
Update on the Potential Use of Natural Triterpenes for the Treatment of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and Metabolic Dysfunction-Associated Steatohepatitis (MASH)

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Review

Update on the Potential Use of Natural Triterpenes for the Treatment of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and Metabolic Dysfunction-Associated Steatohepatitis (MASH)

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Abstract

Background/Objectives: Metabolic dysfunction-associated steatotic liver disease (MASLD) and its progressive inflammatory/fibrotic form, metabolic dysfunction-associated steatohepatitis (MASH), represent a growing global health burden. Their progression driven by complex, interconnected mechanisms involving metabolic dysregulation, chronic inflammation, oxidative stress, and progressive fibrosis. Despite advances in understanding disease pathophysiology, effective pharmacological therapies remain limited. Pentacyclic triterpenes, a structurally diverse class of natural compounds widely distributed in nature, have attracted increasing attention due to their broad biological activities and ability to modulate multiple molecular pathways implicated in chronic liver disease development. This review aims to provide a mechanistic overview of the potential role of pentacyclic triterpenes in MASLD and MASH. **Methods:** A comprehensive review of the literature was conducted using major scientific databases (Pubmed, Scielo, Web of Science) to identify experimental studies investigating pentacyclic triterpenes in the context of metabolic liver diseases. The selected studies were analyzed according to triterpene structural classification, reported bioactivities, molecular targets, and experimental evidence from *in vitro* and *in vivo* models of MASLD/MASH or specific processes involved in the disease progression. **Results:** Pentacyclic triterpenes, specially ursolic acid, oleanolic acid and glycyrrhizin, exhibit pleiotropic hepatoprotective effects, including regulation of lipid metabolism, attenuation of oxidative and endoplasmic reticulum stress, suppression of pro-inflammatory signaling, inhibition of inflammasome activation, and reduction of hepatic stellate cell activation and extracellular matrix deposition. These effects are mediated through modulation of key signaling pathways such as AMPK, NF- κ B, NLRP3, TGF- β , FXR, MAPK, and related metabolic and inflammatory cascades. Preclinical evidence consistently demonstrates improvements in steatosis, inflammation, and fibrosis across multiple experimental models. **Conclusions:** By integrating mechanistic and biological evidence, this review highlights pentacyclic triterpenes as potent multitarget modulators of MASH. However, a transition from preclinical models to well-designed clinical trials is essential to validate their safety and efficacy in humans.

Keywords: pentacyclic triterpenes; metabolic liver diseases; AMPK–mTOR signaling; NLRP3 inflammasome and pyroptosis; hepatic fibrogenesis; oxidative stress–driven inflammation

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) and its progressive inflammatory stage, metabolic dysfunction-associated steatohepatitis (MASH), represent major and growing challenges in hepatology, driven by complex interactions between metabolic imbalance, chronic inflammation, oxidative stress, and progressive fibrogenesis. Despite their increasing prevalence, therapeutic options capable of effectively targeting the multifactorial molecular mechanisms underlying disease initiation and progression remain limited. In this context, pentacyclic triterpenes have emerged as promising bioactive compounds due to their pleiotropic capacity to modulate key signaling pathways involved in lipid metabolism, inflammatory responses, redox homeostasis, and hepatic stellate cell activation. This review aims to integrate current evidence on the role of triterpenes in MASLD and MASH by first outlining the structural characteristics, biological activities and molecular targets of pentacyclic triterpenes. The discussion then contextualizes the pathophysiology of MASLD and MASH, culminating in an analysis of preclinical evidence supporting the direct application of triterpenes in experimental models of metabolic liver disease. This structured approach provides a mechanistic framework that connects triterpene chemistry to biological function and, ultimately, to disease modulation.

Methods

A comprehensive literature search was conducted in major scientific databases (e.g., PubMed, and Web of Science) to identify experimental studies evaluating pentacyclic triterpenes in MASLD/MASH or in relevant pathogenic processes (steatosis, inflammation, oxidative/ER stress, and fibrogenesis). Eligible records were screened for mechanistic endpoints, molecular targets, and in vitro and in vivo outcomes. The selected evidence was organized by triterpene class, primary bioactivities, and pathways implicated in metabolic liver disease progression.

Results

1. Classification and Structural Characteristics of Pentacyclic Triterpenes

Triterpenes constitute a vast class of bioactive compounds characterized by a thirty-carbon skeleton. Synthesized by a wide range of organisms, including bacteria, fungi, and animals, they reach their greatest structural diversity within the plant kingdom, with over 20,000 identified variants [1,2]. Characterized as complex molecules, triterpenes can be found either (i) in their free form, as non-volatile lipophilic substances soluble in organic solvents, acting as components of cellular membranes or as signaling molecules, or (ii) in oxygenated, esterified, or glycosylated derivative forms, which may confer protection to plants against pathogens and pests [3,4].

The fundamental terpene architecture arises from the sequential conjugation of isoprene units ($\text{CH}_2=\text{C}(\text{CH}_3)-\text{CH}=\text{CH}_2$). Terpenes are classified according to the number of isoprene units they contain, as follows: hemiterpenes (one isoprene unit), monoterpenes (two isoprene units), sesquiterpenes (three isoprene units), diterpenes (four isoprene units), sesterpenes (five isoprene units), triterpenes (six isoprene units), tetraterpenes (eight isoprene units), and polyterpenoids (more than eight isoprene units) [5]. Among these, the pentacyclic triterpenes - characterized by five fused rings - stand out for their remarkable pharmacological potential in modulating metabolic and inflammatory pathways. Representative structures of these groups are illustrated in Figure 1.

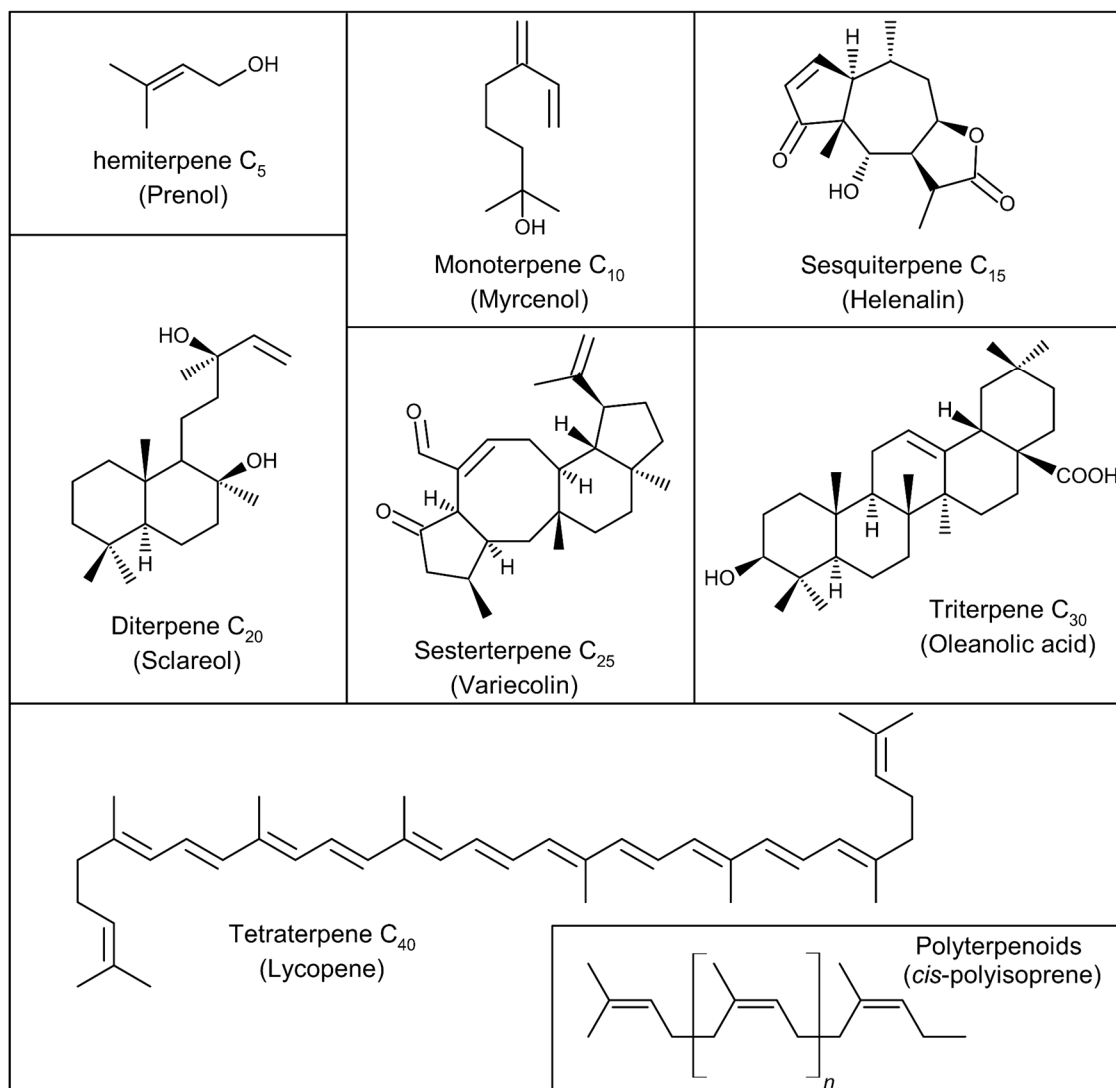


Figure 1. Representative structures of each group of terpenes.

The biosynthetic precursors of terpenes are generated through two independent metabolic pathways: the mevalonic acid (MVA) pathway, which involves the condensation of acetyl-CoA units, and the 1-deoxy-D-xylulose-5-phosphate (DXP) pathway, which proceeds through the condensation of pyruvate and glyceraldehyde-3-phosphate. Regardless of the pathway, both routes yield two isomeric C₅ building blocks: isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP) (Figure 2) [6–9].

Although both pathways produce identical C₅ units, they are compartmentalized and contribute differently to terpene biosynthesis. The MVA pathway occurs predominantly in the cytosol and is mainly responsible for the formation of sesquiterpenes and triterpenes, whereas the plastid-localized DXP pathway primarily supports the biosynthesis of mono-, di-, and tetraterpenes [10].

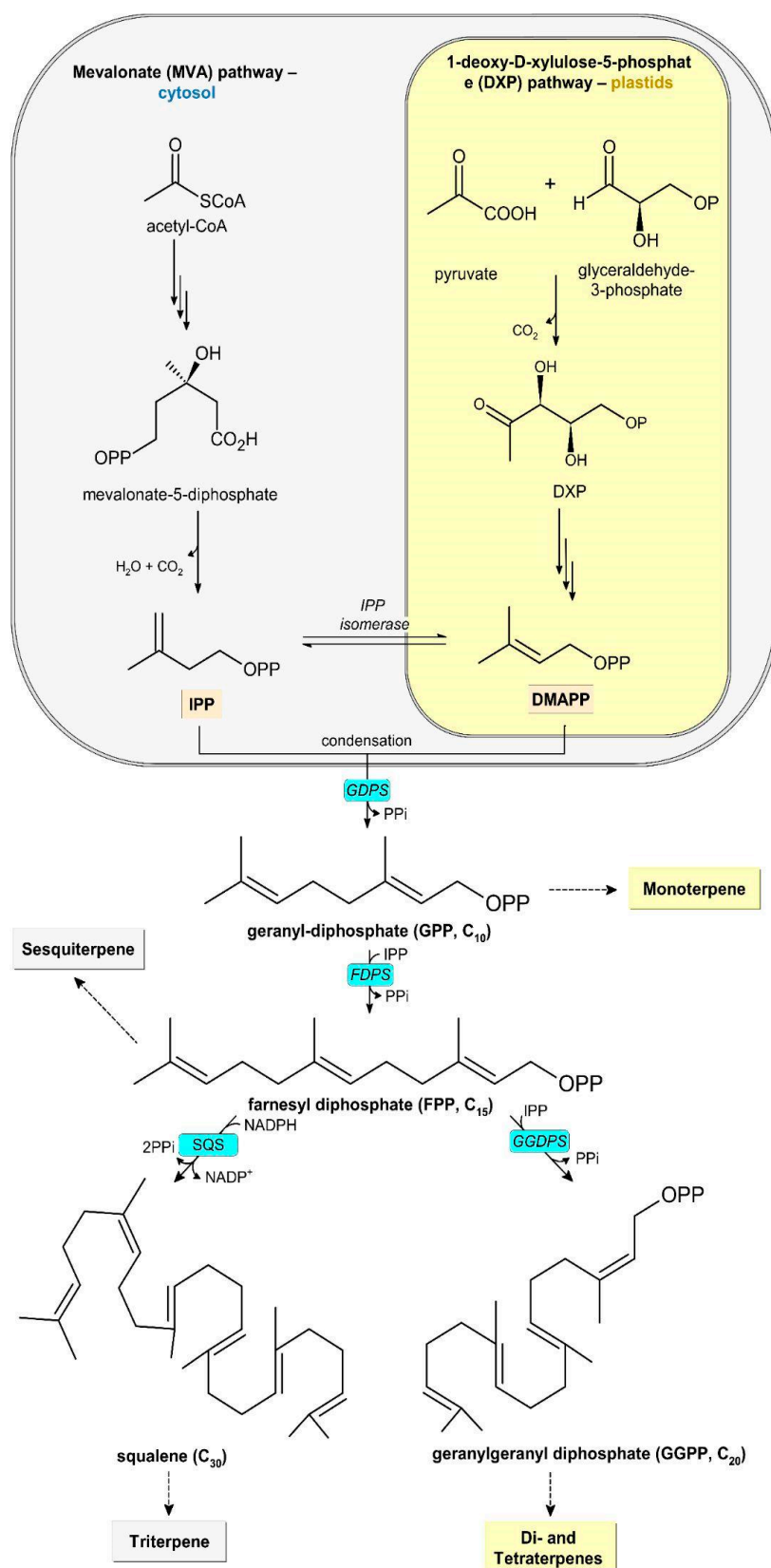


Figure 2. Schematic representation of the synthesis of the direct precursors isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) involved in terpenoid biosynthesis. The mevalonate (MVA) pathway occurs in the cytosol and provides precursors for the production of sesqui- and triterpenes, whereas the plastid-localized 1-deoxy-D-xylulose-5-phosphate (DXP) pathway supports the biosynthesis of mono-, di-, and tetraterpenes. Abbreviations: GDPS, geranyl diphosphate synthase; FDPS, farnesyl diphosphate synthase; GGDPs, geranylgeranyl diphosphate synthase; SQS, squalene synthase.

Terpene biosynthesis is driven by a series of sequential condensation reactions. The process initiates with the condensation of DMAPP and one IPP unit to form geranyl pyrophosphate (GPP), the fundamental precursor of monoterpenes, in a reaction catalyzed by geranyl diphosphate synthase (GDPS). GPP subsequently undergoes condensation with an additional IPP unit to generate farnesyl pyrophosphate (FPP), the C15 precursor of sesquiterpenes and triterpenes, mediated by farnesyl diphosphate synthase (FDPS). Through the action of geranylgeranyl diphosphate synthase, FPP may further condense with IPP to form geranylgeranyl diphosphate (GGPP), the C20 precursor of di- and tetraterpenes.

A critical branch point occurs when two FPP molecules undergo a reductive head-to-head condensation, catalyzed by squalene synthase (SQS), to produce squalene. This hydrocarbon is subsequently epoxidized into 2,3-oxidosqualene, the primary substrate for oxidosqualene cyclases (OSCs), which orchestrate the complex cyclization reactions that define the diverse triterpene skeletons. The stereochemical outcome is dictated by the folding conformation of the substrate: while the chair-boat-chair (CBC) conformation leads to sterol biosynthesis, the chair-chair-chair (CCC) conformation generates the dammarenyl cation. This key intermediate undergoes further ring expansion and rearrangements to yield the characteristic five-fused-ring architecture that defines the pentacyclic triterpene family (Figure 3) [1,8,10–13].

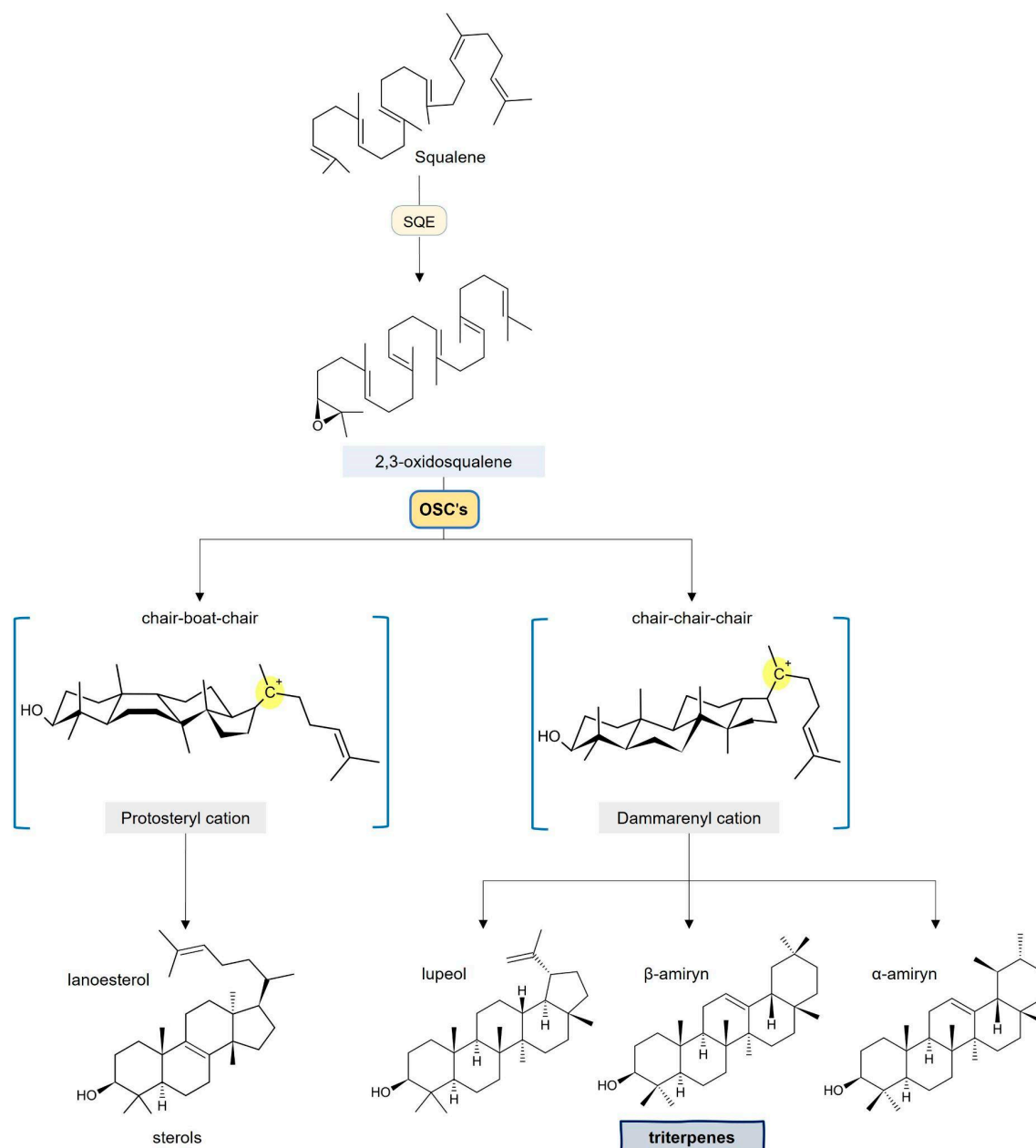


Figure 3. Oxidosqualene cyclase (OSC)-catalyzed 2,3-oxidosqualene cyclization pathways leading to sterols and triterpene compounds through protosteryl and dammarenyl carbocation intermediates, respectively. Abbreviations: OSC, oxidosqualene cyclase; SQE, squalene epoxidase.

Structurally, these pentacyclic triterpenes consist of thirty carbon atoms arranged into five fused rings (A–E), a configuration that allows for immense chemical diversity through functionalization (Figure 4). Based on their core carbocyclic skeletons, these compounds are primarily categorized into three dominant groups: oleananes, ursanes, and lupanes [14]. The distinction between oleanane and ursane types lies in the specific arrangement of methyl substituents on ring E: oleananes feature a gem-dimethyl group at the C20 position, whereas ursanes possess one methyl group at C19 and another at C20. In contrast, lupane-type triterpenes are structurally unique, characterized by a five-membered E ring and a trans-fused D/E ring junction [15–18].

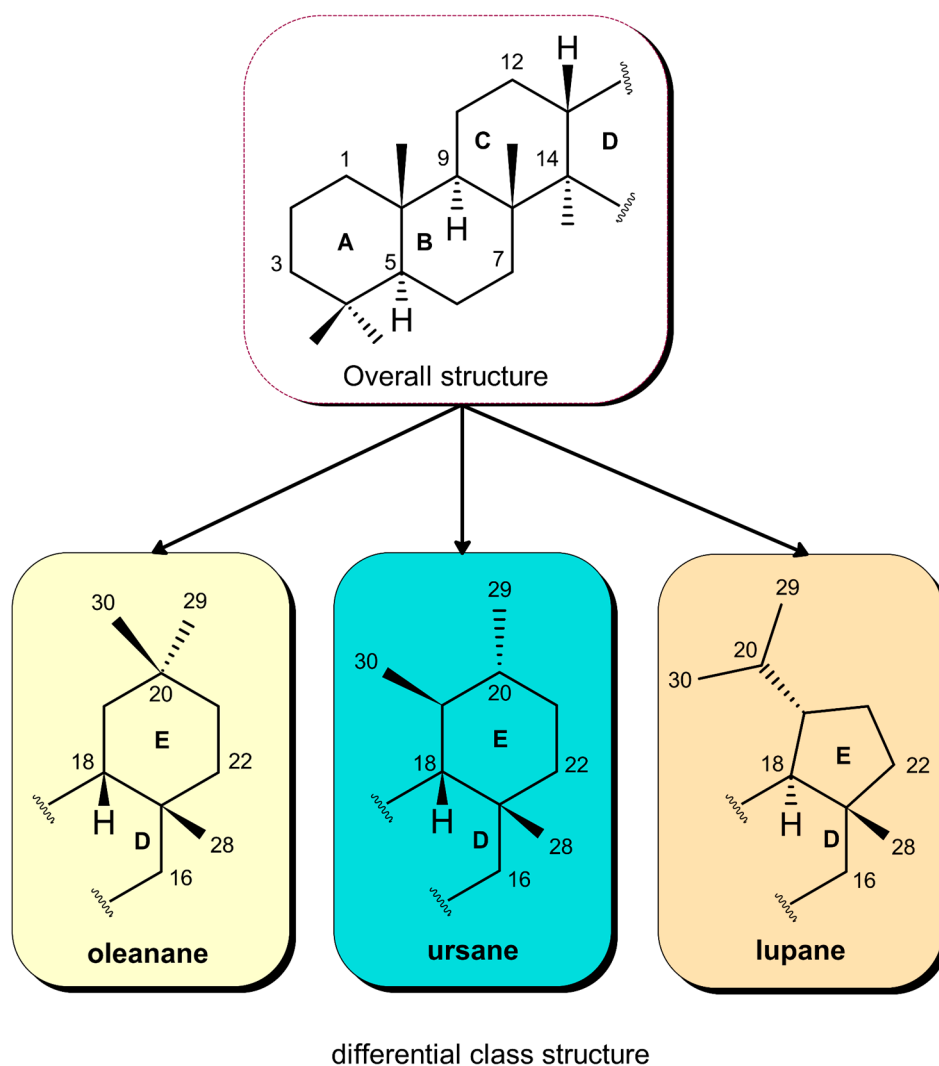


Figure 4. General structure of pentacyclic triterpenes classified according to their carbon skeletons into oleananes, ursanes, and lupanes.

Due to their ubiquitous presence in the plant kingdom and their remarkably broad spectrum of biological activities, pentacyclic triterpenes have emerged as pivotal bioactive natural products. Beyond their ecological roles, these compounds are increasingly recognized as promising lead scaffolds for the development of novel therapeutic agents, particularly in the context of chronic metabolic and inflammatory diseases [19,20].

2. Bioactivity of Triterpenes

2.1. Anti-Inflammatory Action

The therapeutic application of plants rich in pentacyclic triterpenes is deeply rooted in traditional medicine, particularly for managing inflammatory conditions [21,22]. Modern pharmacological research has validated these traditional uses, identifying triterpenoids as potent modulators of the inflammatory cascade. Among these, glycyrrhizin - a triterpenoid saponin abundantly found in licorice root (*Glycyrrhiza* spp.) - stands out due to its broad anti-inflammatory properties. Upon oral administration, glycyrrhizin undergoes microbial transformation in the gut into glycyrrhetic acid, an oleanane-type aglycone that serves as the primary effector molecule [23,24]. Glycyrrhizin exerts anti-inflammatory effects through a sophisticated, multi-target network. It directly inhibits key pro-inflammatory enzymes, including 5-lipoxygenase and cyclooxygenase (COX)-2, thereby reducing the biosynthesis of leukotrienes and prostaglandins [25–27]. A hallmark of its activity is the suppression of the NF- κ B and MAPK signaling axes, which orchestrate the expression of inducible nitric oxide synthase (iNOS) and critical cytokines such as TNF- α , IL-1 β , and IL-6. Notably, glycyrrhizin possesses a unique ability to bind and neutralize to high-mobility group box 1 (HMGB1), a potent damage-associated molecular pattern (DAMP) that drives sterile inflammation by antagonizing HMGB1 activity and modulating Toll-like receptor (TLR) signaling, glycyrrhizin effectively limits neutrophil activation, reduces reactive oxygen species (ROS) production, and downregulates adhesion molecules. These pleiotropic actions collectively attenuate leukocyte infiltration and tissue damage, positioning glycyrrhizin as a formidable candidate for mitigating the chronic inflammatory milieu characteristic of MASH and other metabolic liver disorders [28–30].

Similarly, celastrol, a bioactive triterpenoid isolated from *Tripterygium wilfordii*, exhibits potent anti-inflammatory and immunomodulatory properties by targeting multiple regulatory nodes. Its mechanism of action is uniquely characterized by the of K63-linked deubiquitination of the NLR family pyrin domain containing 3 (NLRP3) inflammasome [31]. Furthermore, celastrol effectively suppresses the HMGB1/NF- κ B axis, dampening the propagation of pro-inflammatory signals [32]. Advanced systems pharmacology and multi-omics analyses have elucidated that celastrol targets key pro-inflammatory mediators, including TNF- α , and IL-6, while regulating pathways such as phosphoinositide 3-kinase (PI3K)/ protein kinase B (Akt), MAPK, transforming growth factor (TGF)- β , and IL signaling. By attenuating immune cell activation, fibroblast invasiveness, cytokine production, and synovial inflammation, celastrol demonstrates a broad anti-inflammatory profile [33]. Beyond its anti-inflammatory profile, celastrol exerts significant anti-proliferative and pro-apoptotic effects. It potentiates TNF-induced apoptosis by downregulating a suite of survival genes, such as IAP1/2, Bcl-2, and c-FLIP, while simultaneously inhibiting mediators of invasion and angiogenesis, including MMP-9 and VEGF [34]. By attenuating cytokine production, fibroblast activation, and oxidative stress, celastrol emerges as a robust therapeutic candidate for chronic inflammatory disorders, particularly those where inflammation and fibrogenesis are closely intertwined, such as MASH.

A pivotal anti-inflammatory mechanism of pentacyclic triterpenes involves the activation of the AMP-activated protein kinase (AMPK) pathway, a master regulator of energy homeostasis and immune signaling. A diverse array of compounds, including oleanolic acid (OA), ursolic acid (UA), betulinic acid (BA), glycyrrhetic acid, and asiatic acid (AA), has been identified as potent AMPK activators, underscoring their therapeutic potential in metabolic-driven inflammation [35].

Specifically, recent investigations into Δ -OA have highlighted its efficacy as a robust AMPK activator. Comparative assays using 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) - a gold-standard AMPK agonist - demonstrated that Δ -OA achieves similar pharmacological outcomes in modulating inflammatory responses. This equivalence to established activators positions Δ -OA and related triterpenoids as promising drug candidates for conditions where AMPK dysregulation is central, such as the chronic inflammatory milieu of MASH [35].

Recent studies have highlighted the anti-inflammatory activity of ursane-type triterpenes, particularly UA with potential applications in the treatment of neuroinflammation. UA has been shown to exert immunomodulatory effects and promote neuronal repair through direct remyelination during the chronic progressive stage of multiple sclerosis [36]. Additionally, UA has demonstrated anti-inflammatory activity in models of Parkinson's disease [37], arthritis [38], type 2 diabetes mellitus (T2DM) [39], and myasthenia gravis [40]. Administration of UA prior to disease onset also prevented encephalopathy development by inhibiting Th17 cell differentiation in a mice model of the disease [41]. Several mechanisms have been associated with its anti-inflammatory effects, including reductions in pro-inflammatory cytokines IL-1 β , IL-6, IL-8, and TNF- α levels, and malondialdehyde (MDA) level, one of the products of lipid peroxidation and a biomarker of liver oxidative damage, along with increases in superoxide dismutase (SOD) and glutathione (GSH) levels, that are key components of the cellular antioxidant system [42].

Another ursane-type triterpene under investigation is boswellic acid. Ammon (2006) demonstrated that boswellic-type triterpenes inhibit the synthesis of the pro-inflammatory enzyme 5-lipoxygenase and its products, including 5-hydroxyeicosatetraenoic acid and leukotriene B4 [43]. This compound also modulates several pathways associated with obesity and T2DM, which are discussed in later sections.

A lupane-type triterpene that has attracted attention due to its anti-inflammatory, antioxidant, and antifibrotic activities is ganoderic acid A, the major triterpenoid extracted from *Ganoderma* mushrooms. In a study conducted by Ma et al. (2021), this compound demonstrated significant biological activity [44].

Despite extensive investigation, it remains unclear whether the carbon skeleton of triterpenes significantly influences their anti-inflammatory efficacy. While some studies suggest that oleanane-type structures may exhibit higher activity than ursane-type compounds [45], other reports indicate comparable effects among oleanane-, lupane-, and ursane-type skeletons [46,47].

2.2. Antioxidant Activity

Oxidative stress is a central driver in the progression of MASLD to MASH, contributing significantly to hepatocyte injury and fibrogenesis. Several studies have demonstrated that pentacyclic triterpenes possess significant antioxidant potential, which directly contributes to their hepatoprotective profile.

Early investigations, such as those Allouche et al. (2010) evaluated the antioxidant and antithrombotic activities of uvaol, erythrodiol, OA, and maslinic acid added to isolated human low-density lipoprotein (LDL), aiming to assess their cardiovascular protective effects. The results indicated that maslinic acid, uvaol, and erythrodiol by assessing their ability to protect isolated human LDL from oxidation [48].

The antioxidant effect of maslinic acid had been previously reported [49,50]. Wang et al. (2006) demonstrated that maslinic acid strongly inhibited copper-induced LDL oxidation *in vitro*, reducing the formation of conjugated dienes by approximately 21% compared with the control group [49]. According to Allouche et al. (2010), this effect was significant at a concentration of approximately 100 μ M, while no effect was initially detected at 10 μ M. However, the same study later reported that even 10 μ M maslinic acid exhibited antioxidant properties [48].

The relevance of this mechanism to hepatic disease was highlighted by Lim et al. (2024) who investigated the protective effects of four triterpenes — AA, asiaticoside, madecassic acid, and madecassoside — in different cell culture models, including Hs68 (human skin fibroblasts), HepG2 (human hepatocytes), RAW 264.7 (murine macrophages), and EA.hy926 (human umbilical vein endothelial cells). Hs68 cells were exposed to UVB radiation, while HepG2 and EA.hy926 cells were challenged with tert-butyl hydroperoxide (TBHP) and hydrogen peroxide, respectively. RAW 264.7 macrophages were stimulated with lipopolysaccharide (LPS). Pretreatment with triterpenes attenuated UVB-induced ROS and MDA generation and preserved GSH levels in skin fibroblasts, while increasing intracellular collagen content. In HepG2 cells, pretreatment significantly improved

cell viability and reduced TBHP-induced ROS, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels. In EA.hy926 cells, triterpenes reduced ROS levels and decreased MDA and GSH expression. In RAW 264.7 macrophages, treatment significantly reduced nitric oxide, TNF- α , and IL-6 production [50].

In another study, Mamadalieva et al. (2021) evaluated the antioxidant activity of fifteen cycloartane-type triterpenes using cell-free assays, including phosphomolybdenum, 1,1-diphenyl-2-picrylhydrazyl (DPPH \bullet), 2,2'-azinobis(3-ethylbenzothiazoline)-6-sulfonic acid (ABTS \bullet^+), cupric ion-reducing antioxidant capacity (CUPRAC), ferric-reducing antioxidant power (FRAP), and metal-chelating activity assays. Most of the compounds exhibited antioxidant activity, despite lacking typical phenolic or catecholic moieties commonly associated with antioxidant effects in natural products such as flavonoids [51].

Ostapiuk et al. (2021) investigated the antioxidant mechanisms of betulin and BA, two lupane-type triterpenes, using triterpene-rich extracts. The results demonstrated a significant reduction in hydrogen peroxide and superoxide anion formation, as well as decreased lipid peroxidation [52].

As observed for anti-inflammatory effects, no clear structure–activity relationship has been established for the antioxidant activity of triterpenes. Nevertheless, most compounds within this class exhibit antioxidant effects to varying extents, underscoring their therapeutic potential in diseases and conditions associated with oxidative stress.

2.3. Antiadipogenic Activity and T2DM Control

Triterpenes have demonstrated considerable potential as antiadipogenic agents. Excessive adipose tissue accumulation is associated with multiple metabolic disorders, including insulin resistance, dyslipidemia, hepatic steatosis, coagulopathies, and hypertension [53].

Peng et al. (2022) evaluated the antiadipogenic effects of lanostane-type triterpenoids by testing forty compounds for their ability to inhibit the differentiation of 3T3-L1 preadipocytes into adipocytes. Several compounds significantly reduced adipocyte differentiation, particularly those containing an A-seco-23 \rightarrow 26 lactone skeleton [54].

Mohsen et al. (2019) demonstrated that BA effectively reduced lipid accumulation in 3T3-L1 cells by downregulating the expression of peroxisome proliferator-activated receptor gamma (PPAR γ) and liver X receptor alpha (LXR α). The study also showed enhanced interaction of steroid receptor coactivator-1 (SRC-1) with PPAR γ and reduced SRC-3 levels [55]. These findings were supported by Melo et al. (2009), who investigated the effects of BA extracted from *Clusia nemorosa* L. (Clusiaceae) in a mouse model of obesity. The treatment resulted in significant reductions in body weight, abdominal fat accumulation, blood glucose levels, plasma triglycerides, and total cholesterol, primarily through inhibition of pancreatic lipase [56].

Betancourt et al. (2021) demonstrated that an extract composed of a mixture of UA, OA, and UA lactone reduced lipid accumulation in 3T3-L1 cells, accompanied by decreased leptin expression [57]. These findings were corroborated by Acín et al. (2021), who showed that C57BL/6J mice fed a high-fat diet and treated with this extract exhibited improved glucose tolerance, reduced body weight, decreased hepatic and adipose fat content, lower plasma lipid levels, and reduced hepatic mRNA expression of PPAR α , CPT1A, and sterol regulatory element-binding protein (SREBP)-1 [58].

In *in vitro* studies using HepG2 cells treated with free fatty acids, UA reduced lipid accumulation and modulated the expression of genes involved in lipid synthesis and degradation, concomitant with increased AMPK phosphorylation. These effects were reversed by the addition of an AMPK inhibitor, confirming that AMPK activation is essential for UA activity. Molecular docking studies further demonstrated binding of UA to AMPK at the 4CFH site, similarly to the agonist Pound-Thirsk compound 1 (PT1) [59].

Bermúdez-Contreras et al. (2025) demonstrated that extracts of *Agave durangensis*, containing approximately 30% triterpenes, reduced triglyceride levels by 59.28% and very-low-density lipoprotein (VLDL) cholesterol by 60.27% in a mouse model of T2DM [60]. Liou et al. (2019) investigated maslinic acid extracted from olive peels and reported reductions in obesity in mice

treated with doses between 10 and 20 mg/kg, along with improvements in hepatic steatosis. These effects were associated with suppression of TNF- α gene expression in the liver and epididymal adipose tissue, reduced serum TNF- α levels, downregulation of SREBP-1c, PPAR γ , CCAAT/Enhancer-binding protein (C/EBP) β , and fatty acid synthase (FAS), and increased expression of adipose triglyceride lipase (ATGL), Sirtuin (Sirt)1, and AMPK phosphorylation [61].

Zaitone et al. (2015) demonstrated that oral administration of boswellic acids reduced food intake, body weight gain, and improved energy expenditure. These effects were associated with reduced pro-inflammatory mediators, decreased systemic insulin resistance, and attenuation of hepatic lipid accumulation, leading to improved liver function [62].

Han et al. (2025) treated human skin fibroblasts with β -boswellic acid, an ursane-type triterpene, and demonstrated safety at concentrations up to 40 μ M. Treatment reduced high-glucose-induced ferroptosis and lipid peroxidation while improving cell migration. Western blot analysis revealed increased levels of phosphorylated signal transducer and activator of transcription (STAT)3. *In vivo*, β -boswellic acid (10 mg/kg, subcutaneous) accelerated wound closure, reduced inflammatory cell infiltration, improved granulation tissue organization, and increased collagen deposition in diabetic rat wounds [63].

Given the strong association between obesity and T2DM, these findings collectively highlight the promising potential of triterpenes for the treatment of metabolic disorders.

2.4. Antifibrotic Activity

Fibrosis is a pathological process resulting from dysregulated tissue repair following persistent or severe injury, most commonly associated with chronic inflammatory conditions. It is characterized by excessive accumulation of extracellular matrix (ECM) components, including collagen and fibronectin [64]. In cases of repetitive injury, continuous ECM deposition leads to progressive disruption of tissue architecture, organ dysfunction, and ultimately organ failure [65,66].

Among the most extensively studied antifibrotic triterpenes is AA, an ursane-type compound isolated from *Centella asiatica*, widely used in traditional African, Ayurvedic, and Chinese medicine. AA exhibits anti-inflammatory, antioxidant, antitumor, and wound-healing properties [67]. *In vitro* studies have shown that AA protects hepatocytes and Kupffer cells from injury by modulating mitochondrial stress and enhancing cellular antioxidant defenses [68].

Tang et al. (2012) demonstrated *in vitro* that AA effectively blocks TGF- β 1-induced myofibroblast differentiation and collagen I expression in hepatic stellate cells (HSCs), suggesting direct antagonism of profibrotic signaling [69]. These findings align with earlier evidence indicating the involvement of TGF- β pathways in hepatic fibrosis [70]. The antifibrotic potential of AA was further confirmed *in vivo* in a rat model of carbon tetrachloride-induced hepatic fibrosis, where treatment significantly attenuated liver fibrosis and preserved hepatic function [71].

UA has also been extensively investigated for its antifibrotic properties. Wang et al. (2011) demonstrated *in vitro* that UA selectively induces apoptosis in activated HSCs, as evidenced by increased caspase-3 cleavage, while sparing hepatocytes [72]. Additionally, UA undergoes *in vivo* biotransformation into an epoxy derivative capable of covalently interacting with Cys-163 in caspase-3, leading to enzyme inactivation [73]. UA treatment was also associated with increased mitochondrial membrane permeability and inhibition of NF- κ B activation, reinforcing its dual proapoptotic and anti-inflammatory mechanisms [72].

Synthetic triterpenoids have also demonstrated strong antifibrotic activity. Wei et al. (2013) evaluated the synthetic oleanane-type triterpenoid CDDO (2-cyano-3,12-dioxoleana-1,9-dien-28-oic acid) using *in vivo* fibrosis models [74]. In a bleomycin-induced skin fibrosis model mimicking the inflammatory phase of systemic sclerosis, CDDO treatment significantly attenuated dermal fibrosis and inflammatory cell infiltration [75,76].

Given the anti-inflammatory properties of CDDO, these effects may result from immunosuppression, inhibition of TGF- β signaling, or both. To isolate its direct antifibrotic action, a complementary inflammation-independent, TGF- β -driven scleroderma model was employed. In this

model, CDDO abolished dermal thickening and myofibroblast accumulation. Consistently, *in vitro* experiments using explanted skin fibroblasts showed that CDDO directly antagonized TGF- β -induced fibrotic responses [77].

Additional evidence for the antifibrotic activity of lupane-type triterpenes was provided by Chang et al. (2021), who evaluated an enriched extract from *Momordica charantia* leaves containing kuguacin R and 3 β ,7 β ,25-trihydroxycucurbita-5,23-dien-19-al. Oral administration of the extract to ICR mice, concomitantly treated with carbon tetrachloride, significantly suppressed hepatic necroinflammation and collagen deposition. Treatment also reduced α -smooth muscle actin (α -SMA) expression, TGF- β 1 levels, pro-inflammatory cytokines (IL-6 and TNF- α), TLR4 expression, and intrahepatic infiltration of Ly6C⁺ monocytes [78].

Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal lung disease of unknown etiology, influenced by genetic susceptibility, epigenetic modifications, aging, and environmental factors [79]. Multiple signaling pathways, including TGF- β , PPAR γ , mTOR, and Wnt, are implicated in IPF progression.

BA, a lupane-type triterpene, has demonstrated antifibrotic activity in pulmonary fibrosis models. BA inhibits Wnt3a-induced fibroblast activation by suppressing Wnt/ β -catenin signaling. *In vivo*, BA treatment was beneficial in a bleomycin-induced pulmonary fibrosis mouse model and exhibited superior pharmacodynamic effects compared with pirfenidone. These findings suggest that BA and its derivatives represent promising candidates for antifibrotic drug development targeting pulmonary fibrosis [80].

2.5. Antitumor Activity

Pentacyclic triterpenes have been extensively investigated for their antitumor properties, largely due to their ability to modulate key signaling pathways involved in cell proliferation, apoptosis, angiogenesis, and metastasis. *In vitro* studies have consistently demonstrated that triterpenes such as OA, UA, and BA exert cytotoxic effects against a broad spectrum of cancer cell lines, including hepatocellular carcinoma, breast, prostate, colon, and lung cancer cells [81–83]. These effects are frequently associated with cell cycle arrest and induction of apoptosis through both intrinsic and extrinsic pathways.

Mechanistically, *in vitro* evidence indicates that UA and BA induce mitochondrial dysfunction, characterized by loss of mitochondrial membrane potential, cytochrome c release, and activation of caspase-9 and caspase-3 [84,85]. These compounds also downregulate anti-apoptotic proteins such as Bcl-2 and Bcl-xL while upregulating pro-apoptotic mediators including Bax and Bad. Additionally, triterpenes have been shown to suppress pro-survival signaling cascades, notably NF- κ B, PI3K/Akt, and STAT3 pathways, thereby sensitizing tumor cells to apoptotic stimuli [86].

Beyond apoptosis, triterpenes interfere with tumor cell proliferation by modulating cell cycle regulators. *In vitro* studies have demonstrated that BA induces G₀/G₁ or G₂/M cell cycle arrest, depending on the tumor cell type, through downregulation of cyclins (cyclin D1, cyclin B1) and cyclin-dependent kinases, accompanied by increased expression of cyclin dependent kinase (CDK) inhibitors such as p21 and p27 [87]. Moreover, triterpenes inhibit angiogenesis-related processes by suppressing VEGF expression and endothelial cell migration, further limiting tumor growth and metastatic potential [88].

The antitumor efficacy of triterpenes has been corroborated in multiple *in vivo* animal models. BA treatment significantly reduced tumor growth in xenograft mouse models of melanoma, breast cancer, and hepatocellular carcinoma, with concomitant increases in tumor cell apoptosis and reductions in microvessel density [89–91]. Similarly, UA administration inhibited tumor progression in chemically induced and xenograft cancer models, effects that were associated with decreased inflammatory signaling and oxidative stress within the tumor microenvironment [92].

Synthetic triterpenoids have also shown enhanced antitumor potency *in vivo*. Compounds such as CDDO and its derivatives (CDDO-Me and CDDO-Im) markedly suppressed tumor growth and metastasis in preclinical models of breast, lung, and pancreatic cancer [93]. These effects were

attributed to simultaneous inhibition of NF- κ B signaling, activation of Nrf2-mediated cytoprotective responses, and induction of apoptosis in malignant cells, highlighting the therapeutic potential of structural modification of naturally occurring triterpenes.

Although robust *in vitro* and *in vivo* data support the antitumor activity of pentacyclic triterpenes, clinical evidence remains limited. Early-phase clinical studies evaluating synthetic triterpenoids, particularly CDDO derivatives, have demonstrated acceptable safety profiles but modest efficacy, underscoring the need for improved bioavailability, optimized dosing strategies, and combination approaches to enhance translational success [94].

Collectively, the bioactivity of triterpenes highlights the substantial therapeutic potential of this class of compounds for the treatment of a wide range of diseases. Among these, metabolic dysfunction-associated fatty liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) are particularly relevant, as their pathogenesis encompasses several of the biological processes modulated by triterpenes. These processes operate at different stages of disease development, acting as predisposing factors - such as obesity and T2DM - as integral components of disease progression, including hepatic steatosis, chronic inflammation, oxidative stress, and fibrogenesis, or as long-term complications, such as hepatocellular carcinoma. In the following section, the pathophysiology of MASH is discussed, with emphasis on the key cellular events and signaling pathways that drive disease initiation and progression.

3. Mechanisms of Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD) and Metabolic Dysfunction–Associated Steatohepatitis (MASH)

Chronic liver diseases (CLDs) and cirrhosis represent major global health challenges, accounting for substantial morbidity and mortality worldwide [93]. According to the Global Burden of Disease Study 2017, viral hepatitis B and C remain strongly associated with the rising prevalence of cirrhosis and other CLDs. In parallel, metabolic dysfunction-associated steatotic liver disease (MASLD) and its progressive form, metabolic dysfunction-associated steatohepatitis (MASH), have emerged as leading contributors to the global burden of liver disease, driving an increasing incidence of cirrhosis and hepatocellular carcinoma (HCC). Autoimmune and genetic disorders further contribute to the complex etiology of CLDs [94].

MASLD is a multisystemic disorder in which insulin resistance and metabolic dysfunction play central roles in disease initiation and progression [95]. The diagnosis is established when more than 5% of hepatocytes exhibit steatosis in the presence of defined metabolic abnormalities, including obesity, T2DM, or dyslipidemia [96]. Clinically, MASLD encompasses a broad spectrum ranging from isolated triglyceride accumulation in hepatocytes — termed metabolic dysfunction-associated steatotic liver (MASL) — to MASH, which is characterized by lobular or portal inflammation and hepatocellular ballooning [97,98]. In advanced stages, persistent injury may culminate in fibrosis, cirrhosis, and ultimately HCC [97].

The early pathophysiology of MASLD is complex and multifactorial [95]. To account for this complexity, the “multiple-hit” hypothesis was proposed (Figure 5), postulating that disease progression results from the simultaneous action of several pathogenic stimuli. These include genetic susceptibility, dietary factors, obesity, insulin resistance, altered lipid metabolism, lipotoxicity, oxidative stress, mitochondrial and endoplasmic reticulum dysfunction, intestinal dysbiosis, and dysregulated cytokine and adipokine production [99]. Collectively, these factors promote activation of pro-inflammatory cascades and inflammasomes, particularly NLRP3, leading to hepatocellular injury, cell death, and fibrogenesis — hallmarks of MASH. Concomitantly, activation of hepatic stellate cells (HSCs) and immune cells enhances extracellular matrix (ECM) deposition, accelerating fibrosis progression [94,95,100].

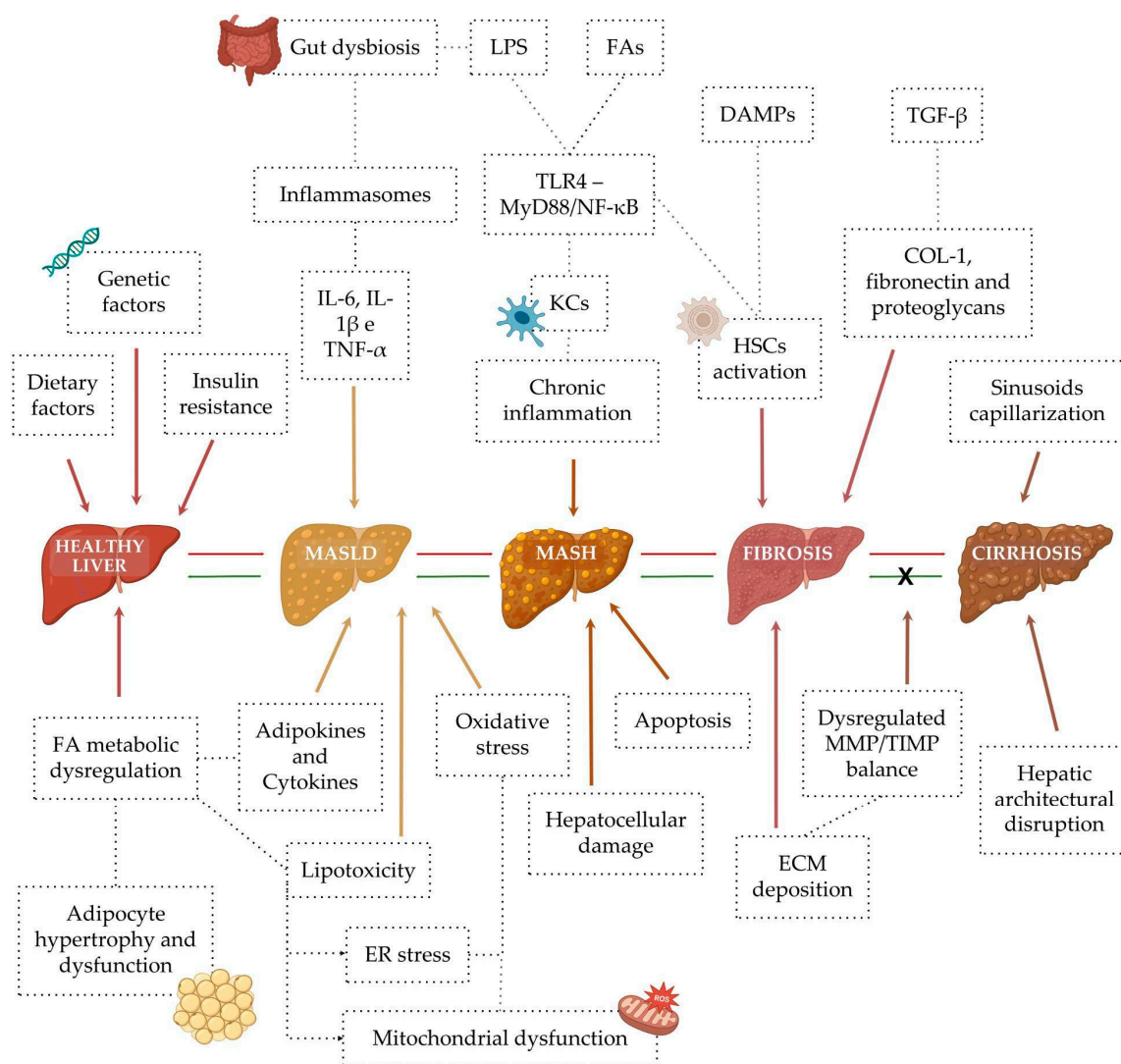


Figure 5. Main mechanisms involved in the development of MASLD/MASH and its complications.

Within this context, dysregulated fatty acid (FA) metabolism has been closely linked to cellular stress and lipotoxicity, triggering inflammation, immune cell recruitment, and hepatocyte death – key drivers of the transition from MASLD to MASH and more advanced liver disease stages [101]. Elevated levels of free FA and cholesterol exacerbate insulin resistance, promote adipocyte dysfunction, and alter gut microbiota composition, leading to increased intestinal permeability and enhanced translocation of lipopolysaccharides (LPS). These events further amplify hepatic inflammation via the gut–liver axis [102].

In the liver, excessive lipid influx and de novo lipogenesis induce oxidative stress, mitochondrial dysfunction, and inflammasome activation, culminating in hepatocyte injury and apoptosis [103]. Lipotoxicity activates pro-inflammatory signaling through Toll-like receptors (TLRs), resulting in increased production of cytokines such as TNF- α , IL-6, and IL-1 β . These mediators amplify inflammatory responses and drive the transdifferentiation of HSCs into myofibroblasts, thereby promoting fibrosis [101]. TLR4, abundantly expressed in Kupffer cells (KCs) and HSCs, is activated by bacterial LPS and FA, triggering the MyD88/NF- κ B pathway and sustaining chronic inflammation.

In parallel, oxidative stress arising from mitochondrial and endoplasmic reticulum dysfunction activates the NLRP3 inflammasome, further intensifying inflammatory and profibrotic signaling [94]. Persistent activation of the IKK/NF- κ B and JNK pathways in HSCs, along with TLR5-mediated NF- κ B and MAPK signaling, contributes to chronic inflammation, tissue remodeling, and fibrosis progression [101].

More recently, pyroptosis has been recognized as an additional driver of hepatic inflammation and fibrogenesis. Pyroptosis is a pro-inflammatory form of programmed cell death mediated by caspase activation and gasdermin D (GSDMD)-dependent pore formation in the plasma membrane, resulting in the release of inflammatory cytokines, lactate dehydrogenase (LDH), osmotic swelling, and cell lysis. This process occurs through canonical (caspase-1-dependent) and non-canonical (caspase-4/5/11-dependent) pathways and has been shown to promote macrophage activation and fibrosis progression [104–106].

Activation of these interconnected pathways compromises hepatic regenerative capacity and promotes excessive ECM deposition, ultimately leading to progressive fibrosis [98]. Regardless of etiology, liver fibrosis shares common molecular mechanisms, including hepatocyte death, chronic inflammation, HSC activation, and disruption of epithelial and endothelial barriers, all of which are closely associated with liver-related mortality [107].

Under physiological conditions, HSCs remain quiescent, storing vitamin A and producing type IV collagen. However, chronic liver injury induces a phenotypic switch characterized by increased proliferation, contractility, and synthesis of type I and III collagen, typical of cirrhotic tissue [103]. This transition is driven by sustained inflammation, whereby hepatocyte death releases damage-associated molecular patterns (DAMPs) and apoptotic bodies that further activate HSCs [94].

TGF- β signaling plays a pivotal role in hepatic fibrogenesis by activating the SMAD pathway and inducing the expression of genes encoding type I collagen, fibronectin, and proteoglycans – key components of the ECM [96]. Additional pathways, including platelet-derived growth factor (PDGF) and VEGF, contribute to HSC proliferation, migration, survival, and ECM production, while also enhancing TGF- β signaling [108]. NF- κ B activation by inflammatory stimuli and inflammasome signaling further reinforces the profibrotic response, perpetuating excessive ECM accumulation [94,95].

The hepatic ECM undergoes dynamic remodeling during fibrogenesis and plays a critical role in CLD progression [109]. Its proteome, comprising structural proteins, proteases, and protease inhibitors, evolves with disease severity, influencing cell–cell communication and inflammatory signaling [108]. Maintenance of ECM homeostasis depends on the balance between MMPs and their tissue inhibitors (TIMPs). Disruption of this balance - through increased TIMP activity or reduced MMP function - results in excessive collagen deposition, increased liver stiffness, and fibrosis progression [110].

As fibrosis advances, ECM deposition predominates due to elevated TIMP-1 expression, which also protects activated HSCs from apoptosis, thereby sustaining fibrogenesis. Activated macrophages and persistent MAPK and NF- κ B signaling further exacerbate ECM dysregulation, aggravating liver injury [108,110]. Ultimately, prolonged fibrotic remodeling leads to cirrhosis, an advanced and often irreversible stage of CLDs characterized by extensive ECM accumulation and regenerative nodule formation, resulting in architectural distortion and functional impairment of the liver [111,112].

Cirrhosis arises from continuous cycles of hepatocyte necrosis and regeneration, leading to sinusoidal capillarization, reduced functional parenchyma, altered hepatic blood flow, and portosystemic shunting. These changes underpin the development of portal hypertension and its complications, including ascites, hepatic encephalopathy, and pulmonary, renal, and cardiac dysfunction, as well as hyponatremia [113].

MASLD is also closely linked to alterations in gut microbiota composition and intestinal barrier integrity, positioning the gut–liver axis as a central component of disease pathophysiology. Metabolic and dietary factors promote intestinal dysbiosis, characterized by depletion of commensal bacteria and expansion of pro-inflammatory Gram-negative species. Inflammatory and hypoxic conditions disrupt tight junction integrity, increasing intestinal permeability and facilitating bacterial translocation and passage of microbial products such as LPS into the portal circulation. These molecules activate KCs via pattern recognition receptors, particularly TLRs, triggering inflammatory cascades mediated by cytokines and ROS [114].

NADPH oxidase 2 (NOX2), a major source of ROS in phagocytes, and the NLRP3 inflammasome are activated by signals derived from the dysbiotic microbiota and impaired epithelial barrier, modulating hepatic inflammation and fibrosis progression [115]. Clinically, cirrhosis presents as a heterogeneous condition with two major prognostic stages: a compensated phase, characterized by preserved liver function, and a decompensated phase marked by complications such as ascites, variceal bleeding, infections, and hepatic encephalopathy [116]. Disease progression may culminate in severe outcomes, including hepatorenal syndrome, acute-on-chronic liver failure (ACLF), and multiple organ failure [117].

4. Current Applications of Triterpenes for MASLD and MASH

Accumulating preclinical evidence supports pentacyclic triterpenes as promising multitarget modulators of metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH). Although these compounds differ in chemical structure and primary molecular targets, they consistently converge on key pathogenic processes, including dysregulated lipid metabolism, oxidative and endoplasmic reticulum stress, chronic inflammation, inflammasome activation, and hepatic fibrogenesis. The multitarget mechanisms by which pentacyclic triterpenes modulate MASLD/MASH pathophysiology are summarized in Figure 6.

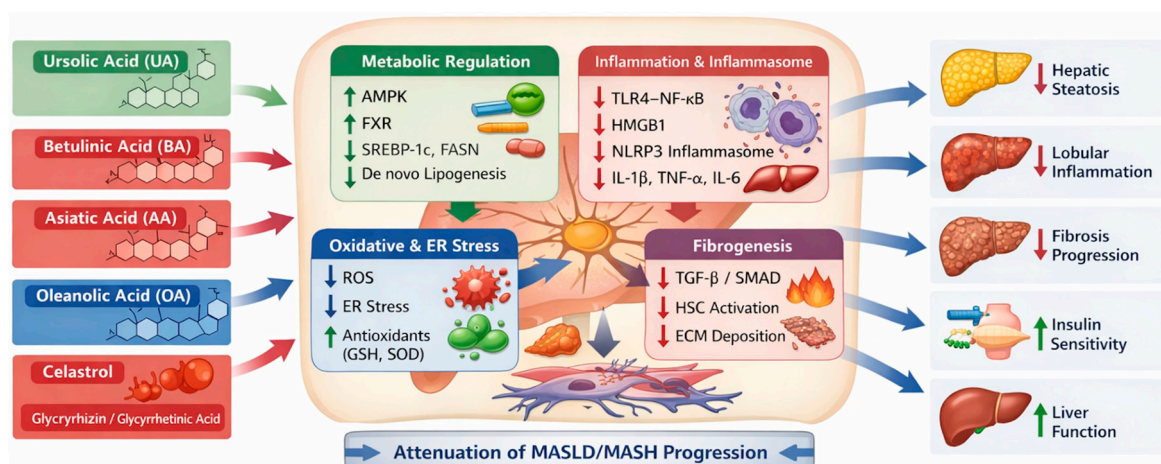


Figure 6. Multitarget mechanisms of pentacyclic triterpenes in MASLD and MASH.

Pentacyclic triterpenes, including UA, BA, AA, OA, celastrol, and glycyrrhizin/glycyrrhetic acid, modulate key pathogenic pathways involved in MASLD/MASH progression. These compounds converge on metabolic regulation (AMPK, FXR, lipogenesis), inflammatory signaling (TLR-NF-κB, NLRP3 inflammasome), oxidative and endoplasmic reticulum stress, and hepatic fibrogenesis (TGF-β/SMAD, HSC activation), resulting in reduced steatosis, inflammation, and fibrosis and improved hepatic function.

A comparative overview of the main triterpenes investigated to date, including their molecular mechanisms, experimental models, therapeutic outcomes, and key supporting references, is provided in Table 1. The following subsections focus on compound-specific mechanistic features and translational insights that extend beyond the comparative framework summarized in the table.

Table 1. Summary of pentacyclic triterpenes in MASLD/MASH models.

Compound	Triterpene class	Main molecular mechanisms	Experimental model	Main outcomes	Key references
Ursolic acid	Ursane	AMPK activation; inhibition of TGF-β/SMAD and NLRP3; antioxidant effects	HFD, MCD, CCl ₄ , TAA MASLD/MASH models	Reduced steatosis, inflammation, fibrosis; improved liver enzymes	[20,119,120]

Betulinic acid	Lupane	AMPK and FXR activation; inhibition of SREBP-1c, YY1/FAS; antifibrotic	HFD- and MCD-fed mice; TAA/CCl ₄ fibrosis	Attenuation of steatosis, insulin resistance, fibrosis	[126,129,131]
Asiatic acid	Ursane	NF-κB and PI3K/AKT/mTOR inhibition; ER stress reduction	HFD-fed mice; CCl ₄ -induced MASH	Reduced lipid accumulation, inflammation, oxidative stress	[133–135]
Oleanolic acid	Oleanane	PPARα activation; NF-κB inhibition; lipogenesis suppression	High-fructose and HFD steatosis models	Improved insulin sensitivity; reduced hepatic lipid content	[142,143,149]
Celastrol	Quinone methide triterpenoid	AMPK activation; SREBP-1c/FASN suppression; NLRP3 and HMGB1/NF-κB inhibition	Diet-induced MASH mouse models	Reduced steatosis, inflammation and fibrosis	[152,155,157]
Glycyrrhizin / Glycyrrhetic acid	Oleanane-type saponin/metabolite	NF-κB, MAPK and NLRP3 inhibition; bile acid homeostasis modulation	MCD-induced MASH; chronic hepatitis clinical use	Attenuation of inflammation and fibrosis; hepatoprotection	[164,169,171, 172]

4.1. Ursolic Acid (UA)

Beyond its well-established hepatoprotective effects summarized in Table 1, UA exhibits a distinctive capacity to simultaneously modulate metabolic reprogramming and fibrogenic signaling.

UA has long been recognized for its hepatoprotective and antifibrotic properties, with early evidence of its therapeutic potential in acute liver injury models dating back to the 1980s [118]. In a seminal study, Martín-Aragón et al. (2001) demonstrated that pretreatment with UA in a rat model of CCl₄-induced acute liver injury significantly reduced lipid peroxidation and serum transaminase levels, while enhancing hepatic antioxidant defenses, including superoxide dismutase, catalase, GSH reductase, GSH peroxidase, and total GSH content [119].

Subsequent studies extended these findings to chronic injury and metabolic contexts. Saravanan et al. (2006) reported that UA administration attenuated ethanol-induced liver injury in rats, reducing serum AST, ALT, and bilirubin levels, lowering lipid peroxidation markers, and restoring circulating antioxidants, with efficacy comparable to silymarin [120]. In diet-induced steatosis models, oral UA administration mitigated hepatic inflammation and fibrosis, in part by increasing decorin expression, a key regulator of extracellular matrix homeostasis, thereby promoting matrix repair and remodeling [121]. Consistently, UA was shown to reduce hepatic lipid accumulation, adipocyte hypertrophy, and circulating lipid levels through activation of AMPK signaling, highlighting its metabolic regulatory capacity [59].

The prophylactic potential of UA against MASLD has also been explored in the context of excessive fructose intake. Using a developmental “multiple-hit” model, Mukonowenzou et al. (2021) demonstrated that early-life UA supplementation significantly attenuated fructose-induced hepatic lipid accumulation and long-term metabolic dysfunction, suggesting a role for UA in metabolic programming and disease prevention [122].

Strong antifibrotic effects of UA have been consistently demonstrated in chemically induced fibrosis models. In thioacetamide (TAA)-induced liver fibrosis, UA treatment reduced fibrotic area, hepatic hydroxyproline content, and expression of α-SMA, Col1a2, and TIMP1, while inducing apoptosis of activated hepatic stellate cells, as evidenced by reduced TUNEL and α-SMA staining [123]. These findings were corroborated by Li et al. (2023), who showed that UA attenuated TAA-induced fibrosis by inhibiting TGF-β₁ signaling, resulting in reduced HSC activation and collagen deposition [20].

Similarly, in CCl₄-induced fibrosis models, UA administration consistently reduced fibrosis scores, collagen accumulation, and serum transaminases, while modulating gut microbiota composition toward a profile resembling that of healthy controls, particularly increasing Firmicutes and Bacteroidetes populations [124]. Comparable antifibrotic effects were observed in a methionine-

and choline-deficient (MCD) diet model [115]. Additional studies demonstrated that UA suppresses fibrogenesis by restoring the balance between MMP and their inhibitors, reducing pyroptosis, inhibiting caspase-1 and gasdermin D activation, and attenuating inflammatory cytokine release [104].

In experimental MASH models, UA exhibited both preventive and therapeutic efficacy, reducing oxidative stress, inflammation, fibrosis, and hepatic dysfunction. These effects were accompanied by downregulation of NADPH oxidase (NOX) isoforms and suppression of NLRP3 inflammasome activation, reinforcing the role of UA in targeting key oxidative and inflammatory pathways involved in disease progression [125]. Collectively, these findings support UA as a potent modulator of oxidative stress, inflammation, and fibrogenesis, with significant therapeutic potential for MASLD and MASH.

4.2. Betulinic Acid (BA)

While the comparative metabolic and antifibrotic outcomes of betulinic acid (BA) are outlined in Table 1, mechanistic studies highlight BA as a potent regulator of lipid synthesis and bile acid signaling.

The first evidence supporting the therapeutic potential of BA in hepatic steatosis was provided in the beginning of the 2010s. Quan et al. (2013) demonstrated that BA reduced lipid accumulation in HepG2 cells by inhibiting SREBP1 maturation and nuclear translocation, leading to downregulation of lipogenic genes and upregulation of lipid oxidation-related pathways. These effects were mediated by activation of the CAMKK-AMPK axis and subsequent suppression of the mTOR/S6K pathway and were both dose- and time-dependent [126]. These molecular mechanisms were later confirmed in vivo in high-fat diet (HFD)-fed mice, validating the relevance of AMPK signaling in BA-mediated metabolic regulation.

In another study, Zhao et al. (2021) demonstrated that BA treatment of TGF- β 1-induced HSCs reduced cell activation, as evidenced by decreased Col1a1 and α -SMA expression, and impaired cell proliferation and migration, as shown by reduced wound closure in a scratch assay. These effects were associated with suppression of Lck expression and activity, a Src-family tyrosine kinase that promotes hepatic stellate cell activation and profibrotic JAK/STAT signaling, along with increased expression of SOCS1, a key negative regulator of cytokine signaling that limits JAK/STAT-driven inflammation and fibrogenesis [127].

Kim et al. (2019) showed that BA administration attenuated HFD-induced obesity, improved insulin sensitivity, and enhanced energy expenditure in mice. These systemic metabolic benefits were associated with AMPK activation across multiple metabolic tissues, including liver, adipose tissue, and skeletal muscle, resulting in suppression of lipogenic pathways and improved energy balance [128].

The relevance of BA in MASLD has been further substantiated by Gu et al. (2019), who demonstrated that BA significantly attenuated hepatic steatosis in murine models induced by either a HFD or an MCD diet. These effects were mechanistically linked to activation of the farnesoid X receptor (FXR) and subsequent suppression of endoplasmic reticulum stress pathways, including protein kinase RNA-like ER kinase (PERK)/eukaryotic initiation factor (eIF)2 α /activating transcription factor (ATF)4/ C/EBP homologous Protein (CHOP) signaling. Importantly, the protective effects of BA were largely abolished in FXR-deficient mice, underscoring the central role of FXR in mediating BA activity [129].

BA has also shown robust antifibrotic activity in experimental models of liver fibrosis. In TAA-induced fibrosis models, BA treatment markedly improved liver histology and function, reducing collagen deposition and suppressing profibrotic mediators such as TGF- β 1, Col1 α 1, and α -SMA, while restoring antioxidant enzyme activity, thereby highlighting its hepatoprotective and antifibrotic profile [130]. These results were corroborated in an experimental model of CCl₄-induced fibrosis in mice, in which BA treatment reduced ALT and AST levels and fibrotic index, associated with decrease in α -SMA and Col1 α 1 levels [127]. Mu et al. (2020) also demonstrated that BA markedly

protected against hepatic steatosis, inflammation, and fibrosis in both HFD- and MCD-induced MASLD/MASH models. The hepatoprotective effects were attributed to inhibition of de novo lipogenesis via suppression of the YY1/FAS signaling axis, thereby limiting triglyceride synthesis and lipid accumulation in hepatocytes [131].

More recently, Zhang et al. (2022) performed the rational design of BA derivatives as intestine-selective antagonists of the FXR for the treatment of MASH. Through structure–activity relationship optimization, a new compound was identified as a potent FXR antagonist with preferential intestinal accumulation and minimal systemic exposure. This compound selectively inhibits intestinal FXR signaling, leading to compensatory activation of hepatic FXR, increased bile acid synthesis, reduced hepatic cholesterol levels, and suppression of NLRP3 inflammasome activation. In two mice models of diet-induced MASH (Gubra Amylin NASH - GAN diet, or high fat methionine choline deficient - HFMCD diet), this compound reduced hepatic steatosis, inflammation, fibrosis, and improved glucose homeostasis, and insulin sensitivity, outperforming the FXR antagonist glyoursodeoxycholic acid (GUDCA). Collectively, these findings establish intestinal FXR antagonism as a viable therapeutic strategy for MASH and highlight BA-derivatives as promising gut-restricted FXR modulators [132].

Taken together, these studies consistently demonstrate that BA exerts hepatoprotective, antifibrotic, and metabolic regulatory effects through modulation of AMPK, FXR, lipid metabolism, oxidative stress, and inflammatory signaling pathways, supporting its potential as a therapeutic candidate for MASLD and MASH.

4.3. Asiatic Acid (AA)

In contrast to other pentacyclic triterpenes, AA displays moderate but consistent efficacy in experimental MASH models, with mechanistic actions primarily linked to oxidative stress and ER stress modulation.

Similarly to BA, the potential use of AA to attenuate MASH development has been reported since the early 2010s. Yan et al. demonstrated that AA treatment (10 or 20 mg/kg/day, oral gavage, for 10 weeks) in HFD-fed mice reduced body weight, water and feed intake, epididymal fat, and plasma and hepatic triglyceride levels, which was associated with downregulation of key lipogenic enzymes (coenzyme A carboxylase - ACC1, FAS, and stearoyl CoA desaturase - SCD-1) and the transcription factor SREBP-1c. In parallel, AA attenuated hepatic steatosis, inflammation, and oxidative stress by suppressing pro-inflammatory cytokine production (IL-1 β , IL-6, TNF- α) and NF- κ B signaling while increasing catalase and GSH-peroxidase activities and GSH level, and improving insulin sensitivity [133]. Concordant findings were reported by Wang et al., in which HFD-fed mice were treated with AA (4 or 8 mg/Kg/day, oral gavage for 10 weeks). Besides attenuation of hepatic steatosis and liver injury, the authors demonstrated reduction on myeloperoxidase (MPO) and MDA levels, while increasing SOD, GSH-peroxidase and GSH-reductase activities. It was also demonstrated that the treatment with AA lead to the reduction of glucose-regulated protein 78 (GRP78), PERK, eIF2 α and CHOP expression in liver tissue, all of these proteins are correlated to the endoplasmic reticulum stress [134].

In a rat model of CCl₄-induced MASH, Wei et al. (2018) demonstrated that AA treatment (5 or 15 mg/kg/day, oral gavage, for six weeks) resulted in modest but consistent hepatoprotective effects, including reductions in serum AST, ALT, and total bilirubin levels, as well as decreases in fibrosis index and circulating fibrosis markers - hyaluronic acid (HA), laminin (LN), collagen type IV (IV-C), and procollagen III N-terminal peptide (PIIINP) - and downregulation of Col1a1 and Col1a3 mRNA expression. In line with findings from HFD-fed mouse models, AA treatment dose-dependently reduced hepatic malondialdehyde (MDA) levels and pro-inflammatory mediators, including TGF- β , COX-2, TNF- α , IL-6, and IL-1 β , while enhancing antioxidant defenses through increased SOD and GSH-peroxidase activities. AA also attenuated CCl₄-induced hepatocyte apoptosis, as evidenced by reduced caspase-3 levels, and inhibited hepatic stellate cell activation, reflected by decreased α -SMA

expression and lower levels of TIMP-1 and TIMP-2. Mechanistically, these protective effects were associated with inhibition of the PI3K/AKT/mTOR signaling pathway [135].

Although studies with AA consistently demonstrate beneficial effects in experimental MASH, the magnitude of improvement does not appear to have been sufficient to justify more in-depth investigations of this compound for the treatment of MASLD and MASH. One plausible explanation is the poor aqueous solubility of AA, reported to be approximately 0.1 mg/mL [136], which may limit its oral bioavailability and, consequently, its therapeutic efficacy. While several studies have explored structural modifications of asiatic acid to enhance its water solubility [137–140], to the best of our knowledge, no investigations have yet evaluated these derivatives in the context of MASLD or MASH, but these are potential molecules to this use.

4.4. Oleanolic Acid (OA)

OA is an oleanane-type pentacyclic triterpene widely investigated for its effects on lipid metabolism, insulin sensitivity, oxidative stress, and inflammatory responses, particularly in experimental models of metabolic-associated steatotic liver disease, obesity, and liver injury.

In vitro evidence demonstrates that OA directly modulates hepatocellular lipid accumulation under metabolic stress conditions. OA significantly reduced intracellular triglyceride and total cholesterol levels and attenuated lipid droplet formation in hepatocytes exposed to free fatty acids, indicating a cell-autonomous anti-steatotic effect [141]. Lin et al. (2018) further showed that, in hepatic and intestinal cell models treated with OA for 24 h or up to 14 days, OA suppressed ligand-induced lipogenesis by inhibiting LXR α - and PXR-mediated transcriptional activity. Specifically, OA reduced the expression of lipogenic markers including SREBP-1c, FAS, SCD-1, ATP-citrate lyase (ACLY), ACC1, and Fatty acid elongase (FAE) in hepatic cells, while preserving or enhancing ATP-binding cassette transporter (ABC)A1 and ABCG1 expression in intestinal cells. These effects were accompanied by increased AMPK phosphorylation in hepatic cells and differential recruitment of nuclear receptor coregulators, characterized by decreased SRC-1 and increased small heterodimer partner-interacting leucine zipper protein (SMILE) binding to the SREBP-1c promoter, as assessed by reporter assays, qRT-PCR, Western blotting, and DNA affinity precipitation analyses [142].

Consistent with these cellular findings, Liu et al. (2013) reported that oral administration of OA (25 mg/kg/day, oral gavage, once daily for 10 weeks) markedly attenuated liquid fructose-induced hepatic triglyceride accumulation in rats. This was accompanied by reductions in hepatocyte ballooning, hepatic collagen deposition, and serum insulin levels, and was mechanistically associated with downregulation of hepatic SREBP-1/1c mRNA and nuclear protein levels, as well as decreased expression of FAS, SCD1, and ACC1. In contrast, Carbohydrate response element-binding protein (ChREBP) expression and PPAR α and PPAR γ signaling were not altered, indicating selective suppression of de novo lipogenesis [143].

Djeziri et al. (2018) further demonstrated that OA administration (15–60 mg/kg/day, oral gavage, once daily for four weeks) significantly attenuated hepatic steatosis in HFD-fed rodents, reducing liver weight and hepatic lipid content and improving histopathological features. These effects were associated with improvements in serum lipid parameters, including reductions in total cholesterol, triglycerides, and LDL, and activation of hepatic AMPK signaling [144].

Nyakudya et al. (2018) provided evidence that early-life exposure to OA exerts long-term metabolic effects. In this developmental programming model, neonatal oral administration of OA (60 mg/kg/day, once daily for 7 days) significantly attenuated the later development of high-fructose diet-induced MASLD in adult rats. Early OA treatment prevented hepatic lipid accumulation, steatosis, low-grade inflammation, fibrosis, increased MASLD activity scores, visceral and epididymal adiposity, impaired glucose metabolism, and excessive body weight gain, demonstrating sustained metabolic modulation originating from neonatal exposure [145].

Wang et al. (2013) reported that OA improves hepatic insulin resistance in leptin receptor-deficient Lep^{db/db} mice. In this model, OA administration (20 mg/kg/day, intraperitoneal injection, once daily for two weeks) restored body, liver, and fat weights and normalized liver morphology

and function. OA lowered fasting blood glucose, improved glucose and insulin tolerance, enhanced hepatic insulin signaling, and suppressed gluconeogenesis. These effects were accompanied by reductions in serum triglycerides, total cholesterol, LDL, free fatty acids, and pro-inflammatory cytokines (IL-1 β , IL-6, and TNF- α), increased HDL levels, attenuation of hepatic lipid accumulation, and decreased mitochondrial ROS production in the liver [146].

Gamede et al. (2019) similarly demonstrated that OA administration in a diet-induced pre-diabetes rat model (80 mg/kg, oral administration, every third day for 12 weeks following 20 weeks of high-fat high-carbohydrate feeding) significantly reduced the liver-to-body weight ratio, plasma triglycerides, and VLDL cholesterol. OA treatment lowered plasma SREBP levels, intrahepatic triglyceride content, ALT and AST activities, and malondialdehyde levels, while increasing superoxide dismutase and glutathione peroxidase activities. Histological analyses confirmed attenuation of hepatic lipid accumulation and structural abnormalities [147].

Yao et al. (2023) investigated OA in fructose-induced models of hepatic steatosis. OA administration in rats (25 mg/kg/day, oral gavage, once daily for 5 weeks) and in mice (75 mg/kg/day, once daily for 7–11 days) significantly reduced hepatic triglyceride accumulation and lipid droplet deposition across multiple genotypes, including SREBP1c^{+/+}, SREBP1c^{-/-}, SCD1^{+/+}, and SCD1^{-/-} mice. OA consistently suppressed SCD1 mRNA and protein expression, while SREBP1c and ChREBP expression remained unchanged under fasting conditions. In fructose plus oleic acid-supplemented models, OA additionally reduced SREBP1c, FAS, and ACC1 expression and altered hepatic fatty acid composition, decreasing oleic acid levels and the C18:1/C18:0 ratio. OA also increased AMPK phosphorylation and CPT1 α expression in SCD1^{-/-} mice, indicating modulation of fatty acid oxidation pathways under specific metabolic contexts [148].

Xue et al. (2021) demonstrated that OA targets the gut–liver axis in high-fat diet-induced obesity and NAFLD. OA administration (25–100 mg/kg/day, oral gavage, once daily for 8 weeks following 12 weeks of HFD feeding) reduced hepatic lipid accumulation, improved serum lipid profiles, and decreased ALT and AST levels. OA suppressed hepatic expression of LXR α , SREBP-1c, FAS, and ACC α , while increasing PPAR α , CPT1, and AMPK phosphorylation. Additionally, OA reduced hepatic and systemic levels of TNF- α , IL-1 β , and IL-6 and inhibited TLR4/NF- κ B signaling. In the intestine, OA enhanced barrier integrity by increasing occludin, claudin-1, and ZO-1 expression, reduced circulating LPS levels, and modulated gut microbiota composition, including reductions in the Firmicutes/Bacteroidetes ratio [149].

Pi et al. (2024) reported that OA alleviates ischemia–reperfusion injury in a rat model of severe steatotic liver IRL. OA was administered orally by gavage at 21 mg/kg/day for 7 consecutive days prior to surgery, followed by 80 min of ischemia and 24 h of reperfusion. OA reduced Suzuki histological scores, serum ALT and AST levels, and circulating IL-6, TNF- α , and IL-1 β . OA also decreased hepatic Fe²⁺, MDA, 4-hydroxynonenal, and TLR4 levels, while increasing glutathione content and GPX4 expression. These effects were associated with activation of the KEAP1/NRF2/ARE signaling pathway, including increased nuclear NRF2 and elevated NQO1 and GCLC expression [150].

In a very recent study published in 2026, Pi et al. demonstrated that OA attenuates intestinal injury secondary to hepatic ischemia–reperfusion under steatotic conditions. Male Sprague–Dawley rats fed a high-fat diet for 20 weeks received OA (21 mg/kg/day, oral gavage, once daily for 7 days) prior to ischemia–reperfusion. OA reduced liver and intestinal injury scores, serum ALT and AST levels, and circulating IL-6, TNF- α , and IL-1 β . OA preserved intestinal barrier integrity by increasing ZO-1 and occludin expression and reducing D-lactate, diamine oxidase, and LPS levels. Mechanistically, OA activated PPARG signaling and promoted macrophage polarization toward an M2 phenotype, evidenced by increased CD206 and ARG1 and reduced iNOS and CD86 expression. Pharmacological inhibition of PPARG with GW9662 reversed these effects, confirming PPARG-dependent signaling in this recently described model [151].

Collectively, these findings demonstrate the substantial potential of oleanolic acid for the prevention, control, and attenuation of disease progression in MASLD and MASH.

4.5. Celastrol

Early in vitro studies demonstrate that celastrol directly modulates hepatocellular pathways involved in lipid accumulation, bile acid metabolism, inflammation, and insulin resistance, corresponding to initial stages of MASLD development.

Hu et al. (2025) employed HepG2 hepatocytes to validate targets identified by multiomic and network pharmacology analyses, showing that celastrol-induced regulation of bile acid metabolism was dependent on CYP7B1, as siRNA-mediated knockdown of CYP7B1 abolished these effects. Celastrol increased CYP7B1 expression and modulated FXR and LXR signaling, indicating activation of the alternative bile acid synthetic pathway; markers analyzed included CYP7B1, CYP27A1, FXR, LXR, and bile acid-related metabolic signatures assessed by RT-qPCR and Western blotting [152]. Complementarily, Li et al. (2025) demonstrated that celastrol reduced lipid accumulation in palmitic-acid-treated AML-12 cells and primary murine hepatocytes while downregulating Notch2 and osteopontin (OPN) expression, thereby suppressing hepatocyte-driven activation of hepatic stellate cells in co-culture systems [153]. In oleic-acid-induced steatosis models, celastrol reduced lipid droplet accumulation and triglyceride content in HepG2 cells, with effects reversed by the PPAR γ agonist rosiglitazone, implicating PPAR γ -dependent signaling [154]. Additional HepG2 experiments showed that celastrol (0.1–0.4 $\mu\text{g/mL}$, 24 h) decreased intracellular triglycerides and cholesterol while increasing FGF21, phosphorylated AMPK, PGC-1 α , PPAR γ , and SIRT3, linking celastrol to mitochondrial and energy-sensing pathways relevant to steatosis control [155].

Inflammatory signaling and insulin resistance - key drivers of MASLD progression - were also addressed in vitro. Han et al. (2018) established a steatotic HepG2 model using free fatty acids (palmitate:oleate) and demonstrated that celastrol reduced triglyceride accumulation and suppressed TLR4/MyD88/NF- κB signaling, with decreased IL-1 β and TNF- α protein levels; TLR4 siRNA further potentiated these effects [156]. Zhang et al. (2018) modeled lipid-induced insulin resistance by treating HepG2 cells with palmitic acid and adding celastrol, restoring insulin-stimulated glucose uptake and implicating the TLR4/MD2 axis in the regulation of insulin signaling [157]. Although performed in renal cells, Kim et al. (2013) further demonstrated that celastrol suppressed fatty acid- and high-glucose-induced inflammatory responses via inhibition of TLR4/MyD88/NF- κB pathways that are central to inflammation-driven insulin resistance in MASLD [158]. Additionally, Ma et al. (2015) showed that celastrol activated HSF1, leading to increased PGC-1 α transcription and enhanced mitochondrial and oxidative metabolism gene expression, establishing a mechanistic link to lipid oxidation and systemic insulin sensitivity [159].

Consistent with these cellular findings, extensive in vivo evidence demonstrates that celastrol attenuates disease progression from hepatic steatosis to steatohepatitis and fibrosis. Hu et al. (2025) induced MASH in mice using Western diet or HFD feeding and administered celastrol (100–300 $\mu\text{g/kg/day}$, i.p. for 4 weeks or 0.75–1.5 mg/kg/day , oral gavage for 28 days), resulting in reduced hepatic steatosis, liver fibrosis index, serum ALT, AST, triglycerides, cholesterol, and total bile acids, alongside correction of the 12 α -hydroxylated/non-12-hydroxylated bile acid ratio; these effects were associated with restoration of CYP7B1 expression and modulation of FXR/LXR signaling [152]. Canová et al. (2025) further showed that celastrol (200 $\mu\text{g/kg}$ i.p., every second day for 4 weeks) administered during either early or late stages of WD/fructose-induced disease attenuated MASLD-to-MASH progression, reducing hepatic triglycerides, lipid peroxidation, liver weight, and improving glucose tolerance, with regulation of SREBP-dependent lipogenic markers and hepatic GalR2 expression [160]. Benmouna et al. (2025) reported that celastrol (100 $\mu\text{g/kg/day}$ i.p. for 4 weeks) reduced hepatic SREBP-1c, FAS, and ACC1 expression and lowered liver triglyceride and cholesterol content, alongside decreased IL-6 and TNF- α , supporting its role in early MASLD [161].

Progression to steatohepatitis and fibrosis was addressed in more severe models. Li et al. (2025) demonstrated that in a Western diet plus low-dose CCl $_4$ -induced NASH model, celastrol (100 or 250 $\mu\text{g/kg/day}$ i.p. for 2 weeks) reduced hepatic triglycerides, collagen deposition, α -SMA expression, and Sirius Red-positive fibrosis through suppression of Notch2/OPN signaling, with hepatocyte-specific Notch2 overexpression abolishing these effects [153]. Xue et al. (2024) showed that celastrol

(1–5 mg/kg/day by gavage for 12 weeks) attenuated HFD-induced MASLD, reducing hepatic steatosis, ALT, AST, triglycerides, and inflammatory cytokines while improving mitochondrial ultrastructure, ATP content, and antioxidant status via activation of the FGF21/AMPK/PGC-1 α pathway [155]. In a combined T2DM–MASLD model, Sun et al. (2020) demonstrated that celastrol (10–100 mg/kg/day orally for 6 weeks) reduced hepatic lipid accumulation, oxidative stress (reduced MDA and increased SOD), hepatocyte apoptosis, and improved liver histology through activation of the Nrf2/HO-1 pathway [162]. Finally, systemic insulin resistance and its hepatic consequences were corroborated in vivo by Zhang et al. (2018), who showed that celastrol reduced hepatic steatosis, suppressed SREBP-1c, activated AMPK/LKB1, and inhibited NF- κ B signaling in HFD-fed mice [157,163], and by Kim et al. (2013), who demonstrated that celastrol (1 mg/kg/day i.p. for 2 months) improved HOMA-IR, fasting glucose, HbA1c, and reduced hepatic lipid accumulation and inflammatory cytokine expression in db/db mice [158].

Collectively, these in vitro and in vivo findings demonstrate that celastrol consistently targets key pathogenic mechanisms across the MASLD–MASH spectrum - attenuating hepatocellular lipid accumulation, bile acid dysregulation, inflammatory and insulin-resistance signaling, mitochondrial dysfunction, and fibrogenic activation - thereby limiting disease initiation and progression under diverse metabolic stress conditions.

4.6. Glycyrrhizin and Glycyrrhetic Acid

Glycyrrhizin and its active metabolite glycyrrhetic acid have been investigated in experimental settings relevant to MASLD and MASH, with early evidence indicating direct effects on hepatic lipid handling and bile acid–related pathways.

Initial in vitro observations by Yamamoto et al. (1970) demonstrated that direct exposure of rat liver slices to glycyrrhizin increased the incorporation of acetate and mevalonate into cholesterol, suggesting stimulation of hepatic cholesterol synthesis. In parallel in vivo experiments, intramuscular pretreatment with glycyrrhizin (10–100 mg/kg/day for 5 days) accelerated biliary and fecal excretion of cholesterol and bile acids and reduced plasma cholesterol and triglyceride levels in cholesterol-fed rats, indicating a coordinated effect on hepatic cholesterol turnover and bile acid elimination rather than lipid accumulation per se [164]. Complementarily, Negishi et al. (1991) identified a specific, high-affinity binding site for glycyrrhetic acid in rat liver membrane fractions, supporting a direct liver-targeted mechanism of action for glycyrrhizin, although this study did not evaluate steatosis, inflammation, or fibrotic endpoints [165].

Subsequent in vivo studies addressed early metabolic alterations that precede MASLD development, focusing on systemic and hepatic lipid homeostasis. Lim et al. (2009) reported that short-term oral administration of glycyrrhizin (50 mg/kg/day, oral gavage, for 7 days) increased lipoprotein lipase (LPL) expression in multiple tissues, including the liver, and improved circulating lipid profiles, as evidenced by reductions in serum triglycerides, total cholesterol, and LDL, alongside increased HDL levels. These changes were accompanied by reduced lipid deposition in peripheral tissues assessed by Oil Red O staining, although hepatic lipid reduction did not reach statistical significance within the short treatment window [166]. These findings were corroborated by studies of Eu et al. (2010) that demonstrated that longer glycyrrhizin treatment (100 mg/kg/day, oral gavage, for 28 days) in HFD–induced obese rats significantly improved insulin sensitivity, reflected by reduced fasting glucose and HOMA-IR, while also lowering serum triglycerides, total cholesterol, LDL, and free fatty acids. These metabolic improvements were accompanied by reduced lipid deposition in several tissues, including the liver, and tissue-specific regulation of LPL expression, interpreted in the context of altered PPAR-associated lipid metabolism [167].

Additional in vivo evidence under combined dietary and stress-related metabolic challenge was provided by Yaw et al. (2015). In this study, glycyrrhizin (100 mg/kg/day, oral gavage for 14 or 28 days) administered to rats fed a high-calorie diet and exposed to short- or long-term stress selectively modulated the expression of lipid metabolism–related genes, including PPAR α , PPAR γ , and LPL, as well as fatty acid elongases and desaturases (ELOVL5 and ELOVL6), in hepatic and extrahepatic

tissues. While stress exposure markedly influenced lipid metabolic pathways, glycyrrhizin did not significantly alter hepatic elongase or desaturase expression, suggesting that its hepatic effects under these conditions were primarily related to lipid uptake and handling rather than de novo fatty acid synthesis or modification. These molecular findings were supported by analyses of serum lipid profiles and tissue fatty acid composition [168].

Shi et al. (2020) employed *in vitro* and *in vivo* approaches centered on retinoid metabolism. In HepG2 cells, glycyrrhizin directly inhibited the activity of aldo-keto reductase family 1 member B10 (AKR1B10), a key enzyme involved in vitamin A metabolism, as demonstrated by enzymatic kinetics, molecular docking, and loss-of-function experiments using AKR1B10-knockout hepatocytes. glycyrrhizin treatment restored intracellular retinoic acid levels, whereas glycyrrhetic acid exerted comparable effects only after conversion to glycyrrhizinic acid. Markers analyzed included AKR1B10 expression and activity, retinol and retinoic acid species, and retinoid-related metabolic genes assessed by RNA sequencing, RT-qPCR, and HPLC. *In vivo*, oral administration of GL (15, 30, or 60 mg/kg/day, once daily for 4 weeks) significantly reduced hepatic lipid accumulation and inflammatory lesions in both HFD-induced MASLD and MCD diet-induced MASH models. These effects were accompanied by normalization of hepatic retinoid metabolism, reduced serum ALT and AST activities, and decreased hepatic triglyceride and cholesterol levels, without evidence of classical PPAR α or PPAR γ agonist activation [169].

Finally, recent studies have linked glycyrrhizin to regulation of inflammatory steatosis through modulation of the hepatic ACE2 axis. Zhou et al. (2025) demonstrated *in vitro* that glycyrrhizin attenuated lipid accumulation and inflammatory injury in HepG2 hepatocytes exposed to free fatty acids (palmitic acid/oleic acid) combined with LPS. Glycyrrhizin reduced intracellular triglyceride content, lipid droplet accumulation, and ALT and AST release into the culture medium. Molecular analyses showed restoration of ACE2 and Mas receptor expression, suppression of Ang II and SREBP-1c overexpression, increased phosphorylation of AMPK α , and reduced total and phosphorylated MDM2 levels. Silencing of ACE2 abolished glycyrrhizin-induced reductions in lipid accumulation and enzyme release, indicating ACE2-dependent signaling [171]. Consistently, *in vivo* experiments by Zhou et al. (2024) showed that oral glycyrrhizin administration (5 or 30 mg/kg/day, once daily for 3 days) significantly attenuated hepatic injury in an LPS/D-galactosamine-induced steatohepatitis mouse model. glycyrrhizin reduced serum ALT and AST activities, hepatic triglyceride accumulation, and histopathological liver damage, while restoring hepatic ACE2/Ang-(1-7)/Mas signaling and modulating AMPK and MDM2 expression in liver tissue [172].

These studies indicate that glycyrrhizin and glycyrrhetic acid exert consistent hepatoprotective effects across early and intermediate stages of MASLD and MASH. The available evidence supports a mechanistic framework in which these compounds modulate hepatic lipid and bile acid metabolism, improve insulin sensitivity, and suppress metabolic inflammation through defined molecular pathways, including regulation of LPL and PPAR-associated lipid handling, AKR1B10-mediated retinoid metabolism, and ACE2/Ang-(1-7)/Mas signaling coupled to AMPK activation and MDM2 inhibition.

Taken together, the sections above highlight that pentacyclic triterpenes can reproducibly attenuate key pathogenic steps along the MASLD-MASH development - ranging from early hepatocellular lipid accumulation and insulin resistance to inflammatory amplification, oxidative/ER stress, and fibrogenic activation - through pleiotropic but convergent mechanisms across multiple experimental models. Nevertheless, despite the breadth of preclinical efficacy and the mechanistic depth now available for several scaffolds, translation remains challenged by compound-dependent pharmaceutical limitations that can substantially constrain systemic exposure and, ultimately, therapeutic effect. Accordingly, the next section summarizes contemporary strategies being pursued to overcome the main barriers that currently limit clinical development - particularly poor aqueous solubility, low and variable oral bioavailability, and inconsistencies in *in vivo* potency across models and dosing regimens.

5. Strategies for Enhancing Triterpenes Bioavailability and Efficacy

Across pentacyclic triterpenes, one major route to improve drug-like exposure has been chemical derivatization, typically aimed at increasing polarity, tuning ionization, and/or strengthening target engagement so that efficacious dosing becomes feasible despite intrinsically low aqueous solubility. For OA, examples include simple scaffold modification such as 3-acetylation (3-acetyl-oleanolic acid) and target-oriented derivatives (e.g., HA-20) designed to enhance functional activity and thereby support practical administration *in vivo*, as well as more systematic structure-optimization programs that introduce amino acid-type conjugation (e.g., 12 β -O- γ -glutamyl OA derivatives) to obtain FXR antagonist/modulator profiles for MASH-oriented applications. In parallel, broader surveys of OA derivatives emphasize the strategy of tailoring the OA scaffold to modulate metabolic nuclear receptors, reflecting a medicinal-chemistry approach in which optimized potency and physicochemical properties can jointly improve the likelihood of sufficient exposure at tolerable doses [173–176].

A second, widely used strategy focuses on formulation-driven solubility and dissolution enhancement, which can markedly improve oral performance for triterpenes that are otherwise poorly absorbed. Multiple studies illustrate “drug-carrier” approaches that keep the parent triterpene unchanged while improving its apparent solubility and release: solid dispersions (e.g., UA in Gelucire 50/13) and self-micelle solid-dispersion systems (e.g., based on inositol hexanicotinate) are used to increase drug dispersion at the intestinal interface and facilitate uptake; cyclodextrin complexation (e.g., hydroxypropyl- γ -cyclodextrin complexes with OA/UA) provides host-guest inclusion to improve aqueous compatibility; and more recently, OA has been incorporated into cyclodextrin metal-organic frameworks (MOFs) via co-crystallization, representing an emerging encapsulation platform intended to improve handling and delivery of highly lipophilic triterpenes. Collectively, these approaches primarily address the “front-end” barrier of poor dissolution/solubilization that limits oral absorption [177–180].

Beyond solubilization, a substantial body of work has applied nanotechnology-based carriers to enhance triterpene delivery by improving dispersion stability, protecting the payload, and enabling more controllable biodistribution—features that can translate into higher effective exposure and more reliable administration. For UA, reported platforms include phospholipid nanoparticles (including freeze-dried preparations to support handling and dosing), polymeric nanoparticles (including block-copolymer systems), liposomes engineered for extended circulation and pH sensitivity, chitosan-based nanoparticles (including ligand-directed variants such as folate-functionalized systems), PLGA nanoparticles, and nanocrystals where particle-size control is used to increase dissolution rate and thereby improve bioavailability. Related engineering efforts extend to prodrug-like dendrimeric constructs for targeted delivery and to nanoemulsions or other nanoplatfoms designed for controlled release in specialized settings. Although several of these examples were developed for non-hepatic indications, they collectively exemplify generalizable delivery principles for triterpenes: increasing apparent solubility, improving stability, and enabling administration via formulations that overcome absorption and distribution constraints [181–190].

Newer studies illustrate how targeted or biomimetic delivery systems can be leveraged for particularly challenging triterpenes (notably celastrol) where oral dosing and tissue selectivity are limiting, and how route-of-administration engineering can help when absorption is inherently poor (as in glycyrrhizin). Celastrol has been formulated into albumin-based nanoparticles (including biodegradable and ligand-decorated versions), polysaccharide-derived hybrid micelles (e.g., chondroitin sulfate-based), and co-assembly systems where hyaluronic acid functions as a self-assembly “chaperone,” all aiming to improve dispersibility, reduce nonspecific exposure, and support effective dosing. A particularly translationally oriented approach is the design of oral celastrol micelles that form a HDL corona to promote hepatocyte targeting, directly addressing both oral delivery and liver selectivity. Separately, for glycyrrhizin—classically recognized as poorly absorbed—systematic evaluation of non-vascular administration routes has been explored to

enhance systemic availability when oral absorption is insufficient, providing a complementary “delivery-by-route” solution distinct from chemical derivatization or nanocarriers [191–196].

Conclusions

Pentacyclic triterpenes emerge from the available evidence as a coherent class of multitarget modulators capable of intercepting key pathogenic processes across the MASLD-MASH continuum. By converging on central nodes of disease progression - namely dysregulated lipid metabolism, oxidative and endoplasmic reticulum stress, chronic inflammation, inflammasome activation, and hepatic stellate cell-driven fibrogenesis - compounds such as ursolic acid, oleanolic acid, betulinic acid, asiatic acid, celastrol, and glycyrrhizin consistently attenuate steatosis, inflammatory signaling, and fibrotic remodeling in diverse experimental models. Despite structural diversity, these triterpenes share common mechanistic themes, including activation of energy-sensing pathways (e.g., AMPK), suppression of lipogenic transcriptional programs (e.g., SREBP-1c), inhibition of pro-inflammatory cascades (e.g., TLR-NF- κ B and NLRP3 inflammasome signaling), and modulation of profibrotic axes (e.g., TGF- β /SMAD), supporting the concept that multitarget intervention is particularly suited to the multifactorial nature of MASH.

However, translation of these promising preclinical findings into effective clinical therapies remains constrained by compound-specific pharmaceutical and biological limitations. Poor aqueous solubility, low and variable oral bioavailability, and heterogeneity of experimental models limit direct extrapolation to human disease. Future progress will require rational prioritization of triterpenes based on translational readiness, coupled with optimized medicinal chemistry, formulation strategies, and delivery platforms that improve systemic exposure and tissue selectivity. Equally important is the need for well-designed, mechanism-informed clinical trials that incorporate appropriate patient stratification, pharmacokinetic–pharmacodynamic assessment, and validated histological and noninvasive endpoints. Within this framework, pentacyclic triterpenes should be viewed not as single-target agents, but as adaptable scaffolds for the development of next-generation therapies aligned with the complex biology of MASLD and MASH.

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