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Original Article

A herbal formula Erchen decoction for non-alcoholic fatty liver disease: a systematic review and meta-analysis of randomized controlled trials

Wanshu Li[1], Yan Wu[2], Wenzai Ge[1], Li Fan[1], Wei Sun[3]

Departments of [1]Pharmacy, [2]Critical Care Medicine, Ningbo Municipal Hospital of Traditional Chinese Medicine, Ningbo, P. R. China; [3]Department of Pharmacy, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, P. R. China

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Abstract: *Background and objective:* Erchen Decoction (ECD) is a traditional Chinese medicinal formula, which is often used in the treatment of a variety of diseases. This systematic review aims to evaluate the efficacy of ECD in treating non-alcoholic fatty liver (NAFLD) disease according to the PRISMA systematic review standard. *Methods:* English and Chinese databases were searched from database inception to February 2017 without language restriction. *Results:* Seven RCTs with 1951 participants were included. Patients receiving ECD with conventional treatment showed a significant increase in clinical improvement, compared with participants receiving conventional treatment alone (RR=1.25, 95% CI: 1.13 to 1.38, P<0.00001, I^2=54%). *Conclusion:* Although a consistent result that ECD might be more effective than conventional treatment in treating NAFLD in this study, further RCTs of higher quality, larger scale and longer follow-up periods are still required to identify the efficacy of ECD.

Keywords: Erchen decoction, non-alcoholic fatty liver disease, meta-analysis

Introduction

The disease spectrum of non-alcoholic fatty liver disease (NAFLD) includes non-alcoholic simple fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH) [1], affecting about one-third of the population in the Western world and Asia [2, 3]. The diagnosis of NAFLD was made on the basis of ultrasound evidence of fatty liver with no statistically significant alcohol consumption [4], and is particularly associated with metabolic syndrome including obesity, hypertension, hyperglycemia, insulin resistance (IR), dyslipidaemia and hyperuricemia [5, 6]. Morbidity of NAFLD increase constantly in population, and it is a principal cause of chronic hepatic disease and lacks effective treatment [7]. Therefore, the drug of curative effect for NAFLD is needed to overcome the disease.

Erchen decoction (ECD), containing four commonly used herbs (Pinelliae Rhizoma, Citri Reticulatae Pericarpium, Poria and Radix Glycyrrhizae), was first recorded in a classic clinical Traditional Chinese Medicine (TCM) book titled The Taiping Huimin Heji Jufang [8]. ECD is used in the treatment of a variety of diseases caused by retention of phlegm dampness, including obesity, hypertension, hyperglycemia and hyperuricemia. The component of ECD has been shown to reduce low-density lipoprotein (LDL) oxidation in atherosclerotic mice and in hypercholesterolemic and normal lipidemia humans [9].

Whether ECD has beneficial effects on patients with NAFLD is unknown, and recent studies have shown inconsistent results on the efficacy of ECD for treating NAFLD. To better understand the effect of ECD on NAFLD, we conducted this meta-analysis of RCTs. We believe that this study will provide new insights into the use of ECD in NAFLD and function as a foundation to expedite development of treatment for NAFLD.

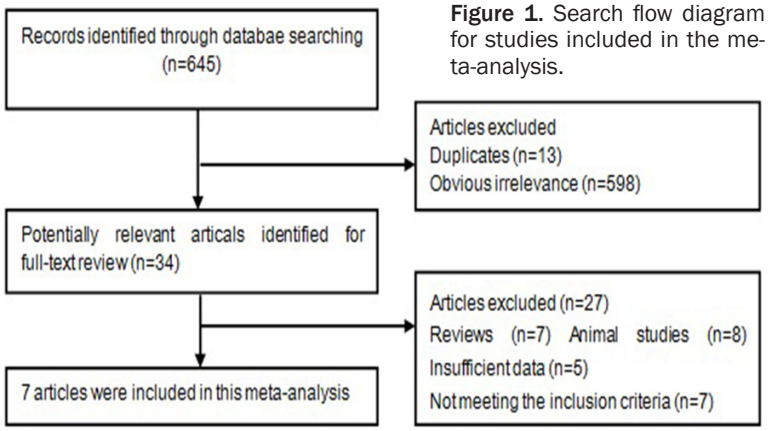

Figure 1. Search flow diagram for studies included in the meta-analysis.

Methods

Search strategy

Search of English and Chinese databases was performed. Databases included PubMed, EMBASE, the Cochrane Library, Chinese Biomedical Database (CBM), China National Knowledge Infrastructure (CNKI), Chongqing VIP (CQVIP), Chinese Biomedical Literature Database (CBM) and Wanfang Medicine Online (WFMO), from database inception to February 2017 without language restriction. The following search terms were used: (Erchen tang or Erchen decoction) and (Non-alcoholic Fatty Liver Disease or NAFLD or Fatty Liver, Nonalcoholic or Nonalcoholic Fatty Liver Disease or Liver, Nonalcoholic Fatty or Fatty Livers, Nonalcoholic or Livers, Nonalcoholic Fatty or Nonalcoholic Fatty Liver or Nonalcoholic Fatty Livers or Nonalcoholic Steatohepatitis or Nonalcoholic Steatohepatitides or Steatohepatitides, Nonalcoholic or Steatohepatitis, Nonalcoholic). Furthermore, we also reviewed the reference lists in the retrieved articles and recent reviews to search for additional studies that potentially met the study criteria.

Eligibility criteria

Inclusion criteria were: (1) completed RCTs published in English or Chinese, with or without blinding; (2) individuals suffering from NAFLD that has been diagnosed by histology or suggestive imaging findings; (3) erchen decoction was given alone or combined with conventional treatment, and compared with conventional treatment or plus placebo (where the same intervention was used in both treatment and comparator groups) and (4) studies with at least 30 subjects to provide enough evidence to approve the outcomes.

Exclusion criteria

The following studies were excluded: (1) reports that did not qualify as an RCT; (2) participants with alcoholic or drug induced, genetic or viral causes of liver injury; (3) studies or case reports enrolling <30 subjects, or manuscripts without sufficient data; and (4) reports in which the data could not be extracted by current mathematical methods.

Study selection and data extraction

All of the articles were searched by two investigators (LF and YW) according to the predefined criteria utilizing a standardized data abstraction form. The form included details of the first author's name, publication year, the number of cases and controls, average age, name and component of Chinese herbs, treatment of the control group, treatment duration and adverse events. To get the details in some studies, emails or phone calls were made to contact the original authors for searching the missing data.

Quality assessment

Two researchers (LF and YW) independently assessed methodological quality of the included studies using the Cochrane risk of bias assessment tool with a potential risk of bias of high, low or unclear. Differences were resolved by agreement after discussion with WS. Studies were assessed based on the following domains: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants, personnel and outcome assessors; (4) incomplete outcome data; (5) selective outcome reporting; and (6) other bias. Studies were assessed as low risk, high risk or unclear risk of bias for each domain.

Data analysis

All statistical analyses were performed in Review Manager (RevMan) Version 5.3. The primary outcome (total effective rate) was presented as a dichotomous variable (presented

Table 1. Summary of randomized controlled trials included in the meta-analysis

Study ID year	T/C (M/F)	Age (yrs)	Intervention (ingredients of ECD formulae)	Control group	Treatment duration	Adverse events
Zhang 2013	T:137 C:111	T:41 C:43	Modified ECD (Rhizoma Pinelliae, Citri Reticulatae Pericarpium, Poria, Radix Glycyrrhizae preparata, Dark Plum fruit, Rhizoma Zingiberis Recens, Rhizoma Bolbostemmae, Lotus Leaf, Raw hawthorn, salvia miltiorrhiza)	Tiopronin Tablets	Two months	NR
Feng 2013	T:63 C:63	T:41.25 C:42.5	Modified ECD (Poria, Rhizoma Zingiberis Recens, Rhizoma Bolbostemmae, Rhizoma Pinelliae, Lotus Leaf, Raw hawthorn, Radix Glycyrrhizae preparata, Dark Plum fruit, Citri Reticulatae Pericarpium, Salvia Miltiorrhiza)	Tiopronin Tablets	Two months	NR
Li 2014	T:29 C:29	43.3±16.7	Modified ECD (Citri Reticulatae Pericarpium, Liquoric Root, salvia miltiorrhiza, Poria, Rhizoma Pinelliae Dark Plum fruit, Radix Glycyrrhizae preparata, Rhizoma Bolbostemmae Raw hawthorn Rhizoma Zingiberis Recens Lotus Leaf)	Liver-protecting tablet+ Vitamin E	Three months	NR
Chen 2011	T:30 C:30	35.8	Modified ECD (Citri Reticulatae Pericarpium, Rhizoma Atractylodis Macrocephalae, Rhizoma Pinelliae, Coix Seed, Poria)	Liver-protecting tablet+ Vitamin E	Three months	NR
Pan 2010	T:42 C:26	T:33-70 C:28-69	Modified ECD (Rhizoma Pinellinae Praeparata, Citri Reticulatae Pericarpium, Poria, Radix Bupleuri, Rhizoma Alismatis, Raw hawthorn, Salvia miltiorrhiza, Red Paeony Root, Radix Glycyrrhizae preparata)	Simvastatin Tablets	Two months	NR
Li 2015	T:86 C:85	43.8±10.2	Modified ECD (Rhizoma Pinelliae Citri Reticulatae Pericarpium, Poria Liquoric Root, Rhizoma Zingiberis Recens, Dark Plum fruit)	Diammonium Glycyrrhizinate Enteric-coated Capsules	One month	NR
Liu 2013	T:66 C:65	41.4	Modified ECD (Citri Reticulatae Pericarpium, Poria Rhizoma Pinelliae, Radix Glycyrrhizae preparata, Rhizoma Zingiberis Recens, Dark Plum fruit, Radix Bupleuri, cortex moutan, Membranous Milkvetch Root, Raw hawthorn, Salvia miltiorrhiza, Rhubarb, Oriental Waterplantain Rhizome, Rhizoma Atractylodis Macrocephalae)	Diammonium Glycyrrhizinate Enteric-coated Capsules	Three months	NR

T = treatment group, C = control group, F = female, M = male, NR = no reported.

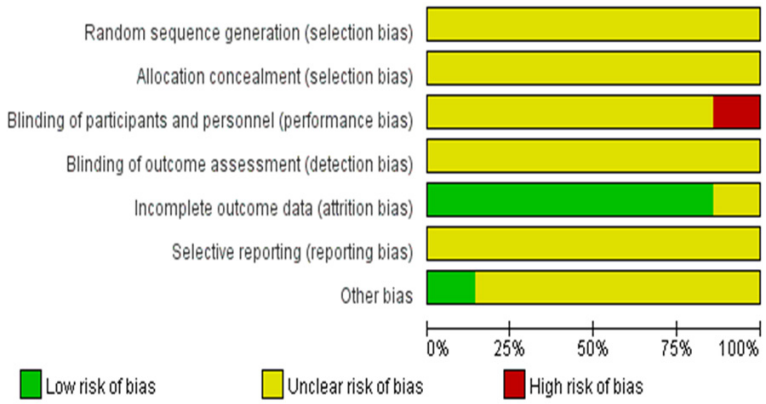

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

as RR with 95% CI). The secondary outcomes (TC, TG, ALT) were assessed as continuous variables (presented as MD and 95% CI). To calculate statistical heterogeneity, the Cochrane's Q test and I^2 statistic were used. When I^2 statistic was less than 50% and the *P* value was more than 0.1, heterogeneity was considered to be low. In cases of low heterogeneity, a fixed effect model was used to pool data; otherwise, a random-effects model was applied.

Results

Literature search

A total of 654 abstracts were retrieved through the electronic databases dated up to February 2017. After initial screening of titles and abstracts using the aforementioned criteria, 34 articles were identified for full-text review. Of these, 27 were further excluded, leaving seven eligible articles [10-16], and a flow chart presenting the study selection process is shown in **Figure 1**. Hence, seven articles involving 862 participants were included in our final meta-analysis. All of the studies were conducted in China. The characteristics of them included in the studies were presented in **Table 1**.

Study characteristics

The studies included 862 participants, of whom 453 were randomized to ECD treatment and 409 to conventional group. The size of the studies varied greatly, the largest study with 248 participants, and the smallest study only had 58 participants. The treatment duration in the included studies ranged from one month to three months. The composition of each treatment group was listed in detail, and all of them were modified ECD.

Methodological quality and risk of bias

As is shown in **Figure 2**, the overall quality of included trials was low. None of the seven trials reported details of random sequence generation or allocation concealment. No trials performed blinding of participants nor mentioned blinding of outcome assessment. Six trials reported all outcomes without missing data [10, 11, 13-16]. All of the studies were published in China, so we could not exclude potential publication bias.

Outcome measures

Assessment of clinical effectiveness is an investigator rated judgment, usually divided into three different levels, including markedly effective, effective and ineffective, based on improvement in type-B ultrasonic of fatty liver, blood lipids and liver function. The reference basis for clinical improvement was the diagnostic criteria of the Chinese Medical Association for nonalcoholic fatty liver disease [13]. These scales are widely used to evaluate clinical efficacy of NAFLD in China.

Seven studies reported the clinical efficacy. Patients receiving ECD with conventional treatment showed a significant increase in clinical improvement, compared with participants receiving conventional treatment alone (RR=1.25, 95% CI: 1.13 to 1.38, P<0.00001, I^2=54%) (**Figure 3**). Conventional therapies included Tiopronin, Liver-protecting + Vitamin E, Simvastatin and Diammonium Glycyrrhizinate Enteric-coated.

TC was reported in 5/7 studies. Overall, ECD-treated patients showed only a statistically significant (P<0.00001) decrease in TC (MD=-0.52 IU/L; 95% CI: -0.65 to -0.40; I^2=0%) compared to the control group (**Figure 4A**). TG

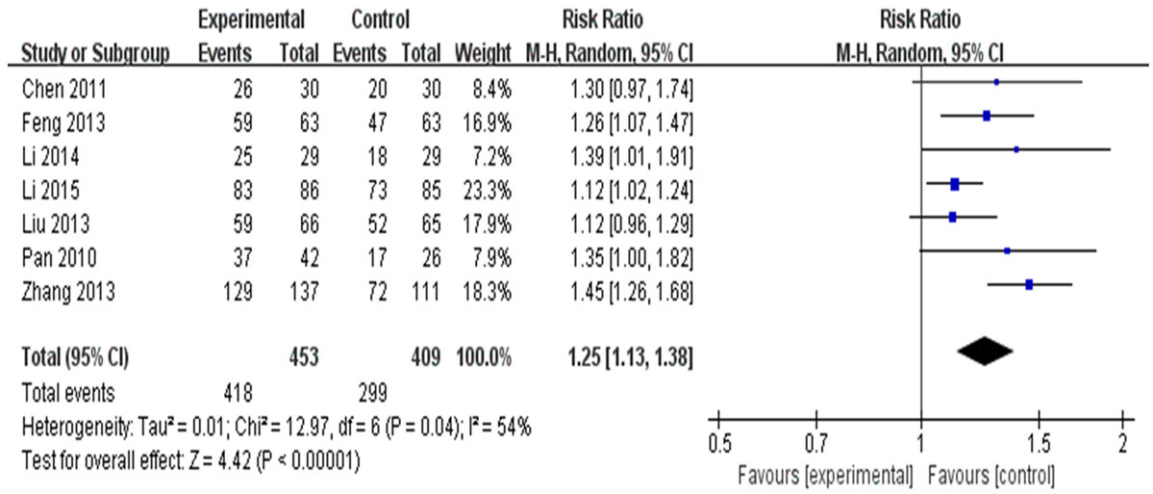

Figure 3. Meta-analysis of the association between Erchen decoction and NAFLD using a random-effects model and a standardized mean difference with a 95% confidence interval.

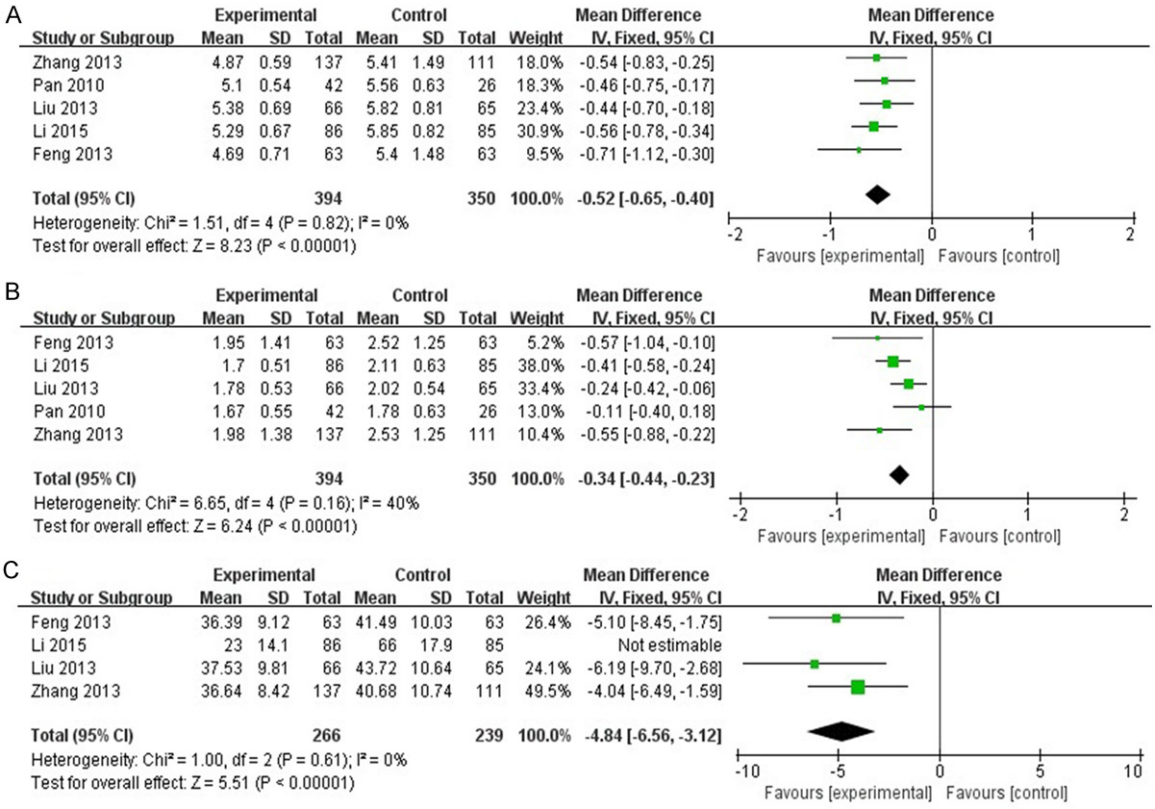

Figure 4. Forest plots of improvement in biochemical and anthropometric variables are shown. A: Serum total cholesterol (TC); B: Triglyceride (TG); C: Alanine aminotransferase (ALT).

activity was evaluated in the included studies. A statistically significant reduction was observed in TG in ECD-treated patients (MD=-0.34 IU/L; 95% CI: -0.44 to -0.23; I^2=40%) (**Figure 4B**). ALT activity was reported in three studies, showing a marked reduction (P<0.00001) in ECD-treated patients (MD=-4.84 mmol/L; 95% CI: -6.56 to -3.12; I^2=0) (**Figure 4C**).

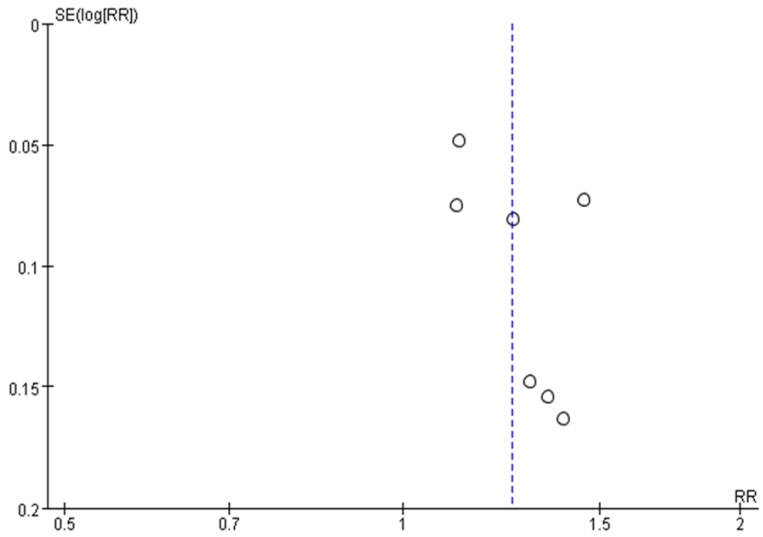

Figure 5. Funnel plot to detect publication bias.

Risk of bias

To determine the potential bias of included studies, the funnel plot was generated in **Figure 5**. The funnel plot was not perfectly symmetrical, suggesting that there might be slight publication bias.

Discussion

This is a systematic analysis to explore the efficacy and safety of ECD for NAFLD. Seven RCTs with 862 participants were included to assess the effects of ECD on NAFLD patients. The pooled analyses showed that ECD therapy was more effective than routine western therapy in improving clinical efficacy, including TC, TG and ALT. However, when we analyzed the subjects with AST, significant difference has not been found. This may be because only two trials with limited data analyzed the AST in ECD supplementation.

In the present study, we conducted this review to assess the efficacy and safety of ECD for the treatment of NAFLD in 4 main Chinese language databases and 3 main English language databases. To the best of our knowledge, this is the first English language systematic review and meta-analysis of RCTs for ECD in treating NAFLD. Compared with the previous study, the strengths of our meta-analysis include the large sample size, which minimized selection bias and led to the relatively stable risk estimation.

The meta-analysis in our study has its own limitations. Most of the trials were with poor methodology according to the current evaluative standards. Although all the included trials stated randomization, none of them mentioned the detailed randomization method. Allocation concealment and blind method were also not mentioned in all the trials. High proportions of positive outcomes were often reported in some Asian countries, so reporting bias and publication bias could not be excluded [17].

Eight English and Chinese electronic databases were searched, but all the seven trials were published in Chinese, leading to publishing bias. The sample size was so small, which could cause exaggerated of weakened results. Therefore, multicenter RCTs with large-scale and long-term follow-up should be conducted to provide more evidence.

Disclosure of conflict of interest

None.

Address correspondence to: Wei Sun, Department of Pharmacy, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou 325027, P. R. China. Tel: +86 139 6880 3162; E-mail: 33sunwei@163.com

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