrated their potential protection on the liver. From the point of TCM theory, the basic pathogenesis of fatty liver was closely correlated to liver stagnation and spleen deficiency [12, 13], and evidence showed CSS could be used for the treatment of liver qi stagnation [7].

Liver stagnation is one of the major syndromes for fatty liver patients, and the application of CSS addition and subtraction treatment has proved to be effective. However, there is no published evidence based on randomized controlled trials (RCTs) to demonstrate that applying CSS is an effective treatment for fatty liver development. Based on the RCTs of CSS for the treatment of fatty liver, the quality and efficacy of these RCTs were systematically evaluated, and this could provide a basis for the treatment of fatty liver by CSS.

Materials and methods

Search strategy

The following databases were retrieved without any language restriction (date last searched: August 2017): the Cochrane Library, PubMed and EMBASE, the China National Knowledge Infrastructure (CNKI), VIP and the WangFang Database. The following terms were used in the search: “fatty liver or fatty or liver”, “Chaihu or Shugan or powders” and “randomized controlled trial or randomized controlled trials”. The reference lists of full-text articles were also screened to avoid omitted studies.

Inclusion and exclusion criteria

Literatures were considered eligible if they met the following criteria: (1) randomized controlled trials; (2) the participants are older than 18 years of age; (3) providing sufficient data to estimate the odds ratio (OR) and 95% confidence intervals (CIs). Studies were excluded if one of the following existed: (1) duplicate publications; (2) case reports, reviews, conference abstracts, letters and animal trials; (3) treatment time of the studies less than 1 month.

Data extraction

Included articles are searched by two authors (Yongyong Zhang and Ying Song) according to the inclusion and exclusion criteria listed above. The disagreement was resolved by discussion until consensus was reached. The extracted information contains the following: the first author’s surname, publication year, country, size of sample, age and sex of subjects, intervention, treatment.
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Outcome indicators

Effective, aspartate transaminase (AST), alanine transaminase (ALT), triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL) and low-density lipoprotein (LDL).

Quality assessment

The RCT methodology was evaluated according to the Cochrane Handbook for systematic review of interventions. Risk of bias for assessing the methodological quality of RCTs mainly included six items: random sequence generation (selection bias), allocation concealment (selection bias), blind subjects and test personnel (implementation bias), blindness outcome evaluation (measurement bias), incomplete data (reporting bias), selection of publication (publication bias), and other bias.

Statistical analysis

We estimate the mean difference (MD) with 95% CIs for continuous outcomes and ORs with 95% CIs for dichotomous outcomes. Heterogeneities were estimated using the $I^2$ statistics. When $I^2 < 50\%$ and $P > 0.10$, the results were considered homogeneous and the fixed-effect model was used; when $50\% \leq I^2 < 75\%$, the results were considered heterogeneous and the random-effect model was used. Subgroup analysis was conducted to identify the causes of the heterogeneity if $I^2 \geq 75\%$. Sensitivity analysis was carried out to evaluate the effect of each individual study on the pooled ORs by excluding studies one-by-one and recalculating the ORs and 95% CIs. A funnel plot was
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Result

Study characteristics

The detailed manuscript screening processes are shown in Figure 1. Using the search terms described above, a total of 426 published records were identified and checking the reference lists, we identified 12 additional publications. After screening the title and abstracts, 38 publications met the crude inclusion criteria and were selected for further assessment. Among them, 1 was excluded for serial publications, 17 not randomized trials and 8 do not match the treatment. Ultimately, 12 studies [14-25] were included in the quantitative synthesis.

All trials had two parallel groups and were described as randomized, and allocation concealment was not reported in any of the Chinese studies. The blinding process was described in only 1 study. The risk of bias, as assessed using the tool from the Cochrane Collaboration, is shown in Figures 2 and 3.

Among the 12 studies, the total number of patients is 1,049 with 526 patients in the treatment group and 523 patients in the control group. The maximum amount of a single RCT sample is 130 cases, and a minimum of 60 cases. The characteristics of studies included are shown in Table 1. For all the studies included, there was no difference between control and treatment groups before these patients were randomly divided into two groups.

Many of the RCT test groups and control groups included routine treatment, which included health education, alcohol consumption, diet control, sports and other basic treatment, and only 1 RCT reported adverse outcomes, including skin itching, nausea, dizziness.

Meta-analysis results

Ten trials reported the data to be effective. We chose a fixed-effects model for the analysis of effective, because of the heterogeneity (Cure $I^2 = 0\%$, Marked effect $I^2 = 45\%$, effective $I^2 = 0\%$, Invalid $I^2 = 0\%$). The results showed that CSS has a significant effect for fatty liver patients compare with control groups (Cure $OR = 2.47$, 95% CI 1.77 to 3.45, $P < 0.00001$; Marked effect $OR = 1.57$, 95% CI 1.16 to 2.12, $P = 0.004$; Effect $OR = 0.65$, 95% CI 0.47 to 0.89, $P = 0.008$; Invalid $OR = 0.23$, 95% CI 0.15 to 0.36, $P < 0.00001$) (Figure 4).

Ten trials reported the data on liver function. The heterogeneity of ALT ($I^2 = 76\%$) is large, so

Table 1. Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size N</th>
<th>Intervention</th>
<th>Control</th>
<th>Duration</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T (M/F)</td>
<td>C (M/F)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cao 2015</td>
<td>36 (23/13)</td>
<td>36 (22/14)</td>
<td>CSS</td>
<td>Ro</td>
<td>6 months</td>
</tr>
<tr>
<td>Cheng 2011</td>
<td>42</td>
<td>42</td>
<td>CSS</td>
<td>Ro</td>
<td>3 months</td>
</tr>
<tr>
<td>Deng 2009</td>
<td>46 (30/16)</td>
<td>46 (32/14)</td>
<td>CSS + Con</td>
<td>Ro</td>
<td>3 months</td>
</tr>
<tr>
<td>Fang 2016</td>
<td>63 (46/17)</td>
<td>63 (45/18)</td>
<td>CSS + Con</td>
<td>Ro</td>
<td>1 month</td>
</tr>
<tr>
<td>Li 2012</td>
<td>30 (23/7)</td>
<td>30 (25/5)</td>
<td>CSS</td>
<td>Ro</td>
<td>2 months</td>
</tr>
<tr>
<td>Pan et al. 2009</td>
<td>41 (29/12)</td>
<td>41 (26/15)</td>
<td>CSS</td>
<td>Dongbao liver Thai</td>
<td>3 months</td>
</tr>
<tr>
<td>Teng 2011</td>
<td>30 (20/10)</td>
<td>30 (19/11)</td>
<td>CSS + Con</td>
<td>Polyene Phosphatidyl choline</td>
<td>3 months</td>
</tr>
<tr>
<td>Wang et al. 2010</td>
<td>54 (29/25)</td>
<td>54 (27/27)</td>
<td>CSS</td>
<td>Ro</td>
<td>3 months</td>
</tr>
<tr>
<td>Xun et al. 2010</td>
<td>51 (24/27)</td>
<td>50 (27/23)</td>
<td>CSS</td>
<td>Ro</td>
<td>14 days</td>
</tr>
<tr>
<td>Zhang 2010</td>
<td>65 (42/23)</td>
<td>65 (41/24)</td>
<td>CSS</td>
<td>Ro</td>
<td>2 months</td>
</tr>
<tr>
<td>Zhang 2013</td>
<td>30 (18/12)</td>
<td>30 (16/14)</td>
<td>CSS</td>
<td>Dongbao liver Thai</td>
<td>3 months</td>
</tr>
<tr>
<td>Zhao et al. 2008</td>
<td>38 (28/10)</td>
<td>36 (27/9)</td>
<td>CSS + Con</td>
<td>Zhibituojuepian</td>
<td>3 months</td>
</tr>
</tbody>
</table>

we chose a random model for liver function. The results indicated that the levels of AST and ALT reduced in fatty liver patients who were treated with CSS than those received other drugs or lifestyle intervention (AST U/L MD = -10.89, 95% CI -12.70 to -9.09; P < 0.00001;
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ALT U/L MD = -13.46, 95% CI -18.25 to -8.67: P < 0.00001 (Figure 5).

All trials reported the data of blood lipids. There was a large heterogeneity in the studies (TG I² = 95%, TC I² = 97%, HDL I² = 92%, LDL I² = 98%), so random model was used for liver function. The results showed that CSS significantly reduced the level of TG and TC in fatty liver patients when compared with those who use other drugs (TG mmol/L MD = -0.88, 95% CI -1.23 to -0.54: P < 0.000001; TC mmol/L MD = -1.29, 95% CI -1.92 to -0.66: P < 0.000001). However, there was no statistically significant in the levels of HDL and LDL in the two groups (HDL mmol/L MD = 0.07, 95% CI -0.12 to 0.27: P = 0.46; LDL mmol/L MD = -0.48, 95% CI -1.02 to -0.06: P = 0.08) (Figure 6).

Discussion

Fatty liver is a common chronic liver disease, and it is one of the important factors in leading to hepatic cirrhosis and liver cancer [26, 27]. Modern pharmacological studies have shown that CSS might work as a significant anti-inflammatory effect in Kupffer cells, and it can also scavenge oxygen free radicals, reduce enzymes released by liver injury, inhibit lipid peroxidation, and have the ability to improve the liver function of damaged hepatocytes [28]. Bupleurum, pericarpium citri reticulatae can decrease the content of TC in hepatocytes and inhibit fiber proliferation and promote fiber absorption [29]; ligusticum wallichii could inhibit TGF-β1 secretion and has the role of anti-hepatic fibrosis [30]; rhizoma cyperi anti-inflammatory could enhance blood circulation; fructus aurantii could promote the digestion of fat food and lower blood fat; Chinese herbaceous peony could improve microcirculation, increase liver blood flow, liver and reduce enzymes and promote liver cell regeneration [31]; licorice could stabilize the liver cell membrane, antagonize or scavenge free radicals, and prevent HSC activation.
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With meta-analysis through 12 studies including 1,049 patients, it demonstrates that CSS has a positive effect on the treatment of fatty liver patients. CSS could improve blood lipid (TG, TC), liver function (AST, ALT) and decrease the TC, TG, ALT and AST level in patients with fatty liver, and the difference is statistically significant compared with other drugs. The effective rate of the experimental group increased significantly when compared with the control group. Some articles refer to the improvement of HDL and LDL in CSS, but there is no difference in this study. The reason may be that the literature is too small and the quality of the literature is low. There are only 12 studies included in this analysis and all of them are Chinese literature. Moreover, the course of treatment is shorter in these studies, of which the longest is Figure 6. The blood lipids of CSS in patients.

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only 3 months, which cannot respond to the long-term use of Chaihu Shugan Scattered for the treatment of fatty liver. All the RCTs are designed for research, assigning implicit and other aspects of the description of the relevant information are inadequate. There was no uniform standard in the related components, quality control, dosage and usage of Bupleurum and Radix Recipe in RCT, which affected the comparability between clinical trials. In addition, articles included in this study did not provide the methods of blind and allocation concealment, and the random allocation concealments of most studies were not described in detail. So we should be cautious about the results of the analysis.

In conclusion, based on the current meta-analysis, CSS has obvious advantages in reducing fatty liver patients with blood lipid (TC, TG) and improve liver function (AST, ALT). However, as the study included in this meta-analysis are all Chinese literature, and limited by the number and quality of articles, the conclusions need to be further validated by more strictly designed multi-centered RCTs with high quality and large scale.

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Disclosure of conflict of interest

None.

Address correspondence to:
San-Qiang Li, The Molecular Medicine Key Laboratory of Liver Injury and Repair, Medical College, Henan University of Science and Technology, Luoyang 471003, Henan, China. Tel: +86-0379-64820863; Fax: +86-0379-64830346; E-mail: sanqiangli2001@163.com

References

[7] Yang QH, Xu YJ, Liu YZ, Liang YJ, Feng GF, Zhang YP, Xing HJ, Yan HZ and Li YY. Effects of Chaihu-Shugan-San and Shen-Ling-Bai-Zhu-
Chaihu-Shugan-San in fatty liver disease


[18] Yuanming Z and Wenli F. Treatment of 38 cases of fatty liver with Chaihu Shugan powder. Strait Pharm J 2008; 20: 82-83.


