


OPEN ACCESS
EDITED BY

 Ioannis Zabetakis,
University of Limerick, Ireland

REVIEWED BY

 Charalampos Proestos,
National and Kapodistrian University of
Athens, Greece
Danyu Cheng,
The First Affiliated Hospital of Xi'an
Jiaotong University, China

***CORRESPONDENCE**

 Paraskevi A. Farazi
✉ e.farazi@euc.ac.cy

RECEIVED 15 December 2025

REVISED 22 January 2026

ACCEPTED 26 January 2026

PUBLISHED 11 February 2026

CITATION

 Kouti T, Christodoulou P,
Christodoulides S, Protopapa F,
Michaeloudes C and Farazi PA (2026)
Polyunsaturated fatty acids as a potential
preventive and therapeutic intervention
for metabolic dysfunction–associated
steatotic liver disease and its progression
to hepatocellular carcinoma.
Front. Nutr. 13:1767917.
doi: 10.3389/fnut.2026.1767917

COPYRIGHT

 © 2026 Kouti, Christodoulou,
Christodoulides, Protopapa,
Michaeloudes and Farazi. This is an
open-access article distributed under
the terms of the [Creative Commons
Attribution License \(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use,
distribution or reproduction in other
forums is permitted, provided the
original author(s) and the copyright
owner(s) are credited and that the
original publication in this journal is
cited, in accordance with accepted
academic practice. No use, distribution
or reproduction is permitted which does
not comply with these terms.

Polyunsaturated fatty acids as a potential preventive and therapeutic intervention for metabolic dysfunction–associated steatotic liver disease and its progression to hepatocellular carcinoma

 Thomai Kouti¹, Panayiota Christodoulou¹,
Stephanos Christodoulides², Foula Protopapa¹,
Charalambos Michaeloudes¹ and Paraskevi A. Farazi^{1*}
¹School of Medicine, European University Cyprus, Egkomi, Nicosia, Cyprus, ²School of Sciences, European University Cyprus, Egkomi, Nicosia, Cyprus

Metabolic dysfunction–associated steatotic liver disease (MASLD) is currently the leading cause of chronic liver disease worldwide and a major cause of hepatocellular carcinoma (HCC), a cancer with poor prognosis. Considering the immense public health impact of MASLD and MASLD–HCC, preventive and more effective management strategies for these diseases are urgently needed. Polyunsaturated fatty acids (PUFAs) appear to improve liver health through modulation of lipid metabolism, inflammation and oxidative stress and therefore could influence MASLD and MASLD–HCC progression. To this end, this review discusses the role of PUFAs, more specifically n-3 and n-6, in MASLD and MASLD–HCC, by critically reviewing evidence from human clinical and observational studies, and experimental models. Human observational and clinical trial studies collectively suggest a beneficial effect of PUFAs in the prevention of MASLD and MASLD–HCC. Evidence in animal models indicate that n-3 PUFA supplementation suppresses the development of MASLD by preventing liver steatosis, inflammation, and fibrosis. These effects are mediated through a shift in lipid metabolism from lipogenesis toward lipolysis and fatty acid oxidation, inhibition of key inflammatory pathways and antioxidant effects. There is evidence from a small number of animal model studies showing a reduction in PUFA levels during MASLD progression to HCC, and a protective effect of n-3 PUFA supplementation against liver tumorigenesis. However, the evidence on the molecular mechanisms mediating this effect is very sparse. The evidence reported in this review suggests consideration of PUFAs, and particularly n-3 PUFAs, as potential preventive modalities for MASLD–HCC and for control of established MASLD–HCC in combination with existing therapies, albeit in a microenvironment context-dependent manner. Finally, the review highlights key gaps in the literature and suggests potential research opportunities to delineate the role of PUFAs in MASLD–HCC.

KEYWORDS

HCC, MASH, MASLD, omega 3 (n-3) polyunsaturated fatty acids, omega-6 PUFAs, PUFA

Introduction

Metabolic dysfunction–associated steatotic liver disease (MASLD), previously known as non-alcoholic fatty liver disease (NAFLD), represents the hepatic manifestation of metabolic syndrome and is now the leading cause of chronic liver disease worldwide (1). 38% of all adults worldwide suffer from MASLD and by 2040, the prevalence is expected to reach 55% (2). A subset of patients progress to metabolic dysfunction–associated steatohepatitis (MASH), characterized by hepatocellular injury, inflammation, and varying degrees of fibrosis. Over time, MASH can evolve into advanced fibrosis, cirrhosis, and eventually hepatocellular carcinoma (HCC), even in the absence of cirrhosis, highlighting the disease's oncogenic potential and its rising global burden (3, 4). HCC is the leading type of primary liver cancer and a significant contributor to cancer-related deaths globally. In addition to MASLD, other chronic liver conditions, such as viral hepatitis and alcoholic liver disease are associated with HCC. However, in recent years, an epidemiologic shift has occurred for HCC with an increasing number of HCC cases now being associated with MASLD (5).

There is currently no available therapy specifically targeting MASLD-HCC patients, who are treated for liver cancer, based on tumor stage, by surgery, non-specific chemotherapy, or immunotherapy. Patients, therefore, experience significant side effects from the chemotherapy, whilst a proportion of patients may respond poorly to immunotherapy (6). Therefore, therapies targeting metabolic dysfunction may enable a more personalized and targeted treatment approach for MASLD-HCC patients.

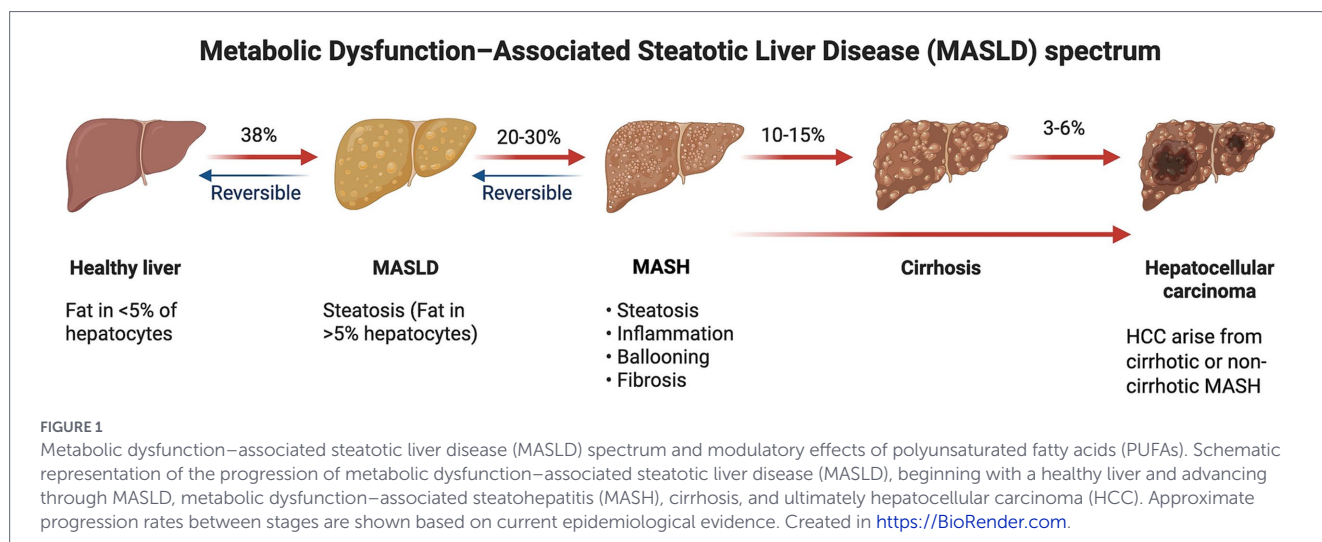
Given the emerging evidence for the role of PUFAs in modulating processes of metabolic dysfunction including lipid metabolism, inflammation, and oxidative stress, it is reasonable to consider their use in the prevention and control of MASLD and MASLD-HCC. Epidemiologic and animal model data support the role of PUFAs, particularly n-3 PUFAs, in the prevention of MASLD. However, although epidemiological evidence supports a potential protective effect of PUFAs against the development of MASLD-HCC, there is a lack of data from experimental models and a poor understanding of the mechanisms involved. To paint a clearer picture on this topic this review will: (1) Synthesize human evidence for PUFAs in preventing and managing MASLD and MASLD-HCC through a comprehensive review of the existing epidemiological, clinical and experimental data; (2) Detail the established mechanisms by which PUFAs improve MASLD and MASLD-HCC; (3) Critically examine the conflicted and emerging evidence for PUFAs in MASLD-HCC, focusing on the unique MASLD tumour microenvironment; and (4) Outline priority research directions to trigger progress in filling the gaps in this area. This review is the first to address the role of PUFAs beyond MASLD and dive into their role in the progression to MASLD-HCC with the aim to highlight controversies and research gaps in this field. Considering the poor survival of MASLD-HCC patients, understanding how PUFAs may impact MASLD-HCC development and the mechanisms associated with their tumor effects are of utmost importance.

Pathogenesis of MASLD/MASLD-HCC

MASLD is the most common cause of chronic liver disease and has a higher prevalence in people with obesity, type 2 diabetes, and

metabolic syndrome. It is characterized by excess lipid accumulation within hepatocytes in the context of metabolic dysfunction, typically linked to insulin resistance. It involves steatosis affecting more than 5% of the liver parenchyma, reflecting an imbalance between lipid acquisition and disposal within the liver (7). In addition, the prevalence of MASLD is associated with genetic polymorphisms in genes such as *PNPLA3*, *TM6SF2*, *MBOAT7*, and *HSD17B13*, which make individuals susceptible to fat accumulation, inflammation, and fibrosis (8). The prevalence of the disease also varies geographically, with higher prevalence reported in South America and the Middle East, and lower prevalence in Africa. These prevalence patterns reflect differences in lifestyle, diet and genetic susceptibility. MASLD is a leading indication for liver transplantation and a rapidly growing risk factor of HCC, even in the absence of cirrhosis (9). MASLD is the recently adopted term that replaces non-alcoholic fatty liver disease (NAFLD) to better reflect its metabolic origins. Traditionally, NAFLD referred to hepatic fat accumulation not caused by excessive alcohol intake and encompassed two stages: non-alcoholic fatty liver (NAFL), characterized by simple steatosis without significant inflammation, and non-alcoholic steatohepatitis (NASH), where steatosis is accompanied by hepatocellular injury, inflammation, and varying degrees of fibrosis (10). In 2023, international liver societies introduced the term MASLD, defining it as hepatic steatosis in individuals with at least one cardiometabolic risk factor such as obesity, type 2 diabetes, dyslipidemia, or hypertension. The progressive form, metabolic dysfunction–associated steatohepatitis (MASH), corresponds to NASH in the older terminology and represents the stage most likely to progress to cirrhosis and HCC (11). The metabolic origins of MASLD render it different from other types of chronic liver diseases, which requires different considerations in prevention and treatment of MASLD and MASLD-HCC.

Progression of MASLD to metabolic dysfunction–associated steatohepatitis (MASH) occurs in about 20–30% of MASLD patients. Individuals with MASH are at increased risk of fibrosis, cirrhosis, and hepatocellular carcinoma (HCC), and among those who develop MASH, approximately 10–15% will progress to cirrhosis (12). Overall, an estimated 3–6% of patients with MASH will eventually develop MASH-associated hepatocellular carcinoma (HCC) (13). Notably, among individuals who develop MASH-related HCC, a substantial proportion arises in the absence of preceding cirrhosis (14, 15) (Figure 1). The histological changes of MASLD follow a pattern of changes very similar to that of the alcohol induced hepatic injury and range from simple fat accumulation to inflammation, fibrosis and cirrhosis. The “multiple hit hypothesis” suggests that the development of MASLD stems from metabolic, inflammatory, and genetic factors. Insulin resistance leads to an increase in adipose tissue lipolysis, and then an influx of free fatty acids into the liver, promoting hepatic steatosis. When free fatty acids, diacylglycerols and ceramides accumulate in the liver, the mitochondrial β -oxidation of these molecules is impaired, resulting in the overproduction of reactive oxygen species (ROS) and oxidative stress. This causes lipid peroxidation, cell membrane damage and hepatocyte apoptosis or necrosis, leading to the release of damage-associated molecular patterns (DAMPs) (16). The gut-liver axis plays a key role in MASLD pathogenesis, as the intestinal dysbiosis increases the permeability of the gut, allowing bacterial endotoxins to reach the liver through the portal vein. DAMPs and endotoxins activate receptors, such as toll-like receptors (TLRs), in Kupffer cells, which trigger inflammatory mechanisms, including transcription factor NF- κ B, mitogen associated protein kinases



(MAPKs) and the NOD-like receptor protein 3 (NLRP3) inflammasome (17). The resulting inflammatory response is associated with the release of cytokines such as $\text{TNF-}\alpha$, IL-6, and IL-1 β , and growth factors, including transforming growth factor (TGF)- β . These mediators promote hepatic stellate cells to transform into myofibroblasts, which in turn produce extracellular matrix components, resulting in fibrosis. As these processes progress, they disrupt the architecture and function of the liver, paving the way for cirrhosis and HCC (18).

HCC develops through a complex interplay of genetic, epigenetic, metabolic, and inflammatory alterations that transform chronically injured hepatocytes into malignant cells. In MASLD and MASH, persistent lipotoxicity and oxidative stress induce DNA damage, mitochondrial dysfunction, and impaired repair mechanisms. ROS and lipid peroxidation products such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) form mutagenic adducts with DNA, promoting genomic instability (19). Continuous activation of inflammatory signaling, notably NF- κ B, JNK, and STAT3 pathways, drives hepatocyte proliferation, survival, and resistance to apoptosis (20). At the same time, metabolic reprogramming in pre-malignant hepatocytes supports tumorigenesis. Enhanced *de novo* lipogenesis, altered β -oxidation, and a shift toward aerobic glycolysis provide energy and biosynthetic precursors for rapid cell growth (21). Oncogenic pathways such as Wnt/ β -catenin, PI3K/Akt/mTOR, and MAPKs become aberrantly activated, either through mutations or chronic signaling, leading to uncontrolled proliferation and angiogenesis (22). Epigenetic modifications, including DNA hypermethylation, histone acetylation, and deregulated microRNAs (e.g., miR-122, miR-21), further silence tumor suppressor genes and enhance oncogene expression (23). Collectively, these molecular alterations enable hepatocytes to escape normal growth controls and acquire malignant potential.

The HCC tumor microenvironment plays a pivotal role in promoting tumor initiation, progression, and immune escape. Chronic liver injury remodels the hepatic niche into a pro-inflammatory, fibrotic, and immunosuppressive milieu. Activated hepatic stellate cells (HSCs) and cancer-associated fibroblasts (CAFs) secrete extracellular matrix components, TGF- β , and vascular endothelial growth factor (VEGF), fostering fibrosis and neovascularization. This fibrotic matrix not only supports tumor cell proliferation but also provides structural scaffolding for invasion and metastasis (24). Kupffer cells and infiltrating macrophages adopt a tumor-promoting (M2-like) phenotype, releasing IL-6, $\text{TNF-}\alpha$, and ROS, which further enhance inflammation and

oncogenic signaling (25). Chronic hypoxia in the fibrotic liver upregulates hypoxia-inducible factors (HIF-1 α and HIF-2 α), stimulating angiogenesis and metabolic adaptation of cancer cells (26). In parallel, the TME becomes immunosuppressive, with regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and exhausted cytotoxic T cells impairing effective antitumor immunity. Tumor cells exploit immune checkpoints such as PD-1/PD-L1 and CTLA-4 to evade immune surveillance (27). Altogether, these cellular and molecular interactions create a self-reinforcing loop of inflammation, fibrosis, and immune tolerance that sustains tumor growth and progression. The unique tumor and microenvironment characteristics in MASLD-HCC require special considerations for the prevention and treatment of the disease, which may be different from HCC of other etiologies.

Current management strategies for MASLD and MASLD-HCC

Although the selective thyroid hormone receptor- β (THR- β) agonist resmetirom is currently the only approved pharmacologic therapy for MASH, the management of MASLD and MASH remains predominantly non-pharmacological (16, 28). Current strategies focus on lifestyle modification, weight reduction, dietary interventions, increased physical activity, and optimization of metabolic comorbidities, which continue to represent the cornerstone of disease prevention and treatment (Figure 2) (7). Particular attention is directed toward the management of key metabolic comorbidities such as obesity, insulin resistance, and dyslipidemia, which constitute major therapeutic targets in slowing disease progression and reducing overall cardiometabolic risk (16, 29, 30). As far as MASLD-HCC is concerned, there are no specific treatments for the disease. Instead, currently available treatments for HCCs of other aetiologies are also used for the management of MASLD-HCC.

Management of MASLD/MASH

Non-pharmacological treatments in MASLD/MASH

The primary objective of disease management is to achieve a clinically meaningful improvement in patient outcomes. In liver disease,

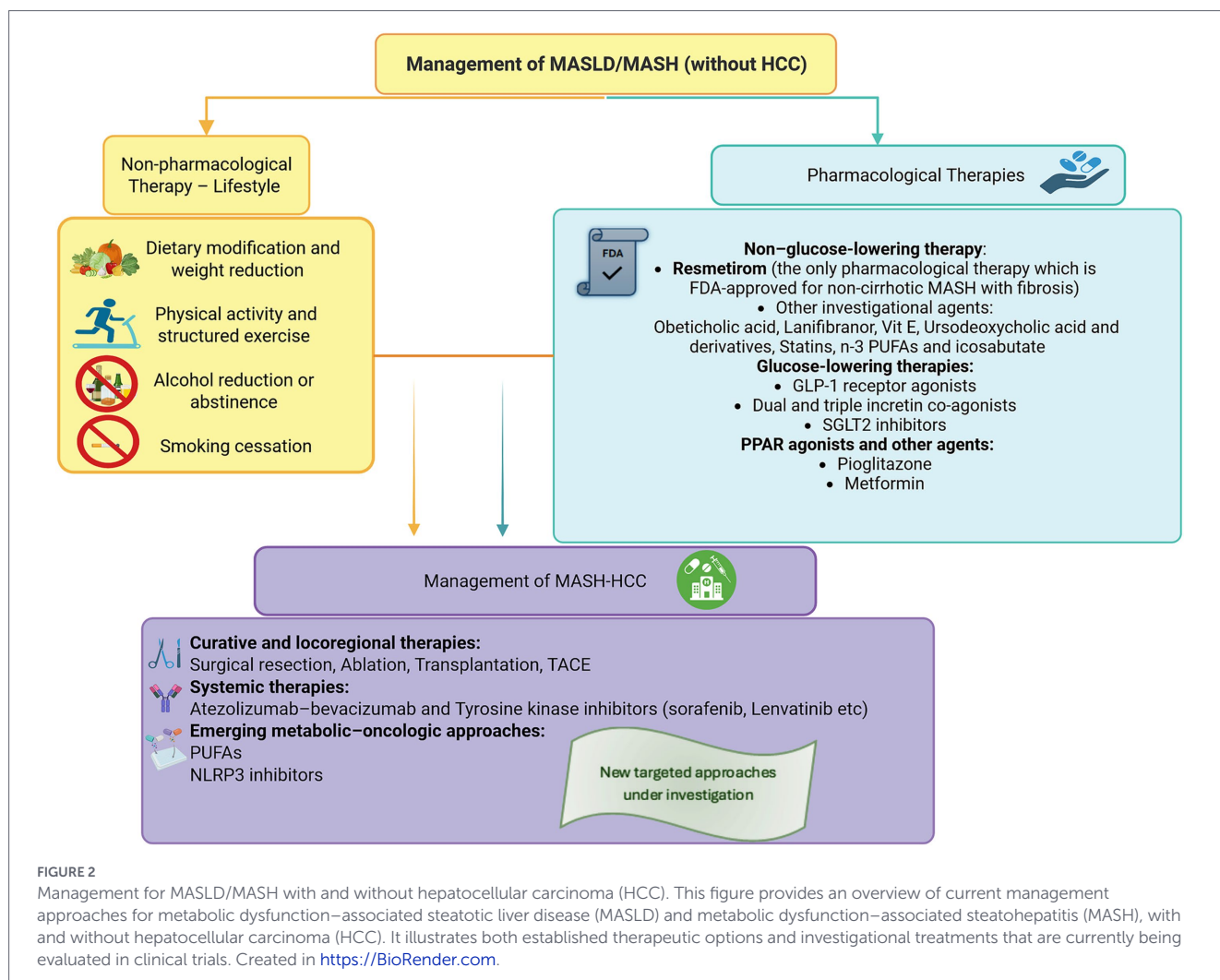


FIGURE 2

Management for MASLD/MASH with and without hepatocellular carcinoma (HCC). This figure provides an overview of current management approaches for metabolic dysfunction–associated steatotic liver disease (MASLD) and metabolic dysfunction–associated steatohepatitis (MASH), with and without hepatocellular carcinoma (HCC). It illustrates both established therapeutic options and investigational treatments that are currently being evaluated in clinical trials. Created in <https://BioRender.com>.

these outcomes typically include the prevention of cirrhosis decompensation, preservation of liver function, reduction in the risk of HCC, and avoidance of liver transplantation (31). Within this framework, non-pharmacological interventions represent a cornerstone in improving clinical outcomes and slowing disease progression, encompassing dietary modification and weight reduction, regular physical activity and structured exercise programs, as well as reduction or abstinence from alcohol consumption and smoking cessation (32).

Weight loss remains the most effective non-pharmacological intervention for managing MASLD, with consistent evidence supporting a dose-dependent reduction in liver fat content, steatohepatitis, and fibrosis (32). According to the EASL–EASD–EASO Clinical Practice Guidelines, targeted weight reduction is a cornerstone in MASLD management, with specific goals tailored to body mass index (BMI) and clinical context. In overweight or obese individuals, a $\geq 5\%$ weight loss reduces hepatic steatosis, while a 7–10% loss is typically needed to improve MASH and hepatic inflammation, and $\geq 10\%$ to reverse fibrosis (33). For patients with class II or III obesity, incretin-based pharmacotherapy or bariatric surgery may be considered, whereas even modest weight loss (3–5%) in individuals with normal BMI can improve hepatic steatosis (7).

Numerous clinical trials have demonstrated that weight loss achieved through caloric restriction leads to improvements in liver enzymes, hepatic steatosis, fibrosis, and MASH progression (33–36).

Furthermore, weight reduction contributes to better glycemic control, lipid profiles, and blood pressure regulation, while also lowering the risk of cardiovascular disease and other metabolic complications (37). However, longitudinal studies indicate that maximal weight loss tends to occur at around 6 months, followed by partial weight regain, with a net average weight loss of approximately 5%, and an associated partial reaccumulation of hepatic fat and stiffness by 12–24 months (7, 38).

Various nutritional approaches have been investigated in this context, including hypocaloric low-carbohydrate and low-fat diets, Mediterranean-style eating patterns, very low-carbohydrate ketogenic diets, and intermittent fasting strategies such as time-restricted eating (TRE). Within this spectrum, the Mediterranean diet has drawn considerable attention, as it emphasizes minimizing the intake of processed and ultra-processed foods, such as processed meats and sugar-sweetened beverages, while increasing the consumption of unprocessed or minimally processed foods. The Mediterranean diet, rich in fruits, vegetables, whole grains, fish, and olive oil, provides a high content of monounsaturated and n-3 PUFAs that can reduce hepatic fat accumulation, enhance insulin sensitivity, and improve steatosis even in the absence of significant weight loss. Additionally, it may modulate the gut microbiota, thereby attenuating hepatic inflammation and supporting metabolic function (39). The Mediterranean diet has demonstrated additional benefits in reducing hepatic lipid

accumulation and enhancing cardiometabolic health, and it may offer greater long-term adherence compared to other dietary approaches (40–42). Beyond the Mediterranean pattern, more restrictive approaches such as very low-carbohydrate ketogenic diets have also been examined. Evidence on the efficacy and safety of very low-carbohydrate ketogenic diets (<20–50 g/day) in MASLD is currently limited, and potential cardiovascular and renal risks warrant caution (43, 44). Another dietary intervention that has gained interest is intermittent fasting, particularly TRE. Currently, evidence comparing TRE with standard daily caloric restriction (DCR) in terms of hepatic fat reduction in individuals with MASLD remains limited. In a randomized controlled trial involving adults with obesity and MASLD, TRE was associated with a ~6% reduction in intrahepatic triglyceride content, an average weight loss of approximately 7 kg, and improvements in metabolic parameters after 12 months. These results indicate that TRE may represent a feasible and effective dietary approach for selected patients, highlighting the importance of tailoring nutritional interventions to individual preferences and tolerability (43, 45).

Beyond dietary interventions, lifestyle modification in MASLD also relies heavily on structured physical activity. According to current recommendations, physical activity in individuals with MASLD should be personalized. It is generally advised to engage in more than 150 min of moderate-intensity aerobic exercise or at least 75 min of vigorous-intensity activity per week, combined with efforts to minimize sedentary behavior, to optimize both metabolic and hepatic outcomes (7). In particular, engagement in non-occupational physical activity has been shown to reduce the prevalence of MASLD and lower all-cause mortality (46). Regular, structured exercise improves insulin sensitivity, promotes weight loss, and reduces hepatic fat content (47). Both aerobic and resistance training modalities have shown beneficial effects in individuals with MASLD (48). However, compared with their well-established cardiometabolic benefits, the evidence supporting the impact of physical activity on histological improvement, non-invasive fibrosis markers, or liver-related clinical outcomes remains limited and inconclusive (7).

Finally, smoking cessation is strongly encouraged, as tobacco use negatively impacts disease progression and increases the risk of HCC and cardiovascular events (7, 49). Similarly, alcohol consumption should be minimized, and complete abstinence is advised for individuals with significant fibrosis (\geq F2) or cirrhosis. Alcohol intake has been shown to promote fibrosis progression in a dose-dependent manner and to synergize with cardiometabolic risk factors, further aggravating hepatic injury (7, 50, 51).

Pharmacologic therapies for MASH

Pharmacological approaches for MASH are currently evolving, with agents targeting distinct pathophysiological mechanisms (52). Among non-glucose-lowering therapies, resmetirom, a liver-directed thyroid hormone receptor- β agonist, is the first FDA-approved drug for non-cirrhotic MASH with fibrosis (F2–F3), demonstrating histological improvements in steatohepatitis and fibrosis (28, 53). Other investigational agents include the FXR agonist obeticholic acid, which was shown to improve fibrosis but was not approved due to safety concerns (54), and lanifibranor, a pan-peroxisome proliferator-activated receptor (PPAR) agonist currently under phase III evaluation (55). Additionally, Vitamin E has shown histological benefit in non-diabetic MASH, while ursodeoxycholic acid and its derivatives, despite biochemical improvements, have failed to consistently

demonstrate histological efficacy (56–59). Similarly, statins are considered safe and may reduce liver-related outcomes in MASLD, but evidence from randomized control trials confirming histological benefit is currently lacking (60). Lastly, n-3 PUFAs (EPA and DHA) possess anti-inflammatory and insulin-sensitizing properties yet have not consistently demonstrated histological benefit in clinical studies (61, 62). Notably, ongoing trials are evaluating modified formulations such as icosabutate—a structurally engineered fatty acid that has shown potential to suppress liver inflammation and fibrosis in preclinical models of MASH (63).

Glucose-lowering drugs, such as GLP-1 receptor agonists (e.g., liraglutide, semaglutide, tirzepatide) show promising results in steatohepatitis resolution through weight loss and metabolic modulation, though effects on fibrosis are limited (64). To enhance the therapeutic efficacy, dual and triple incretin co-agonists, targeting combinations such as GLP-1/GIP or GLP-1/GIP/glucagon, are currently under investigation (65, 66). By contrast, SGLT2 inhibitors such as empagliflozin and dapagliflozin have demonstrated modest reductions in hepatic fat and ALT levels, with no histological efficacy demonstrated to date from randomized trials (67).

Other drugs that have been used for the management of MASH include PPAR agonists, such as pioglitazone, a PPAR γ agonist, which improve histological features of steatohepatitis (68, 69), yet their clinical use is limited by adverse effects and regulatory withdrawal in certain countries (70). Metformin does not appear to improve liver histology but may provide survival benefits in patients with advanced fibrosis or cirrhosis (71, 72). Overall, while resmetirom represents a landmark in MASH pharmacotherapy, further research is warranted to optimize monotherapy approaches, identify patient subgroups most likely to respond, and evaluate the potential of rational combination therapies for sustained disease modification.

Management of MASH-HCC

Currently, there is no approved therapy specifically targeting both MASH-associated HCC (73). The management of MASH-HCC involves treating the liver cancer according to the same oncologic guidelines applied to HCC of other etiologies, based on tumor stage, including resection, ablation, transplantation, transarterial chemoembolization (TACE), or systemic therapies such as atezolizumab, bevacizumab or tyrosine kinase inhibitors (74, 75). Notably, patients with MASH-related HCC may exhibit significant side effects from the chemotherapy, as well as reduced responsiveness to immunotherapy, possibly due to an altered immune microenvironment (6, 73, 76). In light of this, attention has turned to therapies that could target both the metabolic dysfunction and tumor progression. Agents such as polyunsaturated fatty acids (PUFAs) and NLRP3 inhibitors are being investigated for their dual antifibrotic and antitumor potential (77, 78). So far, they remain the only agents specifically investigated for dual action in MASH-HCC.

Biochemistry and physiological role of PUFAs

Polyunsaturated fatty acids (PUFAs) are essential lipids whose physiological roles, despite extensive investigation, remain complex and at times contradictory. They are classified into omega-3 (n-3) and

omega-6 (n-6) families derived from the essential precursors α -linolenic acid (ALA) and linoleic acid (LA), respectively (79). Although long-chain derivatives such as eicosapentaenoic acid (EPA; C20:5), docosahexaenoic acid (DHA; C22:6) and arachidonic acid (AA; C20:4) are widely believed to regulate inflammation and cardio-metabolic health, the conversion of ALA to EPA/DHA and of LA to AA is inefficient, challenging assumptions about the functional adequacy of precursor-based intake (80). Therefore, the main dietary sources of the long-chain n-3 PUFAs EPA and DHA should be obtained from oily fish, whereas the long-chain n-6 PUFA AA should be predominantly obtained from animal-based products, particularly meat and poultry (81).

It is widely acknowledged that modern Western diets are characterized by a substantial insufficiency of n-3 PUFAs, typically exhibiting an n-6/n-3 ratio of 15–20:1 which far exceeds the proposed optimal ratio of approximately 4:1 and the ideal 1:1 ratio (82). However, achieving a more favorable n-6/n-3 balance does not necessitate restricting n-6 PUFA intake. Evidence indicates that higher n-6 PUFA consumption does not elicit adverse effects when accompanied by sufficient n-3 intake (83). Moreover, sufficient dietary provision of both n-3 and n-6 PUFAs is required to support optimal metabolic health and cardiovascular risk reduction (84). Beyond general metabolic health, PUFAs have been increasingly implicated in the prevention and management of MASLD and its progression toward HCC (85).

Role of PUFAs in MASLD and MASLD-HCC prevention and management

Role of PUFAs in the prevention of MASLD in humans

Human observational and genetic studies suggest that both n-3 and n-6 PUFAs may play a protective role in MASLD development (86, 87). In a large population-based analysis, higher circulating levels of total PUFAs and n-6 PUFAs, including linoleic acid, were independently associated with lower MASLD risk, while saturated fatty acids showed strong positive associations with disease prevalence (86). Mendelian randomization further supported a potentially causal inverse relationship between genetically predicted total PUFA levels, along with n-6 proportions, and MASLD risk (OR: 0.73 and 0.80, respectively) (86). n-3 PUFAs also show preventive potential. Large-scale prospective data from the UK Biobank indicate that regular long-chain n-3 supplementation (DHA) reduces the risk of liver disease, including MASLD, by approximately 28% (88) (Table 1). Although these studies provide evidence that PUFA insufficiency manifested by lower n-3 and n-6 levels may contribute to MASLD susceptibility, their observational nature necessitates caution as causality cannot be definitively established.

TABLE 1 Role of PUFAs in the prevention of MASLD and MASLD-HCC in humans.

Study	Country	Study design	Sample size	PUFAs investigated	Outcome measure	Major finding	Effect size
Liu et al., 2025 (86)	UK	Cross-sectional study	3,084	Omega-6 (linoleic acid)	Risk of incident MASLD	Circulating levels were negatively associated with MASLD risk	OR = 0.46 (95% CI: 0.27–0.79); <i>p</i> -value < 0.05
Liu et al., 2024 (88)	UK	Observational study	252,398	Omega-3 (DHA) and Omega-6	Risk of incident of MASLD-HCC	Plasma levels were negatively associated with MASLD-HCC risk	HR = 0.48 (95% CI: 0.33–0.69) and HR = 0.48 (95% CI: 0.28–0.81); <i>p</i> -value < 0.05 respectively
Moussa et al., 2021 (91)	USA	Case-control study	1,675	Omega-3 (EPA, DHA)	Risk of incident of MASLD-HCC	Intake was inversely associated with MASLD-HCC risk	OR = 0.50 (95% CI: 0.33–0.70); <i>p</i> -value < 0.05
Yang et al., 2020 (90)	USA	Prospective cohort study	138,483	Omega-3	Risk of incident of MASLD-HCC	Intake was inversely associated with MASLD-HCC risk	HR = 0.63 (95% CI: 0.41–0.96); <i>p</i> -value < 0.05

OR = odds ratio; HR = hazard ratio.

Role of PUFAs in the prevention of MASLD-HCC in humans

Large-scale human data indicate a strong inverse association between circulating PUFA levels and the risk of progression from MASLD to HCC (89). In the UK Biobank cohort, elevated plasma concentrations of n-3 (DHA) and n-6 polyunsaturated fatty acids were associated with a substantially decreased risk of incident HCC and reduced mortality from chronic liver disease (88). Participants in the highest quartile of plasma n-3 and n-6 PUFA concentrations exhibited approximately a 50% reduction in HCC risk compared with those in the lowest quartile (88). Moreover, population-based studies similarly suggest that low PUFA intake may predispose individuals to MASLD-related HCC (90, 91). An analysis of data from two large U. S. prospective cohort studies indicates that higher dietary intake of PUFAs, particularly the n-3 subclass, is associated with a reduced risk of HCC (90). These findings are supported by results from a hospital-based case-control study, which similarly reported inverse associations between HCC risk and the intake long-chain n-3 PUFAs (EPA and DHA) (91). However, the evidence remains limited by heterogeneous populations and uncertainty regarding the influence of fibrosis stage on the association between PUFAs and HCC (88). Moreover, in a single-arm pilot study evaluating hepatic responses to n-3 supplementation in patients with MASLD and MASH, n-3 PUFA supplementation did not affect hepatic gene expression or histological features associated with HCC, indicating potentially limited effect of PUFAs in the prevention of HCC (Table 1) (92).

Role of PUFAs in the management of MASLD in humans

Human interventional evidence evaluating PUFAs for MASLD management shows clinically meaningful metabolic improvements but inconsistent effects on liver histology (93). Meta-analyses of randomized controlled trials have reported reductions in liver enzyme (i.e., ALT, AST, γ -GT) levels, triglycerides, total cholesterol and liver fat following n-3 PUFA supplementation in MASLD (mainly EPA & DHA, some studies also included DPA) (Table 2) (94–96). However, heterogeneity across trials, particularly variations in dose, EPA/DHA composition and study duration has led to inconsistencies with some RCTs failing to show histological benefit, such as a change in fibrosis (61, 62). Therefore, although n-3 PUFAs have been consistently shown to improve metabolic parameters and reduce hepatic steatosis, their therapeutic efficacy in more advanced stages of disease remains unclear (97). Robust, long-term clinical trials are needed to define optimal dosing strategies and to establish clinically meaningful endpoints.

Role of PUFAs in the management of MASLD-HCC in humans

Although observational studies demonstrate marked alterations in PUFA status among affected patients, findings that may hold therapeutic relevance, the evidence supporting the clinical efficacy of PUFA supplementation in individuals with established MASLD-HCC remains extremely limited (88, 98). Collectively, evidence suggests that while circulating PUFA levels may serve as prognostic biomarkers for adverse hepatic outcomes, there is currently no evidence that PUFA supplementation can alter disease progression once MASLD has progressed to advanced fibrosis or HCC (Table 2) (88). Robust, targeted

randomized controlled trials conducted specifically in MASLD-HCC populations are necessary to generate high-quality evidence before any safe conclusions about therapeutic effectiveness can be made.

Role of PUFAs in MASLD and MASLD-HCC in cell and animal studies

Studies in mouse models and cell lines have also shown MASLD and HCC suppressive properties of PUFAs. Most studies in mouse models have shown the impact of PUFAs in MASLD. These studies involve feeding mice with variations of a high fat diet that induces MASLD and then adding interventions involving PUFAs. These interventions range from adding DHA alone, DHA and EPA, palmitoleic acid n-3 PUFAs, Deuterium-reinforced PUFAs, fish oil, ω -3 algal oil (rich in DHA) and ω -7 sea buckthorn oil (rich in palmitoleic acid), hemp seed oil, krill oil, soybean oil, seed oil of *rosa roxburghii* tratt, canola oil and unsaturated alginate oligosaccharides (99–117) (Table 3). Even though these studies assess slightly different outcomes related to MASLD, such as plasma lipids, hepatic fat, steatosis and fibrosis, all studies have shown that addition of these different PUFA interventions in the diets of mice results in suppression of MASLD progression. Some studies have shown that hepatic PUFA levels are reduced during MASLD progression, further attesting to their disease preventive role (118, 119) (Table 3).

Only a handful of studies in mice have addressed the role of PUFAs in MASLD-HCC progression. In a study of a non-obese MASLD-HCC mouse model, reduced plasma and tumor tissue levels of DHA and EPA were reported, as well an increase of these PUFAs over time in mice that never progress to HCC, implying their potential tumor suppressive role (120). Furthermore, a comparison of obese and non-obese MASLD-HCC mice showed a reduction of PUFAs in both models during tumor progression (121) (Table 3). A different study of Pten deficient mice, showed that EPA supplementation resulted in reduction of severe chronic hepatic inflammation, ROS formation, and HCC development (122). In another model of HCC induced by high fat diet consumption and carcinogen exposure, EPA supplementation resulted in reduction of HCC development (123) (Table 3). Finally, some work regarding the role of PUFAs in HCC was carried out in cell lines derived from HCC of viral etiologies. EPA and DHA treatment resulted in inhibition of HCC cell growth in three different cell lines through inhibition of COX-2 and beta-catenin, thereby providing some evidence of the role of PUFAs in HCC (124).

Mechanisms mediating the effects of PUFAs on MASLD pathogenesis

Several studies have demonstrated a protective effect of n-3 PUFAs in metabolic diseases including MASLD through their effects on lipid metabolism, inflammation and oxidative stress (Figures 3, 4). Indeed, n-3 PUFAs were shown to reduce markers of metabolic dysfunction, oxidative stress, and liver inflammation and injury in a LDLR-deficient western diet-induced mouse model of MASLD (125).

Effect of PUFAs on metabolic dysregulation in MASLD

Metabolic impairment and hepatic lipid accumulation are central to the pathogenesis of MASLD. n-3 PUFAs have been shown to reduce

TABLE 2 Role of PUFAs in the management of MASLD and MASLD-HCC in humans.

Study	Country	Study design	No. of patients	PUFAs investigated	Daily dose (g)	Therapy duration	Major findings	Effect size
Kim et al., 2025 (97)	South Korea	Meta-analysis of 20 randomized controlled trials	1,615	Omega-3	1.5–4.0	3–12 months	Significant effect on gamma-glutamyl transferase (γ GT), but not on AST, ALT, hepatic fat, stiffness or histology	γ GT levels in MASLD: WMD = –5.38 IU/L (95% CI: –9.16 – –1.61); p -value < 0.05
Lee et al., 2020 (95)	Taiwan	Meta-analysis of 22 randomized controlled trials	1,366	Omega-3 (mainly EPA & DHA, some studies also included DPA)	1.0–4.0	3–12 months	Significant effect on triglyceride, total cholesterol and high-density lipoprotein levels in MASLD	Triglyceride levels: MD = –28.57 (95% CI: –40.1 – –16.33) Total cholesterol levels: MD = –7.82 (95% CI: –14.86 – –0.79) High-density lipoprotein levels: MD = 3.55 (95% CI: 1.38–5.73); $p < 0.05$
Argo et al., 2015 (62)	USA	Double-blind randomized, placebo-controlled trial	41	Omega-3 (EPA & DHA)	3.0	12 months	No significant effect for the primary endpoint of NAS reduction ≥ 2 points without fibrosis progression in MASLD	Four of 17 omega-3 (24%) and 3 of 17 placebo-treated patients (18%) had reduction in NAS ($p = 0.99$)
Sanyal et al., 2014 (61)	USA	Double-blind randomized placebo-controlled trial	243	Omega-3 (EPA)	2.7	12 months	Significant effect on triglyceride levels in MASLD, but not on steatosis, inflammation, fibrosis and liver enzymes	Levels of triglycerides: –6.5 mg/dL vs. +12 mg/dL in the placebo group ($p = 0.03$)

AST = aspartate aminotransferase; ALT = alanine aminotransferase; WMD = weighted mean difference; MD = mean difference; NAS = non-alcoholic fatty liver disease activity score.

hepatic steatosis by driving a shift from lipogenesis to lipid catabolism in hepatocytes. More specifically, *in vitro* studies have demonstrated that n-3 PUFAs inhibit the activity of sterol regulatory element-binding protein 1 (SREBP1), which is a transcription factor that regulates genes involved in fatty acid and triglyceride synthesis. This effect is mediated by reducing SREBP1 expression, through inhibition of gene transcription and induction of mRNA degradation, and by preventing the proteolytic release of SREBP1 from the endoplasmic reticulum (126–128). At the same time, n-3 PUFAs are ligands of the nuclear receptors PPAR, which drive lipolysis and fatty acid oxidation, and

inhibit lipogenesis (129, 130). n-3 PUFAs are also known to inhibit the activity of diacylglycerol acyltransferase (DGAT), an enzyme catalyzing the terminal step of hepatic triglyceride synthesis, in the liver (131). These findings are confirmed in clinical and experimental studies of MASLD. A study in obese MASLD patients showed an increased n-6 PUFA/n-3 PUFA ratio, which was associated with increased SREBP1 and decreased PPAR α expression, suggesting increased lipogenesis (132). DHA and olive oil supplementation were also shown to increase PPAR α expression and transcriptional activity, whilst reducing SREBP1 expression and activity, in a high fat diet-induced mouse

TABLE 3 Role of PUFAs in MASLD and MASLD-HCC in animal studies.

Reference	Mouse model	PUFA intervention	Outcomes/results
Antraco et al. (99)	High fat diet (HFD)	Fish oil	↓ body/liver mass, plasma lipids/transaminases, glucose, cholesterol liver content
Liu et al. (100)	HFD	Fish oil	↓ hepatic steatosis
Hirako et al. (101)	High cholesterol	Fish oil	↓ Hepatic fat
Soni et al. (102)	HFD	EPA and DHA	↓ Hepatic triglyceride content, lipid/fatty acid biosynthesis
Hao et al. (103)	HFD	n-3 PUFAs	↓ body weight and fat mass
Wang et al. (104)	HFD	n-3 PUFAs	↓ MASLD
Smid et al. (105)	MCD diet*	n-3 PUFAs	↓ MASLD
Li et al. (106)	MCD diet	D-PUFAs**	↓ MASH
Wang et al. (107)	HFD	Palmitoleic acid	↓ liver injury, hepatitis, and dyslipidemia
Chen et al. (108)	HFD	DHA	↓ MASLD
Zhou et al. (109)	HFD	DHA	↓ MASLD
Nakamoto and Tokuyama (110)	CD ^Δ , 0.1% methionine-HFD	DHA	↓ Inflammation, fibrosis
Li et al. (111)	HFD	ω-3 algal oil (DHA rich) and ω-7 sea buckthorn oil (palmitoleic acid rich)	↓ lipid profiles, hepatic steatosis
Gong et al. (112)	MCD diet	Hemp seed oil	↓ hepatic steatosis, inflammation, fibrosis
Hwang et al. (113)	HFD	Krill Oil	↓ hepatic steatosis
Sanchez et al. (114)	HFD	soybean oil	↓ early MASH, glucose intolerance
Manca et al. (115)	HFD	Canola oil	↓ hepatic and retroperitoneal fat
Ni et al. (116)	HFD	seed oil of <i>Rosa roxburghii</i> Tratt	↓ MASLD progression, lipid accumulation, oxidative stress, inflammatory response
Cha et al. (117)	Growth hormone receptor knockout	Unsaturated alginate oligosaccharides	↓ insulin resistance, hepatic steatosis (lean MASLD)
Ishii et al. (122)	Pten deficient	EPA	↓ severe chronic hepatic inflammation, ROS formation, HCC development
Inoue-Yamauchi et al. (123)	HFD + carcinogen	EPA	↓ HCC development
Yan et al. (118)	HFD	N/A	↓ n-3 FAs, n-3/n-6 in mice fed HFD
Xavier et al. (119)	CD L-amino-defined diet	N/A	↓ PUFAs in MASLD
Vlock et al. (120)	CD HFD	N/A	↓ PUFAs in lean MASH-HCC
Hymel et al. (121)	CD and CS [‡] HFD	N/A	↓ PUFAs in lean and obese MASH-HCC

* Methionine, choline deficient, ** Deuterium-reinforced polyunsaturated fatty acids, ^ΔCD = choline-deficient, [‡]CS = choline supplemented.

model of MASLD (133). Moreover, in a high-fat diet mouse model, EPA reduced hepatic triglyceride levels and altered the composition of VLDL by promoting increased unsaturated fatty acid content. The latter is mediated by inducing the expression of the enzyme stearoyl-CoA desaturase-1 (SCD-1), which catalyzes the conversion of saturated to unsaturated fatty acids (134).

Effect of PUFAs on oxidative stress responses in MASLD

Lipid accumulation in the liver leads to impaired mitochondrial function and subsequently increased production of ROS. This leads to

the development of oxidative stress, resulting in hepatic injury and the release of pro-inflammatory DAMPs. n-3 PUFAs are known to prevent oxidative stress, thus potentially mitigating hepatic damage, and consequently inflammation and fibrosis (Figures 3, 4). EPA and DHA were shown in *in vitro* studies to act as direct antioxidants by scavenging ROS, whilst they can also activate the cytoprotective transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) (135, 136). Indeed, J₃-isoprostanes, products of non-enzymatic n-3 PUFA oxidation were shown to activate Nrf2 by preventing its degradation by the Keap1-Cullin3 E3 ubiquitin ligase complex in hepatocytes (137). Furthermore, in an MCD mouse model of MASH, the DHA-derived mediator Resolvin D1 was reported to induce Nrf2-mediated

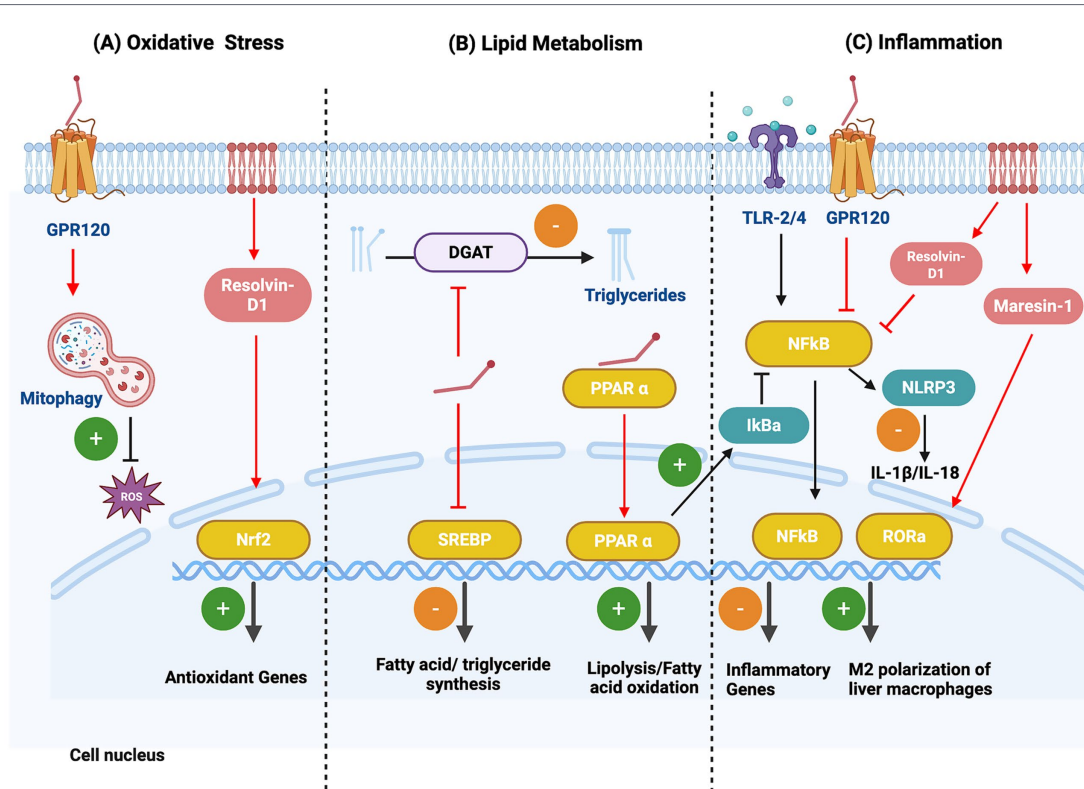


FIGURE 3

Molecular mechanisms mediating the effects of n3-PUFAs on MASLD. n-3-PUFAs have a protective role against the development of MASLD by exerting antioxidant (A) and anti-inflammatory effects (C), and by regulating hepatic lipid metabolism (B). (A) n-3 PUFAs promote mitophagy of damaged mitochondria, by activating the GPR120 receptor, leading to a reduction in ROS levels. The DHA-derived mediator Resolvin-D1 promotes the expression of antioxidant genes by activating the cytoprotective transcription factor, Nrf2. (B) n-3 PUFAs induce lipolysis and fatty acid oxidation by activating the nuclear receptor PPAR α while at the same time reducing fatty acid and triglyceride synthesis through inhibition of the transcription factor, SREBP. Furthermore, n-3 PUFAs reduce triglyceride synthesis by inhibiting the enzyme DGAT. (C) The anti-inflammatory effects of n-3 PUFAs are mediated through inhibition of NF κ B. Specifically, activation of GPR120 receptor and the DHA-derived mediator Resolvin D1 lead to inhibition of TLR-mediated NF κ B activation. Also, PPAR α activation promotes the expression of the NF κ B inhibitor, I κ B α . Inhibition of NF κ B by n-3 PUFAs also leads to reduced NLRP3 inflammasome activity. Finally, the DHA-derived Maresin-1 promotes M2 polarization of liver macrophages, preventing the early development of MASH, by activation of the nuclear receptor, ROR α . Created in <https://BioRender.com>.

Potential modulatory roles of PUFAs in MASLD–MASH–HCC progression

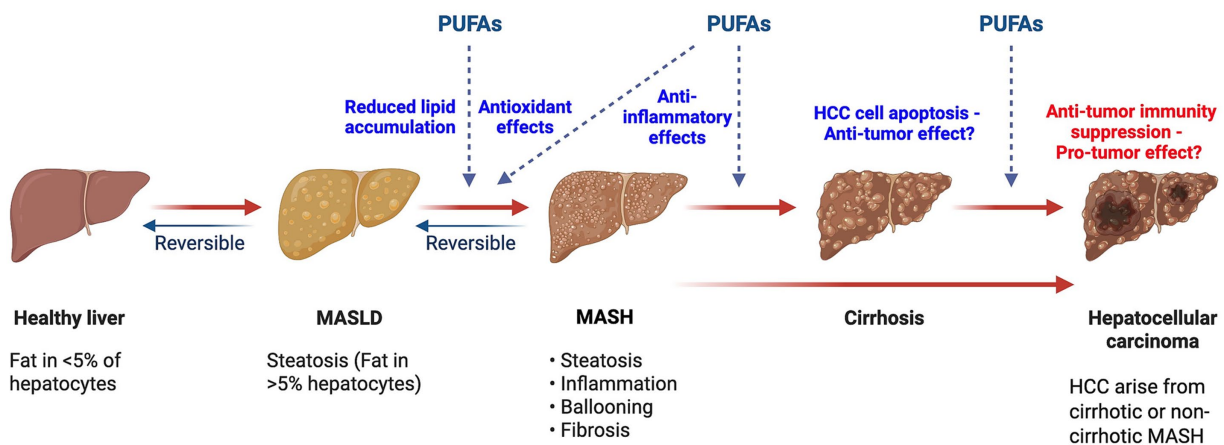


FIGURE 4

The effects of n3-PUFAs on MASLD progression to MASH and HCC. Proposed modulatory effects of polyunsaturated fatty acids (PUFAs) on metabolic dysfunction, inflammatory processes, and potential antitumor effects in HCC across the MASLD–MASH–HCC continuum. Created in <https://BioRender.com>.

antioxidant responses and prevent oxidative damage (138). DHA was also shown to protect hepatocytes from oxidative stress-induced injury by promoting the removal of dysfunctional mitochondria through mitophagy, mediated by GPR120, a G protein-coupled long-chain fatty acid receptor (139).

Effect of PUFAs on inflammatory pathways in MASLD

DAMPs released due to hepatic injury, as well as bacterial endotoxins arising from gut dysbiosis, promote hepatic inflammation and fibrosis through activation of TLRs, particularly TLR-2 and TLR-4, and downstream signaling pathways, including MAPKs, NF κ B and the NLRP3 inflammasome (140–143). n-3 PUFAs have been shown to play a key role in protection against hepatic inflammation in MASH (142) (Figures 3, 4). EPA and DHA were reported to inhibit TLR-2 and -4 activity, by reducing their expression and the systemic abundance of their agonists, in high-fat diet LDLR^{-/-} mouse models of MASH. This effect was associated with a reduction in NF κ B activity and hepatic inflammation and fibrosis (125, 144). In a high fat diet mouse model, activation of GPR120 by n-3 PUFAs was shown to inhibit TLR-mediated signaling in macrophages by inhibition of downstream kinases, and through receptor internalization via its adaptor protein β -arrestin2 (145). n-3 PUFAs also inhibit high fat diet-induced activation of NF κ B, possibly by increasing the expression of its inhibitor I κ B α in a PPAR α -dependent manner (146, 147). Resolvin D1, an endogenous lipid mediator derived from DHA through a lipoxygenase-mediated mechanism, also inhibited TLR-4-induced NF κ B and MAPK activation in an MCD mouse model of MASH (138). Maresin-1, another DHA-derived pro-resolving mediator, was shown to activate the nuclear receptor retinoic acid receptor-related orphan receptor (ROR) α , which drives macrophage M2 polarization inhibiting liver inflammation and preventing early MASH development (148). n-3 PUFAs also inhibit the activation of the NLRP3 inflammasome, a key multiprotein complex that drives the caspase 1-mediated cleavage, maturation, and secretion of the proinflammatory cytokines IL-1 β and IL-18. Activation of NLRP3 depends on two signals; a priming signal that involves TLR/NF- κ B-dependent expression of NLRP3 and pro-IL-1 β , and an activation signal triggered by cellular stressors, including ROS, that induces NLRP3 complex assembly and caspase-1 activation (149). n-3 PUFA supplementation was shown to prevent NLRP3 priming, through NF κ B inhibition, in a high fat diet-induced mouse model of MASH (150).

Mechanisms mediating the effects of PUFAs on HCC development in MASLD

There are a limited number of experimental studies investigating the effect of PUFAs, specifically n-3 PUFAs, on MASLD-HCC development. These studies have shown that the effects of n-3 PUFAs may be context-dependent and can be either protective or detrimental.

Protective effects of PUFAs against MASLD-HCC development

In an alcohol/high-fat/high-sugar mouse model of MASLD, the patatin-like phospholipase domain-containing protein 3 (PNPLA3)

variant I148M, which is associated with increased n-3 PUFAs levels, conferred protection against HCC development (151). Furthermore, a diet-induced lean MASH-HCC mouse model, mice that developed HCC showed lower plasma n-3 and n-6 PUFA levels. The reduction in PUFA levels, possibly caused by a reduction in desaturase expression, was associated with tumor progression (120). These findings indicate a role of n-3 PUFAs in preventing the development of HCC in MASLD patients.

The mechanisms underlying this protective effect are poorly understood. EPA supplementation led to reduced hepatic steatosis and inflammation and prevented the development of HCC in a PTEN-deficient mouse model of MASH. Moreover, EPA reduced the proliferation of primary hepatocytes isolated from the mouse model, by inhibiting extracellular signal-related kinase (ERK)1/2 MAPK activity (122). These results suggest that the anti-tumorigenic effect of n-3 PUFAs may be mediated through inhibition of pro-inflammatory pathways. In a different high-fat MASH mouse model, EPA was shown to suppress the activation of the oncogenic transcription factor STAT3, and prevent diethylnitrosamine-induced HCC development, without affecting hepatic inflammation (123). Furthermore, *in vitro* studies have reported that EPA and DHA promote apoptosis and inhibit the proliferation of HCC cell lines through different mechanisms, including inhibition of the Wnt/ β -catenin and COX-2 activity and activation of c-Jun N-terminal protein kinase (JNK) and p53 signaling pathways (124, 152–156). Nano-liposomes containing 2,6-diisopropylphenol-linolenic acid conjugate were also shown to induce apoptosis and inhibit the migration and adhesion of the HCC line HepG2 (157). Whether this would apply to MASLD-HCC-derived cell lines remains to be determined.

Detrimental effects of PUFAs on MASLD-HCC development

A recent study demonstrated a negative effect of PUFAs on anti-tumor immunity. More specifically, mucosal-associated invariant T (MAIT) cells, which exert liver anti-tumor immunity by inducing HCC cytotoxicity, show accumulation of n-3 and n-6 PUFAs in MASLD patients. The same study demonstrated that arachidonic acid and DHA, promote ROS-dependent impairment of mitochondrial respiration and glycolysis, leading to metabolic exhaustion of MAIT cells. In addition, exaggerated PUFA-mediated lipid peroxidation was shown to trigger MAIT cell ferroptosis. This leads to a reduction in the numbers and bioenergetic capacity of MAIT cells, negatively affecting their tumour-killing ability (158).

The effect of n-3 PUFAs, on HCC development in MASLD patients may therefore be cell type and stage-specific, which introduces another layer of complexity to potential therapeutic applications of PUFAs.

Conclusions/discussion

There is increasing evidence through observational studies involving large cohorts that PUFAs play a role in the prevention of MASLD and MASLD-HCC. In addition, randomized control trials have shown a therapeutic potential of PUFAs in MASLD, however, the evidence remains poor regarding the role of PUFAs in MASLD-HCC treatment. Animal models have also shown extensively that different

combinations of PUFA supplementation results in reduction of MASLD outcomes, further supporting the role of PUFAs in MASLD prevention and management. Evidence for the role of PUFAs in MASLD-HCC prevention stems from observations that PUFA levels are reduced during MASLD-HCC progression and different mouse models showing reduction of HCC development with PUFA supplementation. The mechanistic basis of the role of PUFAs in MASLD and MASLD-HCC lies on their effects in lipid metabolism, inflammation and oxidative stress. Therefore, PUFAs help with reducing fat accumulation, reducing inflammation and alleviating oxidative stress, which contributes to MASLD and MASLD-HCC prevention. On the other hand, understanding the effect of PUFAs in HCC treatment remains elusive and controversial with one study showing that PUFAs may actually have a suppressive role of anti-tumor immune response. This controversial effect may potentially stem from differing effects of PUFAs depending on tumor stage and characteristics, such as tumor microenvironment, which can be rich in ECM (fibrosis/cirrhosis), exhibit inflammation, and/or recruitment of various types of immune cells.

In summary, the evidence for n-3 PUFAs as a preventive agent in early MASLD and its progression to HCC is compelling. Their role in altering the course of established HCC, however, remains a mystery. The role of PUFAs in HCC appears to be context-dependent and may be a double-edged sword, potentially suppressing tumours in some contexts while impairing anti-tumour immunity in others. This paradox represents the key frontier for future research.

Future directions

While there is a lot of evidence supporting the role of PUFAs on MASLD and MASLD-HCC prevention and management, there are some gaps that need to be filled by further research. At the clinical level, design of RCTs specifically in patients with advanced fibrosis (F3-F4), the group at highest risk for HCC, are needed to clarify if PUFA supplementation can delay or prevent carcinogenesis. Such clinical studies can be further supplemented by mechanistic studies using MASLD-HCC-specific models to untangle the cell-type-specific effects of PUFAs and clarify whether PUFAs have a protective effect on hepatocytes and detrimental effect on immune cells. Tools such as single-cell sequencing and metabolomic analyses on PUFA-treated models can provide answers to these questions and potentially contribute to the development of guidelines for context-dependent use of PUFAs in clinical practice based on tumor immune microenvironment status. Furthermore, translational studies can be designed to address the role of PUFAs in combination with existing cancer therapies for MASLD-HCC, such as immunotherapy and tyrosine kinase inhibitors.

References

- Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *Hepatology*. (2023) 78:1966–86. doi: 10.1097/HEP.0000000000000520
- Younossi ZM, Kalligeros M, Henry L. Epidemiology of metabolic dysfunction-associated steatotic liver disease. *Clin Mol Hepatol*. (2025) 31:S32–50. doi: 10.3350/cmh.2024.0431
- Hagstrom H, Shang Y, Hegmar H, Nasr P. Natural history and progression of metabolic dysfunction-associated steatotic liver disease. *Lancet Gastroenterol Hepatol*. (2024) 9:944–56. doi: 10.1016/S2468-1253(24)00193-6
- Motta BM, Masarone M, Torre P, Persico M. From non-alcoholic steatohepatitis (NASH) to hepatocellular carcinoma (HCC): epidemiology, incidence, predictions, risk factors, and prevention. *Cancers (Basel)*. (2023) 15. doi: 10.3390/cancers15225458
- Mathew S, Cussens C, Pericleous M. Hepatocellular carcinoma (HCC): an update on risk factors, surveillance, diagnosis and treatment strategies. *Clin Med (Lond)*. (2025) 25:100532. doi: 10.1016/j.clinme.2025.100532
- Pfister D, Nunez NG, Pinyol R, Govaere O, Pinter M, Szydlowska M, et al. NASH limits anti-tumour surveillance in immunotherapy-treated HCC. *Nature*. (2021) 592:450–6. doi: 10.1038/s41586-021-03362-0
- European Association for the Study of the L, European Association for the Study of D, European Association for the Study of O. EASL-EASD-EASO clinical practice guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). *J Hepatol*. (2024) 81:492–542. doi: 10.1016/j.jhep.2024.04.031
- Lavrado NC, Salles GF, Cardoso CRL, de Franca PHC, Melo M, Leite NC, et al. Impact of PNPLA3 and TM6SF2 polymorphisms on the prognosis of patients with MASLD and type 2 diabetes mellitus. *Liver Int*. (2024) 44:1042–50. doi: 10.1111/liv.15845

Author contributions

TK: Investigation, Writing – original draft, Writing – review & editing. PC: Writing – original draft, Writing – review & editing. SC: Writing – original draft, Writing – review & editing. FP: Writing – original draft, Writing – review & editing. CM: Conceptualization, Writing – original draft, Writing – review & editing. PF: Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

Funding

The author(s) declared that financial support was not received for this work and/or its publication.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that Generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

9. Huang M, Chen H, Wang H, Zhang Y, Li L, Lan Y, et al. Global burden and risk factors of MASLD: trends from 1990 to 2021 and predictions to 2030. *Intern Emerg Med.* (2025) 20:1013–24. doi: 10.1007/s11739-025-03895-6
10. Miao L, Targher G, Byrne CD, Cao YY, Zheng MH. Current status and future trends of the global burden of MASLD. *Trends Endocrinol Metab.* (2024) 35:697–707. doi: 10.1016/j.tem.2024.02.007
11. Targher G, Valenti L, Byrne CD. Metabolic dysfunction-associated Steatotic liver disease. *N Engl J Med.* (2025) 393:683–98. doi: 10.1056/NEJMra2412865
12. Armandi A, Bugianesi E. Natural history of NASH. *Liver Int.* (2021) 41 Suppl 1:78–82. doi: 10.1111/liv.14910
13. Guo Z, Wu D, Mao R, Yao Z, Wu Q, Lv W. Global burden of MAFLD, MAFLD related cirrhosis and MASH related liver cancer from 1990 to 2021. *Sci Rep.* (2025) 15:7083. doi: 10.1038/s41598-025-91312-5
14. Wong CR, Nguyen MH, Lim JK. Hepatocellular carcinoma in patients with non-alcoholic fatty liver disease. *World J Gastroenterol.* (2016) 22:8294–303. doi: 10.3748/wjg.v22.i37.8294
15. Chrysavgis L, Giannakodimos I, Diamantopoulou P, Cholongitas E. Non-alcoholic fatty liver disease and hepatocellular carcinoma: clinical challenges of an intriguing link. *World J Gastroenterol.* (2022) 28:310–31. doi: 10.3748/wjg.v28.i3.310
16. Chan WK, Chuah KH, Rajaram RB, Lim LL, Ratnasingam J, Vethakkan SR. Metabolic dysfunction-associated Steatotic liver disease (MASLD): a state-of-the-art review. *J Obes Metab Syndr.* (2023) 32:197–213. doi: 10.7570/jomes23052
17. Bradic I, Kuentzel KB, Pirschheim A, Rainer S, Schwarz B, Trauner M, et al. From LAL-D to MASLD: insights into the role of LAL and Kupffer cells in liver inflammation and lipid metabolism. *Biochim Biophys Acta Mol Cell Biol Lipids.* (2025) 1870:159575. doi: 10.1016/j.bbalip.2024.159575
18. Geng Y, Faber KN, de Meijer VE, Blokzijl H, Moshage H. How does hepatic lipid accumulation lead to lipotoxicity in non-alcoholic fatty liver disease? *Hepatol Int.* (2021) 15:21–35. doi: 10.1007/s12072-020-10121-2
19. Marra M, Sordelli IM, Lombardi A, Lamberti M, Tarantino L, Giudice A, et al. Molecular targets and oxidative stress biomarkers in hepatocellular carcinoma: an overview. *J Transl Med.* (2011) 9:171. doi: 10.1186/1479-5876-9-171
20. He G, Karin M. NF- κ B and STAT3 - key players in liver inflammation and cancer. *Cell Res.* (2011) 21:159–68. doi: 10.1038/cr.2010.183
21. Yang F, Hilakivi-Clarke L, Shaha A, Wang Y, Wang X, Deng Y, et al. Metabolic reprogramming and its clinical implication for liver cancer. *Hepatology.* (2023) 78:1602–24. doi: 10.1097/HEP.0000000000000005
22. Zheng J, Wang S, Xia L, Sun Z, Chan KM, Bernards R, et al. Hepatocellular carcinoma: signaling pathways and therapeutic advances. *Signal Transduct Target Ther.* (2025) 10:35. doi: 10.1038/s41392-024-02075-w
23. Sharma S, Kelly TK, Jones PA. Epigenetics in cancer. *Carcinogenesis.* (2010) 31:27–36. doi: 10.1093/carcin/bgp220
24. Affo S, Yu LX, Schwabe RF. The role of Cancer-associated fibroblasts and fibrosis in liver Cancer. *Annu Rev Pathol.* (2017) 12:153–86. doi: 10.1146/annurev-pathol-052016-100322
25. Seyhan D, Allaire M, Fu Y, Conti F, Wang XW, Gao B, et al. Immune microenvironment in hepatocellular carcinoma: from pathogenesis to immunotherapy. *Cell Mol Immunol.* (2025) 22:1132–58. doi: 10.1038/s41423-025-01308-4
26. Wilson GK, Tennant DA, McKeating JA. Hypoxia inducible factors in liver disease and hepatocellular carcinoma: current understanding and future directions. *J Hepatol.* (2014) 61:1397–406. doi: 10.1016/j.jhep.2014.08.025
27. Cheng AL, Hsu C, Chan SL, Choo SP, Kudo M. Challenges of combination therapy with immune checkpoint inhibitors for hepatocellular carcinoma. *J Hepatol.* (2020) 72:307–19. doi: 10.1016/j.jhep.2019.09.025
28. Keam SJ. Resmetromir: First Approval. *Drugs.* (2024) 84:729–35. doi: 10.1007/s40265-024-02045-0
29. Nascimbeni F, Pellegrini E, Lugari S, Mondelli A, Bursi S, Onfiani G, et al. Statins and nonalcoholic fatty liver disease in the era of precision medicine: more friends than foes. *Atherosclerosis.* (2019) 284:66–74. doi: 10.1016/j.atherosclerosis.2019.02.028
30. Leith D, Lin YY, Brennan P. Metabolic dysfunction-associated Steatotic liver disease and type 2 diabetes: a deadly synergy. *touchREV Endocrinol.* (2024) 20:5–9. doi: 10.17925/EE.2024.20.2.2
31. Siddiqui MS, Harrison SA, Abdelmalek MF, Anstee QM, Bedossa P, Castera L, et al. Case definitions for inclusion and analysis of endpoints in clinical trials for nonalcoholic steatohepatitis through the lens of regulatory science. *Hepatology.* (2018) 67:2001–12. doi: 10.1002/hep.29607
32. Romero-Gomez M, Zelber-Sagi S, Trenell M. Treatment of NAFLD with diet, physical activity and exercise. *J Hepatol.* (2017) 67:829–46. doi: 10.1016/j.jhep.2017.05.016
33. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. *Gastroenterology.* (2015) 149:367–378.e5. doi: 10.1053/j.gastro.2015.04.005
34. Koutoukidis DA, Koshiaris C, Henry JA, Noreik M, Morris E, Manoharan I, et al. The effect of the magnitude of weight loss on non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Metabolism.* (2021) 115:154455. doi: 10.1016/j.metabol.2020.154455
35. Fernandez T, Vinuela M, Vidal C, Barrera F. Lifestyle changes in patients with non-alcoholic fatty liver disease: a systematic review and meta-analysis. *PLoS One.* (2022) 17:e0263931. doi: 10.1371/journal.pone.0263931
36. Wong VW, Chan RS, Wong GL, Cheung BH, Chu WC, Yeung DK, et al. Community-based lifestyle modification programme for non-alcoholic fatty liver disease: a randomized controlled trial. *J Hepatol.* (2013) 59:536–42. doi: 10.1016/j.jhep.2013.04.013
37. Haase CL, Lopes S, Olsen AH, Satyrganova A, Schnecke V, McEwan P. Weight loss and risk reduction of obesity-related outcomes in 0.5 million people: evidence from a UK primary care database. *Int J Obes.* (2021) 45:1249–58. doi: 10.1038/s41366-021-00788-4
38. Marin-Alejandro BA, Cantero I, Perez-Diaz-Del-Campo N, Monreal JI, Elorz M, Herrero JI, et al. Effects of two personalized dietary strategies during a 2-year intervention in subjects with nonalcoholic fatty liver disease: a randomized trial. *Liver Int.* (2021) 41:1532–44. doi: 10.1111/liv.14818
39. Diaz LA, Arab JP, Idalsoaga F, Perelli J, Vega J, Dirchwolf M, et al. Updated recommendations for the management of metabolic dysfunction-associated liver disease (MASLD) by the Latin American working group. *Ann Hepatol.* (2025) 30:101903. doi: 10.1016/j.aohp.2025.101903
40. Yaskolka Meir A, Rinott E, Tsaban G, Zelicha H, Kaplan A, Rosen P, et al. Effect of green-Mediterranean diet on intrahepatic fat: the DIRECT PLUS randomised controlled trial. *Gut.* (2021) 70:2085–95. doi: 10.1136/gutjnl-2020-323106
41. Kawaguchi T, Charlton M, Kawaguchi A, Yamamura S, Nakano D, Tsutsumi T, et al. Effects of Mediterranean diet in patients with nonalcoholic fatty liver disease: a systematic review, Meta-analysis, and Meta-regression analysis of randomized controlled trials. *Semin Liver Dis.* (2021) 41:225–34. doi: 10.1055/s-0041-1723751
42. Montemayor S, Mascaro CM, Ugarriza L, Casares M, Llompart I, Abete I, et al. Adherence to Mediterranean diet and NAFLD in patients with metabolic syndrome: the FLIPAN study. *Nutrients.* (2022) 14. doi: 10.3390/nu14151816
43. Holmer M, Lindqvist C, Petersson S, Moshtaghi-Svensson J, Tillander V, Brismar TB, et al. Treatment of NAFLD with intermittent calorie restriction or low-carb high-fat diet - a randomised controlled trial. *JHEP Rep.* (2021) 3:100256. doi: 10.1016/j.jhepr.2021.100256
44. Zelber-Sagi S, Grinshpan LS, Ivancovsky-Wajcman D, Goldenshluger A, Gepner Y. One size does not fit all; practical, personal tailoring of the diet to NAFLD patients. *Liver Int.* (2022) 42:1731–50. doi: 10.1111/liv.15335
45. Wei X, Lin B, Huang Y, Yang S, Huang C, Shi L, et al. Effects of time-restricted eating on nonalcoholic fatty liver disease: the TREATY-FLD randomized clinical trial. *JAMA Netw Open.* (2023) 6:e233513. doi: 10.1001/jamanetworkopen.2023.3513
46. Curci R, Bonfiglio C, Franco I, Bagnato CB, Verrelli N, Bianco A. Leisure-time physical activity in subjects with metabolic-dysfunction-associated steatotic liver disease: an all-cause mortality study. *J Clin Med.* (2024) 13. doi: 10.3390/jcm13133772
47. Zhang HJ, He J, Pan LL, Ma ZM, Han CK, Chen CS, et al. Effects of moderate and vigorous exercise on nonalcoholic fatty liver disease: a randomized clinical trial. *JAMA Intern Med.* (2016) 176:1074–82. doi: 10.1001/jamainternmed.2016.3202
48. Xue Y, Peng Y, Zhang L, Ba Y, Jin G, Liu G. Effect of different exercise modalities on nonalcoholic fatty liver disease: a systematic review and network meta-analysis. *Sci Rep.* (2024) 14:6212. doi: 10.1038/s41598-024-51470-4
49. Marti-Aguado D, Clemente-Sanchez A, Bataller R. Cigarette smoking and liver diseases. *J Hepatol.* (2022) 77:191–205. doi: 10.1016/j.jhep.2022.01.016
50. Marti-Aguado D, Calleja JL, Vilar-Gomez E, Iruzoquieta P, Rodriguez-Duque JC, Del Barrio M, et al. Low-to-moderate alcohol consumption is associated with increased fibrosis in individuals with metabolic dysfunction-associated steatotic liver disease. *J Hepatol.* (2024) 81:930–40. doi: 10.1016/j.jhep.2024.06.036
51. Diaz LA, Arab JP, Louvet A, Bataller R, Arrese M. The intersection between alcohol-related liver disease and nonalcoholic fatty liver disease. *Nat Rev Gastroenterol Hepatol.* (2023) 20:764–83. doi: 10.1038/s41575-023-00822-y
52. Tincopa MA, Anstee QM, Loomba R. New and emerging treatments for metabolic dysfunction-associated steatohepatitis. *Cell Metab.* (2024) 36:912–26. doi: 10.1016/j.cmet.2024.03.011
53. Mousa AM, Mahmoud M, AlShuraiaan GM. Resmetromir: the first disease-specific treatment for MASH. *Int J Endocrinol.* (2025) 2025:6430023. doi: 10.1155/ije/6430023
54. Azizoltani A, Niknam B, Taghizadeh-Teymorloei M, Ghoojani E, Dianat-Moghadam H, Alizadeh E. Therapeutic implications of obeticholic acid, a farnesoid X receptor agonist, in the treatment of liver fibrosis. *Biomed Pharmacother.* (2025) 189:118249. doi: 10.1016/j.biopha.2025.118249
55. A Phase 3 Study Evaluating Efficacy and Safety of Lanifibranor Followed by an Active Treatment Extension in Adult Patients With (NASH) and Fibrosis Stages F2 and F3 (NATiV3) (NATiV3). Available online at: <https://www.clinicaltrials.gov/study/NCT04849728> (Accessed February 03, 2026).
56. Song Y, Ni W, Zheng M, Sheng H, Wang J, Xie S, et al. Vitamin E (300 mg) in the treatment of MASH: a multi-center, randomized, double-blind, placebo-controlled study. *Cell Rep Med.* (2025) 6:101939. doi: 10.1016/j.xcrm.2025.101939
57. Perumpail BJ, Li AA, John N, Sallam S, Shah ND, Kwong W, et al. The role of vitamin E in the treatment of NAFLD. *Diseases.* (2018) 6. doi: 10.3390/diseases6040086
58. Lindor KD, Kowdley KV, Heathcote EJ, Harrison ME, Jorgensen R, Angulo P, et al. Ursodeoxycholic acid for treatment of nonalcoholic steatohepatitis: results of a randomized trial. *Hepatology.* (2004) 39:770–8. doi: 10.1002/hep.20092

59. Leuschner UF, Lindenthal B, Herrmann G, Arnold JC, Rossle M, Cordes HJ, et al. High-dose ursodeoxycholic acid therapy for nonalcoholic steatohepatitis: a double-blind, randomized, placebo-controlled trial. *Hepatology*. (2010) 52:472–9. doi: 10.1002/hep.23727
60. Zhou XD, Muthiah MD, Zheng MH. Statins in MASLD: challenges and future directions. *JHEP Rep*. (2025) 7:101372. doi: 10.1016/j.jhepr.2025.101372
61. Sanyal AJ, Abdelmalek MF, Suzuki A, Cummings OW, Chojkier M, Group E-AS. No significant effects of ethyl-eicosapentanoic acid on histologic features of nonalcoholic steatohepatitis in a phase 2 trial. *Gastroenterology*. (2014) 147:377–84 e1. doi: 10.1053/j.gastro.2014.04.046
62. Argo CK, Patrie JT, Lackner C, Henry TD, de Lange EE, Weltman AL, et al. Effects of n-3 fish oil on metabolic and histological parameters in NASH: a double-blind, randomized, placebo-controlled trial. *J Hepatol*. (2015) 62:190–7. doi: 10.1016/j.jhep.2014.08.036
63. Fraser D. A., Wang X., Lund J., Nikolic N., Iruarizaga-Lejarreta M., Skjaeret T., et al. A structurally engineered fatty acid, icosabutate, suppresses liver inflammation and fibrosis in NASH. *J Hepatol*. (2022);76:800–811, doi: 10.1016/j.jhep.2021.12.004
64. Adeghate EA. GLP-1 receptor agonists in the treatment of diabetic non-alcoholic steatohepatitis patients. *Expert Opin Pharmacother*. (2024) 25:223–32. doi: 10.1080/14656566.2024.2328796
65. Newsome PN, Ambery P. Incretins (GLP-1 receptor agonists and dual/triple agonists) and the liver. *J Hepatol*. (2023) 79:1557–65. doi: 10.1016/j.jhep.2023.07.033
66. Targher G, Mantovani A, Byrne CD, Tilg H. Recent advances in incretin-based therapy for MASLD: from single to dual or triple incretin receptor agonists. *Gut*. (2025) 74:487–97. doi: 10.1136/gutjnl-2024-334023
67. Mantovani A, Byrne CD, Targher G. Efficacy of peroxisome proliferator-activated receptor agonists, glucagon-like peptide-1 receptor agonists, or sodium-glucose cotransporter-2 inhibitors for treatment of non-alcoholic fatty liver disease: a systematic review. *Lancet Gastroenterol Hepatol*. (2022) 7:367–78. doi: 10.1016/S2468-1253(21)00261-2
68. Cusi K, Orsak B, Bril F, Lomonaco R, Hecht J, Ortiz-Lopez C, et al. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial. *Ann Intern Med*. (2016) 165:305–15. doi: 10.7326/M15-1774
69. Aithal GP, Thomas JA, Kaye PV, Lawson A, Ryder SD, Spendlove I, et al. Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. *Gastroenterology*. (2008) 135:1176–84. doi: 10.1053/j.gastro.2008.06.047
70. Staels B, Butruille L, Francque S. Treating NASH by targeting peroxisome proliferator-activated receptors. *J Hepatol*. (2023) 79:1302–16. doi: 10.1016/j.jhep.2023.07.004
71. Zhang X, Harmsen WS, Mettler TA, Kim WR, Roberts RO, Therneau TM, et al. Continuation of metformin use after a diagnosis of cirrhosis significantly improves survival of patients with diabetes. *Hepatology*. (2014) 60:2008–16. doi: 10.1002/hep.27199
72. Vilar-Gomez E, Vuppalanchi R, Desai AP, Gawrieh S, Ghabril M, Saxena R, et al. Long-term metformin use may improve clinical outcomes in diabetic patients with non-alcoholic steatohepatitis and bridging fibrosis or compensated cirrhosis. *Aliment Pharmacol Ther*. (2019) 50:317–28. doi: 10.1111/apt.15331
73. Wang X, Zhang L, Dong B. Molecular mechanisms in MASLD/MASH-related HCC. *Hepatology*. (2025) 82:1303–24. doi: 10.1097/HEP.0000000000000786
74. Llovet JM, Willoughby CE, Singal AG, Greten TF, Heikenwalder M, El-Serag HB, et al. Nonalcoholic steatohepatitis-related hepatocellular carcinoma: pathogenesis and treatment. *Nat Rev Gastroenterol Hepatol*. (2023) 20:487–503. doi: 10.1038/s41575-023-00754-7
75. Vogel A, Chan SL, Dawson LA, Kelley RK, Llovet JM, Meyer T, et al. Hepatocellular carcinoma: ESMO clinical practice guideline for diagnosis, treatment and follow-up. *Ann Oncol*. (2025) 36:491–506. doi: 10.1016/j.annonc.2025.02.006
76. Cheu JW, Wong CC. The immune microenvironment of steatotic hepatocellular carcinoma: current findings and future prospects. *Hepatol Commun*. (2024) 8. doi: 10.1097/HC9.0000000000000516
77. Liebig M, Dannenberg D, Vollmar B, Abshagen K. N-3 pufas reduce tumor load and improve survival in a NASH-tumor mouse model. *Ther Adv Chronic Dis*. (2019) 10:2040622319872118. doi: 10.1177/2040622319872118
78. Papadakos SP, Dedes N, Kouroumalis E, Theocharis S. The role of the NLRP3 inflammasome in HCC carcinogenesis and treatment: harnessing innate immunity. *Cancers (Basel)*. (2022) 14. doi: 10.3390/cancers14133150
79. Deckelbaum RJ, Akabas SR. N-3 fatty acids and cardiovascular disease: navigating toward recommendations. *Am J Clin Nutr*. (2006) 84:1–2. doi: 10.1093/ajcn/84.1.1
80. Arterburn LM, Hall EB, Oken H. Distribution, interconversion, and dose response of n-3 fatty acids in humans. *Am J Clin Nutr*. (2006) 83:1467S–76S. doi: 10.1093/ajcn/83.6.1467S
81. Gebauer SK, Psota TL, Harris WS, Kris-Etherton PM. N-3 fatty acid dietary recommendations and food sources to achieve essentiality and cardiovascular benefits. *Am J Clin Nutr*. (2006) 83:1526S–35S. doi: 10.1093/ajcn/83.6.1526S
82. Simopoulos AP. The omega-6/omega-3 fatty acid ratio, genetic variation, and cardiovascular disease. *Asia Pac J Clin Nutr*. (2008) 17 Suppl 1:131–4.
83. Zhao G, Etherton TD, Martin KR, Gillies PJ, West SG, Kris-Etherton PM. Dietary alpha-linolenic acid inhibits proinflammatory cytokine production by peripheral blood mononuclear cells in hypercholesterolemic subjects. *Am J Clin Nutr*. (2007) 85:385–91. doi: 10.1093/ajcn/85.2.385
84. Sokola-Wysoczanska E, Wysoczanski T, Wagner J, Czyz K, Bodkowski R, Lochynski S, et al. Polyunsaturated fatty acids and their potential therapeutic role in cardiovascular system disorders—a review. *Nutrients*. (2018) 10. doi: 10.3390/nu10101561
85. Cheraghpour M, Hatami B, Singal AG. Lifestyle and pharmacologic approaches to prevention of metabolic dysfunction-associated steatotic liver disease-related hepatocellular carcinoma. *Clin Gastroenterol Hepatol*. (2025) 23:685–694.e6. doi: 10.1016/j.cgh.2024.09.041
86. Liu Z, Wang P, Wang Y, Yu J, Wang Q, Li J, et al. Association of circulating fatty acids with metabolic dysfunction-associated steatotic liver disease: a cross-sectional analysis and mendelian randomization study. *Clin Nutr ESPEN*. (2025) 69:294–302. doi: 10.1016/j.clnesp.2025.07.027
87. Ambroselli D, Masciulli F, Romano E, Catanzaro G, Besharat ZM, Massari MC, et al. New advances in metabolic syndrome, from prevention to treatment: the role of diet and food. *Nutrients*. (2023) 15. doi: 10.3390/nu15030640
88. Liu Z, Huang H, Xie J, Xu Y, Xu C. Circulating fatty acids and risk of hepatocellular carcinoma and chronic liver disease mortality in the UK biobank. *Nat Commun*. (2024) 15:3707. doi: 10.1038/s41467-024-47960-8
89. Zeng C, Liu S, Li H, Han X. Inverse association between serum lipid profiles and hepatocellular carcinoma risk: a meta-analysis of epidemiological studies. *Front Oncol*. (2025) 15:1644677. doi: 10.3389/fonc.2025.1644677
90. Yang W, Sui J, Ma Y, Simon TG, Petrick JL, Lai M, et al. High dietary intake of vegetable or polyunsaturated fats is associated with reduced risk of hepatocellular carcinoma. *Clin Gastroenterol Hepatol*. (2020) 18:2775–2783.e11. doi: 10.1016/j.cgh.2020.01.003
91. Moussa I, Day RS, Li R, Kaseb A, Jalal PK, Daniel-MacDougall C, et al. Association of dietary fat intake and hepatocellular carcinoma among US adults. *Cancer Med*. (2021) 10:7308–19. doi: 10.1002/cam4.4256
92. Arendt BM, Teterina A, Pettinelli P, Comelli EM, Ma DWL, Fung SK, et al. Cancer-related gene expression is associated with disease severity and modifiable lifestyle factors in non-alcoholic fatty liver disease. *Nutrition*. (2019) 62:100–7. doi: 10.1016/j.nut.2018.12.001
93. Li YH, Yang LH, Sha KH, Liu TG, Zhang LG, Liu XX. Efficacy of poly-unsaturated fatty acid therapy on patients with nonalcoholic steatohepatitis. *World J Gastroenterol*. (2015) 21:7008–13. doi: 10.3748/wjg.v21.i22.7008
94. Aziz T, Niraj MK, Kumar S, Kumar R, Parveen H. Effectiveness of Omega-3 polyunsaturated fatty acids in non-alcoholic fatty liver disease: a systematic review and Meta-analysis. *Cureus*. (2024) 16:e68002. doi: 10.7759/cureus.68002
95. Lee CH, Fu Y, Yang SJ, Chi CC. Effects of omega-3 polyunsaturated fatty acid supplementation on non-alcoholic fatty liver: a systematic review and meta-analysis. *Nutrients*. (2020) 12. doi: 10.3390/nu12092769
96. Musa-Veloso K, Venditti C, Lee HY, Darch M, Floyd S, West S, et al. Systematic review and meta-analysis of controlled intervention studies on the effectiveness of long-chain omega-3 fatty acids in patients with nonalcoholic fatty liver disease. *Nutr Rev*. (2018) 76:581–602. doi: 10.1093/nutrit/nuy022
97. Kim SJ, Cho SH, Yun JM. Omega-3 polyunsaturated fatty acids and nonalcoholic fatty liver disease in adults: a meta-analysis of randomized controlled trials. *Clin Nutr*. (2025) 50:164–74. doi: 10.1016/j.clnu.2025.05.013
98. Jiao J, Kwan SY, Sabotta CM, Tanaka H, Veillon L, Warmoes MO, et al. Circulating fatty acids associated with advanced liver fibrosis and hepatocellular carcinoma in South Texas Hispanics. *Cancer Epidemiol Biomarkers Prev*. (2021) 30:1643–51. doi: 10.1158/1055-9965.epi-21-0183
99. Antraco VJ, Hirata BKS, de Jesus Simao J, Cruz MM, da Silva VS de da Cunha Sa RDC, Abdala F. M., Armelin-Correa L., Alonso-Vale M. I. C. Omega-3 polyunsaturated fatty acids prevent nonalcoholic steatohepatitis (NASH) and stimulate adipogenesis. *Nutrients* (2021) 13. doi: 10.3390/nu13020622
100. Liu W, Zhu M, Gong M, Zheng W, Zeng X, Zheng Q, et al. Comparison of the effects of monounsaturated fatty acids and polyunsaturated fatty acids on liver lipid disorders in obese mice. *Nutrients*. (2023) 15. doi: 10.3390/nu15143200
101. Hirako S, Kim H, Iizuka Y, Matsumoto A. Fish oil consumption prevents hepatic lipid accumulation induced by high-cholesterol feeding in obese KK mice. *Biomed Res*. (2024) 45:33–43. doi: 10.2220/biomedres.45.33
102. Soni NK, Nookaew I, Sandberg AS, Gabrielson GB. Eicosapentaenoic and docosahexaenoic acid-enriched high fat diet delays the development of fatty liver in mice. *Lipids Health Dis*. (2015) 14:74. doi: 10.1186/s12944-015-0072-8
103. Hao L, Chen CY, Nie YH, Kaliannan K, Kang JX. Differential interventional effects of omega-6 and omega-3 polyunsaturated fatty acids on high fat diet-induced obesity and hepatic pathology. *Int J Mol Sci*. (2023) 24. doi: 10.3390/ijms242417261
104. Wang Y, Chen YF, Cong YX, Wang YP, Liu P, Du YP, et al. N-3 polyunsaturated fatty acids mediate hydroxycholesterol acid-FXR signaling to ameliorate metabolic dysfunction-associated fatty liver disease. *J Nutr Biochem*. (2026) 147:110136. doi: 10.1016/j.jnutbio.2025.110136
105. Smid V, Dvorak K, Stehnova K, Strnad H, Rubert J, Stritesky J, et al. The ameliorating effects of n-3 polyunsaturated fatty acids on liver steatosis induced by a high-fat methionine choline-deficient diet in mice. *Int J Mol Sci*. (2023) 24. doi: 10.3390/ijms242417226
106. Li H, Zhang O, Hui C, Huang Y, Shao H, Song M, et al. Deuterium-reinforced polyunsaturated fatty acids prevent diet-induced nonalcoholic steatohepatitis by reducing oxidative stress. *Medicina Kaunas*. (2022) 58. doi: 10.3390/medicina58060790

107. Wang H, Shan C, Guo G, Ning D, Miao F. Therapeutic potential of palmitoleic acid in non-alcoholic fatty liver disease: targeting ferroptosis and lipid metabolism disorders. *Int Immunopharmacol.* (2024) 142:113025. doi: 10.1016/j.intimp.2024.113025
108. Chen YF, Fan ZK, Wang YP, Liu P, Guo XF, Li D. Docosahexaenoic acid modulates nonalcoholic fatty liver disease by suppressing endocannabinoid system. *Mol Nutr Food Res.* (2024) 68:e2300616. doi: 10.1002/mnfr.202300616
109. Zhou Y, Tian S, Qian L, Jiang S, Tang Y, Han T. DHA-enriched phosphatidylserine ameliorates non-alcoholic fatty liver disease and intestinal dysbiosis in mice induced by a high-fat diet. *Food Funct.* (2021) 12:4021–33. doi: 10.1039/d0fo03471a
110. Nakamoto K, Tokuyama S. Docosahexaenoic acid attenuates the progression of non-alcoholic steatohepatitis by suppressing the adipocyte inflammation via the G protein-coupled receptor 120/free fatty acid receptor 4 pathway. *Pharmacology.* (2022) 107:330–8. doi: 10.1159/000522117
111. Li J, Guo J, Yuen M, Yuen H, Peng Q. The comparative effects of omega-7 fatty acid-rich sea buckthorn oil and omega-3 fatty acid-rich DHA algal oil on improving high-fat diet-induced hyperlipidemia. *Food Funct.* (2025) 16:1241–53. doi: 10.1039/d4fo04961f
112. Gong M, Lu H, Li L, Feng M, Zou Z. Integration of transcriptomics and metabolomics revealed the protective effects of hemp seed oil against methionine-choline-deficient diet-induced non-alcoholic steatohepatitis in mice. *Food Funct.* (2023) 14:2096–111. doi: 10.1039/d2fo03054c
113. Hwang SM, Kim YU, Kim JK, Chun YS, Kwon YS, Ku SK, et al. Preventive and therapeutic effects of krill oil on obesity and obesity-induced metabolic syndromes in high-fat diet-fed mice. *Mar Drugs.* (2022) 20. doi: 10.3390/md20080483
114. Sanchez V, Brandt A, Jin CJ, Rajcic D, Engstler AJ, Jung F, et al. Fortifying butterfat with soybean oil attenuates the onset of diet-induced non-alcoholic steatohepatitis and glucose intolerance. *Nutrients.* (2021) 13. doi: 10.3390/nu13030959
115. Manca CS, Cordeiro Simoes-Ambrosio LM, Ovidio PP, Ramalho LZ, Jordao AA. Effects of different vegetable oils on the nonalcoholic fatty liver disease in C57/BL mice. *Evid Based Complement Alternat Med.* (2023) 2023:4197955. doi: 10.1155/2023/4197955
116. Ni HY, Yu L, Zhao XL, Wang LT, Zhao CJ, Huang H, et al. Seed oil of *Rosa roxburghii* Tratt against non-alcoholic fatty liver disease in vivo and in vitro through PPARalpha/PGC-1alpha-mediated mitochondrial oxidative metabolism. *Phytomedicine.* (2022) 98:153919. doi: 10.1016/j.phymed.2021.153919
117. Cha Q, Zhao W, Ran L, Wang Y, Wang X, Xu F, et al. Unsaturated alginate oligosaccharides alleviate insulin resistance and fatty liver in non-obese NAFLD mice by regulating bile acid metabolism through gut microbiota. *Metab Open.* (2025) 28:100412. doi: 10.1016/j.metop.2025.100412
118. Yan X, Li L, Liu P, Xu J, Wang Z, Ding L, et al. Targeted metabolomics profiles serum fatty acids by HFD induced non-alcoholic fatty liver in mice based on GC-MS. *J Pharm Biomed Anal.* (2022) 211:114620. doi: 10.1016/j.jpba.2022.114620
119. Xavier A, Zaccioni F, Santana-Romo F, Eykyn TR, Lavin B, Phinikaridou A, et al. Assessment of hepatic fatty acids during non-alcoholic steatohepatitis progression using magnetic resonance spectroscopy. *Ann Hepatol.* (2021) 25:100358. doi: 10.1016/j.aohp.2021.100358
120. Vlock EM, Karanjit S, Talmon G, Farazi PA. Reduction of polyunsaturated fatty acids with tumor progression in a lean non-alcoholic steatohepatitis-associated hepatocellular carcinoma mouse model. *J Cancer.* (2020) 11:5536–46. doi: 10.7150/jca.48495
121. Hymel E, Vlock E, Fisher KW, Farazi PA. Differential progression of unhealthy diet-induced hepatocellular carcinoma in obese and non-obese mice. *PLoS One.* (2022) 17:e0272623. doi: 10.1371/journal.pone.0272623
122. Ishii H, Horie Y, Ohshima S, Anezaki Y, Kinoshita N, Dohmen T, et al. Eicosapentaenoic acid ameliorates steatohepatitis and hepatocellular carcinoma in hepatocyte-specific Pten-deficient mice. *J Hepatol.* (2009) 50:562–71. doi: 10.1016/j.jhep.2008.10.031
123. Inoue-Yamauchi A, Itagaki H, Oda H. Eicosapentaenoic acid attenuates obesity-related hepatocellular carcinogenesis. *Carcinogenesis.* (2018) 39:28–35. doi: 10.1093/carcin/bgx112
124. Lim K, Han C, Dai Y, Shen M, Wu T. Omega-3 polyunsaturated fatty acids inhibit hepatocellular carcinoma cell growth through blocking beta-catenin and cyclooxygenase-2. *Mol Cancer Ther.* (2009) 8:3046–55. doi: 10.1158/1535-7163.MCT-09-0551
125. Depner CM, Philbrick KA, Jump DB. Docosahexaenoic acid attenuates hepatic inflammation, oxidative stress, and fibrosis without decreasing hepatosteatosis in a Ldlr(−/−) mouse model of western diet-induced nonalcoholic steatohepatitis. *J Nutr.* (2013) 143:315–23. doi: 10.3945/jn.112.171322
126. Michaeloudes C, Christodoulides S, Christodoulou P, Kyriakou TC, Patrikios I, Stephanou A. Variability in the clinical effects of the omega-3 polyunsaturated fatty acids DHA and EPA in cardiovascular disease-possible causes and future considerations. *Nutrients.* (2023) 15. doi: 10.3390/nu15224830
127. Yoshikawa T, Shimano H, Yahagi N, Ide T, Amemiya-Kudo M, Matsuzaka T, et al. Polyunsaturated fatty acids suppress sterol regulatory element-binding protein 1c promoter activity by inhibition of liver X receptor (LXR) binding to LXR response elements. *J Biol Chem.* (2002) 277:1705–11. doi: 10.1074/jbc.M105711200
128. Xu J, Nakamura MT, Cho HP, Clarke SD. Sterol regulatory element binding protein-1 expression is suppressed by dietary polyunsaturated fatty acids. A mechanism for the coordinate suppression of lipogenic genes by polyunsaturated fatty acids. *J Biol Chem.* (1999) 274:23577–83. doi: 10.1074/jbc.274.33.23577
129. Zuniga J, Cancino M, Medina F, Varela P, Vargas R, Tapia G, et al. N-3 PUFA supplementation triggers PPAR-α activation and PPAR-α/NF-κB interaction: anti-inflammatory implications in liver ischemia-reperfusion injury. *PLoS One.* (2011) 6:e28502. doi: 10.1371/journal.pone.0028502
130. Rudkowska I, Caron-Dorval D, Verreault M, Couture P, Deshaies Y, Barbier O, et al. PPARalpha L162V polymorphism alters the potential of n-3 fatty acids to increase lipoprotein lipase activity. *Mol Nutr Food Res.* (2010) 54:543–50. doi: 10.1002/mnfr.200900085
131. Rustan AC, Christiansen EN, Drevon CA. Serum lipids, hepatic glycerolipid metabolism and peroxisomal fatty acid oxidation in rats fed omega-3 and omega-6 fatty acids. *Biochem J.* (1992) 283:333–9. doi: 10.1042/bj2830333
132. Pettinelli P, Del Pozo T, Araya J, Rodrigo R, Araya AV, Smok G, et al. Enhancement in liver SREBP-1c/PPAR-alpha ratio and steatosis in obese patients: correlations with insulin resistance and n-3 long-chain polyunsaturated fatty acid depletion. *Biochim Biophys Acta.* (2009) 1792:1080–6. doi: 10.1016/j.bbdis.2009.08.015
133. Hernandez-Rodas MC, Valenzuela R, Echeverria F, Rincon-Cervera MA, Espinosa A, Illesca P, et al. Supplementation with docosahexaenoic acid and extra virgin olive oil prevents liver steatosis induced by a high-fat diet in mice through PPAR-α and Nrf2 upregulation with concomitant SREBP-1c and NF-κB downregulation. *Mol Nutr Food Res.* (2017) 61. doi: 10.1002/mnfr.201700479
134. Sato A, Kawano H, Notsu T, Ohta M, Nakakuki M, Mizuguchi K, et al. Antiobesity effect of eicosapentaenoic acid in high-fat/high-sucrose diet-induced obesity: importance of hepatic lipogenesis. *Diabetes.* (2010) 59:2495–504. doi: 10.2337/db09-1554
135. Mason RP, Sherratt SC, Jacob RF. Eicosapentaenoic acid inhibits oxidation of ApoB-containing lipoprotein particles of different size in vitro when administered alone or in combination with atorvastatin active metabolite compared with other triglyceride-lowering agents. *J Cardiovasc Pharmacol.* (2016) 68:33–40. doi: 10.1097/FJC.0000000000000379
136. Sakai C, Ishida M, Ohba H, Yamashita H, Uchida H, Yoshizumi M, et al. Fish oil omega-3 polyunsaturated fatty acids attenuate oxidative stress-induced DNA damage in vascular endothelial cells. *PLoS One.* (2017) 12:e0187934. doi: 10.1371/journal.pone.0187934
137. Gao L, Wang J, Sekhar KR, Yin H, Yared NF, Schneider SN, et al. Novel n-3 fatty acid oxidation products activate Nrf2 by destabilizing the association between Keap1 and Cullin3. *J Biol Chem.* (2007) 282:2529–37. doi: 10.1074/jbc.m607622200
138. Li J, Deng X, Bai T, Wang S, Jiang Q, Xu K. Resolvin D1 mitigates non-alcoholic steatohepatitis by suppressing the TLR4-MyD88-mediated NF-kappaB and MAPK pathways and activating the Nrf2 pathway in mice. *Int Immunopharmacol.* (2020) 88:106961. doi: 10.1016/j.intimp.2020.106961
139. Chen J, Wang D, Zong Y, Yang X. DHA protects hepatocytes from oxidative injury through GPR120/ERK-mediated mitophagy. *Int J Mol Sci.* (2021) 22. doi: 10.3390/ijms22115675
140. Csak T, Velayudham A, Hritz I, Petrasek J, Levin I, Lippai D, et al. Deficiency in myeloid differentiation factor-2 and toll-like receptor 4 expression attenuates nonalcoholic steatohepatitis and fibrosis in mice. *Am J Physiol Gastrointest Liver Physiol.* (2011) 300:G433–41. doi: 10.1152/ajpgi.00163.2009
141. Miura K, Yang L, van Rooijen N, Brenner DA, Ohnishi H, Seki E. Toll-like receptor 2 and palmitic acid cooperatively contribute to the development of nonalcoholic steatohepatitis through inflammasome activation in mice. *Hepatology.* (2013) 57:577–89. doi: 10.1002/hep.26081
142. Jump DB, Lytle KA, Depner CM, Tripathy S. Omega-3 polyunsaturated fatty acids as a treatment strategy for nonalcoholic fatty liver disease. *Pharmacol Ther.* (2018) 181:108–25. doi: 10.1016/j.pharmthera.2017.07.007
143. Li T, Li F, Liu X, Liu J, Li D. Synergistic anti-inflammatory effects of quercetin and catechin via inhibiting activation of TLR4-MyD88-mediated NF-kappaB and MAPK signaling pathways. *Phytother Res.* (2019) 33:756–67. doi: 10.1002/ptr.6268
144. Lytle KA, Wong CP, Jump DB. Docosahexaenoic acid blocks progression of western diet-induced nonalcoholic steatohepatitis in obese Ldlr−/− mice. *PLoS One.* (2017) 12:e0173376. doi: 10.1371/journal.pone.0173376
145. Oh DY, Talukdar S, Bae EJ, Imamura T, Morinaga H, Fan W, et al. GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects. *Cell.* (2010) 142:687–98. doi: 10.1016/j.cell.2010.07.041
146. Tapia G, Valenzuela R, Espinosa A, Romanque P, Dossi C, Gonzalez-Manan D, et al. N-3 long-chain PUFA supplementation prevents high fat diet induced mouse liver steatosis and inflammation in relation to PPAR-alpha upregulation and NF-kappaB DNA binding abrogation. *Mol Nutr Food Res.* (2014) 58:1333–41. doi: 10.1002/mnfr.201300458
147. Buroker NE, Barboza J, Huang JY. The IkappaBalpha gene is a peroxisome proliferator-activated receptor cardiac target gene. *FEBS J.* (2009) 276:3247–55. doi: 10.1111/j.1742-4658.2009.07039.x
148. Han YH, Shin KO, Kim JY, Khadka DB, Kim HJ, Lee YM, et al. A maresin 1/RORalpha/12-lipoxygenase autoregulatory circuit prevents inflammation and progression of nonalcoholic steatohepatitis. *J Clin Invest.* (2019) 129:1684–98. doi: 10.1172/JCI124219
149. Petrilli V, Dostert C, Muruve DA, Tschopp J. The inflammasome: a danger sensing complex triggering innate immunity. *Curr Opin Immunol.* (2007) 19:615–22. doi: 10.1016/j.coi.2007.09.002
150. Sui YH, Luo WJ, Xu QY, Hua J. Dietary saturated fatty acid and polyunsaturated fatty acid oppositely affect hepatic NOD-like receptor protein 3 inflammasome through regulating nuclear factor-kappa B activation. *World J Gastroenterol.* (2016) 22:2533–44. doi: 10.3748/wjg.v22.i8.2533
151. Patsenker E, Thangapandi VR, Knittelfelder O, Palladini A, Hefti M, Beil-Wagner J, et al. The PNPLA3 variant I148M reveals protective effects toward hepatocellular

- carcinoma in mice via restoration of omega-3 polyunsaturated fats. *J Nutr Biochem.* (2022) 108:109081. doi: 10.1016/j.jnutbio.2022.109081
152. Chen YJ, Jiang HT, Wang TF. Influence of docosahexaenoic acid on proliferation and apoptosis in human HepG2 cell line. *Ann Clin Lab Sci.* (2019) 49:72–8.
153. Chang FZ, Wang Q, Zhang Q, Chang LL, Li W. Omega-3 polyunsaturated fatty acid inhibits the malignant progression of hepatocarcinoma by inhibiting the Wnt/beta-catenin pathway. *Eur Rev Med Pharmacol Sci.* (2018) 22:4500–8. doi: 10.26355/eurrev_201807_15504
154. Sun SN, Jia WD, Chen H, Ma JL, Ge YS, Yu JH, et al. Docosahexaenoic acid (DHA) induces apoptosis in human hepatocellular carcinoma cells. *Int J Clin Exp Pathol.* (2013) 6:281–9.
155. Notarnicola M, Messa C, Refolo MG, Tutino V, Miccolis A, Caruso MG. Polyunsaturated fatty acids reduce fatty acid synthase and hydroxy-methyl-glutaryl CoA-reductase gene expression and promote apoptosis in HepG2 cell line. *Lipids Health Dis.* (2011) 10:10. doi: 10.1186/1476-511x-10-10
156. Lee M, Bae MA. Docosahexaenoic acid induces apoptosis in CYP2E1-containing HepG2 cells by activating the c-Jun N-terminal protein kinase related mitochondrial damage. *J Nutr Biochem.* (2007) 18:348–54. doi: 10.1016/j.jnutbio.2006.06.003
157. Khan AA, Alanazi AM, Jabeen M, Hassan I, Bhat MA. Targeted nano-delivery of novel omega-3 conjugate against hepatocellular carcinoma: regulating COX-2/bcl-2 expression in an animal model. *Biomed Pharmacother.* (2016) 81:394–401. doi: 10.1016/j.biopha.2016.04.033
158. Deschler S, Pohl-Topcu J, Ramsauer L, Meiser P, Erlacher S, Schenk RP, et al. Polyunsaturated fatty acid-induced metabolic exhaustion and ferroptosis impair the anti-tumour function of MAIT cells in MASLD. *J Hepatol.* (2025) 83:1364–78. doi: 10.1016/j.jhep.2025.06.006