Systematic evaluation and META analysis of the role of traditional Chinese medicine on the therapeutic effect of metabolism-related steatohepatopathy

Ranran Huang[1]，Fumang Zhang[1]，Ce Zheng[2]

[1]Department of Geriatrics，The Third Affiliated Hospital of Zhejiang Chinese Medical University，310005，China

[2]Department of Infectious Diseases，Hangzhou TCM Hospital Affiliated to Zhejiang Chinese Medical University，310005，China

Introduction. Metabolism-associated fatty liver disease (MAFLD) is a frequent type of common chronic lung disorder, whose prevalence rises significantly with the increase of obesity and metabolic syndrome. Chinese medicines, as an essential part of traditional medical science, and widely utilized in the therapy of a broad range of chronic illnesses, have not been systematically elucidated in terms of their specific effects in the treatment of MAFLD. Therefore, through systematic evaluation and META analysis, this study aimed to comprehensively assess the clinical therapeutic effects and security of Chinese herbal medicine in the management of MAFLD.

Methods. A search of sci-hub, Web of Science, PubMed, EMBASE, China Knowledge Network (CNKI), and Wanfang database was conducted using "traditional Chinese medicine", "non-alcoholic fatty liver disease", "metabolic associated fatty liver disease", and "herbal medicine" as key search terms. hub, Web of Science, PubMed, EMBASE, China Knowledge Network (CNKI), and Wanfang databases with key search terms, and all related rapid controlled trials (RCTs) released up to June 30, 2024 were collected. Through initial screening by reading the abstracts, duplicates and non-compliant literature were excluded and included in all clinical trials of Chinese herbal medicine for the treatment of metabolism-associated steatohepatopathy.The study subjects were patients diagnosed with metabolism-associated steatohepatopathy, the intervention was Chinese herbal medicine, while the comparison group was a placebo or routine treatment, and the major endpoints

included clinical efficacy, liver function indexes (ALT, AST), blood lipid levels (TG, TC, LDL-C, HDL-C). Data extraction and quality assessment were performed from two individual authors, and the quality assessment was performed using the Cochrane Risk of Bias Assessment Tool. Statistics analysis was carried out using RevMan 5.4 software, mainly using random-effects model or fixed-effects model, and the appropriate model was selected according to the heterogeneity results.

Results. Fifteen RCTs that complied with the integration standard were selected, involving 2,034 patients.The results of META assay demonstrated that the TCM treated group was remarkably more favorable than the controlled ones in terms of improving the clinical efficacy, liver function indexes (ALT, AST), and regulating the blood fats levels (TG, TC, LDL-C, HDL-C) ($P<0.05$). Among them, the decreases in ALT and AST levels were particularly significant, indicating that the traditional Chinese medicine had a significant protective effect on hepatocellular injury. In addition, TCM treatment also showed positive effects in regulating lipid levels, which helped to improve the metabolic status of MAFLD patients. The publication bias analysis did not find significant bias, indicating that the results have high confidence.

Conclusion. The present study confirmed the significant effectiveness of herbal medicine in treating MAFLD via systematic evaluation and META analysis. Chinese medicines could not only remarkably reduce liver dysfunction and liver fat content, but also effectively regulate blood lipid levels and body weight, which had a positive impact on the overall health status of MAFLD patients. Nevertheless, this study has some limitations, such as the large heterogeneity of included studies as well as the relatively low qualified of some of them.

Keywords. metabolism-related fatty liver disease; META analysis; traditional Chinese medicine; liver function; lipid indices

INTRODUCTION

With the rapid changes in lifestyle in modern society, the incidence of metabolic diseases has been rising, among which metabolically-associated fatty liver disease (MAFLD) has become globally recognized as on of the most prevalent and chronic

liver conditions, which is closely related to adiposity, model 2 of diabetes mellitus, and those of the meteorological syndrome [1]. MAFLD encompasses a spectrum of liver pathologies characterized by abnormal fat accumulation, varying from pure steatosis to the progression of nutritional fatty liver disease (NASH) and in severe cases to hepatic cirrhosis and hepatocellular carcinoma (HCC) [2].The pathology of MAFLD is marked by the excess fatty deposits in the kidney, disrupting normal liver function and potentially triggering an inflammatory and fibrotic response that leads to irreversible damage [3]. Epidemiologic data show significant regional and demographic variations in the prevalence of MAFLD, but the overall global prevalence is on the rise [4]. In developed countries, MAFLD affects more than 20% of the population and is the leading cause of liver-related death [5]. Its pathogenesis is closely related to the metabolic syndromic constituent parts, inclusive of adiposity, insulation therapy resistance, abnormalities of blood lipid profile and hypertension [6]. Effective management of MAFLD is essential to prevent its progression to advanced liver disease and to reduce the associated morbidity and mortality.The development of MAFLD involves a complex pathophysiological process driven by disorders of hepatic lipid metabolism, oxidative stress, and inflammatory cascade responses. Hepatic steatosis, characterized by excessive accumulation of triglycerides in hepatocytes, triggers a cascade of events that ultimately leads to more severe liver injury [7]. Lipid peroxidation and mitochondrial dysfunction further exacerbate cellular damage and promote inflammation and fibrosis progression [8]. Currently, treatments for MAFLD focus on lifestyle changes such as weight loss, dietary and physical activity changes, and management of comorbidities such as diabetes and dyslipidemia [9]. However, pharmacological treatments specifically targeting MAFLD are limited, highlighting the need for innovative therapeutic interventions. Recently, Chinese Traditional Medicine (TCM) has received much focus for its potential in the treatment of MAFLD due to its holistic approach and individualized treatment strategies. TCM views MAFLD in terms of liver dysfunction, blood stasis, and internal dampness-heat and emphasizes the restoration of metabolic homeostasis

and liver function through herbal medicine, acupuncture, and dietary therapy.

As an important part of TCM, Chinese medicine has special benefits in the cure of chronic diseases. The concept of TCM in treating diseases emphasizes the holistic concept and evidence-based treatment, and achieves the purpose of treating diseases by harmonizing the human body's equilibrium of yin and yang. The main ideas of TCM in treating MAFLD include removing body heat and toxins, harmonizing qi and blood, modulating lipid metabolism and other aspects [10]. These therapeutic strategies are based on the theories of Chinese medicine, which believe that the etiology of MAFLD is closely related to the dysfunction of the liver, stagnation of qi and blood, and internalization of dampness and heat. Therefore, the purpose of removing pathological products from the body, improving liver function, and regulating metabolism can be achieved through the rational combination of Chinese medicines. Commonly used Chinese medicines in clinical practice, such as Poria, Hawthorn, Lycium barbarum and Astragalus, are widely used to improve patients' liver function, reduce fat accumulation and improve insulin resistance. The mechanism of traditional Chinese medicine in the treatment of NAFLD has been shown to involve mainly the modulatory effects of its pleiotropic constituents on several pathologic aspects [11]. Poria cocos is widely utilized in herbal medicine for its diuretic, spleen strengthening and tranquilizing effects. Modern studies have shown that the polysaccharide and triterpenoid components in Poria have a number of bioactive effects such as antiarthritic, lipid-lowering, anti-oxidation and so on [12]. By promoting urinary excretion, Poria can help remove excessive water and metabolic waste from the body and reduce the burden on the liver. In addition, Poria can regulate lipid metabolism and reduce blood lipid level, which has significant effect on the treatment of MAFLD [13]. Hawthorn are extensively used in TCM because of their efficacy in eliminating foodstuffs and stagnation, activating bleeding and dissipating bruises. Its main active ingredients include flavonoids and organic acid compounds, which can inhibit lipogenesis and promote the oxidative decomposition of fat, thus reducing the accumulation of liver fat [14]. Studies have shown that

hawthorn can promote lipid metabolism via modulation of the AMPK signaling pathway, which has a certain scientific basis and clinical application experience [15]. Lycium barbarum was found to be wealthy in a variety of anti-oxidation components, such as polysaccharides, flavenoids, and carotenoids. It has the effect of protecting liver cells, antioxidant, and regulating lipid metabolism. Lycium barbarum can reduce the damage of oxidative stress on hepatocytes, improve insulin resistance, promote the metabolism of liver lipids, and have a positive impact on the restoration of liver function in patients with MAFLD [16]. Astragalus is regarded as a commonly used drug for qi tonic in traditional Chinese medicine, and it has a variety of functions including immune enhancement, anti-oxidant, anti- inflammation, and regulating blood glucose. Recent researches have suggested that Astragalus can minimize hepatic fat accumulation and improve hepatic function by regulating lipid metabolism and anti-oxidative stress [17]. The main active components in Astragalus, such as astragaloside and astragalus polysaccharide, can inhibit lipid peroxidation and protect hepatocytes from damage [18]. In addition, the therapeutic effects of TCM exhibit significant individualization across cultural backgrounds and individual differences. TCM emphasizes evidence-based treatment and develops individualized treatment plans based on patients' specific symptoms, constitution and etiology. For NAFLD patients with liver-depressing and spleen-deficient types, TCM practitioners may use combinations of drugs to ease the liver and strengthen the spleen [19]; while for NAFLD patients with damp-heat internalization types, they may be treated with drugs to clear heat and relieve dampness [20]. This individualized treatment approach can more precisely target the pathological changes and improve the therapeutic effect. This concept of individualized treatment gives TCM a unique advantage in the treatment of complex chronic diseases, such as MAFLD. Traditional Chinese medicine has demonstrated unique advantages and broad application prospects in the treatment of MAFLD. With the deepening of modern medical research, the pharmacological effects and molecular mechanisms of Chinese medicines have been gradually revealed, providing a scientific basis for the clinical application of Chinese

medicines.

Chinese medicine shows great potential in therapy of MAFLD. Characterized by its multi- ingredient a multitarget action, TCM is compatible with the sophisticated pathological mechanism of MAFLD and can intervene in the disease progression from multiple perspectives. Systematic evaluation and META analysis is an important part of modern evidence-based medicine, which can provide more comprehensive and objective evidence by integrating and analyzing the results of multiple studies, helping doctors and patients make more reasonable treatment choices. In the field of TCM treatment for MAFLD, systematic evaluation and META assays can reveal efficacy of different TCM based treatments and safety, and provide a scientific basis for clinical practice.

The aim of this research is to thoroughly assess the efficacy and security of TCM in the therapy of MAFLD through the methods of systematic evaluation and META analysis. Through in-depth analysis of the existing literature, we hope to provide clearer guidance for applying TCM in the therapy of MAFLD, as well as serve as a guide for future lines of inquiry. The significance of this study is not only to promote the scientific research of TCM in the treatment of MAFLD, but also to improve the patient's lifestyle and reduce the medical burden of the society by providing a more effective and safer treatment program.

1 INFORMATION AND METHODS

1.1 Study type and study population

Randomized controlled trials were included. The text type was limited to Chinese and English. The included patients are patients with renal disease combined with endocrine disorders and the total number of patients is not less than 20 cases, and the patients are treated with different traditional Chinese medicines, and the patients' races and nationalities are not limited.

1.2 Database selection

Several academic databases were searched, including sci-hub, Web of Science,

PubMed, EMBASE, China Knowledge Network (CNKI) and Wanfang database in Chinese and English. These databases cover a wide range of literature resources in medicine, biomedicine and related fields.

1.3 Keyword selection

Select a set of keywords associated with the treatment of metabolic fatty liver disease by TCM, including terms related to TCM, such as "traditional Chinese medicine", "proprietary Chinese medicine", "traditional Chinese medicine", etc.; terms related to metabolic fatigue, such as "non-alcoholic fatty liver disease", "metabolic fatty liver disease", etc.; and terms related to efficacy evaluation, such as "efficacy", "efficiency", as well as liver function indexes (ALT, AST, TG, TC, LC, Lipids), regulation of blood lipid levels (TG, TC, LC, LD, LD, LD), and other keywords related to the treatment of metabolic fatigue. Words related to efficacy evaluation, such as "efficacy", as well as indicators of liver function (ALT, AST), regulation of blood lipid levels (TG, TC, LDL-C, HDL-C), etc. We have also used synonyms and synonyms for the terms "metabolic fatty liver disease" and "metabolic fatty liver disease". We also used synonyms and related terms to extend the scope of the keywords and ensure coverage of relevant literature. Appropriate logical operators (e.g., AND, OR) were used to combine keywords and terms to construct the search strategy.

1.4 Inclusion and exclusion criteria

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Criteria for inclusion

(1) Research type: only randomized controlled trials (RCTs) were included because RCTs are considered the gold standard for evaluating treatment effects, which can minimize bias and improve the reliability of study results.

(2) Study population: all patients diagnosed with metabolism-associated fatty liver disease (MAFLD), including non-alcoholic fatty liver disease (NAFLD) and other metabolism-related fatty liver disease types. The age, gender, and duration of disease of the study population were not limited to increase the generalizability of the

findings.

(3) Interventions: the intervention group received Chinese herbal medicine treatment, either a single Chinese medicine or a Chinese medicine compound, and were included. The control group, on the other hand, received conventional treatment, placebo or other medications to compare the unique efficacy of Chinese medicine.

(4) Outcome indicators: The outcome indicators include changes in liver function indicators , clinical efficacy, and lipid levels.

(5) Language of study: To ensure the comprehensiveness of the information, both Chinese and English literature were included, and relevant studies were accessed by retrieval of multiple kinds of data bases, such as PubMed, CNKI, and Embase.

Elimination standards

(1) Non randomized and controlled trials: these include observe research, patient case reports, review articles and so on. Because these types of studies usually present a relatively high level of risk of skewing, which may affect the outcome of META analyses.

(2) Incomplete data: studies were excluded if they failed to provide detailed treatment regimens, outcome indicators, or had incomplete data for valid META analysis.

(3) Repeatedly published studies: If data from the same study were repeatedly published in different literatures, only the most complete or latest version was included to avoid the impact of data duplication on the analysis results.

(4) Unclear interventions: if the specific components of the herbal medicine or the treatment protocol were not clearly described in the literature, making it difficult to conduct an accurate effect assessment, the study would be excluded.

(5) Studies with too small a sample size: Considering that too small a sample size may lead to insufficient statistical efficacy to provide reliable effect estimates, studies with a sample size of less than 20 cases were excluded.

(6) Studies with low quality: studies with unreasonable study design, unreliable methodology or obvious bias were excluded.

1.5 Literature search strategy

Computerized searches were conducted on Chinese and English websites such as CBM, Wanfang Medical Network, China Knowledge Network (CNKI), PubMed, Embase, etc., and the deadline was set to June 2024. Searching for the implementation of herbal treatments for the patients with metabolically related fatty liver disease in randomized controlled trials, two fellows performed document filtering as well as data extractions based on the enrollment standards.

Relevant studies at home and abroad on the effects of different herbal treatments in patients with metabolism-related steatohepatopathy were collected, and initial filtering was carried out by means of reviewing the summary to remove duplicates and non-compliant literature, after which literature extracted and assessed the qualitative evaluation of the included literature, and the clinical efficiency, ALT, AST, TG, TC, LDL-C, HDL-C were analyzed according to the literature inclusion. Statistical analysis was performed, and meta-analysis was performed by applying RevMan5.3 software.

1.6 Methodological quality appraisal of screening of document and incorporation into the study

Documentation and data were separately sieved by two fellows based on entry and elimination criteria, and the data collected were double-checked. Data with different opinions or controversies were discussed by discussion or by a third neurosurgeon and internist. Methods: (1) general data on the study population, including authors, publication date, type of study, sample size, and treatment; (2) Outcome measures, including clinical efficiency, liver function indexes, and lipid indexes. A randomized controlled study was evaluated using the modified Jadad score; this project proposed to evaluate the selected nonrandomized bias risk assessment method by nonrandomization skewness evaluation method (NOS) to evaluate the quality of selected non-randomized controlled trials. The MINORS scale was applied to evaluate the enrolled cases.

1.7 Statistical processing

The RevMan 5.3 software of the Cochrane collaborative network was utilized for Meta-analysis. Secondary variables were analyzed using the ratio of ratios (OR), and continuous variables were analyzed for complication rates using WMD or SWD, both of which were expressed as 95% confidence intervals. Statistical heterogeneity was compared between the two samples, using a fixed-effects model for good homogeneity (P≥0.1,I2≤50%), and when there was heterogeneity in the included study population (P<0.1 and I_2>50%), we will use a random-effects model.

2 RESULTS

2.1 Literature results and general characteristics

A total of 280 papers were found in the preliminary literature search. Among them, 51 articles in Google, 41 articles in sci-hub, 182 articles in Zhi.com, 48 articles in Wanfang, and 46 articles in Wikipedia. This project intends to utilize EndnoteX9 software to eliminate 188 duplicate published articles. Based on reading the remaining 177 articles, 138 case reports, reviews, commentaries, Meta-analyses, etc. were eliminated according to the inclusion criteria, and the titles and abstracts of the remaining 39 articles were read to preliminarily screen 19 suitable documents, and then the screened 19 articles were re-screened to include the following two articles on different topics from the same research unit were excluded and compared with duplicate cases from other research organizations and their relevance to the rest of the literature. Finally, 15 articles were included in the Meta-analysis [21-35]. In Figure 1 the literature screening process is shown.

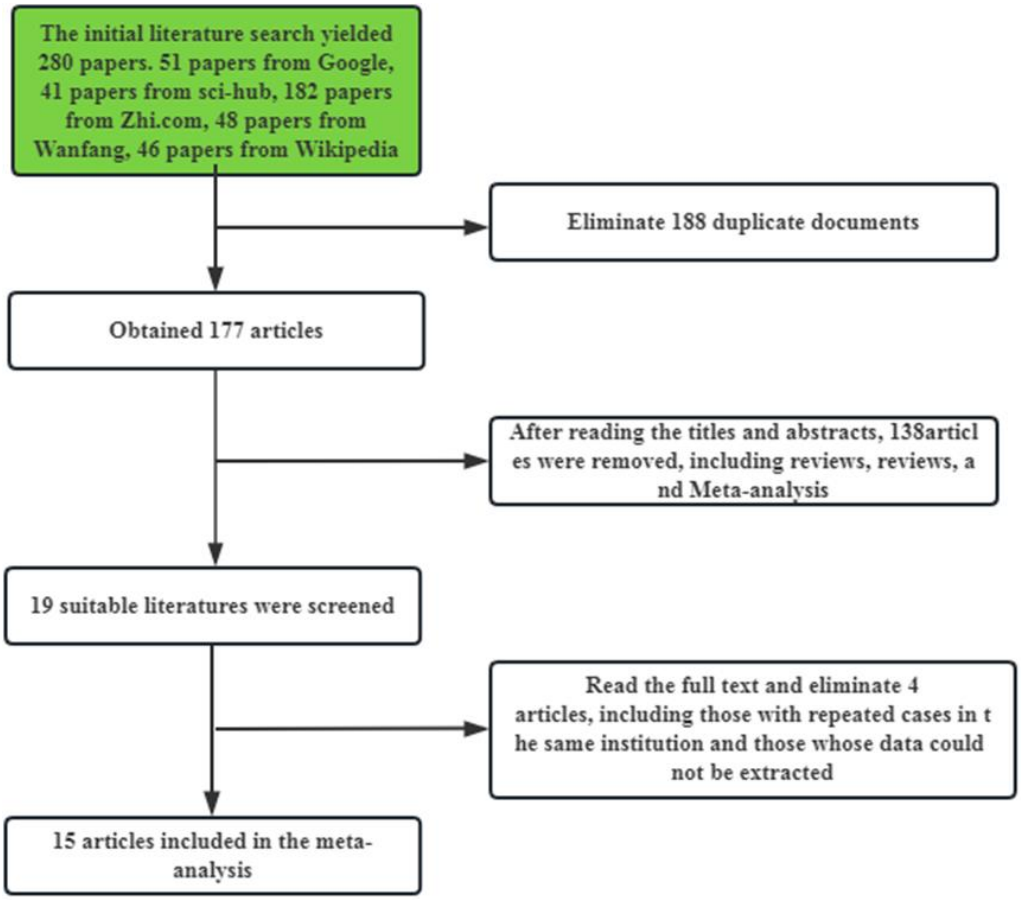

Figure 1 Graph of the literature selection procedure

Fifteen papers including 1282 patients that met the criteria included in this Meta-analysis. No apparent changes were seen in the general profile between the 2 teams within each study. The basic features of the incorporated papers are shown in Table 1.

Table 1 Essential features of the content studies

Incorporation of literature	particular year	Study Type	Grouping（Chinese medicine group/control group，M/C）	Number of patients（M/C）	Chinese Medicine Prescription	outcome indicator
Xie, Weining [21]	2021	Randomized Controlled Trials	M/C	40/40	Chai Hu Liver Relief Essence	①②③
Wang Qian[22]	2023	Randomized controlled trial	M/C	45/45	Wang Jujube and Lotus Leaf Lipid Regulation	②③

					Soup	
Yao Chunmiao[23]	2023	Randomized controlled trial	M/C	60/60	San Ren Tang Combined with Yin Chen Wu Ling San	②③
Yang Fan[24]	2023	Randomized controlled trial	M/C	50/50	Bile Reducing and Yellowing Relief Tang	①②③
Lei Fay [25]	2022	Randomized controlled trial	M/C	35/35	Xiao Chai Hu Tang	①②
Zhao Xiaochao[26]	2022	Randomized controlled trial	M/C	41/41	Liver-Sparing and Lipid-Regulating Soup	①③
Luo Huabing[27]	2022	Randomized controlled trial	M/C	50/50	Ling Gui Zhu Gan Tang	①②③
Liu Yantong[28]	2022	Randomized controlled trial	M/C	28/28	Lotus Leaf Lipid Regulation and Liver Relief Soup	②③
Shi Huilian[29]	2022	Randomized controlled trial	M/C	33/33	San Huang Diarrhea Heart Soup	①③
Shen Yuehua[30]	2023	Randomized controlled trial	M/C	58/58	Lipid-Lowering and Liver-Protecting Soup	①②③
Li Hailing[31]	2022	Randomized controlled trial	M/C	55/55	Lung and Liver Clearing Soup	①②③
Wen Huiling[32]	2022	Randomized controlled trial	M/C	42/42	Ling Gui Zhu Gan Tang	①②③

Gao Wenyuan[33]	2021	Randomized controlled trial	M/C	40/40	Self-designed Liver, Liver and Spleen Enhancement Soup	①②③
Wang Xiaowen[34]	2017	Randomized controlled trial	M/C	34/34	Self-designed Liver Preserving and Lipid Regulating Soup	①②③
Deng Zhaowen[35]	2013	Randomized controlled trial	M/C	30/30	Liver Strengthening Triple Clearing Soup	①②③

Note: ① Clinical efficiency; ② Liver Function Indicators; ③ Lipid Indicators.

A Cochrane risk of bias assessment was performed on the entire included literature, and the results are shown in Figure 2.All studies did not use references to investigator and subject blinding, outcome evaluator blinding, and other sources of bias.

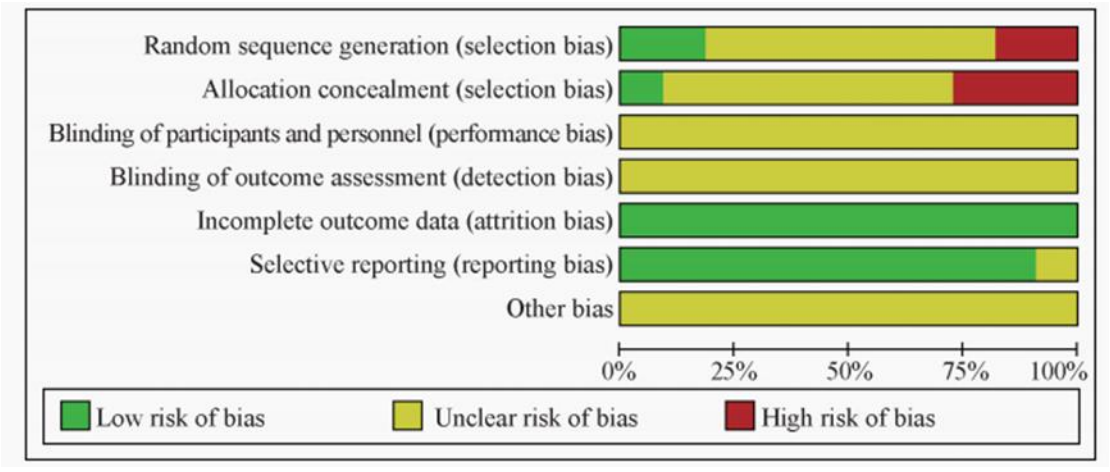

Figure 2 Risk of bias of included literature

2.2 Meta-analysis results

2.2.1 Clinical efficiency

Twelve studies reported [21,24-27.29-35] clinical efficacy rates in 1016 patients with metabolism-related fatty liver disease. By comparing findings with Meta-analysis, the total clinical effectiveness rate was remarkably improved in the TCM group in comparison with the controlled ones (OR=4.12, 95% CI [2.63,6.38], p<0. 001). See Figure 3.

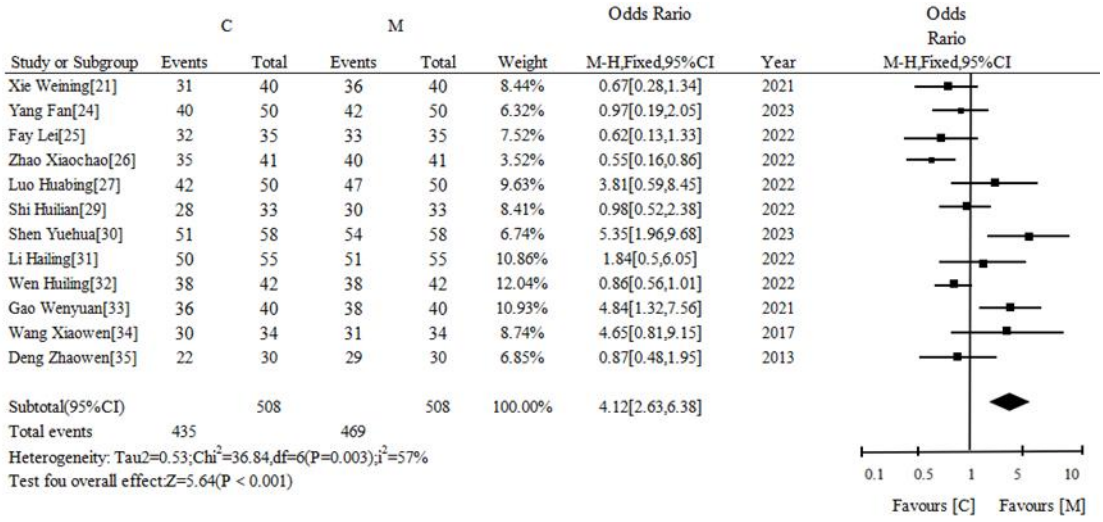

Figure 3 Forest plot of clinical effectiveness

2.2.2 Liver function indices

Thirteen studies [21-25,27,28,30-35] reported hepatic function indices in 1104 patients with metabolism-related fatty liver disorders. Meta-analysis of the findings revealed that liver function indices improved considerably in the TCM group in comparison with the controlled ones (OR=3.84, 95% CI [0.93,5.42], P<0. 001). See Figure 4.

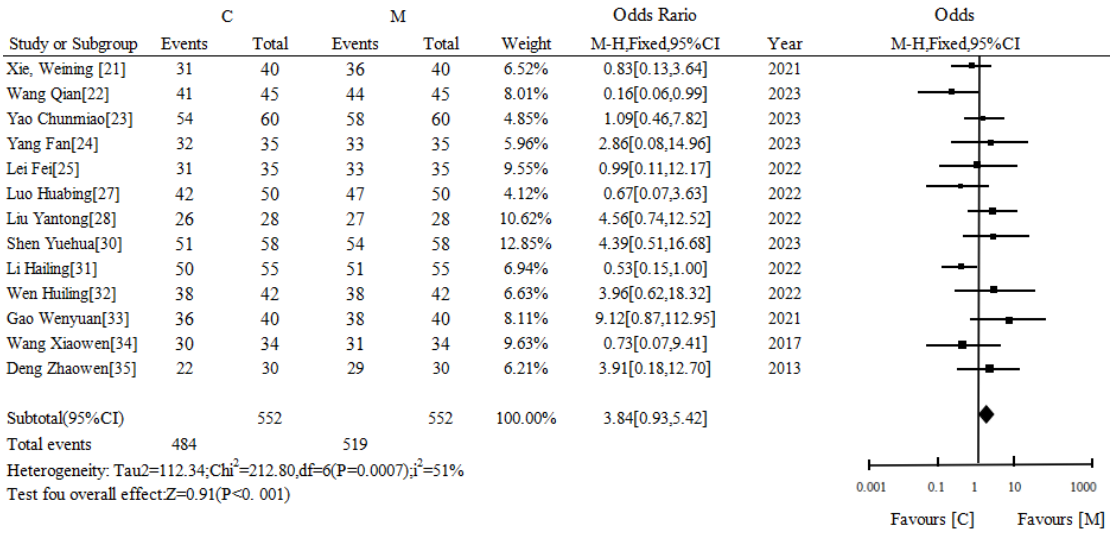

Figure 4 Forest plot of liver function

2.2.3 Lipid indices

Fourteen studies reported [21-24,26-35] lipid indices in 1182 patients with metabolism-related fatty liver disease. Meta-analysis of the findings indicated that lipid indices were markedly ameliorated in the TCM group in comparison with the controlled ones (OR=3.52, 95%CI [2.18,,6.15], p<0. 001). See Figure 5.

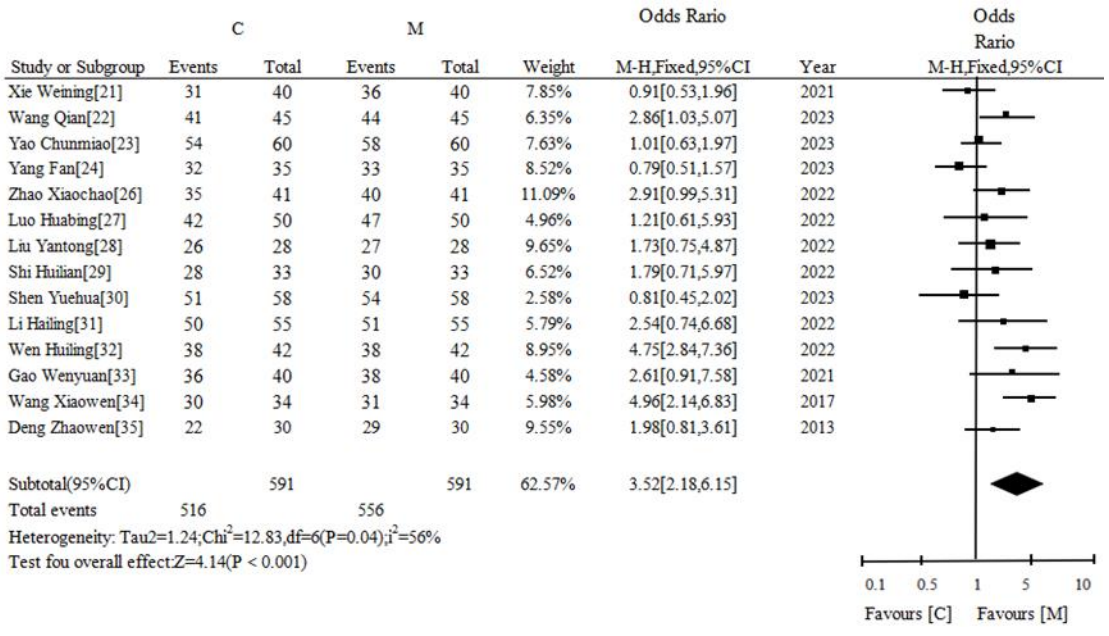

Figure 5 Forest plot of lipid indicators

2.3 Publication bias analysis

We analyzed the meta-analysis of the outcomes and used the "funnel plot" to make a preliminary evaluation of publication bias. We found that the data from the clinical effectiveness meta-analysis showed a roughly symmetrical "funnel" distribution, and were mainly distributed in the middle region, so it can be considered that there is no publication bias. See Figure 6.

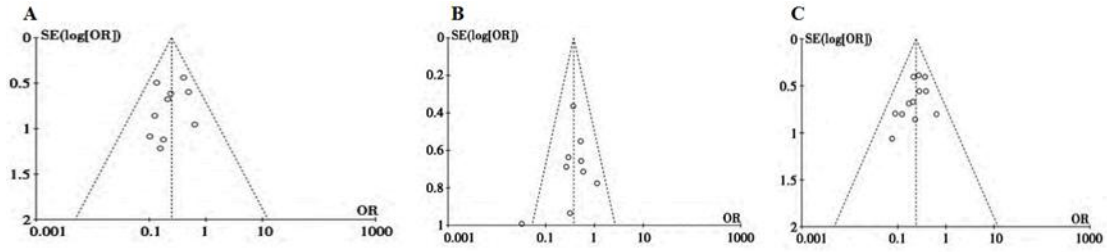

Figure 6 Publication bias analysis (A: clinical effectiveness rate; B: liver function; C: lipid index)

3 DISCUSSION

Metabolism-associated steatohepatopathy is a liver disease caused by metabolic disorders characterized by accumulation of liver fat accompanied by hepatic inflammation and fibrosis. Studies have shown that the pathogenesis of MAFLD is complex and involves a variety of factors, such as insulin resistance, lipid metabolism disorders, intestinal flora dysregulation and genetic factors [36]. Therefore, effective therapeutic strategies for MAFLD are crucial. TCM is an essential tool for the management of MAFLD. Over recent years, increasing attention has been paid to the effect of Chinese medicines in the treatment of MAFLD. It has been found that Chinese medicines modulate the pathogenesis of MAFLD through a multi-target and multi-pathway approach. Commonly used Chinese medicines include Salvia miltiorrhiza, Astragalus membranaceus, Schisandra chinensis, and Ganoderma lucidum, which exhibit a wide range of medicinal effects, including those of anti-inflammatory, antioxidant, lipid-lowering, as well as hepatoprotective properties [37]. Herbal medicines have demonstrated significant efficacy in improving liver

function, attenuating hepatic fibrosis, and regulating lipid metabolism.META is a method of performing statistical methods used to allow for quantification and synthesis of findings from a variety of individual researches in order to improve result reliability with statistical significance. In the current study, META analysis served to integrate the clinic trial data of TCM for MAFLD and to assess the effects of TCM on liver function, liver fat content, liver fibrosis and metabolic indexes.The main steps of META analysis included the calculation of effect sizes, the test of heterogeneity and the analysis of publication bias. The META analysis can provide comprehensive proofs for the herbal medicine in treating MAFLD and offers a solid scientific basis for clinical practice.

Data from a wide range of studies have been synthesized in the findings of the present investigation to provide insight and analysis of the role of herbal medicines in the treatment of metabolism-related steatohepatopathies. For the herbal formulas involved in this study, Chai Hu Shuo Liver San improves the symptoms of liver depletion and spleen deficiency, and may play a role by enhancing immunomodulation [21]. Wang jujube and lotus leaf lipid-regulating soup regulates blood lipids and may improve liver metabolic function through a combination of multiple pathways [22]. San Ren Tang combined with Yin Chen Wu Ling San reduces blood lipids and improves liver function; it integrates the regulation of blood lipids and anti-inflammatory and antioxidant mechanisms [23]. The treatment of non-alcoholic fatty liver disease with choleretic and antioxidant soup may improve liver function through choleretic effect [24]. Xiao Chaihu Tang improved liver function and insulin resistance in patients [25]. Liver-sparing and lipid-regulating soup regulates the levels of inflammatory factors and leptin to obtain lipid-lowering and liver-protecting effects [26]. Ling Gui Zhu Gan Tang reduces the level of oxidative stress and lipid metabolism in patients with spleen deficiency and phlegm stasis [32]. Lotus Leaf Lipid Regulation and Liver Sharing Soup reduces lipid metabolism abnormalities observed in nontoxic fatty liver condition cases [28]. Sanhuang Laxing Tang treats non-alcoholic fatty liver disorder with moist-heat

syndrome [29]. Lipid-lowering and liver-protecting soup improves inflammation in fatty liver and may improve glucose-lipid metabolism and serum adipokines through multiple mechanisms [30]. Lung-cleansing and liver-dispelling soup for the treatment of type 2 mellitus associated with nontoxic fatty liver condition impacts the intestinal flora and related factors [31]. Jian Liver San Qing Tang regulates lipid metabolism, anti-inflammatory and antiviral effects [35].

According to findings of META organization, the traditional medicine treatment team was remarkably more effective than the controlled team in clinical efficacy. Specifically, the general effectiveness rate of clinical efficacy was remarkably elevated in the herbal treatment team, with a ratio (OR) of 4.12, a 95% confidence interval (CI) of [2.63, 6.38], and a p-value of less than 0.001, which demonstrated that the herbal treatment had a high degree of clinical relevance and practical value. The clinical efficacy of TCM in treating MAFLD may be related to its multi-component and multi-target mechanism of action. By harmonizing the balance of yin and yang in the human body, TCM regulates metabolism and promotes hepatic detoxification and repair, thereby improving clinical symptoms and signs [34]. For example, TCM may act through anti-inflammatory, antioxidant, and liver cell regeneration pathways [38]. The literature included in this study covers a variety of herbal formulas, such as Chai Hu Shuo Liver Essence and Wang Zao Lotus Leaf Lipid Regulating Tang, which have shown better clinical efficacy in different studies. This suggests that TCM has wide application potential and flexibility in the treatment of MAFLD, and can be personalized according to the specific conditions of different patients. Many of the components in these herbal formulas have multiple functions such as antioxidant, anti-inflammatory, and immune regulation, which can comprehensively improve liver metabolic function [32]. For example, Chaihu Shuohe San works by regulating immune and anti-inflammatory processes [21]. The synergistic effect between the components in a compound formula may enhance the therapeutic effect. This makes these formulas in the treatment of metabolism-related fatty liver disease, with unique advantages. In addition, modern medical research suggests that these formulas may

play an integrated therapeutic role by integrating multiple pathways, such as regulating blood lipids, antiviral, and improving liver function, and thus achieve better clinical efficacy [39].

In addition, we observed that traditional Chinese medicine performed significantly in improving liver function indicators of patients. In this study, we showed that the herbal medicine treatment group showed significant improvement in the changes of liver function markers such as ALT and AST compare favorably with the controlled team, which indicates that the herbal medicine can reduce the degree of damage to the hepatocytes effectively, and help to recover the liver function. Furthermore, the META analysis revealed that the TC, TG and LDL-C indexes of the patients in the traditional Chinese medicine treatment group were decreased dramatically, while their HDL-C levels were enhanced. These changes suggest that TCM could have latent advantages in regulating lipid metabolism and preventing atherosclerosis and related cardiovascular diseases [40]. Analyzing the reasons for this Chinese herbal formulas usually contain a variety of herbs, each of which contains a variety of chemical components, which act synergistically through a variety of pathways to comprehensively regulate liver function [36,38]. For example, the active ingredients in Chinese herbal formulas are able to comprehensively protect the liver and promote liver function recovery through a variety of mechanisms, including antioxidant, anti-inflammatory, and immunomodulatory mechanisms [25,26]. For example, herbs such as Scutellaria baicalensis, Gardenia jasminoides, and Inulae vulgaris are commonly used for clearing heat and removing toxins, and have significant anti-inflammatory effects. Baicalin and baicalein in Scutellaria baicalensis can reduce the release of inflammatory factors by inhibiting the nuclear factor-κB (NF-κB) signaling pathway, thus reducing the inflammatory response [41]; and geniposide in Gardenia jasminoides is able to reduce the oxidative damage of hepatocytes by inhibiting oxidative stress [42]. Yin Chen in San Ren Tang combined with Yin Chen Wu Ling San is a common heat-clearing and dampness-relieving drug with significant anti-inflammatory effects. Studies have shown that the main active

ingredient in echinocandins can inhibit the expression of a broad range of institutional elements, such as TNF-α and IL-6, thereby reducing the inflammatory response in the liver and protecting hepatocytes [23]. The liver is an important metabolic organ in the human body, and many herbal components can promote the metabolism of hepatocytes, help hepatocytes eliminate metabolites and toxins, and reduce the load on hepatocytes, which in turn can help the recovery of liver function [12]. In addition, some components in traditional Chinese medicine can promote the removal of intracellular wastes by activating the autophagy of hepatocytes and maintain the normal function of the cells. For example, tanshinone in Salvia miltiorrhiza can activate autophagy-related signaling pathways, promote the formation of autophagosomes in hepatocytes, and help remove intracellular metabolic wastes and damaged organelles, thus reducing the burden on hepatocytes and promoting the recovery of liver function [37]. In addition, lipid metabolism disorder is an important etiology of fatty liver disease [12]. Traditional Chinese medicine has shown a role in regulating lipid metabolism, which can improve fat deposition in the liver and reduce the load on hepatocytes through multiple pathways. For example, the lotus leaf in Wang Zao Lotus Leaf Lipotropic Soup has a lipid-lowering effect, which can regulate lipid metabolism and reduce fat deposition in the liver. The components of lotus leaf, such as lotus alkaloids and lotus flavonoids, are able to reduce blood lipid levels and reduce the fat burden of the liver by inhibiting fat synthesis and promoting fat decomposition [22]. The stability and integrity of hepatocyte membranes are crucial for the normal functioning of the liver. Some herbal ingredients can protect liver function by enhancing the stability of hepatocyte membranes and reducing hepatocyte damage. For example, Astragalus in Self-designed Yiqi Shuo Liver and Spleen Strengthening Tang has the effect of protecting liver cell membranes, and Astragaloside and Astragalosan in Astragalus are able to protect hepatocytes by enhancing the stability of the cell membranes and reducing the damage of free radicals to the cell membranes [33]. Chaihu in Chaihu Shuanhe San is also a common liver-protecting herb, and the chaihu saponin in chaihu has the effect of promoting

hepatocyte repair and regeneration, which can reduce oxidative damage to hepatocytes by enhancing the antioxidant capacity of hepatocytes, thus improving the survival rate of hepatocytes. In addition, Chaihu is able to further protect hepatocytes by regulating immune function and reducing inflammatory responses in the liver [21].

The interpretation of these results can be attributed to the multi-target, multi-pathway mechanism of action of Chinese medicines. Many Chinese medicines, such as Salvia miltiorrhiza, Astragalus membranaceus, and Pueraria lobata, have multiple pharmacological effects, such as antioxidant, anti-inflammatory, and immune-regulating effects, which together can effectively improve liver metabolic function, reduce lipid peroxidation, protect hepatocytes, and ultimately achieve the effect of treating MAFLD. For example, Salvia miltiorrhiza reduces hepatocellular damage by inhibiting lipid peroxidation and inflammatory reactions; Astragalus has enhanced immune function and anti-inflammatory effects, which help improve liver function; and Pueraria lobata protects the liver by lowering blood lipids and improving insulin resistance. In addition, the use of herbal compounding has shown unique advantages. The synergistic effect between the components in a compound formula can enhance the efficacy and minimize adverse reactions. For example, "Dan Huang Tang" significantly improves clinical symptoms and laboratory indexes of MAFLD patients by integrating lipid regulation, anti-inflammatory and antioxidant pathways.

In the course of this systematic evaluation and META analysis, although we found that Chinese herbal medicine demonstrated some efficacy in the treatment of metabolism-associated fatty liver disease (MAFLD), there are still some limitations that need to be noted. First, the quality and number of included studies were limited. Although we selected high-quality studies through a rigorous literature search and screening strategy, the number of included studies was insufficient to fully represent the efficacy of all Chinese herbal medicines in treating MAFLD, due to the relatively small number of Chinese herbal medicine studies reported in the international arena. This may affect the breadth and representativeness of our results. Second, the

heterogeneity among studies was high. Due to the diversity of TCM treatment regimens, there were significant differences in the types of TCM, dosage, and treatment duration used in different studies, which led to a high degree of heterogeneity in the study results. Although we used appropriate methods to deal with the heterogeneity in our statistical analyses, we could not completely eliminate this effect. This heterogeneity may make the results of our META analysis somewhat biased. In addition, some of the included studies had a short follow-up time.MAFLD is a chronic disease, and its treatment effect usually takes a long time to show. However, the short follow-up time of some of the studies did not allow us to adequately assess the long-term efficacy of TCM. This limits our comprehensive understanding of the effects of herbal medicines in the long-term treatment of MAFLD. Furthermore, there is a possibility of publication bias. Although we searched the literature through multiple ways and tried our best to include all eligible studies, unpublished studies with negative outcomes may not have been included. Publication bias may have led us to overestimate the therapeutic effects of TCM. In addition, since most of the included studies were from China, there may be cultural and geographical bias, which further affected the generalizability of the results. There was also some subjectivity in the data extraction and quality assessment process. Although we used strict criteria and a two-person independent data extraction method, in practice, it was inevitably influenced by the subjective judgment of the researchers. This subjectivity may have some impact on the results. Finally, our META analysis was limited to the available open literature and we were unable to obtain more raw data for more detailed analysis. Some potential confounding factors, such as patients' lifestyles, dietary habits, and other comorbidities, could not be adequately considered in the analysis. These factors may affect the assessment of the therapeutic effect of herbal medicine. In conclusion, although our study provides preliminary evidence for the treatment of MAFLD with Chinese herbal medicine, further randomized controlled trials (RCTs) with more high-quality, large samples and long-term follow-up are needed to validate our findings. Meanwhile, in future studies,

inter-study heterogeneity should be minimized, follow-up time should be increased, the long-term efficacy of TCM should be comprehensively assessed, and potential confounders should be fully considered in order to provide more reliable and comprehensive evidence to support the use of TCM in the treatment of MAFLD.

In summary, the present study provided strong evidence for the treatment of MAFLD with traditional Chinese medicine through systematic evaluation and META analysis, revealing the potential mechanisms of traditional Chinese medicine in improving liver function, regulating blood lipids, and attenuating fatty liver lesions. This provides a reference for clinical practice and points out the direction for future related research.

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Corresponding Author:

Ce Zheng

Department of Infectious Diseases，Hangzhou TCM Hospital Affiliated to Zhejiang Chinese Medical University，310005，China

E-mail: zczhengce@163.com