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Review Article

MASLD: An Updated Review of Disease Pathogenesis, Diagnostic Approaches, Therapeutic Strategies, and Herbal Interventions in the Transition from NAFLD

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD), renamed metabolic dysfunction-associated steatotic liver disease (MASLD) in 2023, affects roughly three in ten adults worldwide. It ranges from simple steatosis to steatohepatitis (MASH), fibrosis, cirrhosis and hepatocellular carcinoma, and is closely tied to obesity, type 2 diabetes and cardiovascular disease. **Methods:** Narrative review of key trials, meta-analyses and society guidelines, with a dedicated section on herbal products. **Findings:** Fibrosis stage is the main predictor of liver-related outcomes, whereas cardiovascular disease is the leading cause of death. A stepwise pathway using FIB-4 followed by elastography allows efficient risk stratification. Lifestyle change with weight loss remains the foundation of care, and resmetirom and semaglutide are now approved for MASH with moderate to advanced fibrosis. Several herbal products, including silymarin, berberine and curcumin, show promising signals but lack robust histological evidence, and some can themselves cause liver injury. **Conclusions:** Early non-invasive identification, sustained lifestyle modification, cardiometabolic risk control and, where indicated, approved drug therapy form the core of management. Herbal supplements should not replace evidence-based care.

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) has become the most common chronic liver condition in the world. A systematic review of population studies estimated that roughly 30% of adults are affected, and that the figure has risen steadily over

three decades in parallel with the global epidemics of obesity and type 2 diabetes [1]. Prevalence is highest in Latin America and the Middle East, remains high in North America and Asia, and is lower in several African and European populations, although even the lowest regional estimates are substantial. The rise is especially steep across South and Southeast Asia,

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where urbanisation, falling physical activity and rapid dietary change have occurred within a single generation. The disease affects both sexes and all ethnic groups, and it is increasingly recognised in children and adolescents. Because it develops silently over many years, today's prevalence figures reflect exposures that began long ago, and the full clinical consequences of the present burden will become apparent only over the coming decades.

The consequences for health systems are considerable. Fatty liver disease is now one of the leading and fastest-growing causes of cirrhosis, hepatocellular carcinoma and liver transplantation in many countries, and it is becoming a more prominent cause of chronic liver disease in regions where viral hepatitis is increasingly controlled through vaccination and antiviral treatment. Affected patients use more health-care resources than the general population, partly because of their associated diabetes, cardiovascular disease and kidney disease, and the economic cost of the condition is expected to rise as more people are diagnosed. Despite this, public and professional awareness remains low. Many patients are never told that they have fatty liver, many clinicians regard it as a benign incidental finding, and few people at risk of advanced disease are ever evaluated for fibrosis. Closing this gap between the size of the problem and the level of recognition is among the most important tasks facing clinicians who care for people with metabolic disease.

The clinical course of MASLD is heterogeneous, and understanding this heterogeneity is essential to using resources sensibly. Most affected people have simple steatosis, which is characterised by fat accumulation in hepatocytes without significant injury and carries a low short-term risk of liver-related harm. A minority develop steatohepatitis, in which hepatocyte ballooning, lobular inflammation and cell death drive progressive scarring. Over years, fibrosis can advance from perisinusoidal collagen deposition to bridging fibrosis and cirrhosis, although progression is slow, variable and in some patients reversible. In cohorts with paired liver biopsies, fibrosis stage, rather than the degree of fat or inflammation, has proved the dominant predictor of liver-related events and death [2]. Patients who reach advanced fibrosis or cirrhosis face portal hypertension,

ascites, variceal bleeding, hepatic encephalopathy, liver failure and hepatocellular carcinoma, which can occasionally arise even before cirrhosis is established. For this reason, modern care is organised around identifying the minority with significant fibrosis early enough to intervene, while reassuring and supporting the majority with low-risk disease.

The liver is only one of the organs involved. Fatty liver disease shares its origins with insulin resistance, visceral adiposity, atherogenic dyslipidaemia and hypertension, and it both reflects and contributes to systemic metabolic dysfunction. Cardiovascular disease, rather than liver failure, is the commonest cause of death among affected patients, and the condition is also associated with chronic kidney disease, obstructive sleep apnoea, polycystic ovary syndrome, osteoporosis and several extrahepatic cancers, notably colorectal cancer. The relationship with type 2 diabetes is bidirectional: diabetes accelerates the progression of liver fibrosis, while the presence of fatty liver predicts incident diabetes and worsening glycaemic control. MASLD is therefore best understood as a multisystem metabolic disorder with a prominent hepatic manifestation, and its management must address the whole cardiometabolic profile and not the liver alone. This perspective also explains why hepatologists, diabetologists, cardiologists, dietitians and primary care physicians all have a part to play.

Young people are not spared. Pediatric fatty liver disease has become the commonest cause of chronic liver disease in children in many countries, with the highest rates among those with obesity and in some ethnic groups, including South Asian children, who develop metabolic complications at lower degrees of adiposity. Childhood disease can progress to fibrosis before adulthood, and early-onset type 2 diabetes in adolescence is a particularly adverse combination. Women are also affected in distinctive ways: risk rises after menopause, polycystic ovary syndrome is associated with a high burden of steatosis, and metabolic disease in pregnancy can affect both mother and child. These considerations mean that case-finding strategies, lifestyle counselling and drug choices need to be adapted to age, sex and reproductive stage rather than applied



uniformly, an issue that is discussed further in the management section.

The terminology has recently changed. For decades the name non-alcoholic fatty liver disease (NAFLD) defined the condition by what it was not, and non-alcoholic steatohepatitis (NASH) described its inflammatory form. Both labels attracted criticism: they were exclusionary rather than descriptive, they implied that alcohol was irrelevant, and the word fatty was considered stigmatising by many patients. In 2023, a multisociety Delphi consensus replaced these terms with steatotic liver disease as an umbrella category, within which MASLD is diagnosed on positive criteria, namely hepatic steatosis together with at least one of five cardiometabolic risk factors [3]. NASH was renamed metabolic dysfunction-associated steatohepatitis (MASH), and a new category, MetALD, was created for patients with metabolic dysfunction and higher alcohol intake. Because more than 95% of patients previously labelled as having NAFLD satisfy the new definition, earlier research remains largely applicable. This review uses MASLD and MASH for current concepts and NAFLD or NASH when describing historical studies.

The new definition has practical consequences. A diagnosis of MASLD requires evidence of steatosis on imaging, biomarkers or histology, together with at least one criterion among increased BMI or waist circumference, impaired fasting glucose or diabetes, raised blood pressure or its treatment, raised triglycerides or lipid-lowering treatment, and low HDL cholesterol or its treatment. Alcohol intake is quantified rather than simply excluded: patients who drink within defined limits remain in the MASLD category, those with moderate to high intake are classified as MetALD, and those who drink more are classified as alcohol-related liver disease. This acknowledges that metabolic dysfunction and alcohol frequently coexist and interact, and that alcohol accelerates fibrosis in people with metabolic risk. It also shifts the focus of clinical assessment. Instead of searching for reasons to exclude fatty liver as a diagnosis, clinicians are asked to identify and treat the metabolic drivers that explain it, while still excluding other causes such as viral hepatitis, autoimmune liver disease and drug-induced steatosis.

The biology of the disease explains much of its clinical diversity. Insulin resistance in adipose tissue increases the flux of free fatty acids to the liver, while hyperinsulinaemia stimulates hepatic de novo lipogenesis, so that fat accumulates from several sources at once. Certain lipid species, including saturated fatty acids, ceramides and free cholesterol, are directly toxic to hepatocytes, causing endoplasmic reticulum stress, mitochondrial dysfunction and oxidative injury. Injured cells release signals that activate Kupffer cells and recruit immune cells, which in turn activate hepatic stellate cells and promote fibrosis. The gut microbiome and intestinal barrier contribute through bacterial products and bile acid signalling, and genetic variants such as PNPLA3 I148M, TM6SF2 and HSD17B13 modify individual risk. This multiple-hit model, in which several partly independent processes act together, helps to explain why a single therapy rarely works for everyone, and why patients with similar degrees of obesity may have very different liver outcomes.

Several features make the disease especially relevant to South Asia. Affected individuals frequently have a normal body mass index but excess visceral fat, reduced muscle mass and insulin resistance at lower BMI thresholds, so the condition is easily overlooked when screening is restricted to people with obesity. Early-onset diabetes, a strong familial predisposition and rapidly changing diets add to the burden, and rural and semi-urban populations are increasingly affected as well as city dwellers. At the same time, access to elastography, specialist hepatology services and newer medicines is limited, and out-of-pocket costs are a major barrier to care. Cultural beliefs also shape behaviour: many patients prefer traditional and herbal remedies, and some regard dietary and lifestyle advice as insufficient treatment. These factors mean that guidance developed for Western populations cannot simply be transferred, and that practical, affordable and culturally sensitive strategies are particularly valuable in the region.

Treatment has changed in important ways, but lifestyle modification remains its foundation. Prospective histological data show that the degree of weight loss achieved is closely related to improvement, with a loss



of about 5% of body weight reducing steatosis, about 7% to 10% improving inflammation, and 10% or more allowing fibrosis regression in a substantial proportion of patients [4]. Dietary approaches that emphasise vegetables, legumes, whole grains, olive oil and fish while limiting ultra-processed foods and sugar-sweetened beverages are favoured, and regular physical activity reduces liver fat even when body weight does not change. The difficulty is not knowing what works but sustaining it over years. Only a minority of patients achieve and maintain the degree of weight loss associated with fibrosis regression, which explains the interest in pharmacological and surgical adjuncts and in structured, long-term behavioural support.

For the first time, drugs have been approved specifically for MASH. Resmetirom, an oral liver-directed thyroid hormone receptor-beta agonist, improved both steatohepatitis resolution and fibrosis in a large phase 3 trial and in 2024 became the first medicine approved in the United States for adults with non-cirrhotic MASH and moderate to advanced fibrosis [5]. In 2025, semaglutide, a GLP-1 receptor agonist already widely used for diabetes and obesity, followed on the strength of the phase 3 ESSENCE trial [6]. These milestones mark a turning point, but they also raise practical questions. Both drugs were approved on histological surrogate endpoints, with long-term outcome data still maturing. Cost and availability will limit their use in many health systems. And it is not yet clear how best to choose between them, combine them or sequence them with lifestyle and bariatric interventions. A broad pipeline of incretin-based agents, FGF21 analogues and other mechanisms is in late-stage development, and combination regimens are widely anticipated.

Alongside these advances, many patients, particularly in Asia, use herbal and traditional remedies in the hope of reversing fatty liver. The motivations are understandable. Herbal products are perceived as natural, they are widely available without prescription, they are often culturally familiar and trusted, and they are marketed with confident claims of liver protection or detoxification. Some products have biologically plausible effects on lipid metabolism, insulin sensitivity or oxidative stress. However, herbal and dietary supplements are also a recognised cause of drug-induced liver

injury [7], and a patient who already has a diseased liver has less reserve to tolerate additional harm. Products are variably standardised, may be adulterated or contaminated, and are frequently used without the knowledge of the treating physician. Clinicians therefore need balanced, evidence-based information with which to counsel patients, rather than either uncritical endorsement or blanket dismissal.

Current practice guidance from the American Association for the Study of Liver Diseases and from the European societies converges on a stepwise, non-invasive approach to diagnosis [8,9]. Adults with type 2 diabetes, obesity with additional metabolic risk factors, persistently abnormal liver enzymes or incidental steatosis are evaluated first with a simple index such as FIB-4, which combines age, aminotransferases and platelet count. Those with indeterminate or high scores proceed to elastography or an enhanced fibrosis blood test, and a minority undergo liver biopsy when the diagnosis remains uncertain. The pathway is attractive because it conserves specialist resources and avoids unnecessary biopsy, but it depends on primary care physicians applying it consistently. Experience suggests that implementation is patchy, that thresholds may perform differently in older adults and in non-Western populations, and that many patients at highest risk are never tested. The guidelines also stress that management should address cardiovascular risk, and neither recommends any herbal product.

The evidence base for other treatments is more mixed. A phase 2 trial of daily subcutaneous semaglutide provided the first clear signal of steatohepatitis resolution with a GLP-1 receptor agonist [10] and informed the phase 3 programme. Earlier randomised data showed that vitamin E improved histology in non-diabetic patients with biopsy-proven steatohepatitis, and that pioglitazone improved several histological features without meeting its primary end point, although neither is free of long-term concerns, including weight gain and fluid retention with pioglitazone [11]. For eligible patients with severe obesity, bariatric surgery produces durable weight loss and, in prospective biopsy-based cohorts, resolution of steatohepatitis and regression of fibrosis in a majority of patients five years after the procedure [12]. SGLT2 inhibitors and statins serve

mainly as treatments for coexisting diabetes and cardiovascular risk, although they appear safe and may offer liver benefit. Across all these interventions, the central uncertainty is whether improvements in histology translate into fewer cirrhosis complications, cancers and deaths, a question that only long-term outcome trials can answer.

The herbal literature is smaller and less rigorous. Silymarin, derived from milk thistle, is the best-studied product, but the largest randomised trial in biopsy-proven steatohepatitis did not show a significant improvement in its primary histological end point, although a possible effect on fibrosis was seen in secondary analyses [13]. Berberine, a plant alkaloid, improved glucose, lipids and liver fat in randomised trials of modest size [14]. Turmeric and curcumin have been reported to lower liver enzymes in several small studies, yet turmeric supplements, particularly those formulated for high absorption with black pepper, have also been linked to clinically significant liver injury [15]. Concentrated green tea extracts are an established cause of hepatotoxicity [16], and a review of traditional Indian Ayurvedic preparations has documented liver injury associated with several commonly used herbs [17]. Taken together, these data suggest that some herbs may offer small biochemical benefits but that none has been shown to improve long-term liver outcomes, and that safety cannot be assumed simply because a product is natural.

Against this background, several gaps justify a fresh synthesis. Clinicians need a practical way to move from the high prevalence of fatty liver to the identification of the minority at risk, using tools that are available in routine practice. They need clarity on the rapidly changing therapeutic landscape, including where lifestyle intervention, drugs and surgery each belong. And they need an honest appraisal of the herbal products that so many patients ask about, particularly in regions where such products are part of everyday health care. These areas are often addressed in separate publications, and a single integrated account aimed at clinicians in both resource-rich and resource-limited settings may be useful.

This review therefore aims to give clinicians and researchers an integrated and up-to-date account of

MASLD. It summarises the new nomenclature and epidemiology, current understanding of pathogenesis and natural history, the stepwise non-invasive diagnostic pathway, and established and emerging treatments, including special populations such as lean patients, children and women. It then offers a critical appraisal of herbal products and closes with a discussion of unresolved challenges and future directions. Wherever possible, statements are linked to randomised trials, systematic reviews or society guidance, and areas where evidence is limited or evolving are identified explicitly.

1.1 Scope and Methods

This is a narrative review. It draws on landmark randomised trials, systematic reviews and meta-analyses, and the most recent AASLD and EASL guidance [8,9], chosen for their influence on clinical practice. Herbal products are covered in a separate section because patients commonly ask about them. No formal systematic search protocol was used, so the review may under-represent smaller studies. [Authors: add the databases searched, search dates and search terms if the target journal requires them.]

2. Nomenclature: Why NAFLD Became MASLD

The term "non-alcoholic" defined the disease by exclusion, which was criticised as uninformative and the word "fatty" as stigmatising. In 2023, a multi-society Delphi consensus (AASLD, EASL, ALEH and others) introduced new terminology:

- **Steatotic liver disease (SLD)** is the umbrella term for fat accumulation in the liver.
- **MASLD** requires hepatic steatosis plus at least one of five cardiometabolic criteria: increased BMI or waist circumference, impaired fasting glucose or diabetes, raised blood pressure, raised triglycerides, or low HDL cholesterol (or treatment for these).
- **MASH** replaces NASH, denoting steatohepatitis with ballooning and inflammation.
- **MetALD** describes MASLD with higher alcohol intake (about 140 to 350 g per week for women and 210 to 420 g per week for men).



- **ALD** applies when alcohol intake exceeds those ranges.

Studies indicate that over 95% of people previously diagnosed with NAFLD meet MASLD criteria, so existing literature remains largely applicable [3].

3. Epidemiology

Meta-analyses estimate the global prevalence of NAFLD/MASLD at about 30%, up from roughly 25% in earlier estimates, with the highest rates in Latin America and the Middle East and rapidly rising rates in South and Southeast Asia [1]. Prevalence exceeds 60% among people with type 2 diabetes and is higher still in people with severe obesity. In India, community studies commonly report prevalence in the range of 30 to 40%, and notably the disease occurs in people with a normal BMI ("lean MASLD"), reflecting visceral adiposity and insulin resistance at lower BMI thresholds in South Asians.

About 20 to 30% of those with MASLD have MASH, and an estimated 5 to 6% of the general adult population is thought to have MASH. Among those with MASH, a minority progress to advanced fibrosis over years to decades.

4. Pathogenesis

The older "two-hit" model has been replaced by a multiple-parallel-hit model in which several processes act together.

Insulin resistance and lipid overload. Insulin-resistant adipose tissue releases excess free fatty acids, while hyperinsulinaemia drives hepatic de novo lipogenesis. Hepatic fat arises from a combination of adipose-derived fatty acids, dietary fat and newly synthesised lipid.

Lipotoxicity. Specific lipid species, such as saturated fatty acids, ceramides and free cholesterol, cause endoplasmic reticulum stress, mitochondrial dysfunction and oxidative stress, leading to hepatocyte injury and death.

Inflammation and fibrogenesis. Injured hepatocytes release signals that activate Kupffer cells and recruit immune cells. Hepatic stellate cells are then activated and deposit extracellular matrix, producing fibrosis.

Gut-liver axis. Dysbiosis, increased intestinal permeability and endotoxin translocation contribute to hepatic inflammation. Microbial metabolites, including bile acid derivatives and short-chain fatty acids, also modulate disease.

Genetics. Variants in *PNPLA3* (I148M) and *TM6SF2* increase risk of steatosis, MASH and fibrosis, whereas loss-of-function variants in *HSD17B13* appear protective. These findings have created genetically validated drug targets.

5. Natural History and Clinical Outcomes

Fibrosis stage is the strongest predictor of liver-related outcomes and mortality [2]. Patients with stage F3 or F4 fibrosis face substantially higher risk of decompensation, hepatocellular carcinoma and liver-related death. However, in most patients with MASLD, cardiovascular disease is the leading cause of death, followed by extrahepatic cancers and then liver-related events. MASLD is also associated with chronic kidney disease, obstructive sleep apnoea, polycystic ovary syndrome and colorectal neoplasia. Hepatocellular carcinoma can occur in non-cirrhotic MASLD, though most cases arise in cirrhosis.

6. Diagnosis

Case finding. Screening is recommended in high-risk groups: people with type 2 diabetes, obesity with additional metabolic risk factors, persistently abnormal liver enzymes, or incidental steatosis on imaging. Alcohol intake should always be quantified and other causes of liver disease excluded.

Stepwise risk stratification. Current guidelines favour a non-invasive pathway:

1. Calculate the **FIB-4 index** (age, AST, ALT and platelets). A value below about 1.3 makes advanced fibrosis unlikely, with a higher threshold of around 2.0 used in older adults.
2. For intermediate or high FIB-4, perform a second-line test such as **vibration-controlled transient elastography (FibroScan)** or the **Enhanced Liver Fibrosis (ELF)** blood test.
3. Refer patients with persistently elevated risk to hepatology. **Liver biopsy** remains the reference standard for diagnosing MASH, but is reserved for



diagnostic uncertainty or trial settings because of its invasiveness and sampling variability.

Ultrasound detects moderate to severe steatosis but is insensitive for mild disease. Controlled attenuation parameter (CAP) and MRI-PDFF quantify fat more precisely, with MRI-PDFF mainly used in research.

7. Management

7.1 Lifestyle intervention

Lifestyle change remains the foundation of care. Weight loss correlates with histological benefit in a dose-dependent way: about 5% loss improves steatosis, around 7 to 10% improves inflammation, and 10% or more can regress fibrosis in a substantial proportion of patients [4]. A Mediterranean-style diet, limiting ultra-processed foods and sugar-sweetened beverages, and at least 150 minutes of moderate exercise weekly all help, and exercise lowers liver fat even without weight loss. Coffee consumption is associated with lower fibrosis risk. Alcohol should be minimised, and avoided altogether in advanced fibrosis.

7.2 Pharmacotherapy

Until recently no drug was approved for the condition. The landscape has changed substantially.

Resmetirom is an oral liver-directed thyroid hormone receptor-beta agonist. In the phase 3 MAESTRO-NASH trial it improved MASH resolution and fibrosis relative to placebo, and it received US FDA approval in March 2024 for adults with non-cirrhotic MASH and moderate to advanced fibrosis (F2 to F3) [5]. Common adverse effects are gastrointestinal.

Semaglutide, a GLP-1 receptor agonist, showed MASH resolution in a phase 2 trial [10] and subsequently in the phase 3 ESSENCE study, which supported regulatory approval for MASH with fibrosis in the United States in 2025 [6]. GLP-1-based therapies also reduce weight and cardiovascular risk, making them attractive for patients with coexisting obesity or diabetes.

Other agents. Pioglitazone and vitamin E have randomised-trial evidence of histological benefit in selected patients, with vitamin E generally considered in non-diabetic patients with biopsy-proven MASH, and long-term safety concerns limiting use of both [11]. SGLT2 inhibitors reduce liver fat and may help, and statins are safe in MASLD and should be used when indicated for cardiovascular risk.

Table 1: Summary of Pharmacological and Surgical Options in MASLD/MASH

Option	Mechanism	Key evidence	Status and comment
Resmetirom	Liver-directed thyroid hormone receptor-beta agonist	MAESTRO-NASH phase 3 trial [5]	US FDA approved in 2024 for MASH with F2 to F3 fibrosis
Semaglutide	GLP-1 receptor agonist	Phase 2 trial [10]; ESSENCE phase 3 trial [6]	US FDA approved in 2025 for MASH with F2 to F3 fibrosis
Pioglitazone	PPAR-gamma agonist	PIVENS trial [11]	Off-label; weight gain and fluid retention limit use
Vitamin E	Antioxidant	PIVENS trial [11]	Considered in non-diabetic, biopsy-proven MASH; long-term safety concerns
SGLT2 inhibitors	Glucose-lowering, cardiorenal protection	Reduction of liver fat in small trials	Histological benefit unproven; used for diabetes and cardiorenal indications
Bariatric surgery	Sustained weight loss	Prospective cohort [12]	Option for eligible patients with obesity

7.3 Bariatric surgery

For eligible patients with obesity, bariatric surgery produces durable weight loss and resolution of MASH in a majority, with observational data suggesting

reduced liver-related events [12]. It can be considered in compensated cirrhosis in specialised centres.

7.4 Emerging therapies

A large pipeline is in late-stage development. These include dual and triple incretin agonists (tirzepatide,



survodutide, retatrutide), FGF21 analogues (efruxifermin, pegozafermin), the pan-PPAR agonist lanifibranor, and siRNA or antisense approaches targeting *PNPLA3* and *HSD17B13*. Combination therapy is likely to be needed, as in other chronic diseases. Trial results for several of these may have emerged since this review was written, so readers should consult current sources.

7.5 Advanced disease

Patients with cirrhosis require variceal screening, hepatocellular carcinoma surveillance with ultrasound (with or without AFP) every six months, and management of decompensation. MASH is now one of the leading indications for liver transplantation in many countries.

7.6 Special Populations

Lean MASLD. A sizeable share of affected people have a normal BMI, particularly in South and East Asia. They often carry more visceral fat and less muscle than their weight suggests, and share the insulin resistance and genetic risk seen in obesity [1]. A loss of even 3 to 5% of body weight can help, and resistance training is valuable because it builds muscle without needing large changes on the scale.

Children and adolescents. Fatty liver has become one of the commonest causes of chronic liver disease in young people in many countries, with the highest rates in those who are obese. Care rests on family-based changes in food and activity, cutting sugary drinks, and limiting sedentary screen time. Guidance advises checking ALT in children with obesity from about 9 to 11 years of age, and no drug is yet approved specifically for paediatric MASH [8].

Women. Premenopausal women tend to have lower risk than men, but the gap narrows after menopause, probably because the protective effect of oestrogen on fat distribution and insulin sensitivity is lost. Women with polycystic ovary syndrome have a higher burden of MASLD. Pregnancy plans should be discussed before starting newer drugs, since safety data in pregnancy are limited.

Cardiovascular protection. Because heart disease is the leading cause of death in MASLD, blood pressure,

lipids and glucose all need active control, and statins are safe in this group [9]. Patients should also be asked about smoking, sleep apnoea and physical inactivity at the same visit.

7.7 Follow-up in Practice

People at low risk by FIB-4 can usually be reassessed every one to three years, with more frequent review when weight, glucose control or liver enzymes worsen. Those with significant fibrosis should be followed by a hepatologist, and anyone with cirrhosis needs ultrasound surveillance every six months. Success is judged by weight, metabolic control and stable or falling fibrosis markers, rather than by liver enzymes alone, since enzymes can be normal even in advanced disease.

8. Herbal and Natural Products in MASLD

Herbal remedies are widely used by people with fatty liver, often alongside or instead of conventional care, and the topic deserves a balanced look. The overall picture is that several botanicals show promising signals in small or short trials, but none has been proven to improve liver histology or long-term outcomes, and none is recommended by the major AASLD or EASL guidelines [8,9].

8.1 Agents with the Most Clinical Data

Silymarin (milk thistle) and silybin. Silymarin is the most studied herbal product in liver disease. Some studies and meta-analyses have found that silymarin may slightly reduce ALT and AST levels. However, a large randomized controlled trial involving patients with biopsy-confirmed MASH found no significant improvement in the primary disease activity score, although a secondary analysis suggested a possible benefit in reducing liver fibrosis.

Formulations combining silybin with phospholipids and vitamin E have shown some benefit in small studies. Overall, the evidence is inconclusive [13].

Berberine. This plant alkaloid (from *Berberis* species and others) improves glucose, lipids and liver fat in several small randomised trials [14]. Its effect is probably mediated through AMPK activation and gut microbiota changes. Gastrointestinal side effects are common, and it can interact with drugs metabolised by CYP enzymes, including ciclosporin.



Curcumin (turmeric). Meta-analyses suggest modest improvements in liver enzymes and steatosis. Absorption is poor, which has led to the development of high-bioavailability formulations (often containing piperine). Rare cases of turmeric-associated liver injury have been reported, particularly with such concentrated products [15].

Green tea and coffee. Drinking coffee is associated with lower fibrosis risk and is reasonable to encourage.

In contrast, concentrated green tea extract supplements have been linked to liver injury and are best avoided [16].

Others. Ginger, cinnamon, *Salvia miltiorrhiza*, various traditional Chinese medicine formulas and Ayurvedic herbs such as *Phyllanthus niruri* and *Picrorhiza kurroa* have been studied, but trials are mostly small, short and of variable quality.

Table 2: Herbal Products Studied in MASLD: Reported Effects and Safety Concerns

Product	Reported effects	Principal safety concerns
Silymarin	Modest improvement in enzymes; no significant histological gain in the largest trial [13]	Generally well tolerated; mild gastrointestinal upset
Berberine	Improved glucose, lipids and liver fat in small trials [14]	Gastrointestinal effects; drug interactions via CYP enzymes
Curcumin	Modest improvement in enzymes and steatosis	Rare liver injury, particularly with high-bioavailability products [15]
Green tea extract	Inconsistent	Hepatotoxicity with concentrated extracts [16]
<i>Tinospora cordifolia</i> , ashwagandha	Not established	Liver injury reported [17]

8.2 Safety: Herbs Can Injure the Liver

Herbal and dietary supplements are an important cause of drug-induced liver injury, and a patient who already has a damaged liver has less reserve [7]. Reports from India have linked some popular products, including *Tinospora cordifolia* (guduchi) and ashwagandha, to liver injury, sometimes with an autoimmune-like picture [17]. Additional concerns include:

- Poor standardisation, so the dose in a capsule or powder may vary widely
- Adulteration with undeclared drugs, and contamination with heavy metals in some traditional preparations
- Interactions with diabetes, blood-pressure and anticoagulant medicines
- Delayed presentation, since patients often do not mention supplements to their doctor

8.3 Practical Advice

1. Herbal products should be regarded as optional adjuncts, never as substitutes for weight loss, exercise, dietary change and metabolic control.

2. Patients should disclose every herb and supplement to their hepatologist or physician.
3. Avoid high-dose extracts, multi-ingredient "liver detox" blends and unlabelled products.
4. The product should be stopped and medical attention sought if jaundice, dark urine, itching or unexplained fatigue develops.
5. Well-supported food-based measures, such as a Mediterranean-style diet and coffee, are preferable to concentrated supplements.

Herbal evidence is evolving quickly and varies by product; please check current literature or consult a clinician before starting any supplement.

9. Challenges and Future Directions

Key gaps include better non-invasive biomarkers that track treatment response, optimal screening strategies in primary care, and evidence for the right sequencing of drugs and lifestyle therapy. The disease also disproportionately affects populations with limited access to specialist care, and awareness among clinicians and the public remains low. Public health measures addressing diet quality, physical activity and food environments are ultimately essential to reduce incidence.



CONCLUSION

NAFLD, now MASLD, is a common, multisystem metabolic disease whose outcomes are determined mainly by fibrosis stage. Identification through simple, stepwise non-invasive testing, sustained lifestyle modification, and cardiometabolic risk control form the core of care, and for the first time targeted drugs are available for patients with significant fibrosis. The coming years should bring combination regimens and better tools to match therapy to patient.

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