



A COMPREHENSIVE REVIEW ON CHEMICAL AND HERBAL ACTIVE COMPONENTS IN TREATMENT OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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ABSTRACT

Fatty liver disease (FLD) is a rising public health concern, both in India and around the globe. In FLD, liver stores a large amount of fat which if untreated eventually leads to severe hepatic steatosis and irreversible liver damage (cirrhosis). Based on its underlying cause, it is mainly of two types: alcoholic fatty liver disease (AFLD) and metabolic dysfunction-associated steatotic liver disease (MASLD). Extensive research has been conducted on the pathogenesis of MASLD but the underlying mechanisms are still not clear and misinterpreted. This review explores the pathways that trigger fatty liver disease and the severity of MASLD along with the comprehensive analysis of the drug treatments which are in practice or under study. A detailed assessment has been done on plant derived active chemical components as well. Current medications are mostly designed to address insulin resistance, inflammation, and oxidative stress; however, they are susceptible to adverse drug reactions. In addition, a significant amount of research has been conducted on the hepatoprotective effects of a variety of herbal compounds, which are known for their lipid-lowering, antioxidant, and anti-inflammatory properties, alongside maintaining minimal toxicity. Therefore, integrating conventional therapies with plant-based bioactive compounds may offer an additional effective and safer approach for the prevention and management of MASLD.

KEYWORDS: Fatty Liver, Hepatic Steatosis, Therapeutic Drugs, Chemical, Herbal, Hepatoprotective.

Introduction

FLD has emerged as a global health concern of liver and the global and national prevalences of FLD are estimated at 30% and 38.6%, respectively[1]. A large amount of fat is stored in FLD, and MASLD and AFLD are the subtypes. Excessive alcohol causes MASLD, where the alcohol is broken down in hepatocytes by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH). ADH converts alcohol into acetaldehyde, which is harmful due to rapid oxidation to acetate by ALDH. This produces higher amounts of

reduced nicotinamide adenine dinucleotide (NADH) with reduction in nicotinamide adenine dinucleotide (NAD). NADH increases glycerol phosphate production; along with fatty acids produce triglycerides, which affects liver function[2]. Hepatic fat deposition in MASLD leads to several metabolic disturbances. It is stimulated by hepatic steatosis and characterised by hepatocyte damage and inflammation, leading to liver cirrhosis or cancer.

MASLD is a multifactorial and polygenic disease associated with cardiovascular disease (CVD), colonic adenoma,

obstructive sleep apnea (OSA), hyperuricemia, vitamin D insufficiency, pancreatic steatosis, hypothyroidism, and polycystic ovarian syndrome (PCOS). The high incidence of MASLD is stimulated by the pathophysiological link with obesity and type 2 diabetes mellitus (T2DM). About 70% of obese individuals with T2DM develop MASLD. (Stefn and Häring, 2011) Improper treatment of MASLD leads to cirrhosis, end-stage renal failure, and hepatocellular cancer. Recently, several prognostic and therapeutic approaches are available to manage diabetes, cholesterol and triglyceride levels, such as exercise to lose weight and medications (thiazolidinediones and metformin). Our lab prepared metformin-hyaluronic acid-based graphene quantum dots, and their efficacies were tested in both in vitro and in vivo high fat induced-animal models[3,4]. Herbal medications provide effective therapeutic agents against MASLD, maintaining effectiveness and lower side effects. The aim of the study is to analyse the efficacy of medications and herbal agents.

Current Status of MASLD

MASLD is a significant cause of chronic liver disease. 32% of adults suffer from MASLD, indicating a high incidence[5]. Individuals in the US reported low ethanol consumption. A study in England reported a 3% incidence of MASLD. The rate of MASLD in the US ranges from 10% to 30%, with comparable proportions found in Europe and Asia. About 20% of Chinese suffer from fatty liver disease, at a rate of 0.594%. Japanese trial revealed that 308 (10%) of 3147 participants developed MASLD at baseline for a period of 414 days. The prevalence of ultrasonographic MASLD reached 59% in subjects having metabolic syndrome, 70% in diabetic and obese individuals, and 90% in morbidly obese patients, while steatotic hepatitis affected 3% of the average age group population as well as 25%–30% of obese with diabetic patients, including 35% of morbidly obese patients. MASLD significantly contributes to healthcare burden. In a 5-year population-based follow-up study, the diagnosis of MASLD increased the overall healthcare costs by 26%, after controlling for comorbidities. Steatotic hepatitis had been anticipated to be the leading cause of transplantation of liver by 2020. Nonetheless, about one in every five individuals with MASLD develops steatotic hepatitis, and 10% of people with this develop cirrhosis. MASLD is now the second most common cause of liver transplantation in the US[6]. MASLD is more common in people who have prediabetes or T2DM.

Mechanistic Insight into MASLD Progression

Fat accumulation in the liver is a reason for FLD. Elevated lipid levels within hepatocytes enhance reactive oxygen species (ROS) formation via mitochondrial fatty acid β -oxidation, leading to the oxidative stress that causes

damage to the mitochondrial membrane and induces endoplasmic reticulum (ER) stress. Tumor necrosis factor- α (TNF- α), Interleukin-1 (IL-1), IL-6, leptin, angiotensinogen, vascular endothelial growth factor (VEGF), and angiotensin II are among the inflammatory mediators released for macrophage infiltration in hepatic adipose tissue, associated with the pathophysiology of MASLD. These shift the balance between liver cell death, necrosis, and pro-inflammatory and anti-inflammatory processes, impacting hepatocytes and triggering fibrogenesis and steatohepatitis, which translates to cirrhosis.

Mechanism of Fat Deposition in the Liver

The adipose tissues fail to suppress intracellular lipolytic enzymes, adipose triglyceride lipase (ATGL), monoglyceride lipase (MGL), and hormone-sensitive lipase (HSL), leading to breakdown of lipids in the adipose tissue. These enzymes free fatty acids (FFAs) and glycerol.

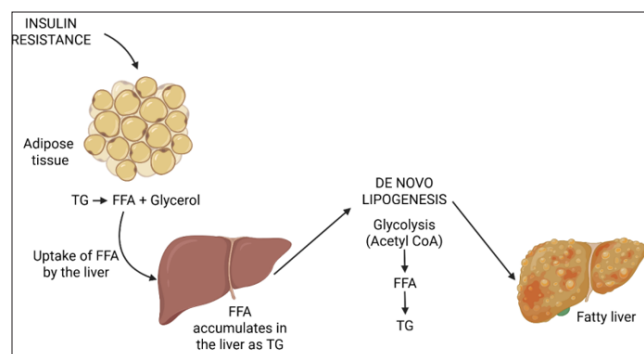


Figure 1. Mechanism of fat deposition in the liver

‘Figure 1’ illustrates how insulin resistance-induced lipolysis in adipocytes results in a huge release of FFAs, which can be taken up by the liver where it accumulates as triglycerides.

Another important pathway is de novo lipogenesis (DNL), which is depicted in Figure 2’, extending the lipid pool in the liver[7]. Glycolysis generates acetyl-CoA, which is converted to malonyl-CoA by the enzyme acetyl-CoA carboxylase (ACC). There are 2 isoforms, ACC1 and ACC2 (Brownsey et al., 2006). ACC1 is present in the cytosol of lipogenic tissues, while ACC2 is produced in skeletal and heart muscle cells in a mitochondria-bound form[8]. Malonyl-CoA acts as the main substrate for fat synthesis and interferes with mitochondrial fatty acid oxidation. Carnitine palmitoyl transferase-1 (CPT1) protein transports long-chain fatty acids into mitochondria. CPT1 is allosterically inhibited by malonyl-CoA. Malonyl-CoA accumulates onto an acyl- carrier protein (ACP) group, leading to malonyl-ACP, an acetoacetate

Moiety. Malonyl-ACP is the template for elongation of the hydrocarbon chains, due to alternating reduction followed by dehydration to produce palmitate (16-carbon-long saturated fatty acid), catalysed by fatty acid synthase (FASN) protein.

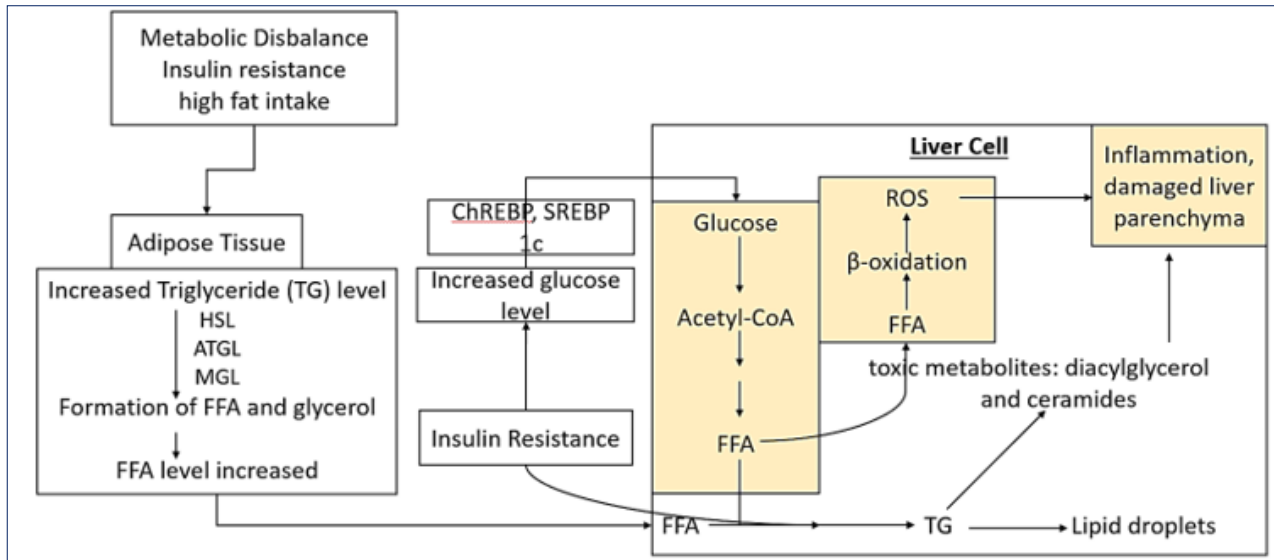


Figure 2. Diagrammatic pathway of fat deposition in the liver

FASN is the regulator of DNL, resulting in FFAs[9]. Surplus FFA disrupts the balance between fat synthesis and breakdown via mitochondrial beta-oxidation and lipophagy, leading to lipotoxicity, steatosis, and inflammation[10].

Control of de novo Lipogenesis

DNL is upregulated by 2 transcription factors, the carbohydrate response element-binding protein (ChREBP) and the sterol regulatory element-binding protein 1c (SREBP1c), activated by glucose and insulin, respectively. Increasing concentrations of metabolites like xylulose-5-phosphate and glucose-6-phosphate upregulate the transcription of ChREBP, affecting the lipogenic genes such as Acc1, Fasn, Elovl6, and Scd1[11]. ChREBP activity is epigenetically modulated by acetylation linked to acetyl-CoA and O-GlcNAcylation of uridine diphosphate-N-acetylglucosamine[12]. Also regulates genes involved in carbohydrate metabolism, such as liver-type pyruvate kinase (L-PK), a key regulator of glycolysis, and glucose-6-phosphatase (G6P).

The activation includes insulin signalling, where the insulin receptor interacts with protein kinase B (PKB)/phosphoinositide-3 kinase (PI3K) to activate SREBP1c. The second depends on nuclear receptor LXR- α -mediated phosphorylation of SREBP1c. It activates gene transcription, encode the genetic transcription such as FFA uptake (e.g., CD36) and FFA synthesis. A qRT-PCR study revealed considerable up-regulation of SREBP-1a, SREBP-1c, ACC α , and FAS genes in a Fas apoptosis inhibitory molecule (FAIM)-deficient liver. The upregulation of SREBP-2 stimulates cholesterol production in the liver by targeting 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR[13]. The production of oxidative stress, inflammation, and damage to the liver due to toxic metabolites such as

diacylglycerol and ceramides[14]. Stearoyl-CoA desaturase (SCD1) protein produces monounsaturated fatty acids (MUFA) from saturated fatty acids and is significant for hepatic lipogenesis. Absence of SCD1 leads to reduced hepatic lipogenesis, as well as obesity resistance, enhanced insulin sensitivity and lipid oxidation, and protection from steatosis.

FFA Overload and Dietary Contributions in MASLD

80% of hepatic fat comes from circulating FFA accumulates due to abnormal lipolysis in adipocytes. 59% of hepatic fat originates from FFAs, lower fraction comes from DNL (26%) and diet (15%). Insulin resistance leads to hyperinsulinemia, predisposing individuals to peripheral lipolysis, and induces hepatic lipogenesis[15].

The farnesoid X receptor (FXR), a nuclear receptor in the liver and small intestine. It regulates triglyceride synthesis, bile acid flow control, and glucose metabolism. MASLD patients have lower levels of hormones like glucagon-like peptide-1 (GLP-1). High consumption of oily fast foods, sugar and sweetened beverages promotes dyslipidemia and insulin resistance. Also, abnormal peripheral lipolysis and DNL in the liver aggravate MASLD progression through reduced mitochondrial β -oxidation, defective lipophagy, and decreased export of triglycerides via very low-density lipoproteins (VLDL).

FFA accumulation leads to lipotoxicity and promotes the development of MASH. Lipotoxicity is described as a disruption of the lipid environment and/or intracellular lipid composition, forming the buildup of bad lipids (VLDL, LDL, and LDL-derived cholesterol esters) which are linked to organelle malfunction, cell damage, and cell death (Figure 3).

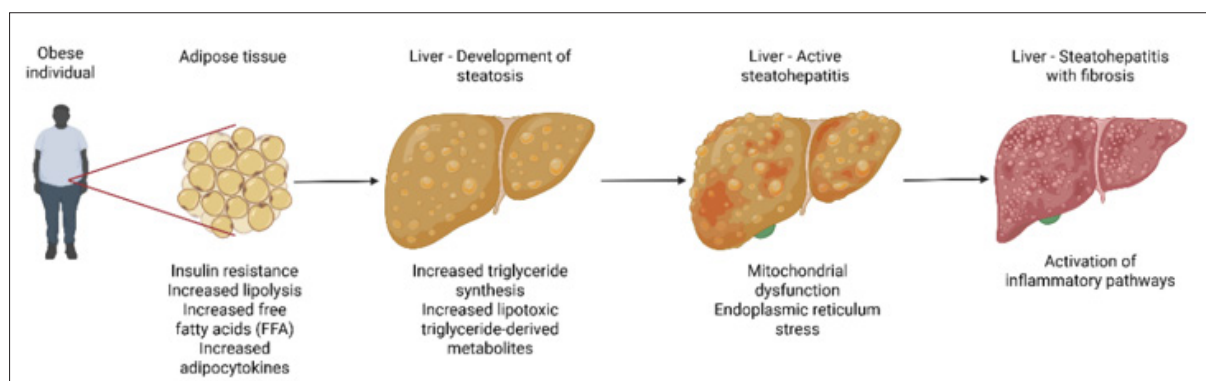


Figure 3.Steps in the pathogenesis of MASLD

It is associated with chronic inflammation (metabolically-triggered inflammation or meta-inflammation). Toxic lipids cause cellular damage through: 1) altering the function of ER and mitochondria; 2) directly altering intracellular

signalling pathways; and 3) interacting with specific pro-inflammatory cellular kinases on the cell surface or in the cytoplasm.

Table 1: Mechanistic Targeting of MASLD Pathways by Chemical Therapeutics.

Sl. No.	Name of the Drug	Key molecular targets	Critical remarks on fatty liver	Ref.
1	Thiazolidinediones (TZDs)	Peroxisome proliferator-activated receptor- γ (PPAR- γ) agonist	Protective against steatosis, inflammation, and fibrosis	[3]
2	Pioglitazone	PPAR α/γ agonist	Improves damage caused by oxidative stress	[17]
3	Saroglitazar	PPAR α/γ agonist	Protective against oxidative stress and hepatic injury	[18]
4	Obeticholic acid (OCA)	Farnesoid X receptor (FXR) agonist	Reduces steatosis, liver weight, hepatic inflammation, and fibrosis	[19]
5	Zafirlukast	Farnesoid X receptor agonist	Reduction in hepatic steatosis, fibrosis, and inflammation	[20]
6	Cilofexor and Tropifexor	Farnesoid X receptor agonist	Decreases hepatic fat via MRI-PDFF	[21]
7	Ursodeoxycholic acid (UDCA)	Farnesoid X receptor antagonist	Decreases necroinflammation, fibrosis, and steatosis	[22]
8	Canagliflozin	SGLT-2 inhibitor	Decreases hepatic fat content and increases hepatic insulin sensitivity	[11]
9	Dapagliflozin	SGLT-2 inhibitor	Decreases hepatic fat content	[23]
10	Pentoxifylline (PTX)	Inhibitor of TNF- α	Reduces inflammation and oxidative stress; improves liver function	[2,24]
11	Orlistat	Lipase inhibitor	Weight loss by reduction of fat absorption	[25]
12	Clofibrate	Lipid-lowering agent	Decreases hepatic triglycerides	[26]
13	Statins	Inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase	Reduces lipid and cholesterol deposition	[27]
14	Ezetimibe combination with Acarbose	Cholesterol absorption inhibitor and alpha-glucosidase inhibitor	Reduces inflammation, steatosis, and fibrosis in the liver	[28]
15	Betaine	Increases S-adenosylmethionine (SAM) levels	Protects against hepatic steatosis	[29]
16	Losartan	Angiotensin II receptor antagonist	Improves aminotransferases and serum markers of fibrosis	[30]
17	Liraglutide	Glucagon-like peptide-1 (GLP-1) receptor agonist	Improves β -oxidation and gluconeogenesis	[31]

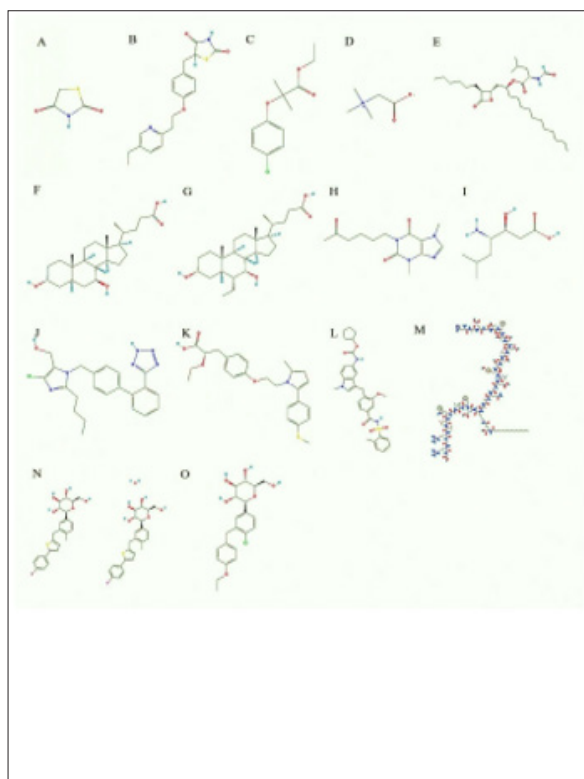


Figure 4. Structures of pre-existing medicines used to treat MASLD.

A. 2,4-Thiazolidinedione (Pubchem ID 5437), B. Pioglitazone (Pubchem ID 4829), C. Clofibrate (Pubchem ID 2796), D. Betaine (Pubchem ID 247), E. Orlistat (Pubchem ID 3034010), F. Ursodiol (Pubchem ID 31401), G. Obeticholic Acid (Pubchem ID 447715), H. Pentoxifylline (Pubchem ID 4740), I. Statine (Pubchem ID 123915), J. Losartan (Pubchem ID 3961), K. Saroglitazar (Pubchem ID 60151560), L. Zafirlukast (Pubchem ID 5717), M. Liraglutide (Pubchem ID 16134956), N. Canagliflozin (Pubchem ID 24997615), O. Dapagliflozin (Pubchem ID 9887712)

Diagnosis and Treatment of MASLD

Several radiology-based methods such as magnetic resonance imaging (MRI), computed tomography (CT), and ultrasound have shown high diagnostic accuracy and

specificity of up to 90% for hepatic steatosis. Of these, ultrasound is the preferred screening method due to its accessibility, affordability, and safety. Despite this, its accuracy and specificity may vary depending on the operator and may be lower in obese individuals[16].

Table 2: Mechanistic Targeting of MASLD Pathways by Potent Herbal active components

S. No.	Plant-derived product	Extracted from	Molecular targets	Detectable effects on fatty liver	Ref.
1	Gypenosides	Gynostemma pentaphyllum	Reduces SREBP-1c, PPAR- γ , FAS, and ACC production	Reduces triglyceride accumulation and liver fat infiltration	[32-35]
2	Palmitine and jatrorrhizine	Coptidis rhizoma	Involved in cholesterol 7 α -hydroxylase A1 (CYP7A1) expression	Promotes bile acid synthesis	[36]
3	Crude extract	Citrus aurantium	Reduces SREBP-1c, PPAR- γ , FAS, and ACC production	Reduces triglyceride accumulation	[37]
4	Berberine	Coptis chinensis	Reduces expression of hepatic stearyl-coenzyme A desaturase 1 (SCD1)	Reduces hepatic TG accumulation	[38]
5	Licochalcone A	Glycyrrhiza uralensis	Induces the AMPK/SIRT-1 pathway	Inhibits hepatic lipogenesis and improves β -oxidation	[39]

6	Ursolic acid crystal	—	Novel liver X receptor α (LXR α) antagonist	Inhibits hepatic lipogenesis through inhibition of LXR α activation	[40]
7	Punicalagin and pomegranate ellagic acid	Punica granatum	Activates CYP7A1/PPAR γ signaling	Promotes hepatic diversion of cholesterol into bile acids	[41]
8	Glycyrrhizin	Glycyrrhizae radix	Restores FXR inhibition	Modulates serum bile acid metabolism	[42]
9	Andrographolide	Andrographis paniculata	Inhibits NF- κ B and the NLRP3 inflammasome	Reduces hepatic steatosis and inflammation	[43]
10	Curcumin	Curcuma longa	Suppresses NPC1L1 expression	Inhibits cholesterol uptake	[1]
11	Lycopene	Solanum lycopersicum	Inhibits cholesterol absorption and NPC1L1	Inhibits cholesterol absorption	[5]
12	ODP-Ia	Opuntia dillenii	Inhibits hepatic HMG-CoA reductase activity	Suppresses hepatic TG levels	[44]
13	Allicin	Allium sativum	Regulates AMPK-SREBPs and PKA-CREB signaling pathways	Reduces TG and TC accumulation	[43]
14	Naringin	Citrus-derived flavonoid	Upregulates hepatic lipase and LCAT expression	Decreases plasma cholesterol and TG levels	[45]
15	Resveratrol (RSV)	Vitis vinifera	Decreases alanine transaminase and plasma inflammatory markers (IL-6, NF- κ B, and hs-CRP)	Reduces liver fat and inflammation	[14]
16	Picroliv	Picrorhiza kurroa	Reduces the activity of alkaline phosphatase, glutamate pyruvate transaminase, and glutamate oxaloacetate transaminase	Protects the liver from biochemical alterations induced by CCl ₄	[15]

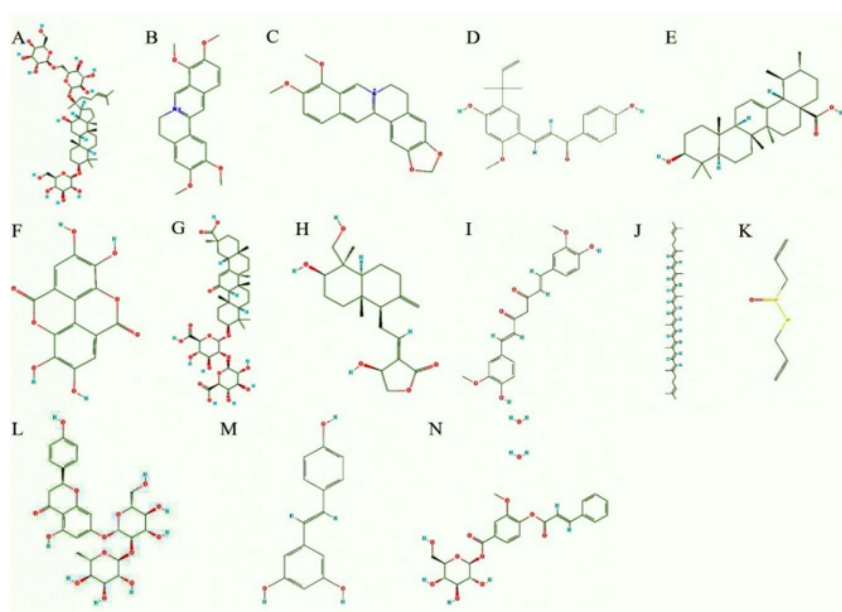


Figure 5: Structures of plant derived bio-active components in the treatment of MASLD

A. Gypenoside (Pubchem ID 44584555), B. Palmatine (Pubchem ID 19009), C. Berberine (Pubchem ID 2353), D. Licochalcone A (Pubchem ID 5318998), E. Ursolic Acid (Pubchem ID 64945), F. Ellagic Acid (Pubchem ID 5281855), G. Glycyrrhizin (Pubchem ID 14982), H. Andrographolide (Pubchem ID 5318517), I. Curcumin (Pubchem ID 969516), J. Lycopene (Pubchem ID 446925), K. Allicin (Pubchem ID 65036), L. Naringin (Pubchem ID 442428), M. Resveratrol (Pubchem ID 445154), N. Picroliv (Pubchem ID 131750182)

Critical Insights of the Various Drug Pathways and Targets in Treatment of MASLD

MASLD is growing problem without any FDA-approved therapy. An appropriate drug for patients should be to increase quality of life, delaying liver-related problems, for prolonged survival[46]. Industry produces chemical-based drugs, on a trial-and-error basis with anti-FLD property. Therapeutic targets against MASLD can be 4 type-targets: carbohydrate and lipid metabolism, lipid toxicity, cell death, inflammation, and extracellular matrix[47].

Peroxisome Proliferator-Activated Receptors (PPARs) are a class of transcription factors, function as lipid sensors, to regulate triglyceride metabolism, adipogenesis, fatty acid oxidation in mitochondria and peroxisome, and liver homeostasis; also boost insulin sensitivity, and control triglyceride accumulation in adipose tissue preventing fibrogenesis. Drugs with agonistic PPARs activity such as, thiazolidinediones, pioglitazone[17], and saroglitazar[18], reduces the influx of fatty acids to the liver and enhances the fatty acid β -oxidation and improve systemic insulin sensitivity (through PPAR- γ). Also, hepatic steatosis, inflammation, liver enzyme levels, and potential fibrosis improved and suppress the oxidative stress and inflammatory signaling[19]. Pilot studies use PPAR agonists like insulin sensitizing medications, metformin and thiazolidinediones[3], pioglitazone[17], and saroglitazar (C et al., 2020), showed high levels of plasma adiponectin, reduced hepatic steatosis, and symptoms of liver damage. PPAR agonists are effective for the treatment of fatty liver disease[3]. Saroglitazar demonstrated low alanine aminotransferase (ALT), liver fat content, triglycerides, and insulin resistance[19].

RCT showed that the insulin-sensitizing agents treat MASLD/MASH. In a double blind RCT among 106 participants, saroglitazar with PPAR- α/γ agonist activity reduces the ALT levels and hepatic fat content. It is also well tolerated[19] and protects liver from metabolic disorders and fibrosis. Pioglitazone targets PPAR γ and improves histological features in MASLD and reduces fibrosis. The RCT study divides patients into two groups (24 females and 42 males) receiving pioglitazone to for the impact of pharmacological agents on insulin resistance reduction. The medication showed the treatment of MASLD, without specific side effects. Drug's impact on lipid profile, blood glucose, serum insulin and its effect to reduce the hepatic aminotransferase[24]. Drugs are limited by propensity to induce weight gain[4].

The farnesoid X-activated receptor (FXR), a bile acid receptor that plays role in metabolism. FXR breaks down glucose and fats and work with other proteins to control lipogenesis-inducing enzymes like SREBP-1 and lowers the bile acid. FXR inhibits hepatic metabolic homeostasis due to lipid buildup, bile acid toxicity, insulin resistance,

inflammation, and fibrosis. FXR inhibition highlights restoration or modification of the FXR signaling. FXR agonism is an auspicious therapeutic strategy for MASLD. Obeticholic acid, zafirlukast, cilofexor and tropifexor[21], are agonists of FXR, to improve the insulin sensitivity in MASLD patients with type 2 diabetes[46]. It reduces steatosis, liver weight, hepatic inflammation, fibrosis and weight loss[21]. In the multicenter, randomized, placebo-controlled "FXR ligand Obeticholic acid in MASH treatment" (FLINT) phase 2 trial, significant improvements observed in inflammation and fibrosis [48]. Obeticholic acid is tested in a large phase 3 long-term trial among 2,400 patients with MASH, including ~2,100 patients with stage 2 or 3 liver fibrosis. Obeticholic acid at a dose of 25 mg daily improved fibrosis and key histological components MASH disease activity. Adverse impact like the itchiness was seen[21]. Zafirlukast may restore the FXR activity and reduces the leukotriene-induced inflammation. Zafirlukast inhibits CysLT1 signaling and lowers NF- κ B activation and the production of pro-inflammatory cytokines. Zafirlukast associated with the metabolic benefits, like less accumulation of fat, insulin sensitivity and low damage in liver due to bile acid. The clinical evidence from RCT evaluates the non-bile acid FXR agonists cilofexor and tropifexor. The non-cirrhotic MASH and advanced fibrosis with the cilofexor and tropifexor, reduces the hepatic steatosis. These indicated the FXR activation suppresses hepatic lipogenesis for metabolic dysfunction[42].

UDCA is a secondary bile acid and weak antagonist to FXR signaling, which detoxifies the bile acid and cytoprotection. The UDCA treatment, is pertinent for bile acid mimetics and effective for treatment of MASLD[47]. This led to decrease in blood AST, γ GT, free fatty acids, total and LDL cholesterol, whereas triglycerides increased. In a study, 40 obese patients were diagnosed with MASLD. 19 participants completed the protocol, while 18 remained in the control groups. Short-term administration of UDCA led to decreased FXR activity, accelerated cholesterol and bile acid and hepatic lipid accumulation. FXR reduces intestinal FGF19 production, which is inversely correlated with hepatic CYP7A1 expression. This is due to CYP7A1 expression, elevated serum levels of bile acid precursors, and diminished FXR/RXR DNA binding activity, reduced FXR's anti lipogenic functions[47]. It decreases hepatic triglycerides, necroinflammation, fibrosis and steatosis[22].

Anti-diabetic drugs show impact on weight loss, reduces MASH. These are agonists of the glucagon-like peptide-1 (GLP-1), promotes insulin secretion in a glucose dependent manner, or inhibitors of the sodium-glucose transport protein 2 (SGLT2), called gliflozins, inhibiting glucose reabsorption. Liraglutide and semaglutide are being tested in MASH and among non-diabetic patients. The pilot study demonstrated improvement of histological features of MASH by liraglutide. SGLT2 inhibitors increase hepatic insulin sensitivity, reducing lipotoxic stress and

gluconeogenesis. Thus, these strategies control metabolic disturbances in MASH. 2 SGLT-2 inhibitors, canagliflozin and dapagliflozin reduces hepatic fat content, increased hepatic insulin sensitivity. The combined impact of AMPK activation, reduced lipogenesis, fatty acid oxidation, insulin sensitivity, and reduced inflammation, dapagliflozin and canagliflozin manage MASLD. Canagliflozin are treatment medicines for MASLD, among individuals of T2DM[10]. The study demonstrated the efficacy of dapagliflozin, on the liver function of T2DM with MASLD when administered with metformin. Dapagliflozin showed impact on body weight loss and lowered ALT levels than DPP4i. Our study showed high body weight in the SGLT2i group, while dapagliflozin reduces body weight than other oral hypoglycemic medications. Dapagliflozin reduced plasma triglycerides but sitagliptin did not[10].

Studies with pentoxifylline (PTX) and orlistat showed inhibition of TNF- α and Lipase, while effective in lowering body weight, decreasing inflammation, oxidative stress, lipid and cholesterol deposition, and treating fatty liver[25]. A 12-month treatment reduced blood aminotransferase levels, reduces hepatocellular damage. This reduction is consistent with the previous interventional studies in MASLD, where biochemical improvement reported minor or histological changes[21]. High obesity (70%) and diabetes (35%) reflect metabolic risk associated with MASLD (Adams et al., 2004). Another study using orlistat demonstrated that weight loss intervention can lead to changes in the liver and metabolism among obese and liver disease patients[25]. Weight loss causes less hepatocellular damage. These biochemical findings are consistent with interventional studies, showing aminotransferases either decreased or back weight-loss therapies[26]. Improvements were correlated with changes in liver enzymes, with fibrosis and steatosis. The weight loss of ≥ 7 –10% was associated with steatohepatitis resolution and fibrosis regression.

Mitochondrial dysfunction increases DNA methylation, leads to metabolic syndrome. DNA cytosine-5-methyltransferases (DNMTs) mediate methylation by catalyzing the transfer of the methyl group from SAM to cytosine. Betaine supplementation elevates DNMT mRNA level in animals. Methylation of betaine aid in lipid metabolism and associated with epigenetic modification of DNA and RNA methylation with lipid. It reduces ROS and rises GSH and glutathione peroxidase to manage anti-oxidative stress[9]. Statins and ezetimibe combination with acarbose helps in FLD treatment. Losartan, an angiotensin II receptor antagonist enhances aminotransferases, serum markers of fibrosis etc and used in MASH trial for histological recovery[4].

The trial drugs are effective to manage factors related to FLD but not effective in treatment; along with few side effects. The advantages of herbal active compounds for MASLD treatment are reported. Also, physicochemical

interactions between active agents and other drugs should be investigated.

Gypenosides from the plant *Gynostemma pentaphyllum* belongs to the family Cucurbitaceae reduces the SREBP-1c, PPAR- γ , FAS, and ACC formation; reduce triglyceride accumulation[32] and liver fat infiltration. These studies showed that gypenosides lowers serum liver enzymes (AST and ALT). Lack of oral bioavailability, standardized extraction techniques, and safety issues human trials have not been conducted. Other active compounds, palmatine and jatrorrhizine, from *Coptis chinensis* express cholesterol 7 α -hydroxylase A1 (CYP7A1). It inhibits cholesterol buildup, reduces oxidative stress, and liver swelling[32]. Crude extract of *Citrus aurantium* (fam. Rutaceae) was assessed for MASLD therapy. Individuals with 400 mg capsules of the herbal mixture showed improvements in the fatty liver and reduces ALT and AST rather than control group. The most prevalent protoberberine alkaloid is berberine, isolated from *Coptis chinensis* and reduces hepatic SCD1 expression. A multicenter, controlled clinical trial on 184 patients with berberine (0.5 g 3 times daily) with lifestyle intervention showed effective body weight, insulin resistance, lipid profiles, and hepatic fat content for a period of 16-week. Licochalcone A showed poor oral bioavailability and water solubility. Study conducted on mice model showed licochalcone A induces AMPK/SIRT-1 pathway[41]. Whereas glycyrrhizin, which restores FXR inhibition and alters the serum bile acid metabolism, isolated from *Glycyrrhiza* species, *G. uralensis* and *G. eradix*[41]. The diammonium glycyrrhizinate lowered serum ALT and AST levels improved the histological grade of hepatic steatosis[24].

Ursolic acid, a novel (LXR α) antagonist is effective intriguing therapeutic possibility for human trials. The reduction in the hepatic steatosis, serum ALT/AST levels, and liver mass[38]. *Punica granatum* produces punicalagin and ellagic acid, activates the CYP7A1/PPAR γ signaling pathway and promote conversion of cholesterol into bile acid[32]. Animal studies showed reduced insulin resistance and liver toxicity enzymes (ALT, AST, ALP, GGT) etc. Human trial with pomegranate peel extract (1500 mg/day for 8 weeks) reduced body weight, BMI, and total cholesterol, improving hepatic steatosis and liver stiffness by FibroScan. Also, pomegranate-derived formulations are high in punicalagin[32].

Andrographis paniculata produces active components like andrographolide inhibit the NF- κ B pathway and the NLRP3 inflammasome[7]. The andrographolide on MASLD patients is the primary stage of development. Randomized control study showed anti-inflammatory activity of the extract with impaired liver. Curcumin, the yellow color *Curcuma longa*, is used in cooking as a spice, antioxidant properties are studied in liver metabolism and suppress NPC1L1

expression. Also inhibit cholesterol uptake, and reduce ALT/AST enzyme. Phytosomal curcumin supplementation decreased hepatic steatosis and fibrosis[49-51]. Solanum lycopersicum, a plant of the family Solanaceae, produces lycopene to control cholesterol absorption and NPC1L1. ODP-1a from *Opuntia dillenii* and allicin from *Allium sativum* suppresses hepatic cholesterol and triglyceride levels[43]. Naringin upregulates hepatic lipase and LCAT expression reducing plasma cholesterol and triglyceride levels. Resveratrol on MASLD patients increases liver function with reduced liver fat and inflammation[14]. Plant-derived products are bio-safe and can be used for treatment of MASLD.

Efficacy Assessment of Chemical and Herbal Drugs

Recent reports show that OCA is safe and effective while 25mg dose of OCA shows adverse response compared to 10mg OCA. Another clinical trial of pioglitazone reported improvement in liver fibro-scan and histology which enhanced risk of weight, fluid retention, bladder cancer and bone fractures. The PPAR agonists thiazolidinediones and saroglitazar are also effective[15]. Another phase III trial medicine, liraglutide, was accepted, with moderate, temporary gastrointestinal complication such as constipation, diarrhea, and lack of appetite. Dapagliflozin and canagliflozin, are effective for MASH [35]. Pentoxifylline is economic and safe, having antioxidant properties treating NASH. Drugs such as orlistat, metformin, losartan with lifestyle interventions showed improved liver histology and weight loss along with gastrointestinal complaints[26].

The safety and efficacy of curcumin was confirmed by clinical trial. It is also an adjunct to standard treatment regimens of patients with cardio-metabolic diseases[4]. Daily intake of 3,000 mg resveratrol showed overweight or obese men with MASLD for 8 weeks. The wistar rats did not show negative alterations after high dosage of tomato lycopene for 4 weeks. Glycyrrhizin enhances blood lipid,

insulin sensitivity and lipoprotein lipase expression.

Contrastingly, the plant components are tested and showed therapeutic efficacy without adverse effects. Though they are effective, there is little to no human trial. Mostly studies are based on animal model and cell lines. Futuristic plant-derived components is a medicine for the development of the health concern.

Futuristic Plant Derived Medicines

Traditional medicines viz, Ayurveda, siddha, Unani and Homeopathy are beneficial to liver health and also reduces the adverse effects of FLD, MASH etc. The leaf extract of *Aegle marmelos*, *Clitoria ternatea*, *Vitex negundo* showed defense against liver damage. *Clitoria ternatea* is anti-oxidants. Whole plant extract of *Amaranthus spinosus* showed protection against CCl₄ induced liver injury in lab mice. Methanolic seed extract of *Apium graveolens* protects liver as examined on rat liver.

Conclusion

MASLD is a condition that is becoming more prevalent with significant morbidity and death rates. Owing to the multiple mechanisms involved in its development and progression, it is very difficult to achieve optimum therapeutic management. Currently available drugs are targeted at insulin resistance, inflammation, and oxidative stress; however, they are prone to adverse drug reactions. In addition, a lot of research has been done on the hepatoprotective effects of various herbal compounds for their lipid-lowering, antioxidant, and anti-inflammatory properties, while having minimal toxicity. Ongoing researches are aimed at investigating both safety and effectiveness of these natural bioactive substances as adjuvant therapy for control of liver disorder. Thereafter, clinical trials are critical for determining appropriate doses, administration modalities, and advantages over time. Therefore, it is essential to explore potential herbal compounds for the treatment of FLD.

Table 3: Names of the future herbal components for the treatment of FLD

Plant Extract	Extracted from	Phyto-active constituents and their effects
Aqueous leaf extract	<i>Aegle marmelos</i>	Active constituents such as luvangetin and marmelosin have hepatoprotective activity.
Leaf extract	<i>Clitoria ternatea</i>	Contains constituents such as rutin, β -amyrin, ursolic acid, and kaempferol, which act as antioxidants and provide liver protection.
Whole plant extract	<i>Amaranthus spinosus</i>	Betanin, β -xanthin, β -sitosterol glucoside, and α -spinasterol have shown protection against CCl ₄ -induced liver injury in laboratory mice.
Seed extract	<i>Apium graveolens</i>	The methanolic extract contains caffeic acid, apigenin, ocimene, and isopimpinellin, which have a significant liver-protective effect, as examined in rat liver.
Leaf extract	<i>Vitex negundo</i>	Shows a liver-protective role in thioacetamide-induced liver damage and fibrosis.

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None

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