Mechanistic pathway of herbs in the amelioration of NAFLD: A systematic review

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Abstract. Non-alcoholic fatty liver disease (NAFLD) is identified by lipid accumulation in the liver and liver injury due to obesity and metabolic syndrome. Herbs have been used in the treatment of various diseases, including liver disease. The present systematic review aimed to identify plants and the doses used in the management and prevention of NAFLD, as well as to assess the safety of these plants and determine their mechanisms of action, providing the preclinical evidence-based usage of herbs. Scientific databases, namely, Scopus, PubMed, Springer, NCBI, Google Scholar, Science Direct, and Web of Science were searched with key words, such as 'non-alcoholic fatty liver disease', 'non-alcoholic steatohepatitis', 'metabolic-associated fatty liver disease', 'medicinal plants', 'hyperlipidemia' and 'plant extracts' from January, 2016 to November, 2023. Manual screening, quality assessment, and data extraction of the search results were performed according to the inclusion and exclusion criteria. Herbs were identified which were able to ameliorate NAFLD symptoms in rodents through lipid metabolism, insulin resistance, inflammation and oxidative stress. These herbs were identified to lead to a reduction in steatosis in the histopathological assessment. The acute or chronic toxicity studies were not found to indicate any signs of toxicity. The present study provides information on the highest dose evaluated and which was effective against NAFLD, with safety assessment in studies using rats. Since chronic liver diseases progress over a long period of time with minimal or no symptoms, the consumption of herbs may provide alternative treatment strategies for the prevention of NAFLD. Further studies are warranted however, to identify their bioactive compounds for drug development or for the standardization of crude extracts. Drug-herb interactions also need to be further evaluated when used concurrently with drugs.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is a type of liver disease that is becoming increasingly common due to the global obesity epidemic (1). It is estimated that approximately one-third of the world's population suffers from this condition (2). Typically, NAFLD is associated with obesity, but it also affects non-obese individuals (3). Notably, NAFLD is often linked to increased mortality rates in individuals with other health conditions, such as cardiovascular complications, type 2 diabetes, chronic kidney disease, hypothyroidism, polycystic ovarian syndrome and psoriasis (4,5).

Understanding its pathogenesis is crucial for developing effective treatment strategies. Of note, two theories, namely the 'two-hit' (6) and 'multiple parallel hit' (7), have been proposed to explain the development of NAFLD/NASH. The two-hit theory suggests that the accumulation of fat in the liver (hepatic steatosis) occurs initially, followed by NASH due to subsequent 'second hits'. On the other hand, the multiple parallel hit theory suggests that the development of steatosis and inflammation occurs simultaneously due to various risk factors such as obesity, insulin resistance, and dyslipidemia. Both theories provide insight into the intricate pathogenesis of NAFLD, which involves the interaction between hepatic fat, inflammation, oxidative stress and insulin resistance (7).

An imbalance in the accumulation and clearance of fat in the liver due to overnutrition causes hepatic steatosis (Fig. 1). This condition is closely related to insulin resistance, which is commonly observed in obese individuals and affects nutrient metabolism and tissue nutrient distribution (8). In cases of peripheral insulin resistance, the liver experiences an inflow of free fatty acids, which leads to the accumulation of fat in the liver in the form of triglycerides. This process is often accompanied by increased levels of lipotoxicity resulting from high levels of free fatty acids, free cholesterol and other lipid metabolites. Consequently, the liver experiences mitochondrial dysfunction, oxidative stress, the production of reactive oxygen species (ROS) and endoplasmic reticulum

(ER) stress-associated mechanisms (9) This triggers the activation of the pro-inflammatory transcription factor, nuclear factor-κB (NF-κB), playing a pivotal role in the regulation of pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-6 and tumor necrosis factor-α (TNF-α) in NAFLD (10), causing both liver damage and an increase in the numbers of inflammatory cells (11). All chronic liver diseases progress over a long period of time, with severe liver disease being more common among older populations (2). Currently, the most reliable method used for the diagnosis of NAFLD is the through histopathological assessment of a liver biopsy (12).

The management of patients with NAFLD involves lifestyle changes, such as weight loss through diet and exercise. Recently, the US Food and Drug Administration approved Rezdiffra (resmetirom) for NASH treatment (13). In addition, lipid-lowering medications, insulin sensitizers and antioxidants have been used for treatment (14). Herbal remedies have been used as an alternative to the current medications.

Herbs have been used in traditional medicine for the treatment of various diseases since ancient times. Some herbs, such as milk thistle or *Silybum marianum*, have been evaluated in clinical trials to assess their efficacy as a treatment for NAFLD. Silymarin, which is extracted from milk thistle and contains a mixture of flavonolignans, is the most extensively studied plant for liver disease (15). In a previous meta-analysis of eight randomized clinical trials of 622 patients (16), silymarin was shown to reduce fasting blood glucose levels, insulin resistance, and triglyceride, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels (Table I).

Berberine, an isoquinoline alkaloid isolated from the traditional Chinese medicinal herb, *Coptis chinensis*, has also been studied in numerous clinical trials. In 18 randomized clinical trial results selected from 1,660 studies related to berberine (17), berberine alone in patients with metabolic disorders was shown to lower lipid and sugar levels, and to ameliorate insulin resistance (Table I). This effect becomes evident with a treatment time >3 months. The lipid-lowering effect of berberine was used as an alternative treatment for patients who do not tolerate statins (18). Statins are widely used as a lipid-lowering drug; however, they can cause side-effects such as high blood glucose levels and cannot be used by diabetic patients (19). Other side-effects included memory and cognitive impairment, which can cause unusual swelling in the neurons of patients taking statins (20).

Resveratrol, a polyphenol found in a variety of plant species, including grapes, peanuts and berries, has been evaluated in some clinical trials; however, the results obtained were rather mixed from the four randomized, double-blinded, placebo-controlled trials involving 156 patients (21). Although some positive effects of resveratrol were observed on metabolic parameters, the improvement in liver function and fatty liver for silymarin (22), berberine (23) and resveratrol (24,25) was less apparent than was expected (Table I). Given the controversial results, larger scale and well-designed population-based clinical studies are recommended to fully elucidate the efficacy of resveratrol.

Although a number of herbs that are traditionally used for the treatment of liver diseases have not undergone clinical trials, they are still used to treat diseases. Since the development of NAFLD takes a considerable amount of time, the long-term consumption of herbs may provide an alternative treatment strategy with which to prevent NAFLD. The present systematic review aimed to identify plants used in the management of NAFLD, and to determine their mechanisms of action and obtain data on their safety.

Data and methods

Search strategy. In order to explore the potential use of natural medicinal plants and plant extracts for the treatment of NAFLD, NASH and metabolic-associated fatty liver disease, a comprehensive search was conducted using relevant key words, such as 'medicinal plants', 'plant extracts', 'non-alcoholic fatty liver disease' and 'non-alcoholic steatohepatitis'. The search was performed across various databases, such as Scopus, PubMed, Springer, NCBI, Google Scholar, ScienceDirect and Web of Science. For this search, studies conducted between January, 2016 and November, 2023 were considered, with a focus on *in vivo* studies that evaluated the effectiveness of natural medicinal plants for the treatment of NAFLD. The mechanisms of action were supported by either *in vitro* or *in vivo* models.

Study selection. The present systematic review was conducted to explore the therapeutic potential of medicinal plants and herbal medicine in the treatment of NAFLD and steatohepatitis. The records for the review were collected from various scientific databases, such as Scopus, PubMed, Springer, NCBI, Google Scholar, Science Direct and Web of Science. The search was conducted using key words, such as 'fatty liver', 'NAFLD', 'plants', 'medicinal', 'herbal medicine' and 'therapeutic uses', and the data were limited to the period from 2016 to 2023. Inclusion criteria for the study were articles written in the English language, basic research studies and non-clinical studies. Conference abstracts, theses, case reports, reviews, commentaries and editorials were excluded. The author NEJ extracted the data, and both NEJ and SMJ independently screened all the retrieved abstracts using the inclusion and exclusion criteria. Any disagreements regarding inclusion were resolved through extensive discussion with the other two authors (RMS and CYC). Articles without liver histopathological assessment or positive drug and single-dose studies were excluded from the screening process.

Data extraction. After carefully applying the inclusion and exclusion criteria, a total of 55 articles were deemed relevant and selected for further analysis (as illustrated in Fig. 2). The information extracted from these articles was then organized and tabulated in an Excel spreadsheet. The key findings were subsequently summarized in three tables as follows: One detailing the traditional uses of the plants under investigation (Table II), the animal dietary model (Table III) and the other presenting the effects of these plants on NAFLD (Table IV).

Results and Discussion

Traditional usage of plants. It is noteworthy that >60% of the world's population, particularly in developing nations, relies mainly on medicinal plants for their healthcare needs. This renders traditional medicine a preferred healthcare system in

Table I. Clinical trial data for silymarin, berberine and resveratrol.

No.	Phytochemical	Glucose	Insulin	Lipids	Liver biochemical properties	Histopathological scores	(Refs.)
1	Silymarin	FBG↓ HbA1c↓	Insulin↓ IR↓ HOMA-IR↓	TG↓ TC and HDL (no effect)	ALT & AST↓ (no clinical relevance)	No data	(16,22)
2	Berberine	FBG↓	HOMA-IR↓	TG↓ TC↓ LDL↓ HDL↓	ALT & AST (No changes)	No data	(17,23)
3	Resveratrol	FBG↓	Insulin & HOMA-IR (no changes)	TC↓ LDL↑ HDL (no effect)	ALT & AST (no changes)	Fibrosis ↑, NAFLD activity score↓	(21,24,25)

↑, Upward arrows indicate an increase; ↓, downward arrows indicate a decrease. FBG, fasting blood glucose; IR, insulin resistance; HOMA-IR, homeostatic model assessment of insulin resistance; TG, triglycerides; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NAFLD, non-alcoholic fatty liver disease.

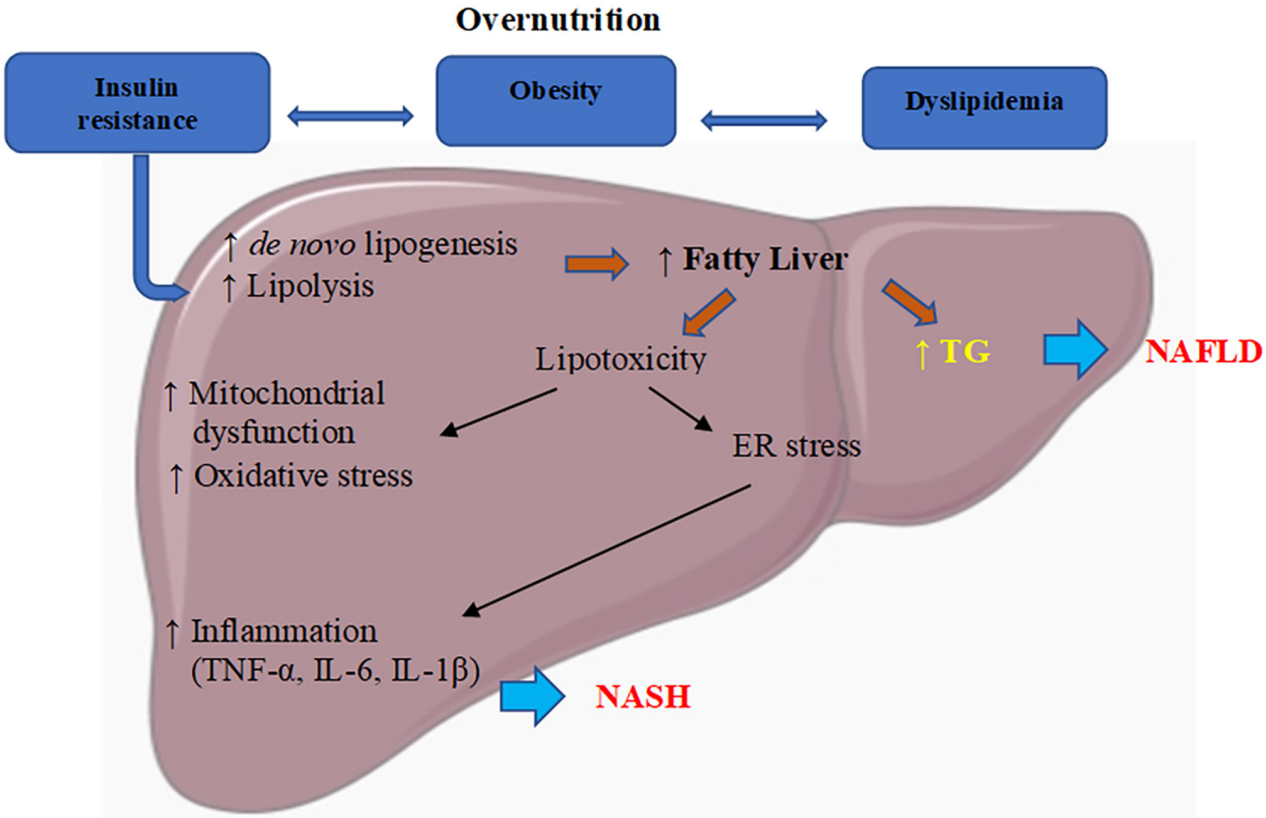

Figure 1. Pathophysiology of NAFLD. Overnutrition causes dyslipidemia, obesity, and IR. IR activates *de novo* lipogenesis and lipolysis, resulting in free fatty acid and triglyceride accumulation in the liver, leading to the development of NAFLD. Free fatty acids induce lipotoxicity, activate mitochondrial dysfunction, and oxidative and ER stress. Subsequently, this induces inflammatory signaling and stimulates the production of TNF-α, IL-6 and IL-1β, causing NASH. ER, endoplasmic reticulum; NAFLD, non-alcoholic fatty liver disease; IR, insulin resistance; TNF, tumor necrosis factor; IL, interleukin; TG, triglycerides.

a number of communities (26) due to its affordability, accessibility and low cost (27). As demonstrated in the present study, all the 20 herbs identified that were found to lead to a reduction in steatosis in liver histopathological analyses were traditionally used as herbal medicines for liver ailments, liver tonics, or for nourishing the liver (Table II) (28-62). This highlights the significance of traditional medicine in promoting liver health.

Animal dietary models. NAFLD is a condition characterized by the accumulation of excessive fat in the liver. This disease progresses from a simple state of liver steatosis to NASH

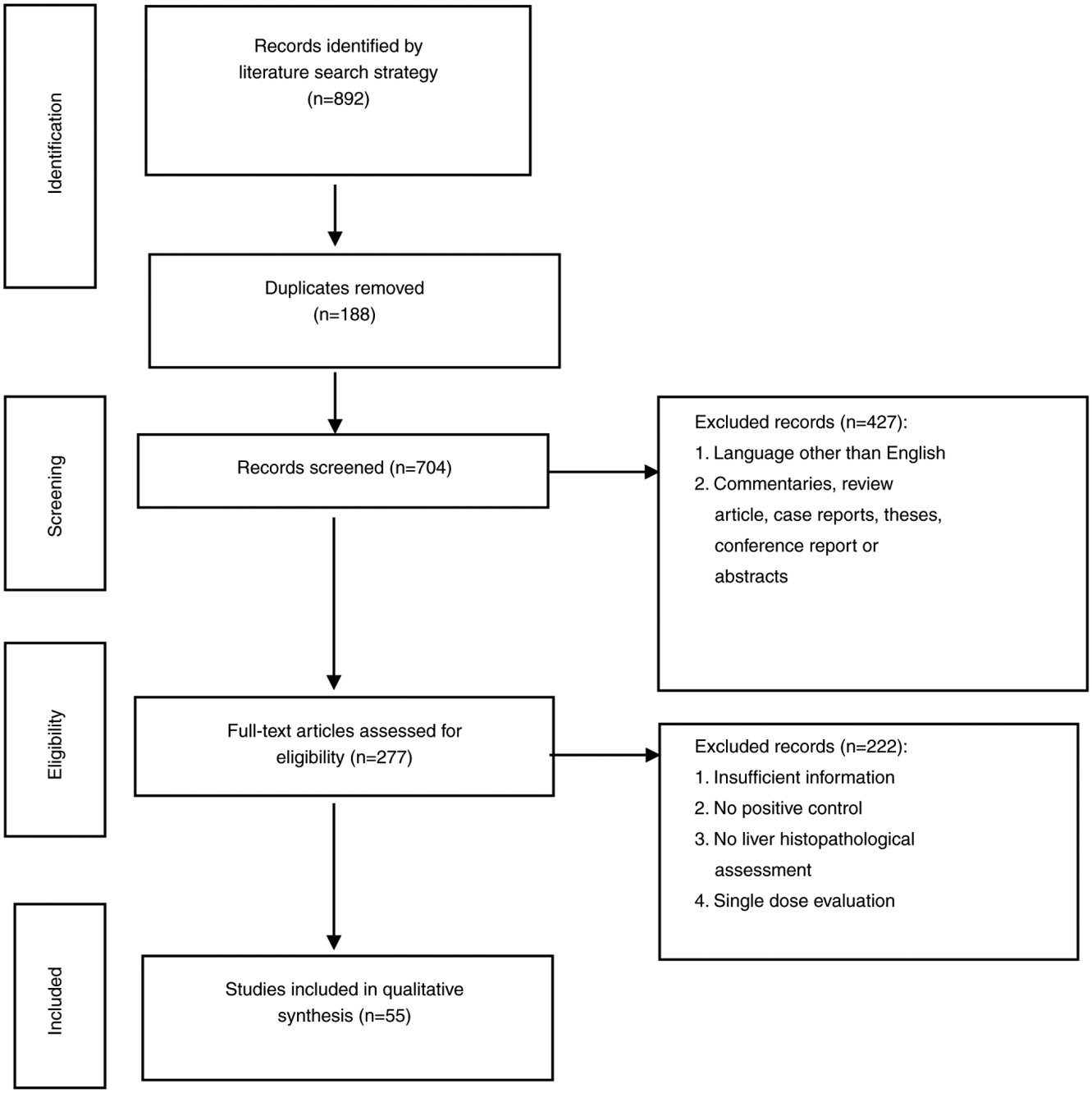

Figure 2. Flow chart demonstrating the process of article selection for the present systematic review.

and ultimately, into liver fibrosis, cirrhosis, and in severe cases, hepatocellular carcinoma (HCC). A review of the pathogenesis and histopathology of the disease in animals revealed that mice and rats are the commonly used models for the study of NAFLD (Table III). The C57BL/6 strain in mice, and the Wistar and Sprague-Dawley (SD) strains in rats are frequently used due to their inherent propensity to develop obesity, type 2 diabetes and NAFLD (63,64). The different stages of fatty liver are induced by altering the diet and chemicals used, including steatosis [confirmed by increased liver triglyceride levels, hepatocyte ballooning and Mallory bodies, also known as Mallory-Denk bodies (MDBs)], NASH, fibrosis and HCC, which are all dependent on the induction period.

When hepatocellular steatosis occurs with concurrent necro inflammatory reactions of the liver and hepatocellular ballooning with or without fibrosis and/or cirrhosis, it is diagnosed as NASH. Lobular inflammation and portal inflammation are both present in NASH, along with other histological lesions, such as hepatocellular ballooning, fibrosis, apoptotic bodies, sinusoidal collagen formation, MDBs, megamitochondria, glycogenated nuclei and iron deposition (64-66). The time of onset, as well as the degree of both NAFLD and accompanying metabolic features, are dependent on species, strain, sex, composition of the gut microbiota and the employed dietary intervention (67,68). Therefore, liver histology from animal models is crucial for elucidating the mechanisms and pathways involved in the pathogenesis of the NAFLD spectrum

Table II. Traditional usage of herbs.

No.	Plants	Family	Location	Part(s) used	Preparation	Traditional usage	(Refs.)
1	*Abroma augusta* L.	Sterculiaceae	India	Root, leaf	Infusions	Diabetes, amenorrhea, dysmenorrhea, urinary system, nourish the liver	(28,29)
2	*Antidesma bunius*	Euphorbiaceae	Bangladesh	Leaves, fruits, bark, roots seeds	Decoction Juices	Cough, stomachache, hepatoprotective	(30)
3	*Aralia elata*	Araliaceae	China	Root, stem bark, leaves	Decoction	Joint pain, bruises,lumps, abscess, hepatitis	(31,32)
4	*Cassia obtusifolia*	Leguminosae	Korea	Seeds	Pounded seeds	Diuretics, laxatives, tonics, dizziness, nourish the liver, constipation	(33,34)
5	*Citrus aurantium*	Rutaceae	China	Peel	Decoction	Laxatives, stomachic, emmenagogue, and dyspepsia, liver tonic	(35,36)
6	*Curcuma longa* Linn.	Zingiberaceae	India	Roots	Decoction Pounded roots	Asthma, liver disorders, anorexia, rheumatism, diabetic wounds, sinusitis	(37)
7	*Crocus sativus* L.	Iridaceae	Turkey	Flower stigma	Decoction	Insomnia, head, heart, asthma, menstrual conditions, liver disease	(38,39)
8	*Cyclosorus terminans*	Thelypteridaceae	Thailand	Leaves, trunk	Decoction	Cough, burn, malaria, edema, inflammation, and external bleeding, liver damage	(40,41)
9	*Glossogyne tenuifolia*	Asteraceae	Taiwan	Whole plant	Decoction	Acute tonsillitis, bronchitis, diarrhea, urinary tract infection, antipyretic, anti-inflammatory, hepatoprotective	(42,43)
10	*Hibiscus sabdariffa* L.	Malvaceae	Africa	Leaves, calyces	Infusions	Diuretic, hypertension, pyrexia, and liver damage.	(44,45)
11	*Moringa oleifera*	Moringaceae	Arabian	Whole plant	Decoction	Fever, headache, constipation, labor pain, liver disease	(46,47)
12	*Morus latifolia*	Moraceae	China	Leaves	Decoction	Coughing up catarrh, fever, dizziness, vertigo, diabetes, liver diseases, blood pressure	(48,49)
13	*Panax notoginseng*	Araliaceae	China	Roots	Pounded roots	cardiovascular, pain, inflammation, hepatitis, and liver cancer	(50,51)
14	*Phyllanthus emblica*	Phyllanthaceae	India	Fruit	Juices	cold and fever, liver tonic, ulcer and dyspepsia	(52)
15	*Picrorhiza kurroa*		India	Leaves	Infusions	Liver and upper respiratory tract, fever, dyspepsia, diarrhea	(53)

Table II. Continued.

No.	Plants	Family	Location	Part(s) used	Preparation	Traditional usage	(Refs.)
16	*Pimpinella anisum* L.	Apiaceae	Italy	Seeds	Pounded seeds	Diuretic, mild expectorant, antifungal, antibacterial, liver disorders	(54,55)
17	*Pluchea indica*	Asteraceae	Indonesia	Leaves	Infusions	Antipyretic, diarrhea, antitussive, nourish the liver	(56,57)
18	*Rosmarinus offcinalis* L.	Lamiaceae	Italy	Leaves	Pounded leaves	Headache, dysmenorrhea, epilepsy, rheumatic pain, spasms, nourish the liver	(58,59)
19	*Rubus ideaus* L.	Rosaceae	Europe	Leaves, Fruit	Decoction	Stomatitis, sore throats, coughs, tonsillitis, fevers, nourish the liver	(60,61)
20	*Trigonella foenum-graecum* L.	Fabaceae	India	Seeds	Pounded seeds	Anti-cholesterolemic, anti-tumor, anti-inflammatory, expectorant, hypoglycemic, nourish the liver	(62)

during the non-clinical stage. In clinical studies, regulatory agencies in the USA require liver histological endpoints in phase 3 studies (69). The ethnopharmacological usage of herbs may provide a reference with which to identify the appropriate animal dietary model. The simple steatosis or NASH observation from a high-fat diet (HFD) or methionine and choline deficiency (MCD) model may be suitable for this purpose.

HFD. The HFD model is the most frequently used dietary model for research in NASH. Research has shown that rats fed a HFD (70) containing 45-75 kcal% develop NASH after 12 weeks. These rats exhibit a phenotype similar to that of humans, characterized by obesity after 10 weeks, insulin resistance indicated by hyperinsulinemia and hyperlipidemia after 10 weeks, and glucose intolerance after 12 weeks (Table III). It is noteworthy that minimal fibrosis is only observable after 36-50 weeks of HFD (70).

MCD diet. The MCD diet is characterized by a high sucrose content and moderate fat content. This means that it typically contains 40% sucrose and 10% fat. However, this diet is deficient in two essential nutrients, choline and methionine. As a result, the ability of the body to oxidize fats and produce very low-density lipoprotein particles is impaired (71). This leads to the accumulation of fat in the liver, which can cause oxidative stress, liver cell death, inflammation and fibrosis after 8-10 weeks.

Notably, mice fed a MCD diet do not exhibit obesity, peripheral insulin resistance, or dyslipidemia (Table III), unlike humans with NASH. Instead, they experience significant weight loss, cachexia and low levels of serum insulin, fasting glucose, leptin, and triglycerides (72). The NASH phenotype with lobular inflammation and metabolic features, as well as ballooning, develops rapidly in these mice within 2-8 weeks (72).

Therefore, this model is suitable for studying NASH and its pharmacological treatment, but inadequate for studying NAFLD due to its multisystemic nature (73). Mouse strains exhibit varying responsiveness to an MCD diet (73).

Choline deficient L-amino acid-defined HFD. A HFD that is deficient in choline and amino acids can lead to the development of NASH with fibrosis in merely 6-9 weeks, even in the absence of significant weight loss (Table III). However, this diet does not fully replicate the metabolic syndrome observed in humans (74).

Streptozotocin (STZ) + HFD. When administered to mice, STZ has been found to damage the pancreatic islets and decrease insulin production. Additionally, a HFD diet beginning at 4 weeks of age, combined with the administration of neonatal STZ, has been shown to cause simple steatosis at 6 weeks (Table III), NASH at 8 weeks, and progressive pericellular fibrosis starting at 8-12 weeks, leading to HCC after 20 weeks (75).

Carbon tetrachloride (CCl_4) + HFD. Exposure to CCl_4 can trigger a response in the liver that leads to an accumulation of harmful lipid and protein peroxidation products, which can in turn, cause necrosis. When combined with a HFD, CCl_4 can exacerbate the development of NASH and fibrosis. In a previous study conducted with mice, it was found that multiple peritoneal injections of CCl_4 over a period of 4 weeks induced not only steatosis, but also hepatocellular ballooning, centrilobular fibrosis and hypertriglyceridemia; weight loss was also observed in the mice (76). Furthermore, the histological features worsened progressively with each administration of CCl_4 (76).

HFD, high-sugar diet and high-fat, high-fructose diet. Consuming fructose can significantly affect glucose and lipid metabolism, leading to several health issues, such as obesity, insulin resistance and lipid accumulation in the liver. Research

Table III. Stages of NAFLD in animal dietary models.

No.	Model	IR	Obese	Steatosis	NASH	Fibrosis	HCC	(Refs.)
1.	High-fat diet (HFD)	Yes >10 weeks	Yes >10 weeks	Yes	Yes >12 weeks	Yes (minimal) 36-50 weeks	Yes 1 year	(70)
2.	Methionine and choline-deficient diet (MCD)	No	No	Yes	Yes 2-8 weeks	Yes 8-10 weeks	No	(71-73)
3.	Choline deficient L-amino acid-defined HFD	No	No	Yes	Yes (6-9 weeks)	Yes (6-9 weeks)	Yes	(74)
4.	STZ + HFD	Yes	Yes	Yes 6 weeks	Yes 8 weeks	Yes 8-12 weeks	Yes>20 weeks	(75)
5.	CCl_4 + HFD	Yes	Yes	Yes	Yes >4 weeks	Yes	-	(76)
6.	High fructose diet	Yes >8 weeks	Yes >8 weeks	Yes >8 weeks	No	-	-	(77)
7.	High fat-high fructose diet (HFHFD)/high-sugar and sigh-fat diet (HSHFD)	Yes >8 weeks	Yes >8 weeks	Yes	Yes >16 weeks	-	-	(77,78)

HFD, high-fat diet; STZ, streptozotocin; CCl_4, carbon tetrachloride; NAFLD, non-alcoholic fatty liver disease.

conducted on rats and mice has demonstrated that drinking fructose-supplemented water for 8 weeks results in simple steatosis without NASH and contributes to obesity and insulin resistance (IR) (77). Additionally, rats that were administered a high-fat, high-fructose diet experienced hepatic inflammation after 16 weeks. Similar results were observed in rats that were fed a high-fat, high-sucrose diet (77). Of note, rats that were fed with glucose and sucrose exhibited a greater weight gain, but lesser hepatic fat accumulation as compared to a high fructose-fed diet (78).

Mechanisms of action. Since NAFLD is associated with IR or obesity, the majority of the pathophysiological observations of the effect of these herbs listed in Table IV were shown to improve: i) lipid metabolism; ii) insulin resistance; iii) inflammation; iv) oxidative stress; and v) endoplasmic reticulum stress, in addition to the reduction of steatosis in the liver histological assessment. However, all rats with steatosis had elevated levels of liver injury markers, such as ALT and AST.

Lipid metabolism. The research results from the 20 plants (Table IV) (28-121) related to markers for liver lipid metabolism revealed marked decreases in triglyceride levels ranging from 11.6 to 72.4%, total cholesterol levels from 13.1 to 50%, low-density lipoprotein levels ranging from 10.8-60.9%, and increases in high-density lipoprotein levels ranging from 13.2-58.2%. These plant extracts exert anti-hyperlipidemic effects that have the potential to reverse or reduce liver steatosis. In hyperlipidemia, the accumulation of high levels of cholesterol and triglycerides in the blood causes fat to accumulate in the liver, resulting in inflammation and oxidative stress (79). The highest dose evaluated and that was found to be effective in reducing liver fat ranged from 100-400 mg/kg body weight in rats (Table IV). Some of these plant extracts, such as *Glossogyne tenuifolia* (80) and *Picrorhiza kurroa* (53) leaves, have been found to be effective at a dose of 150 and 300 mg/kg, respectively. Moreover, neither of these extracts exhibited any signs of toxicity at the highest dose of 5 and 2 g/kg, respectively (Table IV). The extracts of *Antidesma bunius* (82,83), *Aralia elata* (84-86), *Citrus aurantium* (90-93), *Curcuma longa* Linn. (94-96), *Cyclosorus terminans* (101,102), *Panax notoginseng* (109), *Pluchea indica* (114), and *Rosmarinus officinalis* Linn (115,116) have also been shown to reduce the accumulation of lipids in rats fed a HFD through sterol regulatory element-binding transcription factor 1c (SREBP-1c), peroxisome proliferator-activated receptor-α (PPAR-α), fatty acid synthase (FAS), acetyl-CoA carboxylase (ACC), and carnitine palmitoyltransferase (CPT)2 regulation.

The adenosine monophosphate-activated protein kinase (AMPK) pathway plays a crucial role in regulating hepatic lipogenesis and β-oxidation and serves as a vital energy sensor for intracellular energy metabolism. It helps in regulating free fatty acids, *de novo* lipogenesis and hepatic lipid accumulation. The extracts of *C. longa* Linn. (94,95) and *R. officinalis* Linn. (115) can activate AMPK in NASH rats, leading to reduced dyslipidemia and hyperglycemia. Moreover, triggering AMPK signaling, affects adipocytokine production (122), which further highlights the potential of these extracts in regulating metabolic disorders.

Table IV. Herbal plants and their mechanism of actions in NAFLD.

No.	Plants	Chemical constituents	Subject	Dose tested	Effective dose (mg/kg)	Toxicity study	Mechanism of Actions					
							Lipid Metabolism	Insulin Resistance (IR)	Inflammatory Markers	Oxidative Stress Markers	Other	(Refs.)
1	*Abroma augusta L.*	Leaf ethanol extract contains alkaloids, tannins, phenols and flavonoids.	Male Sprague-Dawley (SD) rats on MCD, HFD, CCD, STZ + HFD.	250 and 500 mg/kg, orally, 24 weeks. Positive control (PC): Silymarin (100 mg/kg)	Ethanolic extract at 500 mg/kg	Does not show any sign of toxicity up to 2,000 mg/kg	↓TC, ↓TG, ↓LDL, ↓HDL, ↓FFA,	↓IR	-	↓MDA ↑SOD	↓Steatosis	(28,81)
2.	*Antidesma bunius*	Aqueous fruit extract contain polyphenol, flavonoids, ascorbic acid, gallic acid, (+)-catechin.	HFD, male SD rats	0.38, 0.76, 1.52 g/kg, oral, 12 weeks PC: Statin 10 mg/kg	12 weeks, orally, 1.52 g/kg of extract	500, 1,000, 1,500 and 2,000 mg/kg given orally reported non-toxic in Wistar rats	↓GPAT-1, ↓ACC, ↓SREBP-1c ↓TG	-	↓ TNF-a	↓ MDA	↓Steatosis	(82,83)
3.	*Aralia elata*	Aqueous extract of roots contain flavonoid, total saponins, phenolics.	HFD, C57BL/ 6 mice	100 and 300 mg/kg for 4 weeks. PC: Resveratrol 300 mg/kg	Ethanol extract of 300 mg/kg	5,000 mg/kg for 14 days reported non-toxic in rats	↓TG ↓SREBP-1c ↓FAS ↑ACC1 ↓ACC2 ↑PPARα ↑CPT1	↓Glucose ↓Insulin ↓Akt2 ↓GLUT4 ↑PI3K	-	-	↓Steatosis	(84-86)
4.	*Cassia obtusifolia L.*	Seeds ethanol extract contain anthraquinones	HFD, male Wistar Albino rats	0.5, 1 and 2 g/kg, 6 weeks, oral PC-metformin 0.2 g/kg	1 and 2 g/kg ethanol extract	10 g/kg for 14 days reported non-toxic in rats	↓TG ↓TC	-	↓TNF-α ↓IL-6 ↓IL-8	↑SOD ↑GSH ↓MDA	↓MASH	(87-89)

Table IV. Continued.

No.	Plants	Chemical constituents	Subject	Dose tested	Effective dose (mg/kg)	Toxicity study	Mechanism of Actions					
							Lipid Metabolism	Insulin Resistance (IR)	Inflammatory Markers	Oxidative Stress Markers	Other	(Refs.)
5	*Citrus aurantium* L.	Ethanol extract peel contain flavonoids, limonoids, and alkaloids.	HFD, male C57BL/6 mice	50 and 100 mg/kg of ethanol, 8weeks, PC: Silymarin (200 mg/kg)	100 mg/kg of ethanol extract	400, 2,000 and 4,000 mg/kg, 28 days, extract showed no signs of toxicity.	↓TG ↓TC ↓PPARy ↓SREBP-1c ↓FAS ↑AMPK ↑NRF2	-	↓TNF-α ↓IL-6 ↓IL-1α	-	↓MASH	(90-93)
6	*Curcuma longa* Linn.	Aqueous extracts of *C. longa* roots contained curcumin.	HFD, C57BL/6 mice	300 and 900 mg/kg, oral 8 weeks PC: silymarin 50 mg/kg per oral	Aqueous extracts of 900 mg/kg	250, 500, 1,000 mg/kg for 90 days did not show any signs of toxicity	↓TG, ↓TC ↓SREBP-1c, ↓FAS, ↓ACC ↑AMPK ↑PPAR-α ↑CPT-1	-	↓CD36 ↓FATP5 ↓FATP2	↑CAT ↑SOD ↑GST ↑GPx ↑GR ↑GSH ↓MDA	↓Steatosis ↓ER stress ↓p-mTOR ↓p-S6K ↓p-4-EBP-1	(94-96)
7	*Crocus sativus*	Aqueous *C. sativus* flower stigma extract contained crocetin.	HFD, male SD rats	250 and 500 mg/kg, orally, 4 weeks. PC: Standard botanical mixture 35 mg/kg	4 weeks, 500 mg/kg	1 g/kg, 14 days, showed no mortality or any signs of toxicity.	↓TG, ↓TC, ↓ LDL, ↓ VLDL, ↑ HDL	↓Glucose ↓Insulin	↓TNF-α	↑CAT ↑SOD ↑GST ↑GPx ↑GSH ↓MDA AOPPs ↓NO_2	↓MASH ↓Uric acid	(97-99)
8	*Cyclosorus terminans*	Aerial parts of *n*-hexane extract contained coumarin, furanocoumarins, and dioxocane	HFD, male Wistar rats	100 and 200 mg/kg, oral, 2 weeks. PC: pioglitazone 20 mg/kg	200 mg/kg,	Acute toxicity study of 2 g/kg showed no signs of toxicity for 14 days.	cTG,↓TC ↓LDL, ↑HDL ↓SREBP1c, ↓Fasn ↑PPARα ↑PPARg ↑CPT2	↓Glucose ↓Insulin ↓HOMA-IR, ↑glycogen ↑Slc2a2 ↑Pparg ↑Irs1 &2s ↑Slc2a4	↓TNF-α ↓IL-6	-	↓MASH	(100-102)

Table IV. Continued.

No.	Plants	Chemical constituents	Subject	Dose tested	Effective dose (mg/kg)	Toxicity study	Mechanism of Actions					
							Lipid Metabolism	Insulin Resistance (IR)	Inflamma-tory Markers	Oxidative Stress Markers	Other	(Refs.)
9	*Glossogyne tenuifolia*	Aqueous root and whole plant extract contained phenolics, CGA, and luteolin-7-glucoside.	HFD, male Wistar rats	50 and 150 mg/kg, 4 weeks PC : 20 mg/kg acarbose .	150 mg/kg of aqueous extract	Chronic toxicity study in male mice rats with 5 g/kg for 28 days showed no signs of toxicity	↓TC ↑HDL	↓Insulin	↓IL-6 ↓STAT3 ↓MEK5 ↓ERK5 ↓NFATc3 ↓ANP ↓BNP ↓p-p38 ↓p-JNK, ↓FGF2, ↓p-ERK ½, ↓UPA, ↓MMP2 &9	-	↓Steatosis ↓Apoptosis	(80, 103)
10	*Hibiscus sabdariffa*	Aqueous extract contains total phenolic, flavonoid, carotenoid, and anthocyanin	HFD SD rats	250, 500 mg/kg oral, 8 weeks. PC: Simvastatin 40 mg/kg	Aqueous extract of 500 mg/kg.	Acute 2 g/kg and oral 125, 250, 500 mg/kg for 28 days were safe doses.	↓FAS, ↓ACC, ↓MTP, ↓LDLR, ↑IRS-1, ↑Nrt2, ↑p-Akt	-	↓TNF-α ↓IL6,	↑CAT, ↑SOD, ↑GPx	↓Fibrosis ↓MASH	(104, 105)
11	*Moringa oleifera Lam*	Seed ethanol extract, contains alkaloids, flavonoid, phenolic acids sterols.	HFCS, male SD rats	50 and 500 mg/kg, orally, 12 weeks. PC: Fenofibrate (100 mg/kg)	500 mg/kg seed ethanol extracts	30, 100, 300 and 1,000 mg/kg, no mortality	↓Liver lipids	-	-	-	↓MASH	(46, 106)

Table IV. Continued.

No.	Plants	Chemical constituents	Subject	Dose tested	Effective dose (mg/kg)	Toxicity study	Mechanism of Actions					
							Lipid Metabolism	Insulin Resistance (IR)	Inflammatory Markers	Oxidative Stress Markers	Other	(Refs.)
12	*Morus latifolia*	Ethanol leaf contained chlorogenic acid, rutin, quercetin, caffeic acid and coumaric acid	HFCS, f Wistar Albino rats.	120, 250, 500 mg/kg, orally, 21 days, PC: Orlistat 120 mg/kg	120 mg/kg of leaf extract	Sub-chronic toxicity of 7.5 g/kg and genotoxicity of 10 g/kg showed no mutagenic activity.	↓TC, ↓TG, ↓ LDL, ↓VLDL ↑ HDL	↓Glucose	-	-	↓Steatosis	(107, 108)
13	*Panax notoginseng*	Ethanol extract roots has ginsenoside Rb1, Rg1, Rg2, and Rh	HSHFD of SD rats	30 and 60 mg/kg, oral 8weeks, PC : Simvastatin 1 mg/kg	30 mg/kg of ethanolic extrac	1.2 g/kg for 28 days show no sign of toxicity.	↓TC, ↓TG ↓ PPAR-α ↑CPT-1A ↑CPT-2 ↓SREBP-1c ↑CYP-7A	↓Glucose ↓Insulin	↓TNF-α ↓IL-6 ↓IL-8 ↓IL-1 ↓IL-1β	-	↓Steatosis	(109)
14	*Phyllanthus emblica*	Fruit aqueous extract contained gallic acid, corilagin, and ellagic acid	CDAHFD of C57BL/6J mice	0.9, 1.8, 3.6 g/kg, 6 weeks. PC: Silymarin (84 mg/kg)	Oral administration of 3.6 g/kg extract for 6 weeks	5 g/kg for 14 days showed no mortality or any signs of toxicity.	↑HDL-C, ↓TC, ↓LDL-C, ↓Lipid droplet	-	-	-	↓Steatosis	(110, 111)
15	*Picrorhiza kurroa*	Leaves contained iridoid glycosides.	HFD of male Wistar rats	200 and 400 mg/kg, oral, 4 weeks. PC: Silymarin (50 mg/kg)	Treatment of 400 mg/kg for 4 weeks	No mortality at 2 g/kg after 14 days observation.	↓TC, ↓TG, ↑HDL-C,	-	-	-	↓Steatosis	(53, 112)
16	*Pimpinella anisum L.*	Aqueous seeds extract contains phenolic, ellagic and syringic acids.	CDD with lard of male Wistar Albino rats	25, 50, 100 and 200 mg/kg, 4 weeks. PC: Simvastatin 10 mg/kg	200 mg/kg; 4 weeks	400 and 800 mg/kg, 3 months were safe.	↓TG, ↓TC, ↓LDL-C, ↑HDL-C	-	-	-	↓Steatosis	(113)

Table IV. Continued.

No.	Plants	Chemical constituents	Subject	Dose tested	Effective dose (mg/kg)	Toxicity study	Mechanism of Actions					
							Lipid Metabolism	Insulin Resistance (IR)	Inflamma-tory Markers	Oxidative Stress Markers	Other	(Refs.)
17	*Pluchea indica*	Ethanolic extract leaves contains tannic acid, rutin, quercetin, gallic acid, isoquercetin, catechin, and apigenin.	HFFD, SD rats	100 and 3 00 mg/kg, oral, 6 weeks. PC: Pioglitazone 10 mg/kg	Ethanolic extract at 300 mg/kg	Acute oral toxicity study with up to 2,000 mg/kg for 14 days reported being reasonably non-toxic in rats	↓TG, ↓VLDL-C, ↓LDL-C, ↑HDL-C, ↓FFA ↓SREBP-1c ↓FAS ↑PPARα ↑CPT1 ↑ACOX1 ↓leptin ↓adipocytes	↓Glucose ↓Insulin ↓HOMA-IR	-	-	↓Steatosis	(114)
18	*Rosmarinus officinalis Linn*	Ethanol extract whole grass contain triterpenes, phenolic & diterpenes	HSD, male SD rats	100,200 and 400 mg/kg, oral, 21 days PC: Fenofibrate (50 mg/kg)	400 mg/kg	Does not show any mortality in rats at 2,000 mg/kg given orally	↓TG, ↓TC, ↓FFA, ↓SREBP-1c ↓AMPK ↓FAS ↓GAPDH	-	-	-	↓Steatosis	(115, 116)
19	*Rubus ideaus L*	Ethanol extract of red raspberry fruit contained flavonoids and phenolic acids	HFD, Male Wistar Albino rats	200, 100 and 500 mg/kg, oral, 28 days, PC: Metformin 150 mg/kg	200 mg/kg	Acute toxicity, 2,000 mg/kg, orally was non-toxic.	↓TC ↑HDL ↓TG ↓LDL ↓FFA	↓Glucose ↓Insulin	↓TNF-a	↓MDA ↑SOD ↑GPx ↑GSH	↓Steatosis	(117, 118)

Table IV. Continued.

No.	Plants	Chemical constituents	Subject	Dose tested	Effective dose (mg/kg)	Toxicity study	Mechanism of Actions					
							Lipid Metabolism	Insulin Resistance (IR)	Inflammatory Markers	Oxidative Stress Markers	Other	(Refs.)
20	*Trigonella foenum-graecum* L	Aqueous extract seeds contain galactomannan, phenolic flavonoid, and amino acids	HFD, Wistar rats	0.5 and 1.0 g/kg, 28 days. PC: Orlistat 10 mg/kg	1.0 g/kg of aqueous extract	2 and 5 g/kg, 90 days showed no signs of toxicity.	↓TG, ↓TC, ↓LDL, ↑HDL, ↓VLDL, ↓AI, □CRI, ↓leptin ↓Adiponectin ↓FAS, ↓LDH ↓G6PD ↓Lipase,	↓Glucose ↓ Insulin ↓ HOMA-IR ↓apo-B	-	↑SOD ↑GSH-Px ↓MDA	↓Steatosis	(119-121)

↑↓ indicates an increase or decrease in the value of the respective variable. ACC, acetyl-CoA carboxylase; ACOX1; peroxisomal acyl-coenzyme A oxidase 1; AI, atherogenic indexes; AKT2, protein kinase b type 2; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMPK, adenosine 5□-monophosphate-activated protein kinase; ANP, atrial natriuretic peptide; AOPPs, advanced oxidation protein products; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; CAT, catalase; CCD, cholesterol and chocolate diet; CDAHFD, choline deficient L-amino acid-defined; CD36, cluster of differentiation 36; CPT-1/2, carnitine palmitoyltransferase 1/2; CRI, cardiac risk indexes; CYP-7a, cholesterol 7α-hydroxylase; eIF2, eukaryotic translation initiation factor 2; ER, endoplasmic reticulum; ERK5, extracellular signal-regulated kinase 5; FAS, fatty acid synthase; Fasn, fatty acid synthase; FATP5/2, fatty acid transport proteins 5/2; FFA, free fatty acid; FGF2, fibroblast growth factor 2; G6PD, glucose-6-phosphate dehydrogenase; GADPH, glyceraldehyde 3-phosphate dehydrogenase; GLUT4, glucose transporter 4; GPAT-1, glycerol 3-phosphate acyltransferase; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, glutathione; GST, glutathione-S-transferase; HDL, high-density lipoprotein; HFCD, high-fat high-cholesterol diet; HFCS, high-fructose corn syrup; HFCS, high-fat diet; HFD, high-fat diet; HFFD, high-fat fructose diet; HFHS, high-fat high-sucrose diet; HSHFD, high-sugar and high-fat diet; MCD, methionine-choline-deficient diet; STZ + HFD, streptozotocin + high-fat diet; HNE, 4-hydroxynonenal; HOMA-IR, homeostatic model assessment of insulin resistance; IL, interleukin; IR, insulin resistance; IRS1/2, insulin receptor substrate-1/2; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; MDA, malondialdehyde; MEK5, mitogen-activated protein kinase kinase 5; MMP2/9, matrix metalloproteinase 2/9; MTP, microsomal triglyceride transfer protein; NFATc3, nuclear factor of activated t cells 3; NO_2^-, nitrite; Nrf2, nuclear factor erythroid 2-related factor 2; NRT2, nitrate transporter 2; PC, positive control; p-4-EBP-1, phosphorylated eukaryotic translation initiation factor 4E-binding protein 1; PERK, protein endoplasmic reticulum kinase; PI3K, phosphoinositide 3-kinase; p-JNK, phosphorylated c-Jun N-terminal kinase; p-mTOR, phosphorylated mammalian target of rapamycin; p-p38, phosphorylated p38; PPAR-α/g, peroxisome proliferator-activated receptor-α/g; p-S6K, phosphorylated ribosomal protein S6 kinase; ROS, reactive oxygen species; SCFAs, short-chain fatty acids; Scl2a2, solute carrier family 2 member 2; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; Slc2a4, solute carrier family 2 member 4; SOD, superoxide dismutase; SREBP-1c/2, sterol regulatory element-binding transcription factor 1c/2; STAT3, signal transducer and activator of transcription 3; TC, total cholesterol; TG, triglycerides; TNF-α, tumor necrosis factor-α; UPA, urokinase plasminogen activator; VLDL, very low-density lipoprotein.

Several plant extracts, including *Aralia elata* (84-86), *Curcuma longa* Linn. (94,95), *Cyclosorus terminans* (100-102), *Panax notoginseng* (109), and *Pluchea indica* (114) (Table IV), enhanced fatty acid β-oxidation by activating lipid antioxidant enzymes, such as CPT1 and peroxidation reduction through the activation of AMPK and PPAR-α.

Several plant extracts, including those derived from *Hibiscus sabdariffa*, *Panax notoginseng*, *Antidesma bunius*, *Curcuma longa* Linn., *Aralia elata, Cyclosorus terminans*, *Pluchea indica*, and *R. officinalis* Linn. (Table IV), upregulated the expression leels of SREBP-1c, FAS, ACC, and CPT-1, as well as PPAR-α, a regulator of β-oxidation, in rats that were fed a HFD (83,84,94,95,101,105,109,114,115). This suggests that AMPK activation by these herbal compounds is associated with *de novo* lipid synthesis, which is linked to the suppression of SREBP-1c, PPAR-α, FAS, ACC and CPT-2 expression. Moreover, these plant extracts promote the defense mechanism of β-oxidation, which leads to hepatic fatty acid depletion, by modulating CPT-1 and PPAR-α production.

IR. Carbohydrate metabolism plays a crucial role in IR, as it is regulated by insulin hormone. When the insulin signal fails to prompt glucose absorption in cells due to IR, it leads to hyperglycemia, where glucose levels in the blood remain elevated. The body compensates for this by producing more insulin, which can cause hormonal imbalances and cell damage, particularly in liver cells. Excess insulin production can also lead to liver fat accumulation, which is a common occurrence in IR. Moreover, hyperglycemia and hormonal imbalances can cause inflammation and oxidative stress on liver cells, thus aggravating liver fat accumulation. Therefore, it is essential to manage IR through a healthy diet, regular exercise, and avoiding excessive alcohol consumption to prevent and treat NAFLD. IR leads to the accumulation of free fatty acids in the liver, which triggers *de novo* lipogenesis and causes NAFLD (123,124). Thus, the following studies have shown that certain natural extracts can help manage IR and its associated complications.

It is noteworthy that all the studies cited in Table IV (28-121), examining the effects of herbal plant extracts on IR, found significant decreases in glucose and insulin levels, as well as IR with the oral administration of these herbal extracts, namely, *Abroma augusta* (28,81). *Aralia elata* (84-86), *Crocus sativus* (97-99), *Cyclosorus terminans* (100-102), *Glossogyne tenuifolia* (80,103), *Morus latifolia* (107,108), *Panax notoginseng* (109), *Pluchea indica* (114), and *Rubus ideaus* (117,118), *Trigonella foenum-graecum* (119-121).

For instance, 200 mg/kg hexane extract of *Cyclosorus terminans* administered orally in rats fed a HFD was shown to reduce blood glucose levels, insulin and the homeostatic model assessment of insulin resistance (HOMA-IR) over a period of 2 weeks. This extract increased the expression of genes solute carrier family 2 member 4 (Slc2a4) and solute carrier family 2 member 2 (Scl2a2), thereby stimulating IR in the liver cells and soleus muscle. It also promoted the expression of insulin receptor substrate-1 (IRS1) and insulin receptor substrate-2(IRS2) genes, promoting hepatic and soleus muscle glycogen production (100).

Similarly, treatment with 1 g/kg aqueous *Trigonella foenum-graecum* bark extract for 28 days in rats reversed the effects of IR and lowered the HOMA-IR and apolipoprotein B (apoB) levels in the blood (119). IR is associated with increased secretion and decreased clearance of ApoB, which reduces low-density lipoprotein clearance (125). *Trigonella foenum-graecum* managed to reduce the effects of IR and ApoB, and increase LDL clearance (119).

Inflammation. The oral administration of extracts from various herbs, such as *Antidesma bunius* (83), *Cassia obtusifolia* (87), *Crocus sativus* (97), *Cyclosorus terminans* (101), *Glossogyne tenuifolia* (103), *Hibiscus sabdariffa* (105), *Panax notoginseng* (109) and *Rubus ideaus* (117), were found to lead to an improvement in the levels of inflammatory markers linked to liver damage. These herbal extracts have been found to reduce the levels of pro-inflammatory cytokines and inflammation. The effective dosages of these extracts range from 100-500 mg/kg body weight in rats, and no signs of toxicity were observed even at the highest evaluated dose of 2,000 mg/kg.

According to the study by Park *et al* (126), hepatic adiponectin induction reduced NASH-associated necro-inflammation and fibrosis by antagonizing TNF and regulating each other's secretion. Another study demonstrated that the oral administration of 500 mg/kg *Hibiscus sabdariffa* for 8 weeks reduced the release of pro-inflammatory cytokines, such as IL-6 and TNF-α, which inhibited the development of NASH (105).

Liver inflammation causes inflammatory damage by increasing lipid accumulation and redistribution from adipose tissue to the liver. Hepatic steatosis, steatohepatitis, and fibrosis are the first steps in the evolution of NAFLD caused by liver inflammation (127). Herbal extracts have been found to protect against the advancement of hepatic steatosis to steatohepatitis by reducing liver inflammation. This is achieved by the suppression of inflammatory signaling pathways, controlling dyslipidemia, and enhancing liver function in patients with NAFLD (127). Herbal remedies, such as *Antidesma bunius* (83), *Cassia obtusifolia* (87), *Crocus sativus* (97), *Cyclosorus terminans* (101), *Glossogyne tenuifolia* (103), *Hibiscus sabdariffa* (105), *Panax notoginseng* (109) and *Rubus ideaus L*. (117), and (Table IV) have been shown to reduce the expression levels of hepatic inflammatory cytokines (TNF-α, IL-6, IL-8 and IL-1β) and to further ameliorate liver fibrosis. Hou *et al* (109) demonstrated that 30 mg/kg *Panax notoginseng* ethanol extract reduced the levels of inflammatory markers, namely TNF-α, IL-6, IL-8, IL-1 and IL-1β, and no signs of toxicity were observed at the highest chronic dose evaluated at 1,200 mg/kg for 28 days. From the results presented in Table IV, some of these herbs reduced the biomarker for insulin resistance and lipid metabolism in addition to steatosis reduction. As insulin resistance and lipid accumulation induced steatosis, most likely these herbs will ameliorate IR and lipid accumulation before the development of steatosis. An earlier study on *Hibiscus sabdariffa* aqueous extract at a lower dose of 300 mg/kg for 10 weeks, demonstrated reduced weight gain or obesity in rats fed a HFD through the inhibition of adipogenesis (128), indicating a close link to metabolic syndrome.

Oxidative stress. A total of eight herbal plants, namely *Abroma augusta* (28,81), *Antidesma bunius* (82,83), *Cassia obtusifolia* (87-89), *Curuma longa* (94-96),

Crocus sativus (97-99), *Hibiscus sabdariffa* (104,105), *Rubus ideaus* (117,118), and *Trigonella foenum-graecum* (119-121)_ were found to be safe at the highest toxicity dose evaluated and significantly reduce the levels of pro-oxidants, namely, malondialdehyde, ER stress, ROS and oxidative end products, such as 4-hydroxynonenal (Table IV).

Visceral fat accumulation can lead to oxidative stress, which is a common characteristic of NAFLD. This, in turn, triggers lipid peroxidation, causing oxidative damage throughout the body (105). The development of NAFLD can result in liver damage due to an imbalance between the production of reactive species and antioxidant defense. NAFLD affects lipid metabolism, leading to the production of ROS through fatty acid oxidation. The effective extract dosages ranged from 200-1,500 mg/kg body weight in experimental rats, and all of these plant extracts did not lead to any signs of toxicity at the highest evaluated dose of 2,000 mg/kg (Table IV). The ethanol extract of 200 mg/kg *Rubus ideaus* has been shown to significantly decrease the level of malondialdehyde, while increasing the levels of the antioxidants, superoxide dismutase, glutathione and glutathione peroxidase, thereby reducing liver oxidative stress (117). The extracts of *Aralia elata* (84-86), *Curcuma longa* (94-96), *Cyclosorus terminans* (100-102), *Panax notoginseng* (109), and *Pluchea indica* (114) have been found to significantly promote fatty acid oxidation through the activation of PPAR-α and PPAR-γ.

ER stress. The pathological disorders associated with obesity and NAFLD include the ER stress response as one of the primary characteristics (42). One of the primary characteristics of these disorders is the activation of the ER stress axis (42). However, *Curcuma longa* Linn. has been found to block this axis by activating AMPK, a physiological regulator of the mTOR signaling pathway that helps lower lipid metabolism. By activating AMPK, *Curcuma longa* Linn. can reduce the ER stress response (94). This natural herb has also been found to prevent hepatic dyslipidemia by downregulating the levels of phosphorylated mammalian target of rapamycin (p-mTOR), phosphorylated ribosomal protein s6 kinase (p-S6K) and phosphorylated eukaryotic translation initiation factor 4E-binding protein 1 (p-4-EBP-1), while alleviating ER stress (95). *Curcuma longa* Linn. has been proven to inhibit overnutrition-induced hepatic lipid accumulation, by controlling SREBP-1 and FAS through the protein endoplasmic reticulum kinase/eukaryotic translation initiation factor 2, which regulates lipid metabolism (95). Additionally, *Curcuma longa* Linn. has been found to modulate ER stress response and redox imbalance by impacting mTORC1, demonstrating the role of the mechanistic target of rapamycin complex 1 (mTORC1) activation and protein folding in the pathogenic process of hepatic dyslipidemia (94).

Limitations. The limitations of the studies identified in the present systematic review were the usage of non-standardized extracts, which could affect the reproducibility of their therapeutic effects. Variation in the bioactive synthesis is expected with herbs collected or planted at different locations as the biosynthesis of these bioactive compounds is dependent on the quality of the soil, altitude, environment and the time of harvest.

In conclusion, in the present systematic review, 20 herbs were found to reduce steatosis in histopathological assessment. Of these, 15 herbs, namely *A. augusta* (28,81), *A. bunius* (82,83), *A. elata* (84-86), *C. obtusifolia* (87-89), *C. aurantium* (90-93), *C. longa* (94-96), *C. sativus* (97-99), *C. terminans* (100-102), *G. tenuifolia* (80,103), *H. sabdariffa* (104,105), *P. notoginseng* (109), *P. indica* (114), *R. officinalis* (115,116), *R. ideaus* (117,118) and *T. foenum-graecum* (119-121) exhibited a mode of action involving lipid metabolism, insulin resistance and/or inflammatory markers. The remaining five herbs, namely *M. oleifera* (46,106), *M. latifolia* (107,108), *P. emblica* (110,111), *P. kurroa* (53,112) and *P. anisum* (113) warrant further investigations to establish their cross-link mode of action. These herbs exhibited no signs of toxicity. The herbs were found to exert a positive effect against NAFLD, and understanding its mechanism of action is probably useful for the treatment of other metabolic diseases associated with NAFLD, namely dyslipidemia, diabetes, or hypertension. Further studies are required to identify the bioactive compounds and standardize the extracts. Planning for either *in vivo* or *in vitro* experimental studies is essential to identify the bioactive compounds present in herbs. The traditional usage of these herbs can provide a useful reference for such studies. This process helps in understanding the bioactive components of the herbs and standardizing the extracts to ensure reproducible therapeutic effects. An understanding of the mechanism of action of these herbs is useful for planning more successful clinical trials. The development of NAFLD is time-consuming and herbs may provide alternative treatment to its prevention.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

NEJ extracted the information from the studies in the databases and prepared the initial draft of the manuscript. RMS and SMJ screened and analyzed the extracted information, and edited the manuscript. CYC conceptualized the study, screened the extracted information, and edited the final draft of the manuscript. The authenticity of the raw data was confirmed by NEJ and CYC. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools (Microsoft Word installed with Grammarly and Generative AI) were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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