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Metabolic dysfunction associated fatty liver disease (MAFLD): A review on mechanistic pathways, pathophysiology, and management

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Abstract
Background: Metabolic dysfunction associated fatty liver disease (MAFLD) is a condition in which excess fat accumulates in the liver, without alcohol being a contributing factor. MAFLD can progress to non-alcoholic steatohepatitis (NASH), which can lead to liver cirrhosis and liver failure. Metabolic dysfunction associated fatty liver disease is also regarded as a stand-alone cardiovascular diseases' risk factor.
Objective: In this review, we summarized pathophysiology, mechanistic pathways, symptoms, diagnosis, pharmacological and traditional therapeutic interventions currently being developed for treatment of MAFLD.
Methods: A literature search on various data base *viz* Medline, PubMed, Embase, and Scopus was done using various keywords like MAFLD, NAFLD, steatosis, steatohepatitis, fibrosis, cirrhosis, adiponectin, inflammation,
Results: It has been proposed that the development of MFALD is a two-step process based on this body of evidence. The hepatic deposition of fat, which will worsen insulin resistance, is the initial stage of this process. The second phase of this process consists of alterations in the extracellular matrix, energy homeostasis, cytokine injury, hyperinsulinemia, hepatic iron and/or lipid peroxidation, and oxidation of fatty acids in the liver as a result of various factors. Lifestyle modifications play a central role in managing MAFLD, and early intervention can prevent the progression of the disease to more severe forms, such as nonalcoholic steatohepatitis (NASH) or cirrhosis.
Conclusion: The exact cause of MAFLD is not fully understood, but it is believed to be related to several factors. The pathogenesis of MAFLD has been shown to be profoundly influenced by inflammation and insulin resistance. The primary source of liver damage is the buildup of fat, which is followed by inflammation. A complicated relationship between adipokines and liver disease appears to be critical in the development of MAFLD. Present review aimed to explored pathophysiology of MAFLD and the development of strategies for its therapy.

Keywords: Metabolic dysfunction associated fatty liver disease, steatosis, non-alcoholic steatohepatitis, cirrhosis, adiponectin, inflammation

Introduction
The recently proposed name "metabolic dysfunction-associated fatty liver disease" (MAFLD) is replacing the old term "non-alcoholic fatty liver disease" (NAFLD) in many global countries because it better describes the pathogenesis and cardiometabolic implications of this common liver disease [1]. MAFLD, which is characterized by an increase in triglycerides in hepatocytes, is currently the most prevalent chronic liver disease in many regions of the world. Almost all countries have shown an increase in MAFLD prevalence during the last three decades [1-2]. MAFLD is a complex condition with multiple factors contributing to its pathogenesis. The pathogenesis of MAFLD involves the accumulation of excess fat in the liver, inflammation, and liver damage. Some of the key factors involved in the pathogenesis of MAFLD are insulin resistance, excess fat accumulation in the liver, inflammation, gut micro-biome, Other factors that may contribute to the pathogenesis of MAFLD, is characterized by the hepatic component of metabolic syndrome and is represented by hepatic steatosis. This condition is marked by accumulation of fat in the liver parenchyma without inflammation and occurs in the absence of excessive alcohol consumption (less than 210 ml for men and 140 ml for women) [2]. Simple steatosis, steatohepatitis, cirrhosis and fibrosis comes in the MAFLD spectrum that causes fat to accumulate in the liver parenchyma along with inflammation, hepatocyte ballooning, and globular inflammation [3].

Whereas non-alcoholic steatohepatitis (NASH) progresses to fibrosis and cirrhosis in 20% of individuals over the course of 15 years [4] simple steatosis (SS) rarely progresses to severe illness. Metabolic syndrome is a condition characterized by a cluster of risk factors that include central obesity, dyslipidemia, and type-2 diabetes. MAFLD is strongly associated with metabolic syndrome, with respective relative prevalences of 23%, 51%, 69%, and 43%. The disease burden of MAFLD rose from 15% in 2005 to 25% in 2010, which is attributed to rising obesity rates [5].

Another factor, adiponectin which is a type of adipokine and secreted by adipose tissue, has an inverse relationship with insulin resistance, lipid buildup, inflammation, and MAFLD. Adiponectin generally predicts steatosis grade and severity of MAFLD [6]. Low levels of adiponectin are associated with an increased risk of developing MAFLD. Studies have shown that adiponectin decreases hepatic and systemic insulin resistance and reduced liver inflammation and fibrosis [6].

Fibrosis is indeed considered the primary indicator of poor outcomes in MAFLD. Several studies have shown that the stage of fibrosis is strongly associated with disease-specific mortality and long-term clinical outcomes in MAFLD patients [7]. A study published in Hepatology found that patients with fibrosis stage 3 or 4 at baseline had the worst prognosis [8]. Another systematic review of prognostic accuracy in MAFLD-related events concluded that fibrosis is the strongest predictor for long-term clinical outcomes. Fibrosis progression in MAFLD is usually slow, but approximately 25-40% of patients with non-alcoholic steatohepatitis (NASH) will develop progressive liver fibrosis, which can ultimately lead to cirrhosis (Fig. 1) [9, 11]. Even in the very initial stages of fibrosis, there is a slight enhancement of all-cause mortality, and this increase rises linearly with each stage of the disease's development. However, intermediate fibrosis and cirrhosis have death rates of 7.92 and 23.3 respectively, per 1000 people every year [10]. The development of MAFLD is linked to several pathways and factors. Pathways associated with the development of MAFLD are excessive lipid accumulation within the liver, genetic sensitivity expressed in metabolic derangement situations, higher fat consumption. The double-hit hypothesis is a widely accepted theory for the progression of MAFLD. According to this hypothesis, the first hit is the accumulation of free fatty acids (FFAs) in the liver, leading to steatosis. The second hit is a secondary insult, such as oxidative stress, inflammation, or mitochondrial dysfunction, which triggers the progression of steatosis to non-alcoholic steatohepatitis (NASH) and fibrosis [12, 13].

Epidemiology

Different populations have variable rates of MAFLD, and the methods used to diagnose MAFLD can impact these rates. The main methods used for diagnosis include serum biochemistry, imaging, and histological examination [14]. Liver biopsy, which is considered the gold standard for diagnosis of MAFLD but it cannot be used for screening due to its invasive nature and associated risks. On the other hand, studies that use imaging modalities, such as ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI), can provide a non-invasive assessment of liver fat content and are commonly used for diagnosing MAFLD [14]. However, it is important to note that imaging may not be able to differentiate between simple steatosis and more advanced stages of MAFLD, such as non-alcoholic steatohepatitis (NASH) or fibrosis. Blood tests, including liver function tests and specific biomarkers, can also be used to diagnose MAFLD. However, studies using blood tests alone may frequently underestimate the prevalence of MAFLD compared to studies that utilize imaging modalities. The prevalence of MAFLD as determined by imaging was found to be 25.24% globally in one meta-analysis. Middle East (37.19%) and South America (30.45) had the highest prevalence rates, followed by Asia (27.17%), Adult MAFLD prevalence in India has been estimated to range from 6.7% to 55.1% [14-15]. North America (24.13%), Europe (23.17%), and Africa (13.48%) [16]. NASH was seen in 59.1% of the MAFLD patients who underwent biopsy. Generally, the prevalence of MAFLD varies between 20% and 40% in western countries and 7.9 and 43.3% in eastern countries [17-19].

Pathophysiology

Excessive lipid buildup in the liver, together with genetic predisposition shown in a state of metabolic derangement and linked to an increased consumption of fat, are the processes linked to the incidence and progression of MAFLD [20-21]. High fat intake, which characterizes known Western diets, has been linked to dyslipidemia, insulin resistance, and metabolic/cardiovascular disorders. The general idea for the development of NAFLD is the double-hit hypothesis, while the pathophysiological reasons behind the disease remain unclear. The main insult causing steatosis is IR, which causes decreased fatty acid (FA) transport and hepatic de novo lipogenesis (DNL) [21]. Among many other things, the second hit includes endoplasmic reticulum stress, disruption of autophagy, mitochondrial malfunction, hepatocellular apoptosis, and an increase in inflammatory reactions. Overall, increasing evidence indicates that the pathophysiology of NAFLD involves several interconnected mechanisms. The first hit-fat accumulation in the liver-increases vulnerability to subsequent risk factors, which in turn leads from non-alcoholic steatohepatitis (NASH), a more severe form of NAFLD, to cirrhosis and hepatocellular cancer. The metabolic syndrome (MS), which is characterized by insulin resistance (IR), type 2 diabetes mellitus (T2DM), hyperlipidemia, and obesity, has been linked to NAFLD on several occasions [21-22]. Accordingly, obesity is a major contributor to metabolic syndrome and is associated with a higher risk of non-alcoholic fatty liver disease (NAFLD); however, an increasing percentage of people who are normal weight are also afflicted, suggesting that dyslipidemia is a substantial independent risk factor [22-23].

Diagnosis

MAFLD is frequently asymptomatic and frequently discovered by chance [24]. Physicians should identify the presence of one or more metabolic risk factors and MAFLD in individuals with abnormal liver tests; in fact, the chance of MAFLD rises proportionally with the prevalence of risk factors for metabolic syndrome (Table no. 1 describing the types and symptoms of steatohepatitis) [25]. Alanine transaminase (ALT) and aspartate transaminase (AST) levels in serum readings may not always be abnormal in the parameters of MAFLD, even when utilizing tougher cut-offs for the maximum of normal [26-27]. Numerous research have shown that ALT is an in effective marker for predicting advanced fibrosis in non-alcoholic fatty liver disease patients [28]. Patients with at least 30% steatosis will have an echo-bright liver visible on ultrasound scans, with sensitivity ranging from 64% to 85% and up to 90% [29].

Other techniques for identifying hepatic steatosis include magnetic resonance spectroscopy (MRS), which is regarded to be more sensitive and may also provide a quantitative evaluation of statuses [30], and controlled attenuation parameter software on the Fibro-scan system [31]. Many scoring systems that can identify patients with little or moderate liver fibrosis have been described for the non-invasive evaluation of MAFLD fibrosis [32]. Age, obesity, reduced glucose tolerance, the ratio of AST to ALT, and other factors are shared by many of them. Other noninvasive tests for the identification of liver fibrosis include the Serum European Liver Fibrosis (ELF) panel, which combines the three serum indicators Hyaluronic acid, Pro-collagen III amino terminal peptide, and tissue Inhibitor of metalloproteinase 1 [33]. Transient elastography, like the Fibro-scan, has been approved in MAFLD as an additional non-invasive technique to assess liver fibrosis in the outpatient setting [34-35].

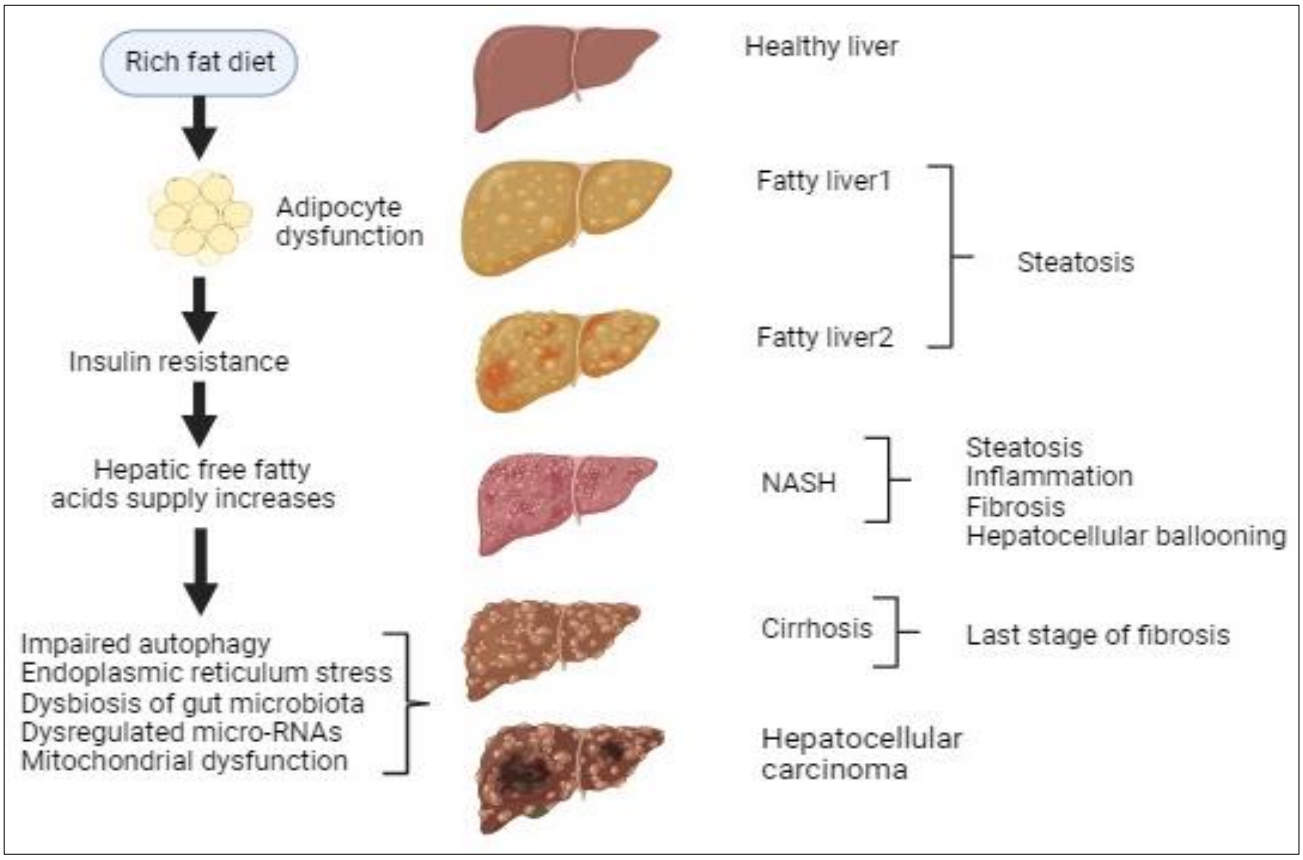

Fig 1: Progression of MAFLD

Table 1: Types and symptoms of non-alcoholic steatohepatitis

Types of NASH	Symptoms of MAFLD
Steatosis	Hepatocyte swelling is a sign of liver cell injury known as ballooning. This is because of intracellular fluid occumulation and various types of toxic cell injury. Patients exhibiting fat accumulation, ballooning degeneration, mallory hyaline, or fibrosis face a higher risk of progressing to cirrhosis and experiencing liver-related mortality compared to those with only fat accumulation or fat accumulation along with lobular inflammation [36-37].
Fibrosis	The normally lobular hepatic parenchyma collapses as a result of fibro genesis' continual death of hepatocytes, which is followed by fibrosis surrounding necrotic liver cells. Increased type 1 and type 3 collagen production in the Disse space is the mechanism of liver fibrosis. Below the sinusoidal epithelium, there is an expansion of fat-storing In to cells, which develop into myofibroblasts and fibrocytes. In addition to collagen, the region of damaged liver cells also has an excessive deposition of the glycoproteins fibronectin and laminin. Growth factors, vasoactive factors, cytokines, lymphokines, and chemokines released by lymphocytes, kuffer cells, endothelial cells, and hepatocytes are all stimulants for fibrosis. Examples include platelet-derived growth factor receptor-beta, transforming growth factor-beta, and metalloprotieneases [38].
Cirrhosis	Hepatic parenchyma's typical lobular architecture is disordered. Different areas of livers may undergo regeneration, forming nodules, following hepatocellular necrosis Nevertheless, because biliary cirrhosis and cirrhosis in hemochromatosis have limited regeneration, regenerative nodules are not absolutely necessary for the diagnosis of cirrhosis [38].

Mechanistic pathways

Molecular events implicated in the development of MAFLDs

The known causes of an excessive formation of triglycerides in hepatocytes are obesity and metabolic disorders like insulin resistance or dyslipidemia. Obese patients have been shown to have increased triglyceride lipolysis and release of fatty acids from adipose tissue. The excessive breakdown of triglycerides affects not only the liver but also other tissues, causing a deposition of fatty acids in the form of diacylglycerol [39].

Transport of fatty acid

Fatty acid transporters, such as CD36, caveolins, and FATP (fatty acid transport proteins), which are found in the plasma

membrane of hepatocytes, are responsible for the uptake of fatty acids into hepatocytes (liver cells) for various metabolic processes, including energy production and lipid synthesis. [40]. Patients with MAFLD have higher quantities of these proteins in their livers, which when combined with hyperlipidemia results in greater FA uptake by hepatocytes. The coordinated action of these transporters allows the liver to efficiently take up circulating fatty acids, which are then utilized for energy production through beta-oxidation, incorporated into triglycerides for storage, or used in the synthesis of complex lipids. Proper regulation of fatty acid transport is essential for maintaining lipid homeostasis and overall liver function [41].

Fate of excess fatty acid uptake

Dysregulation of these processes can contribute to metabolic disorders such as fatty liver disease. Peroxisome proliferator-activated receptor (PPAR), which is a transcription factor that induces the transcription of a large number of genes involved in fatty acid oxidation in the mitochondria and cytochromes, involved in the regulation of lipid metabolism in hepatocytes. Targeting genes involved in de novo lipogenesis (DNL) and FAs import. PPAR alpha (PPARα) is a subtype of PPAR that is differently expressed in MAFLD and non-alcoholic steatohepatitis (NASH) liver [42-43].

The increased hepatic lipid buildup in MAFLD is expected to promote FA oxidation (FAO). Studies examining FAO in MAFLD, including both human and animal research, have provided diverse findings, reflecting the heterogeneity of the disease and the dynamic nature of lipid metabolism.

In the early stages of MAFLD, characterized by simple steatosis, there is often an increase in hepatic lipid buildup. The initial response may involve enhanced fatty acid uptake and storage as triglycerides. However, FAO may also be upregulated as a compensatory mechanism to mitigate lipid overload. In more advanced stages, such as non-alcoholic steatohepatitis (NASH), the situation can become more complex (Fig.1) While some studies suggest that FAO remains elevated or adaptive to cope with increased lipid supply, others indicate that there may be impairments in mitochondrial function and FAO, contributing to the progression of NASH. Studies have reported variable findings regarding FAO in MAFLD. Some studies have observed increased FAO, possibly as an adaptive response, while others have reported impaired FAO in NASH, suggesting mitochondrial dysfunction and oxidative stress [44]. The relationship between hepatic lipid buildup and FAO in MAFLD is nuanced and can vary based on disease progression, individual factors, and experimental conditions. Ongoing research is crucial to further unravel the molecular mechanisms underlying these processes and identify effective therapeutic targets for MAFLD. Another significant mechanism controlling hepatic lipid concentration is liver FA export. FAs delivered to the liver from adipose tissue and the small intestine and released from hepatocytes as water-soluble very low-density lipoprotein (VLDL) particles. Apolipo-protein B100 (apoB100) synthesis and microsomal triglyceride transfer protein (MTTP) activity are essential for the formation of VLDL in the endoplasmic reticulum (ER). As a result, these proteins are thought to be important elements controlling the release of hepatocytes' VLDL. The initial phase involves MTTP catalyzing the loading of ApoB100 with lipids, after which the developing VLDL particle is moved to the golgi apparatus and eventually secreted from hepatocytes [45]. Dysfunctional VLDL production and release is a NASH-specific defect, as Fujita and colleagues have shown [46]. While the blood level of VLDL-TG was lower in the NASH group despite being greater in the MAFLD individuals as compared to controls. According to these findings, MTTP, ApoB100, and PPAR-α expression were shown to be lower in liver biopsies from NASH patients than in MAFLD specimens [47]. (Fig 2)

Increased hepatocyte lipid release during steatosis may partially offset intrahepatic lipid buildup.

However, as MAFLD progresses, lipid outflow from hepatocytes in MAFLD appear to be biphasic, with secretion hitting a plateau and even starting to fall as MAFLD progresses. Dysregulation of lipid homeostasis in hepatocytes leads to hepatic steatosis, which results from an imbalance between synthesis and utilization of lipids. Hepatic lipid acquisition, mediated by increased fatty acid uptake and de novo lipogenesis, is enhanced in MAFLD despite the presence of steatosis. Impaired lipid disposal may also contribute to the accumulation of lipids in hepatocytes [48].

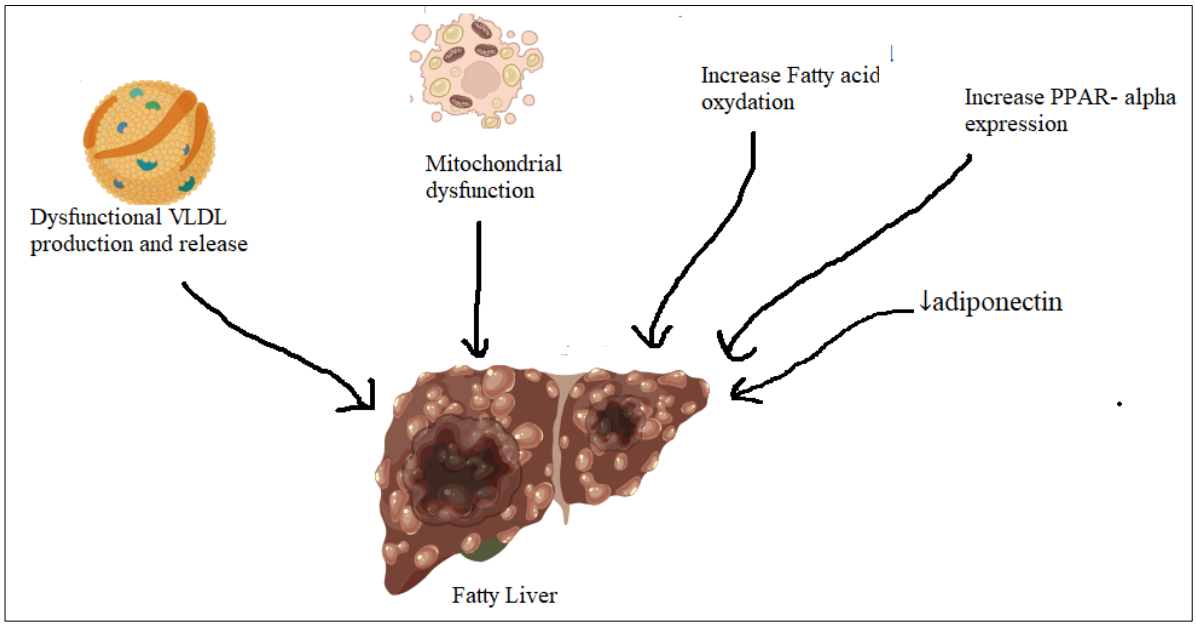

Fig 2: Risk factors for progression of MAFLD. Figure illustrates the most common risk factors associated with the development of MAFLD.

Adiponectin, a hormone released by adipose tissue, plays a crucial role in regulating inflammatory and metabolic processes. It has been shown to have multifaceted effects and metabolic processes thus play a significant role in MAFLD. [49-50]. Research has demonstrated that giving diabetic mice adiponectin can lower their blood levels of FFAs and TAGs while raising their HDL levels. It has been proposed that adiponectin increases insulin sensitivity through activating a number of signaling pathways, including the AMPK and insulin signaling pathways [51-52]. Adiponectin influences AMPK and PPAR-α during the progression of MAFLD. Adiponectin therapy dramatically reduced hypertriglyceridemia and insulin resistance in mice given an HFD, according to earlier studies [53]. According to research by Combs and Marliss adiponectin protects the liver from hepatic steatosis by reducing blood cholesterol levels and glucose synthesis [54]. According to studies, adiponectin stimulates glucose absorption both activating glucose transporters and inhibiting TNF-α [55], In type 2 diabetes mice, adiponectin is thought to reduce glucose synthesis by activating AMPK and concurrently inhibiting the gluconeogenic enzymes phosphoenolpyruvate carboxykinase (PEPCK) and glucose 6 phosphatase (G6pase) [56]. Adiponectin has also been shown for advancement hepatic insulin sensitivity by directly activating ceramidase, a rate-limiting enzyme that facilitates the breakdown of membrane lipids [57-58].

Pharmacological findings on alternative management of MAFLD

Medicinal plants have been known since ancient times and are widely regarded as a rich source of therapeutic measures for the prevention and treatment of various ailments. Indigenous cultures have long used herbs in medicinal practices. Conventional medicinal systems, such as Ayurveda, Siddha, Unani, and Traditional Chinese Medicine, have effectively developed herbal therapies. It is essential to approach herbal treatments with caution, as their safety and efficacy may not be well-established, and they may interact with medications or have unintended effects. Moreover, the quality and purity of herbal supplements can vary widely.

Few traditional therapies used in alternative management systems are discussed here.

Green tea polyphenols [GTP] markedly lowered the levels of TNF-α, IL-6, and malondialdehyde in rats suffering from non-alcoholic fatty liver disease. GTP also decreased the histological alterations in liver tissue that are suggestive of injury while simultaneously noticeably raising AMPK phosphorylation [59]. Berberine and evodiamine (BE) therapy successfully reduced pro-inflammatory factor expression, lowered intestinal epithelial, cell death and improve liver fat formation, tissue damage thereby BE therapy may be a useful for treating NAFLD [60]. Study reported by Sun S. *et al*. (2022) on effect of Alstonia scholaris on non-alcoholic fatty liver disease found significantly decrease in the bodyweight of HFD fed mice. The concentrations of low-density lipoprotein (LDL), triglyceride (TG), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were also decreased significantly in Alstonia scholaris treated mice, accompanied by an increase in high-density lipoprotein (HDL) [61]. Huang T. *et al*. (2015) evaluated the effects of Hibiscus sabdariffa water extract (HSE) on body weight and adipose tissue in HFD-fed hamsters, HSE treatment reduced fat accumulation in the livers of hamsters fed with HFD in a concentration-dependent manner, reduced the levels of liver cholesterol and triglycerides [62]. Dushkin M. *et al*. (2014) evaluated the effects of Rhaponticum cathamoides (ERC) extract, Glycyrrhiza glabra and Punica granatum extract (EGG&EPG). Each of the examined extracts decreased the levels of IL6 and cortisol in the serum brought on by HFD. However, the gains brought about by EGG and EPG were greatly outweighed by the decreasing effects of ERC intake on the serum TNF-alpha level and its restoring effect on the adrenal corticosterone level. Consuming ERC also decreased the buildup of triacylgycerol and boosted PPR-alpha DNA-binding activity in the liver more than EGG and EPG [63]. Zhu W. *et al*. (2017) explored the effects of taurine, tea polyphenols (TPs) on nonalcoholic steatohepatitis rats. Taurine treatment alleviated hepatocyte damage and oxidative stress. TPs treatment improved lipid metabolism and increase hepatic antioxidant activity. Taurine and TPs combination may act as a new effective medicine for treating NASH patients [64]. An study reported by Bansal P. *et al*. (2022), investigated effect of embelin against non-alcoholic fatty liver disease [NAFLD] induced by the high fat diet [HFD]. Embelin reatment reduced oxidative stress and chronic inflammation in obese C57BL/6 mice. When liver tissue was treated with Embelin, obesity biomarkers improved and levels of nuclear factor erythroid 2-related factor and nuclear factor kappa-B protein expression significantly decreased. Treatment with embelin also restores normal thiobarbituric acid reactive substance levels in liver tissue. Histological examination of the liver tissue treated with embelin revealed a notable reduction in necrotic and inflammatory alterations [65]. Abd-Elrazek A. M. *et al*. (2022) investigated effect of *Apium graveolens* [celery] and curcumin against non-alcoholic fatty liver disease induced by high fructose-high fat [HFHF] diet in rats. A histological analysis that identified pathological alterations in the HFHF group confirmed the findings. Additionally, DNA fragmentation was seen, and lysosomal enzyme activity improved. *Apium graveolens* extract and curcumin administration may have ameliorative effects against NALFD development [66]. Miao J. *et al*. (2022) explored the effect of Er-Chen [EC] decoction against the non-alcoholic fatty liver disease [NAFLD] induced by the high fat diet. EC has a variety of ameliorative effects on NAFLD, including improvements in blood lipid levels and liver function as well as the reduction of pathological alterations, oxidative stress, and inflammatory reactions. The mechanism of EC for NAFLD may involve the improvement of gut microbiota change, control of metabolic pathways for taurine and hypotaurine metabolism, cysteine and methionine metabolism, and metabolism of vitamin B6 [67]. Liao M. *et al*. (2022) investigated the effect of the protein-protein interaction network and qPCR experiments, they discovered a number of putative hub proteins against the development of NAFLD. Collectively their findings demonstrated Cori's significant inhibitory effects on NAFLD progression, which were likely mediated by ameliorating insulin resistance and dysregulated lipid metabolism in HFD-fed mice [68].

In line with the previous studies the barley grass juice (*Hordeumvulgare* L.) effect was investigated for the effectiveness to prevent obesity in a high-fat diet model. Body weight, BMI, lipid profiles, and markers of AST, ALT, and ALP, PPAR-gamma and caspase 3 expression were all significantly higher in rats fed a high-fat diet for 60 days, using barley grass juice for 60 days, on the other hand, dramatically lowered body weight, BMI, and liver function

indicators while improving lipid profiles. Barley grass juice treatment also lowers expression of caspase 3 and PPAR-gamma in the liver [69]. Feng W. *et al*. (2018) found that berberine and curcumin exhibited better ameliorative effects on rats with non-alcohol fatty liver disease than lovastatin. The body weight, visceral fat gain, histological inspection and serum parameters were studied to exam in the curative effects. In addition, mediators including SREBP-1c, caveolin-1, pERK, NF-κB, TNF-α, and pJNK were studied. Study showed that berberine and curcumin combination exhibited lower body and fat weight compared with lovastatin group. Biochemical assays showed that LDL-c, ALT, AST, ALP, MDA, LSP level were lower in berberine and curcumin combination treated group compared with lovastatin group. Lower expression of SREBP-1c, pERK, TNF-α, and pJNK were also observed in berberine and curcumin group [70].

Sodum N. *et al*. (2022) investigated effect of cinnamoyl sulfonamide hydroxamate by activating SIRT1, high-fat diet (HFD) in CCl4-induced NASH/NAFLD. HFD and CCl4 together changed how lipids were metabolized, causing CF-1 male mice to store cholesterol and triglycerides in their hepatocytes. However, in both *in-vivo* and in-silico investigations, the hydroxamate derivative NMJ-3 and sodium valproate decreased the accumulation of lipid content in hepatocytes. Comparatively to vorinostat, the NMJ-2 and NMJ-3 can suppress NOTCH-1 overexpression in NAFLD/NASH via activating SIRT-1. In-depth research is necessary for confirmation at the molecular level. Liver sample NMJ-3 therapy decreased inflammation, fibrosis, and necrosis [71]. Lv Y. *et al*. (2019) studied hepatoprotective effect of apigenin (API) against NAFLD and further investigate its potential mechanism. Improve insulin sensitivity and significantly reduce lipid accumulation. Moreover, API could reverse the HFD-induced activation of the NLRP3 inflammation, further reduce inflammatory cytokines IL-1β and IL-18 release, along with the inhibition of xanthine oxidase [72]. Ren S. *et al*. (2021) explored that defatted walnut powder extract (DWPE) has an anti-NAFLD effect in C57BL/6 mice and this effect was induced by changing the compositions and abundances of the gut microbiota. In comparison to the HFD group, DWPE demonstrated a decrease in NF-B and MAPKs family protein expression [73].

Modern therapeutic intervention for MAFLD

Natural products and modifications to lifestyle are being considered as potential MAFLD treatment alternatives. These natural compounds have the potential to address many elements of MAFLD pathogenesis, such as oxidative stress, lipid metabolism and inflammation. The therapeutic treatments of MAFLD are mainly focused on inflammation, fibrosis, and hepatic steatosis. Development of pharmaceutical therapies for MAFLD indeed focused on addressing multiple pathophysiological mechanisms associated with the condition. These mechanisms include insulin sensitivity, inflammation, weight loss, antifibrotic effects, and lipid metabolism.

To date, there is no drug officially licensed specifically for the treatment of MAFLD. Due to the close association between MAFLD and metabolic disorder such as obesity and type 2 diabetes, several drugs, initially developed or approved for other medical conditions, were indeed being investigated for their potential efficacy in treating MAFLD. Many of these drugs were repurposed from other therapeutic areas, particularly type 2 diabetes (T2D), given the strong association between insulin resistance and MAFLD. Some of the classes of these drugs include: SGLT-2 inhibitors originally developed for treating diabetes, have been investigated for their potential benefits in MAFLD, possibly through improvements in insulin sensitivity, improved visceral fat, hepatic steatosis, reduced ALT. and other metabolic effects [71-76].

GLP-1 receptor agonists used for managing type 2 diabetes such as liraglutide, have shown promise in improving liver health and reducing liver fat content in individuals with MAFLD [68-70].

Thiazolidinediones (TZDs) these drugs, such as pioglitazone, have insulin-sensitizing properties and have been studied for their potential benefits in MAFLD. Activation of PPAR-γ receptor by this drug, have been investigated for its potential therapeutic effects in MAFLD, particularly in the more advanced form known as non-alcoholic steatohepatitis (NASH) [77].

Conclusion

The prevalence of MAFLD, can affect children as well as adults suffer from conditions ranging from simple steatosis, inflammation, fibrosis and cirrhosis. While its pathophysiology is still not completely understood, it is known that hepatic steatosis results from a complicated interaction between the environment, nutrition, and adipose and liver tissues. Because fibrosis increases overall mortality from cardiovascular, hepatic, and cancerous causes, it is crucial for determining the disease's prognosis. There is strong evidence that alterations in adiponectin blood levels brought on by adipose tissue growth not only contribute to the initiation and progression of metabolic syndrome but also to MAFLD, NASH, and even NASH-related cirrhosis. Adiponectin can serve as a good disease marker in this approach. Since that cardiovascular disease causes the bulk of fatalities from MAFLD, addressing these two factors concurrently will be difficult but may show promising results.

The main ways to improving MAFLD outcomes include weight loss and lifestyle changes like as eating a balanced diet, exercising regularly, and avoiding alcohol intake. Diet should be rich in micronutrients, protein, carbohydrate, and fat. Protein should be from vegetable sources, carbohydrate source should be rich in fibers and of low glycemic index, and fat from the poly and mono unsaturated fatty acid sources. Balanced diet and lifestyle changes ameliorate metabolic syndrome, which leads to an improvement in MAFLD. It's important to highlight that the management of MAFLD is multifaceted and should be tailored to individual needs. Regular monitoring, lifestyle changes, and collaboration with healthcare professionals are essential components of the therapeutic approach.

Conflict of Interest

No conflict of interest to be declared

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