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Integrated Study Master's Final Thesis

Evidence-Based Herbal Treatment in Liver Disease

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Abbreviation

ALD – Alcoholic Liver Disease

ALP – Alkaline Phosphatase

ALT – Alanine Aminotransferase

APRI – AST to Platelet Ratio Index

ASCVD – Atherosclerotic Cardiovascular Disease

AST – Aspartate Aminotransferase

BMI – Body Mass Index

CAP – Controlled Attenuation Parameter

CC14 – Carbon Tetrachloride

CHB – Chronic Hepatitis B

CHC – Chronic Hepatitis C

CLD – Chronic Liver Disease

COX-2 – Cyclooxygenase-2

CRP – C-reactive Protein Test

DNA – Deoxyribonucleic Acid

ERK – Extracellular Signal-Regulated Kinases

FBS – Fasting Blood Sugar

FDA – U.S. Food and Drug Administration

FIB-4 – Fibrosis-4 Index

GGT – Gamma-Glutamyl Transferase

GSHPx– Glutathione peroxidase

HbA1c – Haemoglobin A1c Test

HBeAg – Hepatitis B e-antigen

HBsAg – Hepatitis B Surface Antigen

HBV – Hepatitis B Virus

HCV – Hepatitis C Virus

HDL – High-Density Lipoprotein

HOMA-IR – Homeostatic Model Assessment of Insulin Resistance

hs-CRP – High-Sensitivity C-Reactive Protein

IFN-α1b – Interferon Alpha-1b

LDL – Low-Density Lipoprotein

MASLD – Metabolic Dysfunction-Associated Steatotic Liver Disease

MDA – Serum Malondialdehyde

MELD – Model for End-Stage Liver Disease

MetS – Metabolic Syndrome

NAFLD – Non-alcoholic fatty liver disease

NAS – NAFLD Activity Score

NASH – Non-Alcoholic Steatohepatitis

NF-κB – Nuclear Factor Kappa Light Chain Enhancer of Activated B Cells

ox-LDL – Oxidized Low-Density Lipoprotein

PROSPERO – International Prospective Register of Systematic Reviews

RCT – Randomized Controlled Trial

RNA – Ribonucleic Acid

SNMC – Stronger Neo-Minophagen C

TAA – Thioacetamide

TAC – Total Antioxidant Capacity

TCA – Tricarboxylic Acid cycle

TNF-α – Tumour Necrosis Factor-Alpha

T2DM – Type 2 Diabetes Mellitus

WMD – Weighted Mean Difference

Abstract

This thesis aims to critically examine the evidence supporting herbal treatments for liver diseases, with particular attention to their mechanisms of action, efficacy, and safety. While herbal medicine has been used since ancient times for disease prevention and treatment, there has been a recent increase in scientific interest in incorporating medicinal plants into contemporary therapeutic methods. (1) Researchers are increasingly drawing on traditional herbal knowledge to understand the mechanisms behind the therapeutic effects of various plants, especially in managing liver disease. (1) Much of this renewed interest comes from studies showing that many plant-derived compounds have anti-inflammatory, antioxidant, and anti-apoptotic effects. (1) This thesis is a literature review examining current research on the clinical use of medicinal plants in liver disease. The review will examine major liver conditions and evaluate the evidence for specific herbal treatments, giving a thorough narrative review of their roles and therapeutic potential.

Šiuo baigiamuoju darbu siekiama kritiškai išnagrinėti įrodymus, pagrindžiančius augalinių gydymo metodų taikymą kepenų ligoms gydyti, ypatingą dėmesį skiriant jų veikimo mechanizmams, veiksmingumui ir saugumui. Nors augalinė medicina ligų prevencijai ir gydymui naudojama nuo seniausių laikų, pastaruoju metu didėja mokslinis susidomėjimas vaistinių augalų įtraukimu į šiuolaikinius terapinius metodus. (1) Tyrėjai vis dažniau remiasi tradicinėmis žiniomis apie vaistažoles, siekdami suprasti įvairių augalų terapinio poveikio mechanizmus, ypač kepenų ligų gydymo kontekste. (1) Didelė dalis šio atsinaujinusio susidomėjimo kyla iš tyrimų, rodančių, kad daugelis augalinės kilmės junginių pasižymi priešuždegiminiu, antioksidaciniu ir antiapoptoziniu poveikiu. (1) Šis baigiamasis darbas yra literatūros apžvalga, kurioje nagrinėjami dabartiniai moksliniai tyrimai apie vaistinių augalų klinikinį taikymą sergant kepenų ligomis. Apžvalgoje bus aptariamos pagrindinės kepenų ligos ir vertinami įrodymai apie konkrečius augalinius gydymo būdus, pateikiant išsamią naratyvinę jų vaidmens ir terapinio potencialo apžvalgą.

Key Words

Herbal Treatment, Chronic Liver Diseases, Literature Review

1. Introduction

1.1. Thesis Structure

This master’s thesis will be a literature review on evidence-based herbal treatments for CLD. It will examine RCTs on herbs used to treat different types of CLD and evaluate the research conducted and the results reported in each article. First, (1.2), the thesis’s introduction will outline the basic knowledge on CLD necessary for conducting the literature review. It will highlight the historical use of herbs in treating medical conditions. Then, (1.3) will provide a brief overview of CLD, covering epidemiology, etiology, and clinical manifestations. After establishing the basic understanding of CLDs, it will analyse RCTs conducted to treat various liver conditions using: silymarin (2.1-3), curcumin (3.1-3), berberine (4.1-3), resveratrol (5.1-3), glycyrrhizin (6.1-3), Phyllanthus (7.1-3), green tea (8.1-3), artichoke (9.1-3), and ginger (10-3). Finally, the thesis will discuss its findings and present its recommendations (11.1). As mentioned above, this thesis will focus on RCTs, which provide evidence of the benefits of herbal treatment for liver conditions, and on meta-analyses, which assess a wide range of data from RCTs conducted on this topic. The exclusion criterion of this thesis is reviews, as they are less comprehensive than meta-analyses and survey a narrower database.

1.2 Background

The use of plants and herbs in medicine dates to the prehistoric period, when fossils from 60,000 years ago revealed that humans used plants as medicine. (2) Archaeological findings dating back 5,000 years show the use of plant-based medicine, as evidenced by a Sumerian slab containing 12 herbal medicine recipes. (3) In Western culture, evidence of herbal medicine appears in Homer's Iliad, written around 800 BCE, which mentions 63 plant species. (3) The classical world used herbal treatments, as documented by Greek physician Hippocrates (459-370 BCE), who recorded 300 medicinal plants. (3) The use and study of herbal medicine continued worldwide throughout the Middle Ages. (3) During the Early Modern Period, from the 16th to the 18th century, the demand for compound drugs grew as medical practitioners combined herbs with animal-based remedies. (3) In the 19th century, advances in chemical techniques resulted in the discovery of active substances in some medicinal plants. (3)

The development of synthetic techniques in the 19th century reduced the importance of natural products in the development of medical drugs, despite continued reliance on them in drug research. (2) During this period, active compounds were extracted from medicinal plants and used either alongside or in place of the whole plant. (3) This development led to the mass production of chemically synthesized drugs worldwide in the 20th century, transforming the medical system. (4) However, the long-lasting effects of alkaloid drugs were quickly recognized, triggering renewed interest in herbal-based medicine during this period. (3) Today, all pharmacopoeias worldwide include herbal medicines that have proven medical value. (3) These herbs are used to treat chronic and acute conditions, various ailments, and to boost the immune system. (4) The popularity of herbal medicine is increasing, especially in the treatment of CLD. (5)

1.3 Brief Overview of Chronic Liver Disease (CLD)

1.3.1 CLD Definition

CLD is defined as a sustained impairment of liver function lasting more than six months. (6) During which key hepatic processes, including the synthesis of clotting factors and essential proteins, detoxification of metabolic byproducts, and bile secretion, progressively deteriorate. (6) Ongoing liver injury and inflammation in CLD can eventually cause fibrosis, which, if not treated, may progress to cirrhosis. (6)

1.3.2 Epidemiology

The prevalence of CLD cases affects 1.5 billion people worldwide each year. (7) The most common diseases causing CLD are as follows: 59% MASLD (formerly NAFLD); 29% HBV; 9% HCV; and 2% ALD. (7) It is noteworthy that alcohol may cause more cases of CLD than are reported, as people and countries tend not to disclose alcohol-related cases because of cultural reasons. (7)

Therefore, to understand the various CLD presentations, it is necessary to review the major related diseases. MASLD is a group of metabolic disorders characterized by fat accumulation (steatosis) affecting over 5% of hepatocytes and is associated with metabolic risk factors without excessive alcohol consumption. (8) Its prevalence has increased over the past 40 years, now affecting around 25% of adults. (8) However, only about 10% of people with MASLD develop liver-related complications. (8) Despite this, MASLD continues to challenge medical practitioners in identifying patients at risk of complications. (8) A 2023 meta-analysis study concluded that, regionally, MASLD prevalence varies considerably. (9) Latin America recorded the highest rates (44.4%), followed by the Middle East and North Africa region (36.5%), South Asia (33.8%), South-East Asia (33.1%), North America (31.2%), East Asia (29.7%), Asia Pacific (28.0%), and Western Europe (25.1%). (9) These figures differ from those reported in an earlier meta-analysis, which covered only four regions and yielded notably different estimates: Africa (56.8%), North America (47.8%), Europe (32.6%), and Asia (31.6%). (9)

HBV is a double-stranded, hepatotropic DNA virus that can cause persistent and chronic infections through immune anergy. (10) This virus is primarily transmitted via blood and bodily fluids. (10) Currently, 3.5% of people worldwide are chronically infected with HBV. (10) HCV is a hepatotropic RNA virus that causes progressive liver damage and is mainly transmitted through blood. (11) Currently, 64 to 103 million people worldwide are infected with this virus. (11) ALD is an umbrella term identifying alcohol-related liver injuries. (12)

In conclusion, liver diseases cause about 2 million deaths worldwide each year, with roughly 1 million resulting from complications of cirrhosis, making it the 11th leading cause of death worldwide. (13) Additionally, another 1 million people die annually from complications related to viral hepatitis and hepatocellular carcinoma. (13) Liver cancer itself ranks as the 16th leading cause of death worldwide. (13) Moreover, alcohol use and obesity, which are

rising in some areas worldwide, contribute to the increasing prevalence of CLD in the global population because they are risk factors for liver-related diseases. (7)

1.3.3 Etiology

MASLD is linked to MetS, which includes obesity, hyperlipidemia, and diabetes mellitus. (6) Some patients progress to NASH, resulting in liver fibrosis. (6) Liver fibrosis is a healing response to liver injury caused by an insult. (14) If left untreated, it can progress to cirrhosis and may eventually lead to liver cancer or failure. (14) Cirrhosis results from prolonged liver inflammation, causing extensive hepatic fibrosis. (15) During this process, normal liver structure is replaced by regenerative nodules, which can ultimately lead to liver failure. (15)

HBV refers to a hepatic condition caused by infection with the hepatitis B virus. (16) It can be either acute, which is short and severe, or chronic, lasting a long time. (16) CHB may lead to serious health issues, such as a high risk of death from cirrhosis and liver cancer. (16) Luckily, HBV can be prevented with a safe and effective vaccine. (16) The vaccine is usually given soon after birth, with booster doses administered a few weeks later. (16) HCV infection can cause acute hepatitis C. (11) After the initial infection, it may progress to CHC infection, bringing about prolonged inflammation. (11) This ongoing inflammation can result in liver fibrosis, cirrhosis, hepatocellular carcinoma, and potentially death. (11) In many regions, HCV is the leading cause of liver transplants. (11)

1.3.4 Clinical Manifestation

CLD often presents with vague and nonspecific symptoms such as fatigue, loss of appetite, and unintentional weight loss. (6) However, these signs can also show underlying complications that the patient has developed. (6) These complications usually stem from portal hypertension, including oesophageal varices and ascites, as well as liver failure symptoms like jaundice, hepatic encephalopathy, and hepatocellular carcinoma. (6)

In some cases, simple hepatic steatosis can progress to NASH. (17) MASLD includes various liver conditions defined by fat buildup, primarily triacylglycerols. (17) Lifestyle changes are the main strategies for preventing and managing liver diseases. (1) For centuries, herbs have been used for the prevention and treatment of liver diseases because of their anti-apoptotic, anti-inflammatory, and antioxidant properties. (1)

MetS is recognized as a combined risk factor for ASCVD, including atherogenic dyslipidaemia, characterized by elevated triglycerides, increased apolipoprotein B-containing

lipoproteins, and decreased HDL cholesterol, along with high blood pressure, hyperglycaemia, and prothrombotic and proinflammatory states. (18) Metabolic disorder pathophysiology is mainly driven by insulin resistance, with high free fatty acid flux and a proinflammatory state also playing important roles. (19) Due to its strong link to type 2 diabetes and cardiovascular disease, high-risk individuals need targeted treatment. (19) First-line management focuses on lifestyle changes, particularly weight loss and enhanced physical activity, although medication may be necessary to lower the risk of diabetes and heart-related problems. (19)

2. Silymarin

2.1. Introduction

Silybum marianum (milk thistle) is among the oldest known herbal medicines, with documented use dating back to ancient times. (20) Among plants investigated for the treatment of liver disease, Silybum marianum has the most extensive body of research to date. (21) Silybin is the most biologically active component, and milk thistle extracts are usually standardized to contain 70-80% silybin. (20) Silymarin is a lipophilic extract derived from milk thistle seeds, consisting of three isomeric flavonolignans (silybin, silydianin, and silychristin) first isolated in 1968. (21) Silybin is the most biologically active component, making up 50-70% of silymarin. (21) While silymarin is found throughout the plant, it is most concentrated in the fruit and seeds, which also contain betaine (a recognized hepatoprotective agent) and essential fatty acids that may further enhance silymarin's anti-inflammatory properties. (20)

Image: Silymarin (purple flower) (22)

Milk thistle is a commercially significant medicinal crop in Europe, with Poland alone cultivating approximately 2,000 hectares for seed and medicine production, and its importance has been growing in North America. (21) The whole plant is used medicinally,

with young stems and sprouts also valued in traditional practice for liver and biliary tract conditions, and approximately 25-30% oil by weight is also present in the seeds. (21) Silymarin is recognized as a potent antioxidant with demonstrated capacities to promote liver cell regeneration, reduce blood cholesterol, and exert anticancer effects. (21) Overall, the strongest clinical evidence for silymarin is in MASLD, whereas evidence in ALD and viral hepatitis remains limited and inconclusive. More rigorous randomized trials are needed to clarify its effects across different liver diseases.

2.2. Studies on Silymarin Treatment for Liver Diseases

Several studies suggest that silymarin may be beneficial in some liver diseases. A study, conducted in Iran in 2008, found that silymarin shows promise as an accessible and affordable treatment for MASLD, pending further studies to optimize dosing and treatment duration. (23) The study was a two-month randomized, placebo-controlled trial that enrolled 50 patients with MASLD, confirmed by elevated liver enzymes and hepatic steatosis on sonography. (23) They were randomized to silymarin 140 mg daily (n=25) or placebo (n=25). (23) Neither group demonstrated meaningful alterations in body weight or BMI throughout the study. (23) However, the silymarin group showed considerable reductions in ALT (103.1 to 41.4 IU/mL) and AST (53.7 to 29.1 IU/mL), both statistically significant ($p<0.001$), compared to modest, non-significant reductions of 7.8 and 2.2 IU/mL, respectively, in the placebo group. (23)

A 2017 double-blind, placebo-controlled randomized trial lasting 48 weeks was conducted at a tertiary hospital in Kuala Lumpur, Malaysia, involving 99 adult participants confirmed with biopsy-confirmed NASH and a NAS of at least 4. (24) Participants were assigned to receive either silymarin 700 mg (n=49) or a placebo (n=50) three times daily. (24) The primary outcome (a 30% or greater reduction in NAS) did not show a significant difference between groups (32.7% vs. 26.0%, p=0.467). (24) However, a significantly higher proportion of the silymarin group achieved a histological fibrosis reduction of at least 1 point (22.4% vs. 6.0%, p=0.023) and a 30% or greater reduction in liver stiffness (24.2% vs. 2.3%, p=0.002). (24) The silymarin group also showed considerable improvements in fibrosis-related indices, including the AST to APRI, the FIB-4 index, and the MASLD fibrosis score, none of which were observed in the placebo group. (24) Adverse event rates were similar between groups, supporting silymarin's favorable safety profile. (24) Overall, while silymarin did not significantly reduce NAS, its antifibrotic effects warrant confirmation in larger trials. (24)

An American study, published in 2019, reported that silymarin is safe to administer for the treatment of NASH and HCV. (25) The "Silymarin in NASH and C Hepatitis" study, a phase II, placebo-controlled, double-blind, randomized, in five healthcare centers in the United States, examined how two doses of a standardized silymarin preparation performed against placebo. (25) The patients were recruited for about three years, from May 2008 to August 2011, with the follow-up study finished in November 2012. (25) Eligible patients were adults with AST or ALT >40 IU/L, biopsy-confirmed NASH without cirrhosis, and a NAS of 4 or more. (25) All participants received dietary consultation, and they were grouped according to diabetes status at the time of randomization. (25) The study concluded that silymarin preparation at higher than usual doses was safe and well-tolerated. (25) However, the researchers noted that future trials should employ refined diagnostic methods for NASH and optimize liver biopsy sampling when relying on histological endpoints. (25)

Furthermore, a RCT published in 2022, conducted in Iran, enrolled 52 candidates with morbid obesity undergoing bariatric surgery (BMI 47.84 ± 6.48 kg/m²; mean age 38.90 ± 10.28 years) with MASLD. (26) Participants were assigned to either eight weeks of silymarin supplementation at 560 mg daily (140 mg four times daily) or a placebo group. (26) Considerable improvements were observed in the AST/ALT ratio, BMI, and sonographic grading of hepatic steatosis ($p < 0.05$), while fibroscan staging, FIB-4, and MASLD scores showed no significant changes. (26) The researchers concluded that silymarin, when combined with caloric restriction, improved ultrasound fatty liver grading and liver enzyme levels in this population after only two months, without adverse effects. (26)

A 2023 study supporting the administration of silymarin for supportive treatment of MASLD is a 12-week randomized, double-blinded, placebo-controlled trial, conducted in Brazil, that recruited adult MASLD outpatients, randomized to either silymarin 700 mg combined with vitamin E 8 mg and phosphatidylcholine 50 mg daily (intervention group), or an identical capsule containing maltodextrin in place of silymarin (control group). (27) The primary outcome was a change in MASLD stage, assessed as the difference in the liver-to-spleen attenuation coefficient on CT imaging at baseline and at the end of the study, with monthly face-to-face consultations and weekly telephone contact maintained throughout. (27) The authors noted that findings from this trial may inform whether silymarin can serve as adjuvant therapy for MASLD and provide a basis for future clinical trials. (27)

In addition to the clinical trials mentioned earlier, two Chinese meta-analyses (conducted in 2017 and 2024) of RCTs are available. (28,29) These meta-analyses, which draw on multiple medical databases, collectively report that silymarin can regulate energy metabolism, reduce liver injury, improve liver histology, and lower transaminase levels in MASLD patients, supporting its function as a phytotherapeutic agent for this condition. (28,29) However, the researchers of both studies noted that further confirmatory research is needed. (28,29) Taken together, these meta-analyses suggest possible benefit, but the evidence is still not strong enough for firm conclusions.

Outside MASLD, the evidence on silymarin is still limited, particularly in ALD and viral hepatitis. This lack of research leads to limited evidence and uncertainty about using silymarin to treat liver diseases other than MASLD. Early research from 1989 in Austria on silymarin showed a reduction in mortality among patients with liver cirrhosis. (30) A prospective, double-blind, randomized trial involved 170 patients with cirrhosis diagnosed within two years prior to the study; about two-thirds were newly diagnosed. (30) Liver biopsies confirmed the diagnosis in 70% of patients, while the rest could not undergo biopsy due to coagulopathy. (30) Patients were randomly assigned to receive silymarin (n=87) or a placebo (n=83), with both groups well matched for cause, severity, age, sex, and baseline biochemical markers. (30) The study results indicated that extended use of silymarin was associated with lower death rates in patients with liver cirrhosis. (30)

Nevertheless, while the Austrian 1989 research showed a reduction due to the administration of silymarin in mortality in alcoholic liver patients, another study showed its lack of effectiveness. (31) An early Spanish study, a randomized, double-blind, multicentre trial, enrolled 200 alcoholic patients with histologically or laparoscopically confirmed liver cirrhosis between February 1986 and June 1989, randomized to silymarin 450 mg daily (150 mg three times daily; n=103) or placebo (n=97) with survival as the primary outcome. (31) 125 patients completed the two-year study period, and 29 deaths occurred overall (15 in the silymarin group, 14 in the placebo group). (31) Survival did not differ markedly between groups, and this finding was consistent regardless of sex, continued alcohol intake, severity of liver dysfunction, or presence of alcoholic hepatitis on biopsy. (31) Silymarin had no significant effect on disease progression, though no adverse effects were reported in either group. (31) The authors concluded that silymarin does not improve survival or clinical course in alcoholic liver cirrhosis. (31)

This research gap is further evident in the medical literature. This is evident, for example, in a Danish 2007 Cochrane review, which assessed the beneficial and harmful effects of silymarin versus placebo in patients with alcoholic and/or HBV or HCV liver diseases, including 13 RCTs involving 915 patients. (32) Methodological quality was low overall, with adequate allocation concealment reported in only 23% of trials and adequate double-blinding in only 46% of trials. (32) Silymarin had no significant effect on overall mortality, liver disease complications, or liver histology. (32) While liver-related mortality was significantly reduced across all trials, this effect was not maintained when analysis was restricted to high-quality trials alone. (32) From a safety standpoint, no meaningful elevation in adverse event rates was detected. (32) The authors concluded that the evidence does not support the beneficial effects of silymarin in these populations and called for adequately conducted, high-quality RCTs. (32)

Another study that highlights this gap is a 2012 systematic literature review from Switzerland that screened 525 references and retained 36 to detailed analysis, assessing the clinical efficacy and safety of silymarin across liver disease indications. (33) In ALD, although no clinical endpoints were reported, histological improvement was noted in two trials; prothrombin time improved significantly when the two trials were pooled; and liver transaminase levels were consistently lower in silymarin-treated groups, leading the authors to suggest that silymarin may be useful as an adjuvant therapy in this context. (33) In spite of these outcomes, the researchers could not reach definitive conclusions about silymarin's therapeutic function in viral hepatitis or cirrhosis, while admitting its pharmacological characteristics. (33) This suggests that its cell-regulatory actions, beyond its antioxidant effects, may support additional clinical applications. (33) The authors importantly emphasized that the absence of evidence of effect should not be interpreted as evidence of no effect. (33)

2.3. Silymarin Conclusion

Overall, the evidence on silymarin is mixed and varies by the type of liver disease. The best evidence is in MASLD, where several RCTs and meta-analyses report improvements in liver enzymes, fibrosis markers, and steatosis, with few safety concerns. Evidence for its use in ALD and viral hepatitis remains limited and methodologically heterogeneous, with early trials pointing to potential benefit in cirrhosis-related mortality and liver histology that has not been consistently replicated in better-quality studies. The 2007 Cochrane review and the 2012 systematic review both point out the same basic limitation: the existing trial base is

insufficient in quality and size to support definitive conclusions in these indications. (32,33) Even so, its antioxidant and antifibrotic properties make it worth studying further. Future RCTs should use larger samples, standardized dosing, clearer outcome measures, and longer follow-up.

3. Curcumin

3.1. Introduction

Curcumin is a yellow-pigmented substance obtained from turmeric (*Curcuma longa*), first identified over a century ago. (34) Curcumin is recognized globally for its various health-promoting properties and is incorporated into everyday products across many cultures. (35) Across India, it is considered an essential element in curry dishes; in Japan, it is consumed as tea; in Thailand, it is used in cosmetics; and in China, it functions as a natural colorant. (35) In Korea, it is added to beverages; in Malaysia, it is used as an antiseptic; and in Pakistan, it is esteemed for its anti-inflammatory properties. (35) In the United States, it appears in a range of food products (from condiments and dairy to snack foods) functioning as both a natural colorant and preservative, and is additionally sold as a dietary supplement. (35)

Image: Curcumin rhizome (36)

While turmeric's anti-inflammatory properties have been recognized for centuries, scientific research conducted over the past two decades has established that these effects are attributable specifically to curcumin, chemically known as diferuloylmethane. (34) Diferuloylmethane is believed to possess anti-inflammatory effects by modulating a wide range of biological targets, including transcription factors, cytokines, protein kinases, adhesion molecules, and redox-related enzymes. (34) This wide-ranging regulatory ability holds special significance considering that chronic inflammation has been identified as a contributing factor in the development of many disease conditions, including neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune, and cancerous

disorders. (34) Current evidence suggests that curcumin may improve liver enzymes and some metabolic markers, but most of the stronger results come from animal studies. In humans, its clinical value remains uncertain, especially with regard to fibrosis and steatosis.

3.2. Studies on Curcumin Treatment for Liver Diseases

Some studies have found that curcumin may be beneficial for liver diseases. A 2007 study on rats yielded positive results. (37) Histopathological findings from an Israeli rat study, where liver cirrhosis was induced by twice-weekly intraperitoneal injections of TAA (200 mg/kg) over 12 weeks, showed that TAA-exposed rats treated with curcumin had significantly less hepatic nodule formation, fibrosis, inflammation, and hepatocyte necrosis and apoptosis than those receiving TAA alone. (37) The study concluded that curcumin prevented the development of TAA-induced hepatic cirrhosis in rats. (37) Given its established safety profile in humans, the authors suggested that curcumin may offer therapeutic benefits in CLD defined by persistent hepatic necroinflammation. (37)

Another American study from 2018 examined curcumin's role in both preventing and treating NASH with fibrosis in female Wistar rats. (38) The animals were fed a high-fat, high-cholesterol western diet with fructose water. (38) To accelerate the development of NASH with fibrosis, the rats received intraperitoneal injections of CCl4 (a commonly used method for inducing hepatic fibrosis, cirrhosis, and acute liver injury in rodent models) at weeks 1, 2, 4, and 6. (38) The rats were then divided into four groups fed freely. (38) The study found that curcumin supplementation showed partial effectiveness in preventing and managing NASH in female rats, mainly by reducing hepatic steatosis and liver inflammation, with possibly greater benefits in treatment. (38) Because the current lack of FDA-approved drugs for MASLD exists, curcumin is a credible, safe, and affordable option to slow down NASH progression. (38)

A 2020 Iranian systematic review and meta-analysis of 9 RCTs evaluated the effects of curcumin supplementation on metabolic and anthropometric markers in patients with MASLD, searching five major databases until September 2019. (39) Curcumin significantly decreased ALT, AST, total cholesterol, LDL, FBS, HOMA-IR, insulin, and waist circumference. (39) However, no significant changes were observed in serum triglyceride, HDL, HbA1c test, body weight, or BMI. (39) Subgroup analyses, however, showed significant reductions in serum triglyceride with adjustments for age and baseline total cholesterol, and notable BMI changes by dosage and duration. (39)

While some research suggests that curcumin may be beneficial for treating liver diseases, other studies have shown no significant effects. A 2019 randomized, double-blind, placebo-controlled trial assessed curcumin's effectiveness in liver disease and found that combining curcumin with lifestyle modification offered no additional benefit over lifestyle changes alone in reducing inflammation or improving markers of hepatic steatosis and fibrosis. (40) The study included adults aged 18 and older with confirmed hepatic steatosis from Taleghani Hospital in Tehran, Iran. (40) Inclusion required minimal alcohol intake (below 20 g/day for women, 30 g/day for men), the absence of other hepatic, systemic, or metabolic disorders, and no medication use in the prior three months. (40) Exclusion criteria comprised pregnancy, poor supplement adherence, participation in another trial, and hypersensitivity to the supplement. (40) Out of 50 enrolled patients, 48 completed the study, with two withdrawing due to lack of interest. Curcumin was well-tolerated with no reported side effects. (40) At baseline, both groups had similar demographic and metabolic profiles. (40) After the intervention, both groups showed significant reductions in body weight, BMI, waist circumference, and daily caloric intake, with no significant differences between them. (40) Physical activity increased more in the curcumin group. (40) In the curcumin group, hepatic fibrosis and NF-κB activity significantly decreased relative to baseline; however, hepatic steatosis, liver enzymes (ALT, AST), and TNF-α improved significantly in both groups. (40) No differences between groups were observed for any outcome. (40)

Another 2019 study conducted in Iran raised concerns about the effectiveness of curcumin in treating MASLD. (41) In a randomized, double-blind, placebo-controlled parallel trial, MASLD patients were recruited from 22 Bahman Hospital (Neyshabur, Iran) between January and August 2017, with diagnoses confirmed by ultrasound. (41) Of 58 eligible participants, 49 completed the study. (41) Inclusion criteria included ultrasound-confirmed fatty liver, age 25-65 years, and non-smoking, non-alcoholic status. (41) Exclusion criteria comprised other hepatic or systemic disorders and pregnancy. (41) The research concluded that after eight weeks of curcumin supplementation in patients with MASLD, there were changes in amino acid profiles, the TCA cycle, bile acids, and the gut microbiota. (41) These effects may reflect curcumin's antioxidant and anti-inflammatory properties, which have been shown to reduce oxidative and inflammatory mediators. (41) These findings do not provide strong evidence for a clear clinical benefit of curcumin, and further studies are needed. (41)

A more recent, 2025 Iranian double-blind, randomized, placebo-controlled trial examined the effects of 80 mg/day nano-curcumin over 16 weeks in 55 adults (aged 30–70) with MASLD-

related fibrosis. (42) Liver fibrosis and steatosis were assessed using fibroscan and FIB-4, along with liver function tests and anthropometric measurements. (42) Both groups showed improvements in fibrosis and steatosis, with no significant differences between them. (42) However, nano-curcumin notably decreased the FIB-4 index, ALT, AST, GGT, and LDH, with significant between-group differences observed for liver enzymes. (42) Anthropometric measures did not show significant differences between groups. (42) While nano-curcumin showed considerable improvements in liver enzyme profiles, it did not outperform placebo in reducing fibrosis or steatosis, indicating the need for further long-term studies. (42)

Yet 2019 Chinese research might help explain the results of studies conducted on human subjects. (43) Upon oral administration, curcumin exhibits poor bioavailability due to limited intestinal absorption, rapid metabolism, and swift elimination. (43) Three gastrointestinal barriers are responsible: physical barriers such as the mucus layer and epithelial tight junctions restrict absorption; chemical barriers, including gastric acid, bile, and digestive enzymes, promote degradation; and biochemical obstacles, such as metabolic enzymes and p-glycoprotein efflux, inactivate curcumin and return it to the gut lumen. (43) Hepatic first-pass metabolism further limits its systemic availability. (43) Curcumin's oral bioavailability is remarkably low, resulting in minimal plasma concentrations even when administered intravenously. (43) Therefore, combining multiple delivery strategies (such as lipid-based lymphatic transport via nanoparticle formulations) is essential to enhance systemic absorption. (43) Various pharmaceutical approaches have shown potential to improve curcumin's oral bioavailability whilst maintaining an acceptable safety profile, though further dedicated research is still necessary. (43)

3.3 Curcumin Conclusion

Collectively, the available evidence suggests that curcumin indicates promise as a complementary intervention for liver disease, particularly in improving liver enzyme profiles and metabolic markers. However, its potency in directly reducing hepatic fibrosis and steatosis remains inconclusive, with several studies reporting no significant between-group differences compared to placebo. While animal studies show more consistent benefits, human trials yield mixed results, stressing the need for larger, well-designed RCTs with longer follow-up periods before curcumin can be recommended as a definitive therapeutic option for liver disease. A key challenge limiting curcumin's clinical translation is its remarkably poor oral bioavailability, driven by limited intestinal absorption, rapid metabolism, and extensive first-pass elimination. Advancing pharmaceutical strategies (such as nanoparticle-based and

lipid-mediated delivery systems) to enhance systemic absorption might be critical in unlocking curcumin's complete therapeutic potential.

4. Berberine

4.1. Introduction

The genus Berberis (Berberidaceae) includes around 500 species found across Central and Southern Europe, the northeastern United States, and South Asia, especially Northern Pakistan. (44) Among these species, Berberis is widely recognized, with its fruits often used in traditional rice dishes, juices, and herbal teas made from the plant's bark. (44) In addition to its cooking uses, various parts of the plant (such as the roots, bark, leaves, and fruits) have long been used in Iranian folk and traditional medicine. (44) The stem and root barks are valued for their cathartic, diuretic, febrifuge, anti-bilious, and antiseptic properties. (44) At the same time, leaf decoctions are used as an anti-scorbutic remedy for dysentery, scurvy, angina, and sore throat. (44) Berberis species have been integral in Ayurvedic and traditional Chinese medicine, used to treat inflammation, infections, diabetes, constipation, obesity, and other conditions, with the earliest recorded use dating back to 650 BCE. (45)

Image: *Berberis lyceum* (family member of berberine) (46)

The main bioactive compound accountable for these effects is berberine, a non-basic quaternary isoquinoline alkaloid of significant importance in pharmacology and medicinal chemistry. (45) Derived directly from the roots, rhizomes, and stem tubers of Berberis and related plants, berberine acts as a key foundation for developing new therapeutic agents through structural alterations and calculated functional-group substitutions. (45) Berberine extracts have traditionally been valued in various medical systems for their wide antimicrobial activity. (45) Plants containing berberine have a long history of medicinal use worldwide, treating conditions ranging from inflammatory and microbial disorders to skin diseases, tumours, and digestive and respiratory ailments. (45) In spite of the challenges of

extraction, growing clinical and experimental evidence demonstrates berberine's extensive pharmacological potential, including immune regulation, antioxidant effects, cardiovascular protection, and liver support. (45) Although berberine shows promise in improving liver function, lipid profiles, and inflammatory markers (similar to the herbs presented above), the evidence remains mixed and inconclusive, requiring larger, high-quality RCTs to establish its definitive role in liver disease management.

4.2. Studies on Berberine Treatment for Liver Diseases

Some studies investigating whether berberine can treat liver diseases have found it may be beneficial. A 2015 randomized, open-label, parallel-controlled clinical trial enrolled 184 MASLD patients in China and assigned them to one of three 16-week interventions: lifestyle intervention alone, lifestyle intervention plus pioglitazone 15mg daily, or lifestyle intervention plus berberine 0.5g three times daily. (47) Berberine combined with lifestyle intervention resulted in a significantly greater reduction in hepatic fat content than lifestyle intervention alone (52.7% vs. 36.4%), along with better improvements in body weight, HOMA-IR, and lipid profiles. (47) Berberine also outperformed pioglitazone in reducing body weight and improving lipid profiles, with only mild, mostly gastrointestinal adverse effects. (47) As the authors stated, animal model data further showed favourable hepatic accumulation of berberine and changes in the expression of metabolism-related genes, suggesting that berberine's therapeutic effect on MASLD may be mediated by direct regulation of hepatic lipid metabolism. (47)

Another 2016 study conducted in China from March 2008 to August 2011 found similar results. (48) A lipidomic sub-analysis using liquid chromatography-mass spectrometry examined serum samples from 80 participants (41 received berberine, 39 underwent lifestyle intervention only) before and after treatment, identifying and quantifying 256 serum lipid molecular species. (48) While both interventions affected lipid classes involved in key metabolic pathways (including free fatty acids, phosphoglycerates, and glycerides), berberine caused substantially wider changes across serum lipid species compared to lifestyle intervention alone. (48) Notably, berberine significantly lowered circulating ceramide and ceramide-1-phosphate levels, suggesting that modulation of ceramide metabolism may play a part in its beneficial effects in fatty liver disease. (48)

Effective results in treating liver diseases with berberine were observed in a 2019 Chinese murine study that investigated berberine's therapeutic potential in NASH-associated

hepatocellular carcinoma, using a model established by streptozotocin injection followed by a high-fat, high-cholesterol diet. (49) Histological, biochemical, and molecular analyses demonstrated that berberine reduced tumour incidence, improved NASH, and significantly lowered ALT, AST, glucose, HDL, LDL, and total cholesterol levels. (49) Transcriptomic sequencing and bioinformatics analysis showed berberine's suppressive effects on genes involved in lipogenesis, inflammation, fibrosis, and angiogenesis, with mechanistic findings indicating inhibition of p38MAPK and ERK phosphorylation, as well as downregulation of COX-2 expression. (49) Collectively, these results show that berberine exerts its antitumor effects mainly through the p38MAPK/ERK-COX2 pathway. (49) Overall, these results show berberine as an encouraging therapeutic candidate for NASH-associated hepatocellular carcinoma, with well-characterized antitumor activity and a plausible underlying mechanism. (49)

A 2016 Chinese meta-analysis of RCTs retrieved from Embase, PubMed, the Cochrane Library, and other databases evaluated the effectiveness of berberine in the treatment of MASLD. (50) Berberine showed positive effects on lipid profiles, blood sugar control, liver function, insulin resistance, and liver fat accumulation. (50) The authors noted, however, that the small number of trials and methodological weaknesses point to the need for more large-scale, well-designed RCTs to confirm these outcomes. (50) This means the researchers conclude that additional clinical trials are necessary to determine whether berberine is effective in treating MASLD.

Furthermore, a 2024 Chinese systematic review and meta-analysis, whose protocol was prospectively registered with PROSPERO, analysed 10 RCTs involving 811 MASLD patients across six databases through September 2023 to assess the clinical effectiveness of berberine. (51) Berberine significantly lowered liver enzymes (ALT, AST, GGT), lipid markers (TG, TC, LDL-C), insulin resistance (HOMA-IR), and BMI, while HDL-C showed no significant change. (51) Adverse effects were limited to mild gastrointestinal symptoms. (51) Overall, berberine demonstrated a favourable safety profile and promising effectiveness at improving liver function, lipid profiles, and insulin sensitivity, supporting its capacity as an adjunct therapy for MASLD. (51)

Another 2026 study showed inconclusive results about berberine's effectiveness in treating liver disease. (52) Preformed across 11 hospitals in China, a 2023 double-blind randomized trial enrolled 337 non-diabetic people with obesity and MASLD. (52) They were assigned to

receive either berberine (n=169) or a placebo (n=168) for six months. (52) Visceral fat area and liver fat content did not differ markedly between the two groups, indicating that berberine had no major effect on these primary outcomes. (52) However, berberine was linked to considerable reductions in LDL-cholesterol, apolipoprotein B, and hs-CRP compared to the placebo, with a similar side-effect profile. (52) These results suggest that berberine is safe but not effective at reducing visceral adipose tissue or liver fat in this population, though its lipid-lowering and anti-inflammatory benefits remain notable. (52)

Another inconclusive study with limited evidence on the effectiveness of berberine for liver disease is an Iranian 2019 systematic review and meta-analysis that searched six databases until July 2019 and included 12 RCTs for evaluating the effects of berberine on anthropometric parameters, CRP levels, and liver enzymes. (53) The inverse variance method was used to combine data from the included studies. (53) Berberine treatment led to modest but statistically significant reductions in body weight (WMD = -2.07 kg), BMI (WMD = -0.47 kg/m²), waist circumference (WMD = -1.08 cm), and CRP levels (WMD = -0.42 mg/L), pointing to a potential indirect role in improving clinical outcomes in metabolic disorders. (53) However, berberine administration had no significant effect on liver enzymes, with ALT and AST levels remaining unchanged compared to controls. (53)

4.3. Berberine Conclusion

In conclusion, the present body of evidence shows mixed results regarding the effectiveness of berberine in liver disease. Several studies have shown considerable improvements in hepatic fat content, liver enzymes, lipid profiles, insulin resistance, and inflammatory markers, with some evidence suggesting direct regulation of hepatic lipid metabolism and antitumor activity through the p38MAPK/ERK-COX2 pathway. However, other well-designed trials have produced inconclusive or negative results, especially concerning berberine's ability to lower visceral adipose tissue and liver fat in patients with MASLD. Additionally, multiple meta-analyses point out that the limited number and varying quality of existing trials make it difficult to draw firm conclusions. Although more heterogeneous than the results seen with other herbs discussed in this thesis, additional research is necessary to evaluate its true potential. In other words, while berberine generally has a favourable safety profile with minimal adverse effects at standard doses, larger, high-quality, multicentre RCTs are necessary to confirm its clinical benefits, ascertain optimal dosing and duration, and identify patient groups most likely to benefit.

5. Resveratrol

5.1. Introduction

Resveratrol was first identified in the roots of Veratrum grandiflorum by Japanese scientists and was later isolated from Polygonum cuspidatum, a plant used in traditional Chinese medicine for thousands of years. (54) Plants produce the natural phenol and phytoalexin, resveratrol, in response to injury or pathogen attack, including bacterial and fungal infections, as part of their defence mechanisms against ecological stress. (54) It has since been found in a wide variety of plant species and is present in many commonly consumed foods, such as grapes, peanuts, blueberries, bilberries, cranberries, and their derived products, such as juices. (54) Beyond the fruit itself, resveratrol is found in various parts of the grapevine (including leaves, roots, and shoots) and is preserved in multiple products like juice, raisins, dried powders, and grape pomace. (55)

Image: Sources of resveratrol (56)

Resveratrol has been studied for a wide range of potential health benefits, although most evidence so far comes from preclinical cellular and animal studies. (57) In these models, it has shown cardioprotective, neuroprotective, antitumor, antidiabetic, antibacterial, and anti-aging effects, partly through influencing glucose metabolism, oxidative stress, inflammation, and cell death. (57) The clinical evidence on resveratrol in MASLD is still inconsistent and inconclusive. Some studies suggest a benefit, while others show no significant effect, and at least one has raised safety concerns, including increased liver enzyme levels. The research centers almost entirely on MASLD, with little evidence regarding other liver conditions, drawing attention to the need for further studies to fully understand resveratrol's role among different liver diseases.

5.2. Studies on Resveratrol Treatment for Liver Diseases

Some studies support using resveratrol for MASLD treatment. A 12-week Iranian randomized, double-blind, placebo-controlled trial published in 2014 showed a positive effect of resveratrol on MASLD. (58) The study included 50 adults with MASLD, diagnosed by ultrasound steatosis grade ≥2, FIB-4 >4 kPa, and elevated ALT levels (>30 IU/L in men, >19 IU/L in women), with minimal or no alcohol intake. (58) Patients were randomly assigned to receive 500 mg of trans-resveratrol daily or a medium-chain triglyceride placebo, with both groups following standardized dietary and physical activity guidelines. (58) One patient in the resveratrol group withdrew for personal reasons, and one in the placebo group was excluded due to >10% weight loss; the remaining 49 patients adhered to the protocol, and no significant adverse effects were reported. (58) The researchers concluded that resveratrol, combined with lifestyle changes, reduced ALT and hepatic steatosis in patients with MASLD. (58) They partly attributed these improvements to reductions in inflammatory markers and hepatocellular cell damage. (58)

Another 3-month randomized, double-blind, placebo-controlled 2015 Chinese trial reported a positive effect of resveratrol on liver enzymes. (59) It enrolled 60 MASLD patients between October 2012 and February 2013, who were assigned to receive resveratrol 300 mg twice daily (600 mg/day) or a placebo. (59) Compared to the placebo, resveratrol significantly reduced AST, ALT, glucose, total cholesterol, LDL cholesterol, and insulin resistance (HOMA-IR). (59) In the resveratrol group, levels of TNF-α, cytokeratin-18 fragment, and fibroblast growth factor 21 were significantly lowered, while adiponectin levels increased. (59) The authors concluded that resveratrol supplementation may benefit patients with MASLD. (59)

While these two studies reported positive results, a 2014 8-week Australian randomized, placebo-controlled trial showed different findings, indicating that resveratrol was ineffective. (60) The study involved 20 overweight or obese men with MASLD, who were assigned to receive either 3000 mg of resveratrol daily (n=10) or a placebo (n=10). (60) Outcomes measured included insulin resistance via euglycemic-hyperinsulinemic clamp, hepatic steatosis and abdominal fat distribution by MR spectroscopy and imaging, plasma markers of inflammation, metabolic and antioxidant functions, and target gene transcription in peripheral blood mononuclear cells. (60) Resveratrol did not decrease insulin resistance, hepatic steatosis, abdominal fat distribution, plasma lipids, or antioxidant activity compared to placebo. (60) Notably, ALT and AST levels significantly increased in the resveratrol group

relative to the placebo up to week 6, implying increased hepatic stress rather than benefit. (60) The researchers concluded that resveratrol not only failed to improve any features of MASLD but may have negatively impacted liver enzyme levels, and they called to conduct further research to determine whether calorie restriction-mimicking agents are safe and effective in treating obesity-related liver diseases. (60)

Another 2016 randomized, double-blind, placebo-controlled Danish trial, conducted between October 2011 and February 2014, produced less encouraging outcomes than the previous studies. (61) The study enrolled 28 overweight patients with hypertransaminasemia and histologically confirmed MASLD, randomly assigning them 1:1 to receive resveratrol 1.5 g daily or a placebo. (61) Twenty-six participants completed the trial with full clinical and biochemical assessments, including MR spectroscopy, and 19 agreed to redo liver biopsies. (61) Resveratrol was not better than placebo regarding the primary outcome of ALT reduction ($p=0.51$). (61) A 3.8% decrease in liver lipid content was observed within the resveratrol group ($p=0.03$), but this did not differ significantly from the placebo group ($p=0.38$), and no histological improvements were seen. (61) Resveratrol failed to increase insulin sensitivity or MetS markers, aside from a temporary reduction in systolic blood pressure; gene expression analysis showed no major changes. (61) One serious adverse event (fever and bicytopenia) was reported in the resveratrol group. (61) The researchers concluded that high-dose, long-term resveratrol had no consistent therapeutic effect on clinical or histological MASLD. (61) However, a modest ameliorating effect on liver fat accumulation could not be excluded. (61)

Furthermore, a study supporting similar findings is a 12-week Iranian randomized, double-blind, placebo-controlled trial that included 60 MASLD patients (aged 20-60 years, BMI 25-35 kg/m²). (62) Participants were randomly assigned to receive 600 mg of resveratrol daily (2×300 mg trans-resveratrol; n=30) or a placebo (n=30). (62) Published in 2018, the study intended to evaluate resveratrol's effects on oxidative and antioxidative status by measuring MDA, ox-LDL, TAC, and activities of erythrocyte superoxide dismutase and GSHPx. (62) Resveratrol supplementation showed no significant impact on any oxidative stress marker compared to the placebo (all $p>0.05$), and changes in liver enzymes (ALT, AST, GGT, and ALP) were similarly non-significant in both groups. (62) The researchers concluded that resveratrol supplementation did not alter oxidative or antioxidative status in MASLD patients, and stressed the need for further human research to investigate its potential antioxidant effects and to identify the best therapeutic dose. (62)

Another study published in 2018 suggests that its administration might increase liver enzyme levels. (63) The largest randomized, placebo-controlled trial of resveratrol to date, conducted in Germany from 2012 to 2016, enrolled 112 overweight, obese, and insulin-resistant subjects in a 12-week intervention. (63) Although the trial aimed to investigate the effects and safety of resveratrol on liver fat content and cardiometabolic risk factors in this population (not specifically in MASLD patients), the inclusion of subjects with significant hepatic steatosis at baseline (range 0.09-37.55%; median 7.12%) allows meaningful inferences about resveratrol's effects on the liver. (63) During the study, liver fat content decreased modestly in the placebo group (-0.7%) but remained almost unchanged in the resveratrol group (-0.03%), a difference that was statistically significant in both the intention-to-treat ($p=0.018$) and per-protocol ($p=0.0077$) populations. (63) No effects of resveratrol on any cardiometabolic or secondary metabolic endpoints were observed. (63) Resveratrol was well-tolerated and safe. (63) Despite this, the researchers concluded that resveratrol not only failed to reduce liver fat content but also performed significantly worse than placebo on this primary endpoint. (63)

Meta-analyses of resveratrol research reveal a complex attitude toward its use for liver diseases, with claims that more research is needed to determine its effectiveness. A Chinese meta-analysis searched EMBASE, PubMed, Science Citation Index, Elsevier, and Cochrane Library databases through July 2016, identifying four randomized, double-blind, placebo-controlled trials enrolling 156 MASLD patients. (64) Fixed-effect or random-effects models were used to estimate mean differences and 95% confidence intervals. (64) Despite promising preclinical evidence (including inhibition of hepatic lipogenesis via LXRα inactivation and TNF-α suppression), clinical trial results were conflicting. (64) The pooled analysis found that resveratrol paradoxically increased LDL and total cholesterol levels, with no significant benefit on any other parameter. (64) The authors concluded that large-scale, well-designed, population-based trials are needed to better define the efficacy of resveratrol in MASLD. (64)

An Egyptian meta-analysis conducted in 2017 reached a similar conclusion: further clinical research is necessary to evaluate the efficacy of resveratrol in liver diseases. (65) The study was a systematic review and meta-analysis that searched PubMed, Scopus, Web of Science, and Cochrane Central using relevant keywords, with data extracted and synthesized using RevMan 5.3, including subgroup and sensitivity analyses. (65) Based on the available evidence, the authors concluded that the effectiveness of resveratrol in treating MASLD could not be adequately supported. (65) That resveratrol neither attenuates liver fibrosis nor significantly improves any fibrosis-related outcome parameters. (65) The same conclusion

was made in a 2020 Polish meta-analysis that searched PubMed, Medline, and Embase through March 2020, including seven RCTs enrolling 302 MASLD patients, who received resveratrol at doses of 500-3000 mg daily for 56-180 days. (66) Resveratrol supplementation showed no significant effect on any parameter analysed, regardless of dose or duration, except for a considerable increase in ALT ($p=0.041$) (a worrying rather than beneficial finding). (66) The authors concluded that the current evidence does not confirm resveratrol's effectiveness in the treatment of MASLD and called to further research to clarify existing contradictions in the literature. (66)

5.3. Resveratrol Conclusion

In conclusion, the clinical evidence regarding resveratrol in MASLD is still inconsistent and inconclusive. While two early trials reported improvements in liver enzymes, inflammatory markers, and hepatic steatosis at lower doses combined with lifestyle changes, most studies (including higher-dose and longer-duration trials) failed to show significant benefits. Compared to other herbs discussed above, some studies indicated that resveratrol might have a negative effect. Few trials found resveratrol performed notably worse than placebo on the primary endpoint of liver fat reduction. Three independent meta-analyses collectively support this view, finding insufficient evidence to confirm resveratrol's effectiveness in managing MASLD, with one raising concern about a paradoxical increase in ALT. Research on resveratrol in liver disease has primarily focused on MASLD, yet even within this area, results are inconsistent. Some studies suggest a benefit, while others report no significant effect, and at least one highlights safety issues such as elevated liver enzymes. This variation, combined with the limited evidence for other liver conditions like ALD and viral hepatitis, reinforces the urgent need for more research to thoroughly assess resveratrol's therapeutic potential in liver disease.

6. Glycyrrhizin

6.1. Introduction

Glycyrrhiza (liquorice), a perennial herb in the Leguminosae family, is found worldwide, mainly cultivated in Asia and Europe, with smaller populations in the tropical and subtropical regions of the Americas and Africa. (67) China is both the largest producer and consumer of liquorice and leads in exporting it. (67) Three species are recognized as official pharmacopeial sources: Glycyrrhiza uralensis, Glycyrrhiza glabra, and Glycyrrhiza inflata, with the roots and rhizomes serving as the medicinal parts. (67) Traditionally, liquorice is

believed to have a wide range of medicinal properties, including tonifying qi, clearing heat, detoxifying, acting as an expectorant and antitussive, providing analgesia, and harmonizing other medicines in compound formulations. (67) Glycyrrhizin and its aglycone, glycyrrhetinic acid, have a wide range of pharmacological properties, including anticancer, anti-inflammatory, hepatoprotective, and antiviral effects. (67) It remains one of the most used medicinal materials in China and is highly esteemed in the United States and Japan, where it is called "Fairy Herb" or "Divine Herb." (67)

Image: Glycyrrhiza (67)

The chemical components of liquorice have been thoroughly studied, including glycyrrhizin, various triterpene saponins, and flavonoids (the latter of which are also used in cosmetic products). (68) This review suggests that the clinical evidence consistently supports glycyrrhizin's hepatoprotective role in CHB and CHC, where it reliably reduces transaminase levels with a favourable safety profile. However, effects are not sustained post-treatment, and histological benefits have not been demonstrated. Evidence in MASLD remains limited to a single trial, and more high-quality research is necessary to establish glycyrrhizin's role across the wider spectrum of liver disease.

6.2. Studies on Glycyrrhizin Treatment for Liver Diseases

All studies reviewed below indicate that administering glycyrrhizin to treat hepatitis B and hepatitis C is beneficial. A Dutch randomized, placebo-controlled trial published in 1999 enrolled 57 European patients with CHC who were non-responders or unlikely to respond to interferon therapy (genotype 1/cirrhosis). (69) These patients were assigned to receive intravenous glycyrrhizin at 240, 160, or 80 mg or a placebo, administered three times weekly for 4 weeks. (69) The study intended to evaluate the effects of glycyrrhizin on serum ALT and HCV-RNA levels, as well as its safety profile in European patients with CHC. (69) Within 2 days of starting treatment, ALT levels declined by 15% from baseline across all active-dose groups ($p < 0.02$), with an average reduction of 26% by the end of the treatment period. (69)

In comparison, the placebo group experienced only a 6% reduction. (69) No clear dose-response relationship was observed (reductions of 29%, 26%, and 23% for 240, 160, and 80 mg doses, respectively), and ALT normalization occurred in only 10% of treated patients. (69) The effect on ALT was not sustained after stopping therapy. (69) Treatment did not lead to a considerable decrease in HCV-RNA levels, and no serious adverse effects were reported during the study. (69) The authors concluded that intravenous glycyrrhizin safely reduces ALT during treatment but has no impact on viral load. (69)

The same main authors from the previous trial later conducted a follow-up randomized study in 2001, assessing the short-term feasibility and effectiveness of intravenous glycyrrhizin given three or six times weekly for four weeks in 72 European patients with CHC who were either non-responders or unlikely to respond to interferon therapy. (70) No significant changes in ALT were seen in the placebo group. (70) The mean ALT reductions from baseline at the end of treatment were 26% and 47% for the three-times and six-times weekly groups, respectively (both $p<0.001$ compared to placebo), with ALT normalization achieved in 10% and 20% of patients in each group. (70) The ALT-lowering effect did not last after stopping treatment, and no major adverse effects were observed. (70) The authors concluded that glycyrrhizin administered six times weekly was more effective than three times weekly, and that both regimens were feasible for European outpatients. (70)

A separate randomized trial conducted in 2002 across nine Chinese hospitals evaluated the therapeutic effectiveness and safety of two dosage levels of stronger SNMC (an intravenous formulation in which glycyrrhizin is the main active component) in 194 patients diagnosed with CHB. (71) These patients had ALT levels exceeding twice the upper limit of normal (>80 IU/L). (71) Participants were assigned to receive either 100 mL of SNMC (Group A, n=99) or 40 mL (Group B, n=95) daily for four weeks, followed by oral glycyrrhizin (GLYCYRON) at nine tablets daily for the next four weeks. (71) By week 8, the primary endpoint (ALT falling below 60 IU/L) was achieved in 74% of Group A and 79% of Group B, with ALT normalized to under 40 IU/L in 58% and 57% of the respective groups. (71) SNMC was discontinued in 4 patients (2%) due to mild, reversible side effects. (71) The authors concluded that SNMC is safe and effective in reducing ALT levels among CHB patients in China and that the lower dose of 40 mL is sufficient to achieve maximum results. (71)

Furthermore, a 2002 Japanese randomized clinical trial evaluated the therapeutic effects of intermittent intravenous SNMC administered three times weekly for 12 weeks, comparing

doses of 40 mL (n=59) and 100 mL (n=53). (72) Participants receiving the 100 mL dose showed significantly greater overall treatment responses (p=0.0243), with ALT levels decreasing by 50% from baseline versus a 29% reduction in the other group (p=0.0002). (72) Minor adverse effects occurred in 20% and 12% of patients in the 100 mL and 40 mL groups, respectively, none of which required treatment. (72) The authors concluded that intermittent SNMC suppresses ALT in a dose-dependent manner in chronic viral hepatitis, and that its favourable tolerability profile facilitates long-term use to maintain quality of life and treatment compliance. (72)

A 2006 randomized trial from the Netherlands enrolled HCV-RNA-positive individuals with elevated ALT levels and significant fibrosis or necro-inflammation who were not suitable candidates for interferon-based treatment. (73) During the initial phase, all participants received six weekly intravenous glycyrrhizin infusions over 4 weeks. (73) Those who responded with ALT improvement (72 out of 121; 60%) were randomly assigned to continue treatment for an additional 22 weeks at either six, three, or once weekly infusion frequencies. (73) By the end of the treatment period, ALT response was maintained in 60%, 24%, and 9% of patients across the respective frequency groups ($p<0.001$). (73) Necro-inflammation scores improved non-significantly in ALT responders compared to non-responders, and no significant histological improvement was observed after 6 months. (73) Quality of life, measured by SF-36, improved in treated patients regardless of ALT response. (73) The researchers concluded that glycyrrhizin-induced ALT responses could be sustained in some CHC patients, provided they received at least three injections per week. (73) However, this biochemical improvement did not translate into meaningful histological changes benefit. (73)

In a 2017 randomized trial from Taiwan, 60 patients with severe acute exacerbation of CHB were randomly assigned to either combination therapy with tenofovir and intravenous glycyrrhizin (Group A, n=30) or tenofovir alone (Group B, n=30). (74) Group A experienced significantly greater reductions in AST and ALT from baseline at days 3, 5, 8, and 15 (all $p<0.05$), and the MELD score significantly decreased from week 1 in Group A, while remaining unchanged in Group B at weeks 1 and 2. (74) At 24 weeks, one patient in Group A and four patients in Group B had either died or underwent liver transplantation. (74) Multivariate analysis identified the baseline MELD score as an independent predictor of these clinical outcomes. (74) No differences were observed between groups in rates of grade 3 hypertension, hypokalemia, or ascites. (74) The researchers concluded that early initiation of

glycyrrhizin therapy is well tolerated and may provide clinical benefits for patients experiencing severe acute exacerbation of CHB. (74)

In addition to these RCTs, a 2021 systematic review and meta-analysis is noteworthy; it searched PubMed, Web of Science, SinoMed, CNKI, Wanfang, and VIP databases from their inception through February 2020. (75) The review identified 18 two-armed RCTs involving 1,915 participants that evaluated the use of compound glycyrrhizin injection in CHB. (75) The methodological quality of most included studies was generally low. (75) Pooled analysis showed that compound glycyrrhizin injection was better than comparators in advancing overall clinical effectiveness and lowering AST levels across several comparisons. (75) However, differences in ALT normalization rates were usually not statistically significant. (75) When combined with other common medications, compound glycyrrhizin injection consistently outperformed comparator combinations in reducing both ALT and AST levels and augmenting overall clinical response. (75) Mild adverse reactions were reported in a few studies. (75) The authors concluded that compound glycyrrhizin injection has a measurable beneficial effect on liver damage in CHB, but the evidence is not strong enough to draw definitive conclusions and called for larger, well-designed RCTs. (75)

All the studies mentioned above discuss the treatment of hepatitis B and hepatitis C. However, only one article has documented a beneficial effect of glycyrrhizin administration in the treatment of MASLD. (76) This study is an Iranian 12-week randomized, double-blind, placebo-controlled trial conducted between November 2019 and January 2020, which enrolled 60 women with MASLD. (76) Participants were assigned to receive either glycyrrhizin root extract powder (1,000 mg daily) or a placebo. (76) Both groups were advised to follow a weight-loss diet and maintain a healthy lifestyle. (76) Women taking glycyrrhizin root showed statistically meaningful improvements compared to the placebo group in ALT ($p < 0.001$), insulin levels ($p = 0.002$), insulin resistance ($p = 0.003$), malondialdehyde ($p < 0.001$), and ultrasound-assessed hepatic steatosis grading ($p < 0.001$). (76) The researchers concluded that supplementing with glycyrrhizin root, along with lifestyle changes, provided greater therapeutic benefits for MASLD than lifestyle modification alone. (76)

6.3. Glycyrrhizin Conclusion

To summarize, the clinical evidence regarding glycyrrhizin in liver disease is more consistent than that for the other herbs reviewed in this thesis. Multiple randomized trials in CHB and

CHC show that glycyrrhizin (mainly given as intravenous SNMC) reliably lowers serum transaminase levels and generally has a safe profile. However, several major limitations were noted: the ALT-lowering effect was not sustained after treatment was stopped, viral load remained unchanged, and histological improvements were not observed in longer-term studies. A meta-analysis of compound glycyrrhizin injection in CHB highlights that, while biochemical benefits are evident, the overall quality of evidence remains low. Evidence supporting glycyrrhizin's use in MASLD is limited to a single trial in women that showed promising results but needs to be replicated in larger, more varied populations. Overall, glycyrrhizin seems to be a useful hepatoprotective adjunct in viral hepatitis, especially for patients who cannot receive standard antiviral therapy. However, more high-quality research is needed to determine its role in MASLD and whether its biochemical benefits translate into meaningful long-term clinical outcomes.

7. Phyllanthus

7.1. Introduction

Phyllanthus (Euphorbiaceae) is a large genus with over 700 species found in tropical and subtropical areas, including Africa, the Americas, Asia, and Oceania. (77) It is divided into 11 subgenera. (77) Among these, 24 well-known species from the subgenera Kirganelia, Cicca, and Phyllanthus hold traditional medicinal importance among different ethnic groups. (77) The genus has a long history of use in herbal medicine in China, India, Brazil, and Southeast Asia. (77) In India, it is especially used in Ayurvedic medicine for digestive, genitourinary, respiratory, and skin issues. (77) Chinese traditional medicine uses it for HBV, high blood pressure, edema, and sore throat. (77) Communities in Thailand, Latin America, and Africa also use these plants for jaundice, kidney stones, and malaria, respectively. (77)

Image: Phyllanthus (78)

The antidiabetic properties of Phyllanthus stem from its ability to regulate glucose levels, increase insulin sensitivity, and protect cells from oxidative damage through various pathways. (78) Main mechanisms include stimulating insulin release from pancreatic β-cells, increasing insulin responsiveness in peripheral tissues, inhibiting carbohydrate-metabolizing enzymes like α-amylase and α-glucosidase to reduce post-meal blood sugar spikes, promoting the regeneration of pancreatic islets and restoring islet cell structure, and decreasing oxidative stress to support proper β-cell function and lower insulin resistance. (78) As I will demonstrate, despite findings in two studies, the overall clinical evidence from RCTs suggests that Phyllanthus has limited efficacy as a standalone treatment for liver diseases, with most trials failing to achieve considerable improvements in primary outcomes, such as reductions in viral load and NAS. Nevertheless, its notable effects on antioxidant levels and fibrosis reduction show potential biological activity that warrants additional investigation through larger, well-designed trials.

7.2. Studies on Phyllanthus Treatment for Liver Diseases

A Chinese RCT published in 2001 showed considerable efficacy of a Phyllanthus amarus compound in the treatment of HBV. (79) A total of 55 patients with CHB were randomly assigned to two groups. (79) The treatment group (n=30) received a Phyllanthus amarus compound for three months, while the control group (n=25) received recombinant human IFN-α1b over the same period. (79) The overall treatment effectiveness in the Phyllanthus amarus compound group was 83.3%, like that in the control group ($p>0.05$). (79) The treatment group showed significantly higher rates of ALT, A/G, and SB normalization- 73.3%, 80.0%, and 78.2%, respectively, compared to the control group ($p<0.05$), while HBeAg and HBV-DNA negative conversion rates of 42.3% and 47.8%, respectively, did not differ significantly compered to those in the control group ($p>0.005$). (79) These results indicate that Phyllanthus amarus compound exhibits considerable potency in managing CHB, especially in restoring liver function and inhibiting HBV replication. (79)

Nonetheless, another study demonstrated partial effectiveness of Phyllanthus in treating liver conditions. (80) A 2021 Indian, block-randomized, double-blind, parallel-arm, placebo-controlled trial evaluated the efficacy of Phyllanthus niruri on liver and kidney function parameters, as well as on total oxidant and antioxidant levels, in patients with mild-to-moderate alcoholic hepatitis over four weeks. (80) Patients were screened using the CAGE questionnaire, and those with confirmed mild-to-moderate alcoholic hepatitis based on laboratory results and Maddrey's discriminant function score were randomly assigned to

treatment or placebo groups. (80) Clinical assessments took place at baseline, 2 weeks, and 4 weeks. (80) Of 454 screened patients, 100 were enrolled, and 71 were analysed using a modified intention-to-treat approach. (80) Liver and kidney function parameters showed no significant improvement with Phyllanthus niruri. (80) However, total antioxidant levels were significantly increased in the treatment group (P=0.034), along with a considerable appetite-stimulant effect (P=0.03). (80) Four weeks of Phyllanthus niruri administration in patients with mild-to-moderate alcoholic hepatitis resulted in improved total antioxidant levels and appetite stimulation compared to placebo, although no significant benefit was observed in liver or kidney function parameters. (80)

While the two trials mentioned above suggested a potential positive effect of Phyllanthus in treating liver conditions, others have reported it to be ineffective. A Chinese RCT published in 2003 assessed the antiviral potential of Phyllanthus urinaria in HBeAg-positive patients with CHB who had HBV DNA levels exceeding 500,000 copies/mL and elevated ALT levels. (81) Participants were randomly assigned to receive Phyllanthus urinaria at 1, 2, or 3 g three times daily for six months, or a placebo. (81) The study mainly measured HBV DNA reduction, with HBeAg seroconversion and ALT normalization as additional outcomes. (81) Intention-to-treat analysis showed no significant difference in HBV DNA reduction among the treatment groups relative to placebo. (81) Rates of HBeAg seroconversion and ALT normalization were also not significantly different across groups. (81) At the 24-week follow-up after treatment, no delayed reactions were observed, and the intervention was not linked to any serious adverse events. (81) Overall, six months of Phyllanthus urinaria administration demonstrated no measurable antiviral effect in patients with CHB. (81)

Furthermore, a 2018 Italian double-blind, placebo-controlled, parallel-group trial examined the efficacy and safety of 12 months of treatment with Phyllanthus niruri in subjects with CHB infection. (82) Participants underwent clinical evaluations at baseline and at monthly intervals of 1, 3, 9, and 12 months during the treatment period, with an additional assessment conducted 6 months after treatment ended. (82) Over the first two years, 50 eligible subjects enrolled, of whom 47 completed all study visits (a 6% dropout rate): 24 of 26 (92%) in the Phyllanthus group and 23 of 24 (96%) in the placebo group. (82) At the 12-month point, viral load levels did not show a significant difference between the study groups, and none of the participants achieved clearance of HBsAg. (82) Regarding safety, renal function parameters remained unchanged in both groups throughout the treatment period, and no serious adverse events were reported. (82) The study was discontinued at the end of the second year due to a

lack of demonstrable treatment benefit. The results do not support the use of Phyllanthus niruri in managing CHB. (82)

Regarding RCTs carried out to assess the effectiveness of Phyllanthus on MASLD, an example is a 2013 Chinese placebo-controlled, double-blind RCT that investigated whether Phyllanthus urinaria was more effective than placebo in improving the histological NAS in 60 patients with confirmed NASH. (83) Participants were randomized to Phyllanthus (n=40) or placebo (n=20) for 24 weeks. (83) Changes in NAS, steatosis, lobular inflammation, ballooning, fibrosis, liver biochemistry, and metabolic profile showed no significant differences between the two groups. (83) Although modest reductions in hepatic steatosis and ballooning were observed within the Phyllanthus group, these changes had limited clinical significance. (83) Overall, Phyllanthus was not more effective than placebo in improving the NAS in NASH patients. (83)

Another 2023 study in Malaysia evaluated the effectiveness of Phyllanthus for MASLD through a 12-month RCT. (84) It assigned adults with mild-to-moderate MASLD (CAP score >250 dB/m, fibrosis score <10 kPa) to receive standardized Phyllanthus niruri 3,000 mg daily (n=112) or a placebo (n=114). (84) The primary outcomes included changes in the CAP score and liver enzyme levels. (84) No significant differences between the groups were observed in CAP score or liver enzyme levels. (84) However, the intervention group showed a significantly greater reduction in fibrosis score compared to the placebo group, and no clinically significant adverse events were reported. (84) Although Phyllanthus niruri did not significantly improve CAP scores or liver enzymes in patients with mild-to-moderate MASLD, its notable impact on fibrosis score warrants further investigation. (84)

7.3. Phyllanthus Conclusion

In conclusion, the clinical evidence on Phyllanthus for liver diseases shows a mixed picture. While two trials, especially those against interferon, suggested promising hepatoprotective effects (particularly in restoring liver function in CHB), subsequent well-designed RCTs have largely failed to show significant antiviral or hepatoprotective benefits over placebo. In both HBV and fatty liver disease, Phyllanthus demonstrated limited effectiveness in achieving primary outcomes, including viral load reduction, HBsAg clearance, and improvement in the NAS. Notable exceptions include increased total antioxidant levels in alcoholic hepatitis and a considerable reduction in fibrosis score among MASLD patients. These data indicate that although Phyllanthus may exert modest biological effects (especially in diminishing oxidative

stress and fibrosis), its clinical utility is still uncertain. The existing trials are further limited by small sample sizes, high risk of bias, short follow-up periods, and inconsistent reporting of outcomes. Subsequent research should focus on larger, well-powered RCTs applying standardized Phyllanthus preparations, clearly defined patient populations, and comprehensive outcome measures to better assess its value in the treatment of liver disease.

8. Green Tea (Camellia sinensis)

8.1. Introduction

Green tea (Camellia sinensis) is an unfermented variety of tea that largely retains the natural compounds found in fresh leaves. (85) Tea has an extensive historical heritage, originating in China and spreading worldwide via various channels. (85) Today, about 3 billion people drink it, making it one of the most popular non-alcoholic beverages. (85) Different countries classify tea using their own standards. (85) Chinese tea is divided into six main categories based on the level of fermentation: green tea, black tea, white tea, yellow tea, Oolong tea, and dark tea. (85) As the earliest known type, green tea is unfermented and retains more natural compounds from fresh leaves, with minimal vitamin loss. (85) This gives green tea its distinctive qualities: a clear brew, a bright green color, and a strong astringent taste. (85) Several studies have shown that green tea contains various bioactive compounds with important effects on human health. (85)

Image: The leaves of Camellia sinensis (86)

The chemical composition of green tea is remarkably varied and complex, comprising multiple compound classes, including polyphenols, alkaloids, proteins, minerals, vitamins, and amino acids. (87) Its general popularity is mainly attributed to its well-documented health-promoting properties, including anticancer, antioxidant, anti-hypercholesterolemic, and antimicrobial activities, as well as its demonstrated role in supporting body weight

reduction. (87) The available RCTs, reviews, and mechanistic studies suggest that green tea may improve liver enzymes, lipid profile, body measurements, and oxidative stress markers in MASLD. Still, the studies are limited by small samples, short duration, and inconsistent dosing, so stronger trials are needed before firm conclusions can be made.

8.2. Studies on Green Tea as Treatment for Liver Diseases

An example of evidence supporting green tea as a treatment for MASLD comes from a 2013 Japanese randomized, double-blind study conducted over 12 weeks. (88) This study examined the effects of high-density catechin green tea on 17 MASLD patients, who were randomly assigned to receive either high-density catechin green tea, low-density catechin green tea, or a placebo. (88) Ultrasonography and CT scans were performed at baseline and after 12 weeks, with serum ALT levels and urinary 8-isoprostane monitored at 4, 8, and 12 weeks. (88) After 12 weeks, the high-density catechin group showed significant reductions in body fat, an improved liver-to-spleen CT attenuation ratio, and decreased serum ALT levels. (88) It also reduced urinary 8-isoprostane excretion compared to both the placebo and low-density catechin groups. (88) These results indicate that daily consumption of 700 ml of green tea containing more than 1 g of catechins over 12 weeks can reduce liver fat content and inflammation in patients with MASLD, indicating that catechins may have therapeutic potential in treating this condition. (88)

Another study showing a beneficial use of green tea in treating MASLD is a 2017 RCT in Pakistan, conducted from April to July 2016, which evaluated the effect of green tea extract supplementation on patients with MASLD. (89) Eighty overweight, non-diabetic, and dyslipidemic MASLD patients (diagnosed by ultrasound and aminotransferase levels) were randomly assigned to receive either green tea extract 500 mg capsules (n=40) or placebo capsules (n=40) twice daily. (89) Before and after treatment, assessments of anthropometric measurements, liver enzyme levels, inflammatory markers, and hepatic ultrasound imaging were performed and analysed using dedicated statistical software. (89) Green tea extract therapy resulted in considerable improvements in metabolic, biochemical, inflammatory, and radiological parameters in non-diabetic, dyslipidemic patients with MASLD, suggesting that dietary supplementation with green tea extract is a beneficial therapeutic option given the limited efficacy of available pharmacological treatments. (89)

A similar 2016 Iranian double-blind, placebo-controlled randomized clinical trial conducted over 90 days further supports these outcomes by examining the impact of green tea intake in

individuals with MASLD. (90) Eighty participants aged 20-50 years with MASLD, diagnosed via ultrasonography and having elevated ALT and AST levels, and no other liver diseases, were randomly assigned to receive either 500 mg green tea extract tablets daily or a placebo. (90) Weight, serum ALT, AST, and ALP levels were measured at baseline and at the end of the intervention in a fasting state, along with dietary data collection. (90) The green tea extract group showed significant reductions in ALT and AST levels after 12 weeks, while the placebo group exhibited non-significant reductions in the same markers. (90) ALP levels decreased significantly in both groups after 12 weeks. (90) These results indicate that green tea extract supplementation can effectively reduce hepatic enzyme levels in individuals with MASLD and may serve as a beneficial treatment strategy for improving liver biochemistry parameters. (90)

Another Iranian double-blind randomized clinical trial, published in 2017, assigned MASLD patients to receive either 550 mg of green tea tablets daily with nutritional education (n=21) or a placebo with the same protocol (n=24) for three months. (91) Significant differences between the groups were observed in BMI, AST, and FBS, while changes in total iron-binding capacity, ferritin, ALT, HOMA-IR, and body weight were not significant. (91) Green tea showed positive effects mainly on anthropometric, liver enzyme, and metabolic parameters. (91) However, the authors noted that the limited findings could be due to the short duration, small sample size, lower extract dose compared to other studies, and the confounding effects of routine treatments both groups received. (91)

Based on searches of PubMed, Scopus, Web of Science, and Google Scholar up to October 2017, a 2017 Iranian systematic review and meta-analysis combined findings from four studies examining the effects of green tea supplementation on MASLD. (92) Considerable improvements were noted across several parameters, including ALT, AST, BMI, triacylglycerol, total cholesterol, and LDL cholesterol, although no significant changes were observed in HDL cholesterol or HOMA-IR levels. (92) These data collectively support the potential role of green tea supplementation in MASLD management strategies. (92)

While other studies were conducted in humans, another RCT was performed in mice. (93) A 2024 Chinese study explored possible pathways through which epigallocatechin gallate in green tea may improve MASLD, identified interaction sites between epigallocatechin gallate and dipeptidyl peptidase-4, and proposed new clinical treatment strategies. (93) This controlled trial examined the effectiveness of green tea epigallocatechin gallate in patients

with MASLD by comparing relevant indices before and after treatment. (93) MASLD animal models were created using male mice fed a high-fat diet, intending to evaluate the liver effects of green tea and epigallocatechin gallate while investigating the underlying biological mechanisms. (93) The interaction between green tea epigallocatechin gallate and dipeptidyl peptidase 4 was further studied using HepG2 cell lines treated with oleic acid and palmitic acid, along with plasmids with disrupted sites to identify effective interaction points. (93) Green tea, epigallocatechin gallate, was found to reduce lipid accumulation, inhibit inflammation, restore disrupted lipid metabolism, and improve MASLD development by lowering dipeptidyl peptidase 4 expression and activity. (93) These data suggest that green tea, epigallocatechin gallate, has a protective effect on MASLD and affords promising opportunities for safe and effective clinical application management. (93) The significance of this finding resides in its potential for translation, indicating that the therapeutic benefits of green tea seen in experimental models could also apply to human MASLD patients.

8.3. Green Tea Conclusion

In conclusion, the evidence from RCTs, systematic reviews, and mechanistic studies consistently indicates that green tea supplementation could be a beneficial addition to managing MASLD. Multiple studies show that green tea and its main bioactive compound, epigallocatechin gallate, have led to considerable improvements in liver enzymes, lipid profiles, anthropometric measures, and oxidative stress markers. The discovery of how epigallocatechin gallate interacts with dipeptidyl peptidase 4 further supports its hepatoprotective effects at the molecular level. However, several limitations remain in the existing research, such as small sample sizes, short durations, varying dosages, and confounding effects from other treatments. To better confirm green tea's therapeutic potential for MASLD and turn promising initial findings into routine clinical practice, future studies ought to focus on well-designed, adequately powered RCTs with standardized preparations and longer follow-up periods.

9. Artichoke

9.1. Introduction

Artichoke (Cynara) is a small genus native to the Mediterranean region, comprising two cultivated species (globe artichoke and cardoon) and their wild ancestor, wild cardoon. (94) The earliest mention of artichoke dates back to the 4th century BC, credited to the ancient Greek writer Theophrastus (c. 371- c. 287 BCE), with the plant being highly valued by

Greeks and Romans of ancient times for its culinary and medicinal uses. (94) Globe artichoke has the most extensive documentation in folk medicine among the three artichoke varieties. (95) It has been utilized in its leaf, root, and immature flowerhead forms, traditionally employed for a range of therapeutic purposes, including improving liver function, lowering lipids, and relieving dyspepsia. (95)

Image: An artichoke (96)

The secondary products derived from artichoke (including its leaves, outer bracts, and stems) contain a wide variety of bioactive compounds that have been thoroughly investigated and documented. (97) These components are notable for their low-fat content and elevated levels of vitamin C, insoluble dietary fiber, inulin, and key minerals, including potassium, sodium, and phosphorus. (97) Additionally, these by-products contain significant quantities of phenolic compounds and their derivatives, particularly flavonoids and hydroxycinnamic acids. (97) This review suggests that clinical evidence consistently supports artichoke leaf extract as an encouraging liver-protecting agent in MASLD management, exhibiting significant improvements in liver enzymes, lipid profiles, and sonographic parameters over multiple studies. However, limitations such as small sample sizes and variable dosages point to the need for further well-designed research to confirm these outcomes.

9.2. Studies on Artichoke Treatment for Liver Diseases

A few RCTs evaluated the effectiveness of artichoke in treating MASLD. All of them showed positive results. A 2016 Iranian randomized, double-blind clinical trial assessed the therapeutic effects of artichoke (Cynara scolymus) on biochemical and liver biomarkers in 60 NASH patients diagnosed based on elevated liver enzymes and sonographic findings. (98) Participants meeting inclusion criteria were those with ALT/AST levels above 30 µ/L and fatty liver confirmed by sonography, along with one or more of the following metabolic indicators: elevated total cholesterol, reduced HDL, raised triglycerides, elevated FBS,

obesity as defined by BMI, or hypertension exceeding 130/85 mmHg. (98) Administration of Cynara scolymus produced significant reductions in body weight, ALT, AST, blood sugar, total cholesterol, LDL, triglycerides, and systolic blood pressure. (98) By contrast, the placebo group showed significant reductions only in body weight, ALT, and AST, while blood sugar and lipid profiles remained unchanged. (98) The researchers attributed these beneficial effects to artichoke's active constituents (particularly flavonoids and caffeoylquinic acid), which have demonstrated hepatoprotective and hypolipidemic properties. (98)

Another RCT with similar results is a 2018 Iranian randomized, double-blind, placebo-controlled parallel-group trial that evaluated the therapeutic utility of artichoke leaf extract in 100 patients with ultrasound-diagnosed MASLD, who were randomized to receive 600 mg of artichoke leaf extract daily or a placebo for two months. (99) MASLD response was assessed using liver ultrasound and serological markers, including the AST/ALT ratio and the APRI score. (99) Ninety patients completed the study (49 on ALE, 41 on placebo) with no reported side effects. (99) Compared to the placebo, treatment with artichoke leaf extract showed significant improvements across several parameters: Doppler sonography showed increased hepatic vein flow, a narrowing of the portal vein diameter, and a reduction in overall liver size, all reaching statistical significance. (99) There were also statistically significant decreases in serum ALT and AST levels, along with improvements in the AST/ALT ratio, APRI score, and a decline in total bilirubin levels. (99) Additionally, artichoke leaf extract significantly lowered total cholesterol, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, and triglyceride levels. (99) These data suggest that artichoke leaf extract supplementation offers meaningful benefits to ultrasound liver parameters and serum hepatic markers in patients with MASLD. (99)

A recent study from 2026 is a German randomized trial, the first to investigate artichoke leaf extract in bariatric surgery candidates. (100) It assigned 40 participants to either receive artichoke leaf extract or a placebo for six weeks. (100) Hepatic steatosis was measured using fibroscan, while liver size was assessed via ultrasound. (100) Secondary outcomes included serum parameters and body composition measured by bioelectrical impedance measurement. (100) The study found that artichoke leaf extract significantly lowered fibroscan scores and liver lobe diameters compared to placebo, with improvements seen as early as three weeks. (100) Female participants showed reductions in total and LDL cholesterol levels, although AST levels increased in the group taking artichoke leaf extract. (100) Fat mass percentage also decreased. (100) Overall, the extract effectively reduced liver fat and volume and

improved body composition in patients with obesity and MASLD. (100) However, the researchers concluded that additional research in this population beyond the pre-bariatric setting is warranted. (100)

Adding to these findings, a 2022 Egyptian systematic review and meta-analysis adhering to PRISMA guidelines synthesized evidence from RCTs examining the use of artichoke leaf extract in patients diagnosed with MASLD, with relevant studies retrieved through systematic electronic database searches. (101) The meta-analysis showed that artichoke leaf extracts significantly reduce AST, ALT, and ALP levels in patients with MASLD, supporting its use as a safe and effective hepatoprotective agent in MASLD management. (101) In addition to confirming clinical effectiveness, the review provides preliminary insights into how artichoke leaf extract exerts its biological effects, attributing these to the complex interactions among its phytochemical components. (101) However, the authors note that these mechanistic findings are still preliminary and need confirmation through more detailed clinical studies using isolated compounds. (101) Furthermore, whether combining artichoke leaf extract with other natural agents, such as bergamot, or synthetic drugs, like pioglitazone and rosiglitazone, can improve therapeutic results while allowing for lower doses remains an open question that warrants further investigation. (101)

9.3 Artichoke Conclusion

In conclusion, the existing clinical evidence from RCTs and meta-analyses consistently shows that artichoke leaf extract has significant therapeutic potential for managing MASLD and NASH, with notable improvements in liver enzyme levels, lipid profiles, and sonographic parameters. Its well-known bioactive compounds (especially flavonoids and caffeoylquinic acid) seem to be responsible for its hepatoprotective and hypolipidemic effects. However, current studies are limited by small sample sizes, varying dosages, and short follow-up periods, and some findings, such as the AST elevation observed in obese patients, require further research. Future well-designed trials with standardized artichoke leaf extract preparations, larger sample sizes, and longer follow-up periods are necessary to fully determine its therapeutic role and investigate the potential benefits of combined therapies for MASLD.

10. Ginger

10.1. Introduction

Ginger (Zingiber officinale Rosc.) originates from the Indo-Malayan region and is now widely distributed throughout the tropics of Asia, Africa, the Americas, and Australia, with India and China regarded as the primary centers of origin. (102) Although cultivated ginger is sterile, it shows significant variation in rhizome morphology and vegetative traits. (102) Growing recognition of this plant's diverse healing properties across various ailments has gradually established it as a crop of substantial medicinal value. (102) Key factors influencing end-product quality include yield traits and chemical constituents such as essential oil, fiber, and oleoresin content, along with both volatile and non-volatile compounds. (102) The essential oil fraction of ginger contains a wide range of monoterpenes and sesquiterpenes, including zingiberene, sesqui-phellandrene, bisabolene, camphene, phellandrene, curcumene, cineole, geranyl acetate, terpineol, borneol, geraniol, limonene, linalool, and farnesene, many of which are linked to therapeutic benefits. (102)

Image: A ginger root (102)

In traditional Chinese medicine, fresh ginger and dried ginger are considered two separate herbal medicines, differing in cultivation, appearance, functional properties, and traditional uses applications. (103) They are used for stomachache, diarrhea, nausea, cholera, asthma, respiratory disorders, and rheumatism. (102) Its use extends to African, West Indian, and Mediterranean traditions, where it is used for arthritis, muscular discomfort, and various other ailments. (102) In folk and ethnic medicine, ginger acts as a remedy for pain, convulsions, fever, indigestion, and tuberculosis, while fresh ginger juice is traditionally given during labor to help with delivery. (102) In some tribal practices, ginger combined with Piper longum has also been used as an abortifacient. (102) Although promising evidence from RCTs and a meta-analysis shows significant improvements in ALT, insulin resistance, and inflammatory markers with ginger supplementation in MASLD, the consistently null findings

concerning AST and hepatic fibrosis across studies require further large-scale, longer-duration trials to clearly determine its therapeutic role.

10.2. Studies on Ginger Treatment for Liver Diseases

All RCTs I reviewed assessing the effectiveness of ginger in treating MASLD have shown it to be beneficial. In a 2016 Iranian 12-week randomized, double-blind, placebo-controlled trial, 44 patients with MASLD were assigned to receive either 2g/day of ginger supplementation or a placebo, along with a modified diet and physical activity program. (104) Ginger supplementation resulted in significant reductions in ALT, γ-glutamyl transferase, inflammatory cytokine levels, the insulin resistance index, and hepatic steatosis grade compared to placebo. (104) However, there was no meaningful effect on hepatic fibrosis or AST levels from the intervention. (104) The authors concluded that 12 weeks of ginger supplementation provided beneficial effects on several MASLD parameters and recommended further research to determine the long-term impact of supplementation. (104)

Another Iranian study from 2020 supports previous findings. (105) A 12-week randomized clinical trial enrolled 46 MASLD patients and split them into two groups: one receiving 1,500 mg/day of ginger in three 500 mg capsules, and the other a placebo. (105) All participants followed a structured diet and exercise plan. (105) Liver ultrasonography, anthropometric measurements, and biochemical tests were conducted at the start and end of the study. (105) Ginger supplementation significantly reduced ALT, total cholesterol, LDL-C, fasting blood glucose, HOMA-IR, hs-CRP, and fetuin-A compared to the placebo. (105) However, no statistically significant differences were observed in body weight, fasting insulin, HDL-C, triglycerides, adiponectin, TNF-α, TAC, GGT, AST, fatty liver index, fatty liver grade, or blood pressure. (105) The authors concluded that ginger supplementation could be a helpful complementary therapy for reducing insulin resistance, liver enzymes, and inflammation in MASLD patients. (105)

Favourable outcomes were also reported in a 2023 Iranian study, which enrolled 76 patients with concurrent T2DM and MASLD in a two-arm, double-blind, placebo-controlled trial. (106) Participants were randomly assigned to receive twice-daily 1,000 mg ginger powder capsules or a placebo for three months. (106) Anthropometric, blood pressure, biochemical, and imaging parameters were measured at baseline and after the intervention. (106) Both groups showed significant reductions in BMI, waist and hip circumferences, and liver transaminases. (106) In the ginger group, notable improvements were also observed in

systolic and diastolic blood pressure, serum insulin, HOMA-IR, and HDL-cholesterol compared to baseline. (106) However, no meaningful differences between groups were found in inflammatory markers or fibroscan-derived indices, including steatosis percentage and CAP. (106) The researchers concluded that while ginger supplementation improved blood pressure, insulin resistance, and HDL-cholesterol, it did not meaningfully impact inflammatory markers or fibroscan imaging parameters, and recommended further trials with longer durations and larger sample sizes. (106) It should be noted, however, that this study enrolled patients with concurrent T2DM and MASLD, representing a distinct metabolic subpopulation compared to previous trials, which may limit how directly its findings can be compared to studies conducted in MASLD patients without diabetes. (106)

A 2023 Chinese meta-analysis of RCTs confirmed the results presented above. (107) It searched PubMed, Embase, Web of Science, EBSCO, and the Cochrane Library through November 2021 to assess the effectiveness of ginger supplementation versus placebo in MASLD. (107) Four RCTs involving 177 patients were included, with analysis conducted using a random-effects model. (107) Compared to placebo, ginger supplementation resulted in significant reductions in both ALT levels and HOMA-IR values. (107) No notable effects were seen on AST, total cholesterol, LDL, or BMI. (107) The researchers concluded that ginger supplementation offers benefits in managing MASLD, especially in improving liver enzyme levels and insulin resistance. (107)

10.3. Ginger Conclusion

In summary, the available clinical evidence consistently supports the hepatoprotective potential of ginger supplementation in managing MASLD. Multiple RCTs and a meta-analysis show that ginger supplementation significantly improves ALT, insulin resistance, and inflammatory markers, with some studies also noting benefits in lipid profiles and blood pressure. However, its effects on AST and hepatic fibrosis remain consistently non-significant across studies. These findings suggest that ginger is a promising complementary therapy for MASLD, but further large-scale, long-term trials are necessary to establish its role more clearly.

11. Discussion

This literature review systematically evaluated the clinical evidence on nine distinct herbal medicines used to manage CLD, with a focus on results from RCTs and meta-analyses. The findings explicitly indicate the extent to which each herbal intervention demonstrates

efficacy, safety, and therapeutic potential for specific liver conditions. In the following summary, the main conclusions and clinical implications drawn from the collective body of evidence are clearly outlined:

Table:

Herb	Liver Disease	Attributed Properties	Study Type	Study Results	Conclusion
Silymarin	MASLD, NASH, ALD, Viral hepatitis, Cirrhosis	Antioxidant, antifibrotic, hepatoprotective, anticancer, Promotes liver cell regeneration	RCTs, meta-analyses, Cochrane review, systematic review	Potential for benefit in MASLD (liver enzymes, fibrosis indices, steatosis); inconsistent results in ALD and viral hepatitis	Potential benefit evidence in MASLD; insufficient evidence in other liver diseases; further high-quality trials needed
Curcumin	MASLD, NASH, Cirrhosis	Anti-inflammatory, antioxidant, modulates cytokines, transcription factors, and kinases.	RCTs, animal studies, meta-analysis	Beneficial in animal models; mixed results in humans; improvements in liver enzymes and metabolic markers, but no significant between-group differences in fibrosis/steatosis in several trials	Promising but inconclusive in humans; poor bioavailability is a key limitation; nanoparticle delivery may improve efficacy.
Berberine	MASLD, MASLD, NASH	Immune-regulatory, antioxidant, cardioprotective, hepatoprotective, lipid-regulating	RCTs, meta-analyses, animal studies, lipidomic analysis	Positive effects on hepatic fat, liver enzymes, lipid profiles, and insulin resistance in several trials; no significant effect on visceral fat or liver fat in one large trial	Mixed evidence; favorable safety profile; larger high-quality RCTs needed

Resveratrol	MASLD	Antioxidant, anti-inflammatory, antidiabetic, cardioprotective, and modulates oxidative stress.	RCTs, meta-analyses	Two early trials showed benefit at lower doses; higher dose trials showed no significant effect; few trials showed worse outcomes than placebo; three meta-analyses found insufficient evidence.	Inconsistent and inconclusive; safety concerns regarding elevated liver enzymes; further research needed
Glycyrrhizin	CHB, CHC, MASLD	Anticancer, anti-inflammatory, hepatoprotective, antiviral	RCTs, meta-analysis	Consistent ALT reduction in hepatitis B and C across multiple trials; effect not sustained post-treatment; no viral load reduction; no histological benefit; single MASLD trial showed promising results	Most consistent evidence among reviewed herbs in viral hepatitis: biochemical but not histological benefit; MASLD evidence limited to one trial
Phyllanthus	CHB, Alcoholic hepatitis, MASLD/NASH	Antioxidant, antidiabetic, modulates glucose homeostasis, enhances insulin sensitivity	RCTs, meta-analysis	Limited efficacy in primary outcomes across most trials; significant antioxidant improvement in alcoholic hepatitis; significant fibrosis reduction in one MASLD trial; no antiviral benefit demonstrated	Limited clinical efficacy overall; modest biological activity in oxidative stress and fibrosis; high risk of bias across trials; further research warranted

Green Tea	MASLD	Anticancer, antioxidant, anti-hypercholesterolemic, antimicrobial, body weight reduction	RCTs, meta-analysis, animal and cell studies	Consistent improvements in ALT, AST, lipid profiles, BMI, and oxidative stress markers across multiple trials.	Consistently beneficial in MASLD; limited by small sample sizes and short durations; larger standardized trials needed
Artichoke	MASLD, NASH	Hepatoprotective, hypolipidemic; active constituents: flavonoids and caffeoylquinic acid	RCTs, meta-analysis	All identified RCTs showed beneficial results; significant improvements in liver enzymes, lipid profiles, sonographic parameters, and portal vein parameters.	Consistently positive evidence in MASLD; limited by small sample sizes and variable dosages; further research needed
Ginger	NAFDL	Antioxidant, anti-inflammatory, hypolipidemic, insulin-sensitizing; active constituents: gingerols, shogaols, zingiberene	RCTs, meta-analysis	All identified RCTs showed beneficial results in ALT, insulin resistance, and inflammatory markers; consistently null findings for AST and hepatic fibrosis.	Promising complementary agent in MASLD; evidence base limited to small, short-duration trials; larger trials needed

The methodological limitations identified across the reviewed literature collectively undermine the strength and applicability of the current evidence on herbal interventions for liver disease. Specifically, many trials suffer from small sample sizes, short intervention periods, inconsistent dosing protocols, and heterogeneous or poorly defined patient populations. These factors limit both the generalizability of individual studies and the validity of cross-study comparisons. Additionally, research efforts have disproportionately focused on herbal treatments for MASLD, while conditions such as ALD, viral hepatitis, and cirrhosis

remain underrepresented in the evidence base. Glycyrrhizin constitutes a notable exception, having been more extensively evaluated in the context of viral hepatitis.

Another challenge is the consistent gap between animal and human study results, evident with curcumin, which demonstrated strong hepatoprotective effects in rodent models yet yielded mixed or inconclusive findings in human trials. This pattern likely reflects both species-specific differences in metabolism and, in curcumin's case specifically, poor oral bioavailability driven by limited intestinal absorption and rapid metabolic degradation. These limitations collectively constrain the ability to draw robust conclusions about clinical efficacy or inform practical therapeutic recommendations for the broader spectrum of liver diseases.

12. Conclusion

This thesis aimed to critically analyse the evidence for herbal treatments for liver diseases, focusing on their mechanisms of action, effectiveness, and safety. From a broader perspective, the findings of this review indicate that herbal medicines may be promising complementary agents in the management of chronic liver diseases, particularly given the limited availability of approved pharmacological treatments for conditions such as metabolic dysfunction-associated steatotic liver disease. It is important to clarify, however, that based on current evidence, none of the herbs reviewed should be recommended as a primary or standalone therapeutic intervention for chronic liver disease. Rather, their use should remain limited to adjunctive or supportive care until more robust and conclusive research is available.

The consistently favourable safety profiles reported across most herbs support their continued evaluation in clinical research, though future investment should be prioritized toward the most promising candidates (particularly artichoke, green tea, and glycyrrhizin) which demonstrated the most consistent positive findings across reviewed trials, while compounds such as resveratrol, which showed both weak efficacy and safety concerns, warrant more cautious further investigation. Future studies should focus on methodologically strict randomized controlled trials employing standardized herbal preparations, validated outcome measures, and extended follow-up periods. Further research into combination therapies and optimized dosing strategies (particularly for compounds with limited bioavailability, such as curcumin) is warranted. By clearly defining these boundaries, future investigations can help bridge the gap between the pharmacological potential of herbal compounds and their evidence-based clinical application.

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