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REVIEW

Natural Product Treatment for Metabolic Dysfunction-Associated Steatotic Liver Disease: Targeted Mitochondrial Quality Control

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Abstract: Metabolic dysfunction-associated steatotic liver disease (MASLD) is characterized by progressive mitochondrial dysfunction that disrupts hepatocellular metabolism, redox homeostasis, and inter-organelle communication. Hepatic metabolic zonation, maintained by spatially specialized mitochondrial networks, coordinates β-oxidation, oxidative phosphorylation, and lipid synthesis under physiological conditions. Chronic nutrient excess and insulin resistance disrupt this zonal organization, particularly in pericentral hepatocytes, leading to oxidative imbalance, defective mitochondrial quality control (MQC), and lipid accumulation. Mitochondrial injury is not confined to hepatocytes. The release of mitochondrial DNA (mtDNA), cardiolipin, and other mitochondrial danger-associated molecular patterns activates Kupffer cells and hepatic stellate cells through TLR9- and cGAS-STING-dependent pathways, thereby amplifying inflammatory and fibrogenic responses. Recent studies indicate that selected natural compounds improve mitochondrial function by enhancing AMPK-SIRT1-PGC-1α-dependent biogenesis, promoting PINK1/Parkin-mediated mitophagy, and attenuating mito-DAMP–driven innate immune activation. This review integrates liver metabolism and mitochondrial stress signaling pathways, elucidates the mechanistic framework of liver-mitochondrial interactions in MASLD, and explores pharmacological strategies targeting organelles to restore liver metabolic homeostasis.

Plain Language Summary: Mitochondrial dysfunction, particularly mitochondrial quality control failure (including imbalanced dynamics, impaired autophagy, reduced biogenesis, and disrupted protein homeostasis), is a core driver of MASLD onset and progression. Various natural products (such as flavonoids and glycosides) and traditional Chinese medicine formulas can restore mitochondrial homeostasis by targeting specific MQC modules (such as promoting fusion, restoring autophagy, and activating biogenesis), thereby improving steatosis, inflammation, and liver injury.

Keywords: metabolic dysfunction-associated steatotic liver disease, mitochondrial quality control, oxidative stress, lipid metabolism, natural products

Introduction

Metabolically associated steatotic liver disease (MASLD), formerly termed non-alcoholic fatty liver disease (NAFLD), has emerged as the most common chronic liver disease worldwide, affecting roughly one-third of the adult population and up to two-thirds of individuals with type 2 diabetes or obesity.[1] It is primarily characterized by hepatic steatosis and the presence of at least one cardiometabolic risk factor, including obesity, type 2 diabetes mellitus (T2DM), insulin resistance, hypertension, or dyslipidemia.[2] The diagnosis requires exclusion of other primary causes of steatosis, such as

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alcohol-related liver disease, drug-induced liver injury, viral hepatitis, or other chronic liver diseases, monogenic disorders, and other secondary causes of steatotic liver disease, in accordance with current EASL/AASLD consensus definitions.[3] In 2023, a multisociety Delphi consensus adopted the MASLD/MASH nomenclature to reflect metabolic roots and enhance clinical clarity, an agenda now integrated into hepatology guidance and coding.[4] This terminological shift reflects a deeper conceptual reframing: MASLD is no longer just passive hepatic fat accumulation, but rather an active manifestation of systemic metabolic derangement encompassing insulin resistance, dyslipidemia, ectopic lipid deposition, and altered hepatic lipid flux.[5] At the cellular level, mitochondria are central integrators of nutrient flux, redox homeostasis, and hepatocyte fate. Accumulating evidence indicates that impaired mitochondrial metabolism and defective mitochondrial quality control (MQC), encompassing dynamics, mitophagy, biogenesis, and proteostasis, are early and persistent drivers of MASLD progression.[6] Hepatic lipid overload and insulin resistance impose sustained metabolic pressure on hepatocyte mitochondria, leading to β-oxidation overload, increased electron transport chain flux, excessive ROS production, and lipid peroxidation.[7] MQC defects can further amplify these damages, including mitochondrial fusion/fission imbalance and suppressed mitophagy.[8,9] The recent approval of the thyroid hormone receptor-β agonist resmetirom, along with encouraging data for GLP-1 receptor agonists such as semaglutide and newer incretin-based polyagonists, represents a milestone in pharmacotherapy; however, these agents primarily target systemic metabolic pathways and do not directly engage MQC circuitry.[3,10] In parallel, a growing body of preclinical and early clinical studies suggests that natural products, including traditional Chinese medicine–derived compounds and formulas, can remodel mitochondrial homeostasis and attenuate steatosis, inflammation, and cell death in MASLD models, often through multi-target, network-level actions.[11]

Building on prior reviews that have independently examined mitochondrial dysfunction in NAFLD and the hepatoprotective properties of natural products, this article foregrounds MQC as the overarching mechanistic architecture that integrates these domains. Within this unified framework, we systematically delineate how natural products recalibrate mitochondrial integrity in MASLD through their actions on dynamics, mitophagy, biogenesis, and proteostasis, while simultaneously providing a critical appraisal of their pharmacological mechanisms, potential toxicological liabilities, and the extent to which these agents can be advanced as MQC-targeted therapeutic candidates in translational settings.

Overview of Mitochondrial Quality Control Modules

Mitochondrial quality control is a multilayered defense system that enables cells to preserve the structural and functional integrity of mitochondria, maintaining energy metabolism and cellular homeostasis by repairing damaged components, clearing dysfunctional mitochondria, and replenishing new organelles. At the molecular level, mitochondrial proteostasis is maintained by molecular chaperones and proteases, and the mitochondrial unfolded protein response (UPR^{mt}) is triggered when protein damage exceeds the repair capacity.[12] Chaperones (eg, HSP60, HSP10) and proteases (eg, LONP1, CLPP) remove or refold damaged proteins; when this capacity is exceeded, UPR^{mt} is activated.[13] At the organelle level, selective removal of dysfunctional mitochondria via PINK1–Parkin-mediated mitophagy is a core mechanism; loss of Parkin, a RBR E3 ubiquitin protein ligase (PARKIN), accelerates steatosis and fibrosis in fatty liver models, and restoring mitophagy ameliorates disease progression.[9,14] MQC also governs the selective propagation of functional mtDNA and metabolic rewiring that preserves ATP homeostasis under stress.[15] Significantly, these MQC modules are differentially perturbed in MASLD, making MQC both a mechanistic nexus of disease progression and a promising therapeutic target.

The term "mitochondrial dysfunction" is frequently invoked in MASLD, yet it conflates several mechanistically distinct processes, offering little precision for biomarker development or targeted therapy. Accumulating experimental and clinical evidence indicates that specific arms of MQC (dynamics, mitophagy, and biogenesis) are differentially impaired in MASLD, driving disease progression. In human NASH liver biopsies, the fusion protein mitofusin 2 (MFN2) is markedly reduced, and hepatocyte-specific Mfn2 deletion in mice induces steatosis, inflammation, and even hepatocarcinogenesis, highlighting fusion failure as a discrete pathogenic node rather than generic "dysfunction".[8] Likewise, mitophagy loss represents an early and measurable vulnerability: PARKIN-deficient mice develop accelerated steatosis, insulin resistance, and fibrosis, and a TNFα/Miz1 feedback loop that suppresses mitophagy has been shown to propagate NASH.[9] Mitochondrial biogenesis is also selectively compromised; fatty liver models exhibit inadequate induction of

PGC-1α-dependent biogenesis during metabolic stress, while biopsies from NAFLD patients display reduced markers of mitochondrial turnover and impaired fatty acid oxidation.[16] Together, these findings underscore that "mitochondrial dysfunction" is too broad to be mechanistically or therapeutically beneficial. The pathogenesis of MASLD is better understood by identifying which MQC modules fail, and therapeutic strategies—including natural products—should be evaluated for their ability to restore these specific MQC axes.

Liver–Mitochondria Interaction in MASLD

The liver is a solid organ composed of parenchyma and interstitium, supplied by a dual blood supply from the portal vein, rich in nutrients, and the hepatic artery, which delivers oxygenated blood to the liver.[17] The interstitium is covered by a dense connective tissue capsule that extends into the parenchyma, dividing the liver into many lobules. Hepatocytes exhibit different functions and organelle characteristics depending on their position along the portal-central vein axis.[18] Peri-portal hepatocytes show higher levels of oxidative phosphorylation and enhanced fatty acid β-oxidation, while peri-central vein hepatocytes are enriched in glycolysis and primarily focused on lipid synthesis.[19,20] This partitioning reflects spatial differences in mitochondrial structure and function, highlighting the heterogeneity of mitochondrial function and structure across liver regions. The walls of the sinusoids are composed of porous sinusoidal endothelial cells containing Kupffer cells and lymphocytes. Between the endothelial cells and hepatocytes lies a narrow Disse lumen containing hepatic stellate cells.[21] Under physiological conditions, hepatocytes maintain the oxygen/redox gradient, regulate lipid metabolism, and balance energy throughout the liver lobules. However, chronic metabolic overload disrupts this regional distribution, with significant regional-specific changes in triglycerides, diglycerides, sphingolipids, and ceramides, redistributing from the peri-central venous region to the peri-portal venous region, and increased fibrosis in the peri-portal venous region.[22] Excessive ROS production, mitochondrial depolarization, and impaired adaptive biosynthesis occur, particularly in hepatocytes prone to lipid accumulation and oxidative stress.[23]

Under stress, hepatocyte mitochondria release mitochondrial damage-associated molecular patterns (mito-DAMPs), including oxidized mitochondrial DNA (mtDNA), cardiolipin, and N-formyl peptide.[24] Due to the structural similarity of mtDNA to bacterial DNA, it can act as a pattern recognition receptor and an endogenous ligand for the cyclic GMP-AMP synthase (cGAS)-STING pathway, activating NF-κB, IRF3, and downstream pro-inflammatory cytokines,[25,26] thereby linking hepatocyte mitochondrial stress to NAFLD/NASH. Mitochondrial release of mitochondrial DAMPs from damaged hepatocytes directly activates hepatic stellate cells, the fibroblasts in the liver, and drives liver scarring.[27] Conversely, innate immune cells within the hepatic sinusoids, particularly Kupffer cells, can recognize leaked mtDNA via TLR9 and STING, promoting macrophage polarization toward a pro-inflammatory M1 phenotype and enhancing cytokine production.[28]

In summary, MASLD is a disease characterized by dysregulation of liver-mitochondrial interactions, in which regional mitochondrial dysfunction alters hepatocyte metabolic progression. A deeper understanding of the mechanisms of this bidirectional interaction is crucial for developing organelle-targeting therapies.

Mitochondrial Dysfunction and Quality Control Failure in MASLD

Mitochondrial dysfunction lies at the core of MASLD. Hepatic lipid overload, oxidative stress, and organelle crosstalk collectively impair mitochondrial bioenergetics, dynamics, and turnover. Instead of a vague "mitochondrial dysfunction," MASLD is now understood as a progressive collapse of MQC encompassing mitochondrial genetics, calcium homeostasis, dynamics, mitophagy, biogenesis, and proteostasis.

Mitochondrial Genetics

mtDNA is a small circular genome located in the mitochondrial matrix that encodes 13 essential polypeptides of the oxidative phosphorylation (OXPHOS) system, as well as 2 rRNAs and 22 tRNAs required for translation within mitochondria.[29] The functional integrity of mtDNA is fundamental to the normal assembly of oxidative phosphorylation complexes, ATP production, and mitochondrial bioenergetics.[30] Unlike nuclear DNA, mtDNA lacks protective histones and has limited DNA repair capabilities, making it more susceptible to oxidative damage and mutations during physiological and pathological oxidative stress.[31] The proximity of mtDNA to the electron transport chain (ETC) and

its relatively inefficient base excision repair mechanism make mtDNA more susceptible to oxidative base damage, strand breaks, point mutations, and deletions.[32,33]

Lipid Accumulation

Hepatic lipid overload occurs when the balance between lipid uptake and clearance is disrupted. Insulin resistance in adipose tissue and the liver is a key factor leading to metabolic imbalance in MASLD. Excess free fatty acids (FFAs) produced by diet and adipose tissue are not only stored in lipid droplets as triglycerides (TG),[34] but also give rise to lipid intermediates such as saturated fatty acids, diacylglycerols (DAG), sphingosine/sphingomyelin, and free cholesterol. These metabolites interfere with insulin signaling, activating inflammatory and pro-apoptotic pathways.[35,36] Hyperinsulinemia upregulates de novo lipid synthesis (DNL) in hepatocytes while restricting very low-density lipoprotein (VLDL) secretion, thereby providing lipogenic substrates.[37] This lipid burden forces excessive mitochondrial β-oxidation.

ROS Production

Excessive β-oxidation of fatty acids leads to an overproduction of reducing NADH and $FADH_2$, which overloads the mitochondrial ETC. Because the ETC has limited capacity, this results in over-reduction of electron carriers, particularly at Complex I and III, causing electrons to leak prematurely and react with oxygen to form mitochondrial reactive oxygen species (mtROS), such as superoxide and hydrogen peroxide.[6,38] Elevated mtROS levels damage respiratory chain complexes, mitochondrial membranes, and mitochondrial DNA, impairing electron transport and weakening the proton gradient, ultimately reducing OXPHOS efficiency and ATP production.[39] In the livers of NAFLD mice, increased markers of mitochondrial autophagy, decreased mitochondrial respiratory chain complex activity, and reduced ATP content were associated with defects in oxidative phosphorylation subunits.[40] mtDNA mutations, particularly in the MT-CYB gene encoding Complex III core subunit, are associated with advanced NASH, metabolic disorders, and biomarkers of oxidative damage.[41] It also oxidizes inner-membrane lipids and damages respiratory-chain proteins, as shown in diet-induced NAFLD mouse models, which exhibit decreased stability and activity of multiple oxidative phosphorylation subunits, including complexes I and IV.[42]

Inflammation

Excessive mtROS, together with endoplasmic reticulum (ER) stress, activate stress-responsive signaling pathways, including c-Jun N-terminal kinase (JNK) and nuclear factor-κB (NF-κB), thereby initiating pro-inflammatory transcriptional programs.[43] Simultaneously, mitochondrial damage leads to the release of mtDAMPs, particularly oxidized mtDNA, into the cytoplasm and extracellular space. These mtDAMPs stimulate the NLRP3 inflammasome, thereby exacerbating liver inflammation and driving metabolic reprogramming.[18] In addition, mitochondrial DNA released into the cytosol can activate the cyclic GMP-AMP synthase (cGAS) and stimulator of interferon genes (STING) pathway, further linking mitochondrial damage to innate immune activation and type I interferon responses.[44] Clinical studies have confirmed that reduced mtDNA copy number and base deletions in the livers of MASLD patients, as well as mitochondrial DNA copy number and deletion levels, may affect susceptibility to non-alcoholic fatty liver disease.[15] Mitochondrial genome sequencing of livers from NAFLD patients revealed increased mutation rates and heterogeneity, particularly in genes encoding ETC proteins, with more severe disease phenotypes exhibiting higher mtDNA variant loads.[45]

Fibrosis

Persistent mitochondrial dysfunction and unresolved inflammation ultimately drive the progression from steatosis to fibrosis. A central event in fibrogenesis is the activation of hepatic stellate cells (HSCs), which transdifferentiate into myofibroblast-like cells in response to inflammatory and oxidative cues.[46] mtROS and oxidized mtDNA contribute to this process both directly and indirectly. On the one hand, ROS promotes transforming growth factor-β (TGF-β) signaling, a master regulator of fibrogenesis, thereby enhancing collagen synthesis and extracellular matrix (ECM) deposition.[47] On the one hand, ROS promotes transforming growth factor-β (TGF-β) signaling, a master regulator of fibrogenesis, thereby enhancing collagen synthesis and ECM deposition. On the other hand, mtDNA-mediated activation of innate immune

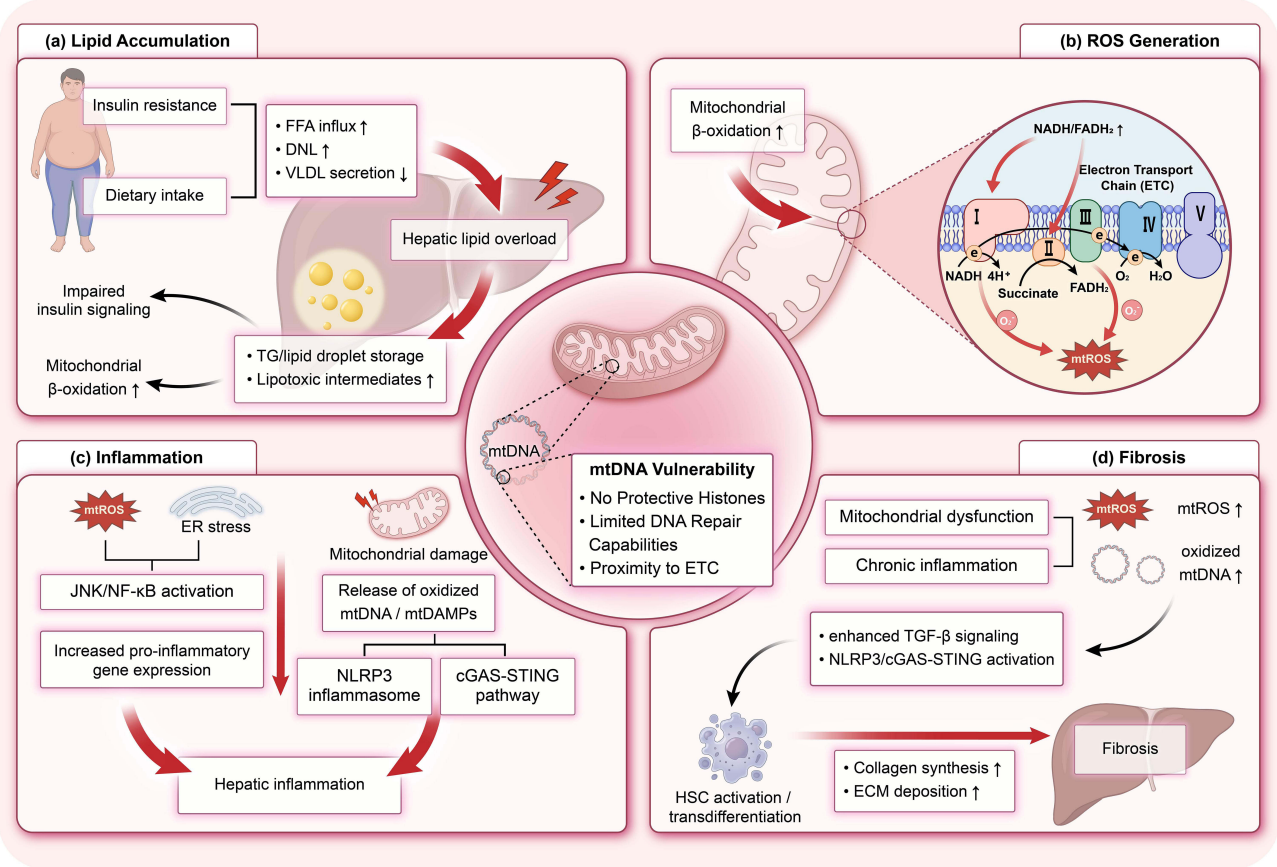

Figure 1 Integrated mitochondrial quality control failure drives the progression of MASLD from lipid overload to inflammation and fibrosis.

pathways, NLRP3 and cGAS–STING, sustains a pro-fibrotic inflammatory milieu.[48] Increased mtDNA mutation loads correlate with more severe fibrosis stages in NASH patients.[41,45]

These changes impair ATP synthesis, lead to the continuous production of ROS, and create a self-reinforcing cycle of oxidative damage (Figure 1). This mitochondrial genetic instability is an early and crucial pathological change in the progression of MASLD.

Mitochondrial Calcium Dysregulation

Under physiological conditions, intracellular calcium (Ca^{2+}) acts as a dynamic second messenger that regulates mitochondrial metabolism, ATP production, and cell fate decisions.[49] In healthy hepatocytes, the functional contact between the ER and mitochondria is called the mitochondrial-associated endoplasmic reticulum membrane (MAMs), and mitochondrial Ca^{2+} levels are strictly regulated by MAMs.[50] Ca^{2+} is pumped from the ER into the mitochondrial matrix through molecular complexes such as the IP_3 receptor (IP_3R), GRP75, and voltage-dependent anion channels (VDACs).[51–53] Ca^{2+} overload activates key dehydrogenases in the tricarboxylic acid cycle, enhancing oxidative phosphorylation capacity.[54] Normal Ca^{2+} cycling thus maintains energy homeostasis and prevents undue oxidative stress. In MASLD, mitochondrial dysfunction is associated with ER stress, organelle contact signaling, and programmed cell death. Chronic ER stress leads to Ca^{2+} dys-homeostasis at MAMs, where excessive ER-to-mitochondria Ca^{2+} transfer triggers mitochondrial Ca^{2+} overload, enhanced mtROS production, and further ER dysfunction.[55] Both clinical and animal studies have confirmed that in NAFLD, lipid overload and persistent ER stress promote mitochondrial Ca^{2+} overload.[56] Hepatocellular ER stress and Ca^{2+} dysregulation promote JNK/NF-κB activation and NLRP3 inflammasome assembly, thereby converting organelle stress into sterile hepatic inflammation.[57] These inflammatory signals trigger multiple modes of regulated cell death, including apoptosis, necroptosis, and, particularly, ferroptosis, which is driven by

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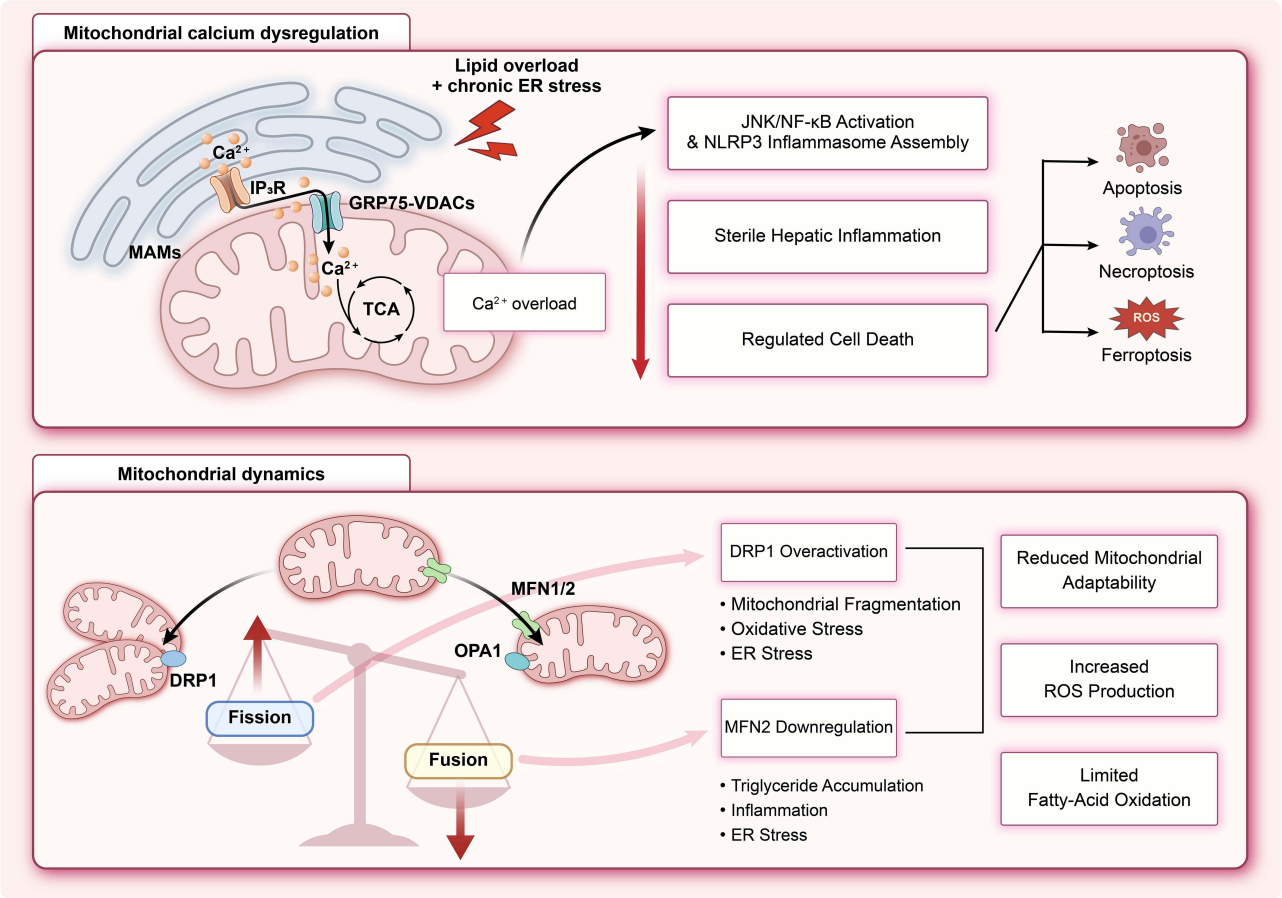

Figure 2 Dysregulation of Mitochondrial Calcium Homeostasis and Dynamics Drives Hepatocellular Stress and Metabolic Dysfunction in MASLD.

mitochondrial lipid peroxidation and the production of iron-dependent reactive oxygen species.[58] Studies have found that inhibiting mitochondrial Ca^{2+} influx using Xestospongin-C can significantly reduce mtROS production and ER stress-induced damage responses, suggesting that Ca^{2+} overload and its downstream ROS signaling are key nodes connecting ER stress and mitochondrial dysfunction.[56] These organelle stress responses converge on mitochondria but affect distinct quality-control arms. Thus, disrupted Ca^{2+} signaling forms a crucial link between organelle stress, inflammation, and hepatocellular death in MASLD (Figure 2).

Mitochondrial Dynamics

Mitochondrial dynamics is primarily regulated by a series of characteristic fusion and splitting proteins, making it a structurally well-defined module within the MQC that can serve as a therapeutic target. Mitochondrial fusion is mediated by MFN1/2 on the outer mitochondrial membrane and optic atrophy protein 1 (OPA1) on the inner mitochondrial membrane, thereby enabling mitochondrial elongation, content mixing, and mtDNA complementarity. In hepatocytes, mitochondrial fusion maintains mitochondrial membrane potential, optimizes OXPHOS, and supports efficient fatty acid β-oxidation.[59] Conversely, mitochondrial division is primarily driven by dynein-associated protein-1 (DRP1),[60] which is recruited from the cytosol to the mitochondria via receptors such as FIS1, MFF, and MiD49/51.[61] Fission facilitates mitochondrial distribution, quality control, and the selective removal of damaged organelles via mitophagy.[62,63]

MFN2 not only regulates mitochondrial junctions and fusions but also acts as a receptor for PINK1-mediated Parkin recruitment, linking mitochondrial dynamics to mitophagy. MFN2 expression is significantly reduced in liver biopsy tissues from human non-alcoholic steatohepatitis (NASH); specific knockout of the MFN2 gene in mouse hepatocytes

leads to triglyceride accumulation, endoplasmic reticulum stress, and inflammation.[8] OPA1 is a dynamin-associated GTPase protein located in the inner mitochondrial membrane and is a key regulator of mitochondrial inner membrane fusion. OPA1 deficiency can activate ATF5-mediated UPR^{mt} and induce FGF21 expression, thereby improving systemic glucose homeostasis and protecting against diet-induced obesity and insulin resistance.[64] Gene knockout of OPA1 can prevent macromitochondrial formation and liver damage. Targeting OPA1 to block mitochondrial fusion can alleviate NASH pathology.[65]

DRP1 overactivation promotes mitochondrial fragmentation, leading to loss of membrane potential, impaired ETC function, and increased mtROS production.[66] Clinical studies have confirmed that Drp1 expression gradually increases from NAFLD to NASH, then to NASH-related fibrosis, and finally to cirrhosis, and is mainly expressed in Kupffer cells.[67] The ketogenic diet reduces Fis1 and Drp1 levels, increases ATP levels, and increases key genes for fatty acid oxidation, improves mitochondrial dysfunction, alleviates lipid deposition, restores mitochondrial homeostasis, and improves mitochondrial dysfunction in the liver of MASLD mice.[68] Activation of DRP1/MFF induces excessive mitochondrial fission, inhibits Nrf2/HO-1, increases intracellular ROS, induces macrophage and liver inflammation, activates HSCs, leading to ECM deposition, and ultimately promotes liver fibrosis.[69] MiD49/51 can independently mediate DRP1 recruitment, independent of Fis1 and MFF. Targeting MiD49/51 may block fatty acid-induced abnormal mitochondrial fission, and combined targeting of MiD51 and MFF enhances the anti-fission effect.[70] The mitochondrial fission inhibitor Mdivi-1 can reduce mitochondrial ROS levels and decrease the expression of fibrosis markers.[71]

In summary, mitochondrial dynamics, comprising fusion and fission proteins, constitute the core regulatory axis of MASLD (Figure 2). Dysregulation of these proteins leads to mitochondrial dysfunction, metabolic stress, inflammation, and fibrosis, making them highly attractive targets for precision medicine strategies (Table 1).

Mitophagy and Lysosomal Clearance

Mitophagy removes dysfunctional mitochondria through selective recognition and lysosomal degradation. In MASLD, impaired mitophagy leads to the persistence of damaged organelles, exacerbating oxidative stress, lipid accumulation, inflammation, and fibrosis. Mitophagy mechanisms primarily occur through two pathways: a ubiquitin-dependent PINK1-Parkin pathway and a receptor-mediated pathway involving outer membrane proteins BNIP3, NIX, and FUNDC1.

PINK1–Parkin–dependent mitophagy is the primary pathway for tagging dysfunctional mitochondria. When membrane potential collapses, PINK1 accumulates on the outer membrane and recruits Parkin, which ubiquitinates multiple substrates to initiate autophagosome assembly.[72,73] Parkin overexpression reduces lipid accumulation and restores mitochondrial morphology.[74] Conversely, liver-specific Parkin deficiency impairs mitophagy, accelerates steatosis, promotes insulin resistance, and increases fibrosis.[75] In addition to the PINK1–Parkin axis, receptor-mediated mitophagy

Table 1 Expression Changes of Key Mitochondrial Dynamics Proteins in MASLD

Category	Key Proteins	Localization	Alteration in MASLD	Therapeutic Implication
Fusion	MFN2[8]	Outer membrane	Mfn2 deficiency reduces phosphatidylserine transfer and phospholipid synthesis, leading to ER stress.	Restore fusion, improve β-oxidation
	OPA1[65]	Inner membrane	OPA1 deficiency blocks mitochondrial fusion and prevents liver damage.	Maintain OXPHOS integrity
Fission	DRP1[67]	Cytosol, mitochondria	Drp1 expression gradually increases from NAFLD to NASH, and then to NASH-related fibrosis and cirrhosis.	Oligomerization shrinks and cuts mitochondria
	FIS1[68]	Outer membrane	Decreased Fis1 and Drp1 levels alleviate lipid deposition and restore mitochondrial homeostasis.	Participate in the initial recruitment of DRP1
	MFF[69]	Outer membrane	Activation of DRP1/MFF induces excessive mitochondrial division.	Participate in the initial recruitment of DRP1
	MiD49/51[70]	Outer membrane	Targetes MiD49/51 to block mitochondrial division	Participate in the initial recruitment of DRP1

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provides an alternative mechanism for the selective removal of damaged mitochondria. Mitochondrial outer membrane proteins BNIP3, NIX (BNIP3L), and FUNDC1 contain LC3 interaction region (LIR) motifs, enabling them to directly bind to LC3 on the autophagosome membrane and promote the formation of autophagosomes around mitochondria.[76,77] Their deficiency reduces mitochondrial clearance, thereby exacerbating liver damage and steatosis.[78]

Growth differentiation factor 15 (GDF15) is a circulating biomarker of mitochondrial stress and impaired mitophagy. Clinical studies have found that serum GDF15 is positively correlated with non-hepatic mitochondrial respiration in obese individuals, but negatively correlated in patients with liver fibrosis.[79] Circulating GDF15 levels in patients with MASLD are higher than in the control group, and GDF15 levels in the MASH subgroup are positively correlated with fibrosis.[80]

Mitochondrial Biogenesis and NAD^+/SIRT1 Axis

Mitochondrial biogenesis compensates for organelle loss and restores oxidative capacity after injury. PGC-1α/SIRT1 axis constitutes the central transcriptional regulatory hub orchestrating this process. SIRT1 directly deacetylates and activates PGC-1α in hepatocytes, linking nutrient and redox status to mitochondrial transcriptional programs.[81,82] Activated PGC-1α regulates mitochondrial biosynthesis by co-activating nuclear transcription factors, particularly NRF1/2. These transcription factors subsequently induce the expression of nuclear-encoded mitochondrial genes, including mitochondrial transcription factor A (TFAM).[83] TFAM, along with mitochondrial transcription factors B1 and B2 (TFB1M and TFB2M), binds to mtDNA and regulates its transcription and replication. This coordinated transcriptional program ensures proper maintenance of mtDNA and promotes the expression of OXPHOS components, thereby maintaining mitochondrial bioenergetic function.[82] Suppression or loss of hepatic PGC-1α reduces mitochondrial content, lowers fatty-acid oxidation, and promotes triglyceride accumulation.[16] High-fat or Western diet feeding downregulates hepatic SIRT1–PGC-1α signaling, decreases mtDNA copy number, and exacerbates steatosis.[84] Proteomic mapping of NAFLD liver reveals reduced turnover and abundance of OXPHOS subunits, consistent with defective renewal of the mitochondrial pool.[40] Restoring the SIRT1–PGC-1α pathway increases mitochondrial biogenesis, enhances β-oxidation, and attenuates steatosis in vivo.[85] Pharmacological activation of PPARα/PGC-1α increases mtDNA content and reduces hepatic lipid and oxidative stress in preclinical NAFLD models.[86] Human biopsy studies further confirm reduced hepatic PGC-1α in MASH, and liver-specific Pgc-1α deletion promotes fibrosis and respiratory dysfunction in vivo.[87] Collectively, impaired biogenesis in MASLD represents a failure of mitochondrial regeneration, reducing functional organelle reserves and amplifying susceptibility to oxidative injury (Figure 3).

Mitochondrial Proteostasis and UPR^{mt}

Mitochondrial protein homeostasis encompasses the folding, assembly, and proteolytic clearance of mitochondrial proteins, and depends on molecular chaperones (HSP60/HSP10, mtHSP70), matrix proteases (ClpP, LONP1), and the mitochondrial unfolded protein response. Molecular chaperones HSP60/HSP10 and mtHSP70 constitute the first line of defense against mitochondrial protein misfolding. HSP60, a highly conserved molecular chaperone, works in concert with its co-chaperone HSP10 to facilitate the folding and assembly of newly imported precursor proteins into their native conformations within the mitochondrial matrix,[88] while matrix proteases, such as the LONP1 and ClpXP complex (ClpP/ClpX), clear irreversibly damaged or misfolded proteins.[89,90] Emerging evidence indicates that aberrant HSP expression and function contribute to NAFLD pathogenesis. In liver irritation from diet or toxins, HSP60 and LONP1 are upregulated, thereby maintaining OXPHOS assembly and limiting acute mtROS expansion. LONP1 controls PINK1 processing and thus modulates mitophagy initiation.[91] Upregulation of LONP1 can improve mitochondrial structure and function in a fatty liver model.[92] In both MASH patients and high-fat diet-induced MASH mouse models, the expression of LONP1 in hepatocytes was significantly reduced, and this reduction was closely related to the degree of liver fibrosis.[93] ClpP abundance affects OXPHOS subunit turnover.[94] Recent studies further reveal that LONP1 collaborates with mtHSP70 to couple folding surveillance with degradation decisions.[95] In patients with NASH and mice, MRG15 levels are elevated in the liver. TUFM deacetylation is accelerated by the mitochondrial ClpXP protease system, leading to impaired mitophagy, increased oxidative stress, and activation of the NLRP3 inflammasome pathway.[96]

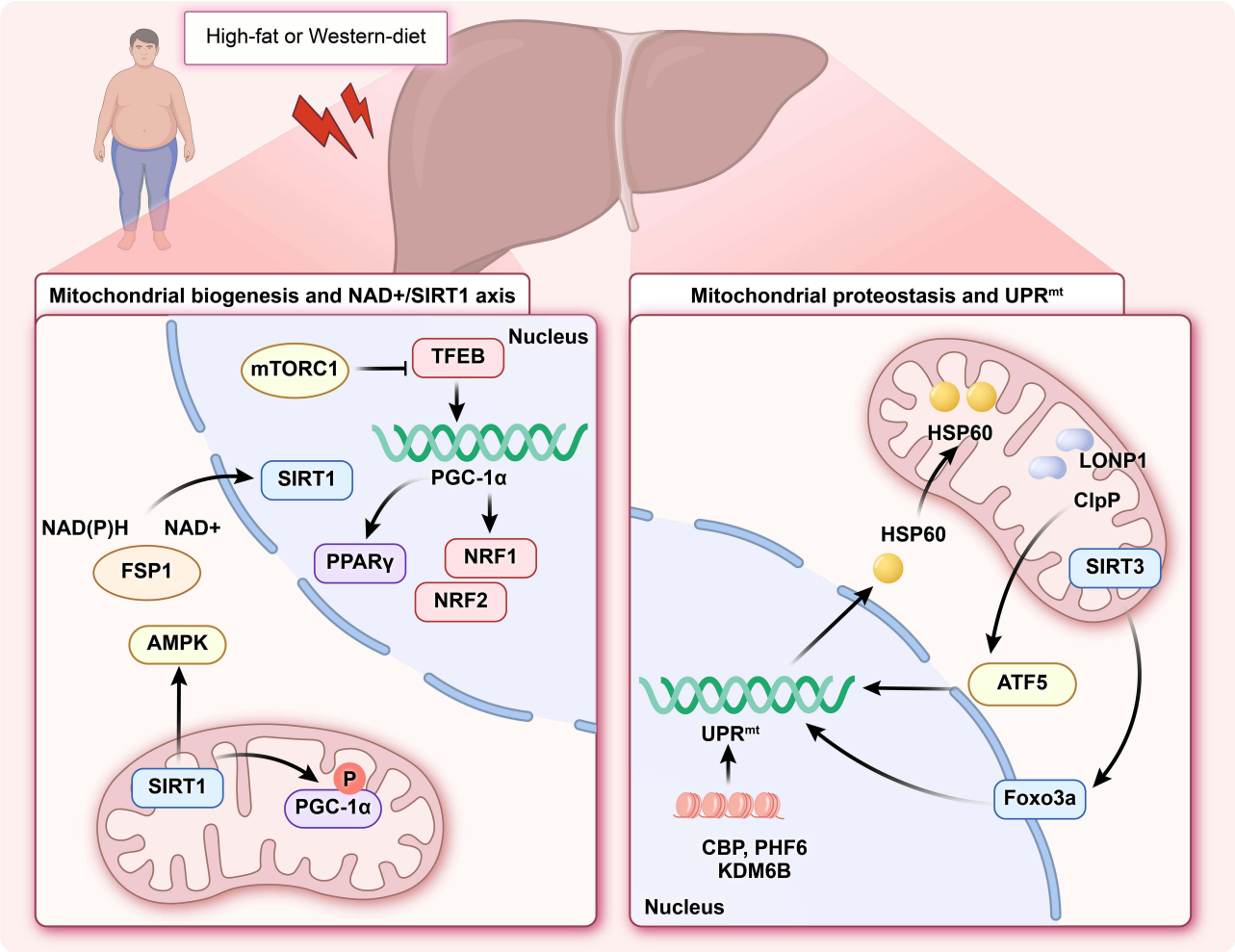

Figure 3 Regulation of Mitochondrial Biogenesis and Proteostasis via the NAD^+/SIRT1 Axis and UPRmt Signaling in MASLD.

UPR^{mt} is a nuclear-driven transcriptional program that upregulates these effector factors when mitochondrial protein toxicity stress accumulates.[97] With persistent metabolic overload, however, UPR^{mt} can become maladaptive. Chronic elevation or dysregulation of proteases/chaperones associates with mitochondrial swelling, defective β-oxidation, and inflammatory priming in NASH.[98] NAD^+ repletion and redox modulators restore components of UPR^{mt} (HSP60/ClpP/LONP1), improve OXPHOS assembly, and reduce steatosis or toxin-induced injury in animal and cell models.[99] UPR^{mt}-induced FGF21 secretion is significantly enhanced during early UPRmt activation and declines in late disease stages due to excessive lipid deposition.[100] Functionally, FGF21 exerts a pleiotropic protective effect by promoting autophagy and mitochondrial respiration while inhibiting lipogenesis, glucose production, inflammation, and fibrosis signaling, thereby reducing metabolic stress and promoting fibrosis regression in MASLD.[101]

Natural Products Targeting MQC in MASLD: Molecular Mechanisms and Pharmacology

Natural Products Modulating Mitochondrial Dynamics

MFN1/2 and OPA1 primarily mediate mitochondrial fusion, whereas fission is orchestrated by DRP1 and mitochondrial fission protein 1 (FIS1). Loss of MFN2 has been causally linked to hepatic steatosis, ER stress, and progression to NASH.[8] Conversely, DRP1 is a crucial player in mitochondrial fission and liver function. Its deficiency alters inter-organelle communication, enhancing mitochondria lipid droplet and ER mitochondria lipid droplet contacts while

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weakening mitochondria ER lipid droplet interactions.[102] Several natural compounds have been shown to restore mitochondrial dynamic equilibrium, thereby mitigating lipid accumulation and oxidative injury in NAFLD models.

Oroxylin A, a flavonoid, can upregulate the expression of the MFN2 transcriptional coactivator PGC-1α, thereby enhancing MFN2 expression and promoting mitochondrial fusion, improving lipid deposition, and inhibiting excessive mitochondrial ROS production.[103] Similarly, hesperetin, a flavanone glycoside, decreases Drp1 and its phosphorylated forms (Drp1-pS616, Drp1-pS637), as well as mitophagy-related proteins (PINK1, Parkin), while increasing MFN2 and OPA1 levels, thereby favoring mitochondrial fusion and improving cellular redox balance.[104] Dihydromyricetin, a dihydroflavonol, improves mitochondrial structure, restores membrane potential, and rebuilds fusion-fission balance by enhancing antioxidant enzyme activity, scavenging ROS, and regulating the expression of key mitochondrial dynamic proteins (Mfn1/2, Opa1, Drp1, Fis1).[105] Likewise, Rutin, a flavonol glycoside, attenuates hepatic steatosis by suppressing DRP1, inhibiting excessive mitochondrial fission, and promoting mitochondrial functional recovery and cell viability.[106]

Peanut Shell Extract has also been reported to normalize mitochondrial homeostasis in diabetic mice, as evidenced by reduced hepatic DRP1, PINK1, and TNFα levels, alongside elevated MFN1, MFN2, OPA1, TFAM, PGC-1α, and NRF2 expression.[107] Peanut shell extract is primarily composed of Flavonoids, Phenolic acids, and General polyphenolic antioxidants.[108] Astaxanthin, a Carotenoid, downregulates ER stress–related genes (GRP94, GRP78, ATF4, ATF6, PERK, eIF2α, IRE1, CHOP) and rebalances mitochondrial dynamics by inhibiting fission (DRP1, Mff) and promoting fusion (OPA1, MFN1, MFN2).[63] Diosgenin, a Steroidal saponin aglycone, exerts hepatoprotective effects by modulating the PERK and IRE1 branches of the unfolded protein response (UPR), thereby reducing ER stress and de novo lipogenesis. It concurrently inhibits DRP1 and upregulates MFN1/MFN2, mitigating mitochondrial dynamic disruption in NAFLD.[109] In contrast, bavachin, a Flavonoid, exacerbates hepatic injury by activating DRP1-mediated excessive mitochondrial fission and ER stress–related apoptosis through the Wnt/β-catenin signaling pathway, highlighting the detrimental impact of unrestrained fission activity.[110]

Collectively, these findings underscore the pivotal role of mitochondrial dynamics as a therapeutic target in NAFLD. Natural products that promote mitochondrial fusion, inhibit excessive fission, and alleviate ER stress may provide multifaceted protection by restoring mitochondrial integrity, suppressing oxidative stress, and improving hepatocellular metabolism (Table 2).

Natural Products Enhancing Mitophagy

Mitophagy failure represents a central metabolic vulnerability in MASLD, in which impaired PINK1 stabilization, defective Parkin recruitment, and redox overload converge to impede mitochondrial turnover. Many natural products can activate the PINK1/Parkin pathway, reduce mitochondrial reactive mtROS levels, restore membrane potential, and protect hepatocytes from lipotoxicity. Cyanidin-3-O-glucoside promotes AMPK activation, increases PINK1 and Parkin expression, and enhances mitophagy. This facilitates the removal of damaged mitochondria and lowers mitochondrial ROS in ethanol-injured hepatocytes.[114] Corilagin restores autophagic flux in HFD-fed mice. It increases LC3-II levels, enhances LC3–Parkin colocalization with mitochondria, elevates mitophagosome formation, and reduces mtROS. These changes restore mitochondrial membrane potential (Δψm) and attenuate steatosis and oxidative injury.[127] Quercetin also downregulates autophagy-related genes (ATG5, ATG7, Beclin-1, LC3A/B) and necroptosis-related genes (Fas, Bcl-2, Drp1, RIPK1), reducing LC3-I, LC3-II, and the LC3-II/LC3-I ratio.[111] It further increases PINK1, Parkin, BNIP3, and LC3-II, and reduces p62, TOM20, and VDAC1.[112] Baicalin and its nanoliposome rescue ΔΨm and reduce oxidative stress. They activate PINK1/Parkin-dependent mitophagy, clear damaged mitochondria, and restore mitochondrial function in toxin-induced liver injury.[128] Sesamin and corn peptides activate PINK1/Parkin-mediated mitophagy in HepG2 cells. They increase mitochondrial autophagy, improve mitochondrial homeostasis, enhance fatty acid metabolism, and reduce lipid accumulation.[129,130] These studies reveal a common mechanism: Parkin translocation restoration, reduction of mtROS, and restoration of membrane potential.

Although the PINK1/Parkin pathway dominates the literature, some natural products can also activate the BNIP3, FUNDC1, and pyroptosis-related mitophagy pathways. Ginsenoside Rb1 activates PINK1/Parkin-dependent mitophagy, reduces mtROS, suppresses NLRP3 activation, and limits pyroptosis in immune-injured hepatocytes.[116,131] Ginsenoside Rg1 stabilizes Δψm and triggers mitophagy via the same pathway, protecting liver tissue during ischemia-reperfusion.[132]

Table 2 Representative Natural Products Targeting MQC in MASLD

Natural Products	MQC Core Modules	Key Pathways	Experimental Evidence	Representative Mechanisms	Dosage	Methods of Administration
Oroxylin A[103]	Mitochondrial dynamics	PGC-1α/MFN2	Alcoholic liver disease	Promotes mitochondrial fusion and biogenesis, reduces mtROS	40 mg/kg	Oral gavage
Hesperetin[104]	Mitochondrial dynamics	AMPKα-DRP1/PINK1-Parkin	Non-alcoholic steatohepatitis	Reshapes the fission-fusion balance and activates mitophagy	100 and 200mg/kg (in vivo)	Oral gavage
Dihydromyricetin[105]	Mitochondrial dynamics	Nrf2-MFN2/DRP1	Lipopolysaccharide–induced hepatic injury	Regulates the balance between mitochondrial fusion and fission	20 μM, 40 μM and 80 μM (in vitro)	Cell treatment
Astaxanthin[63]	Mitochondrial dynamics/ER–mitochondria axis	PERK/IRE1–DRP1	Ochratoxin A-Induced Liver Injury	Suppressing ER stress-related excessive fission	100 mg/kg (in vivo)	Dietary supplementation
Quercetin[111–113]	Mitophagy	AMPK–PINK1/Parkin	Lipopolysaccharide–induced hepatic injury/alcohol-induced liver/ nonalcoholic fatty liver disease	Clears damaged mitochondria and improves lipid metabolism	20mg/kg, 80mg/kg, 100 mg/kg (in vivo), 10–100 μM (in vitro)	Injection, cell treatment and cell treatment
Cyanidin-3-O-glucoside[114]	Mitophagy	AMPK–PINK1/Parkin	Ethanol-induced liver injury	Enhances mitochondrial quality control and inhibites mtROS	50 μg/kg (in vivo), 1μg/mL (in vitro)	Oral gavage and cell treatment
Punicalagin[115]	Mitophagy	PINK1/Parkin–BNIP3	Diabetic Liver Injury	Restoring ΔΨm and reducing oxidative stress	20 mg/kg (in vivo)	Oral gavage
Ginsenoside Rb1[116]	Mitophagy	PINK1/Parkin–NLRP3	Concanavalin A-induced hepatocyte	Mitochondrial autophagy inhibits pyroptosis	25 mg/kg and 50 mg/kg (in vivo),	Oral gavage
Resveratrol[117–120]	Mitophagy/ Biogenesis	SIRT1–PGC-1α	Multiple liver injury cell models	Coordinating mitochondrial renewal and anti-inflammatory responses	500 mg/kg (in vivo), 10, 20, or 40 μg/mL (in vitro)	Oral gavage and cell treatment
Polydatin[121]	Mitophagy/ Biogenesis	SIRT3–FOXO3–BNIP3	Nonalcoholic fatty liver disease	Enhances mitochondrial renewal and antioxidant capacity	40 mg/kg	Oral gavage
Luteolin[122]	Biogenesis	AMPK–PGC-1α	Nonalcoholic fatty liver disease	Increases mtDNA copy number and ATP production	20 mg/kg	Oral gavage

(*Continued*)

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Table 2 (Continued).

Natural Products	MQC Core Modules	Key Pathways	Experimental Evidence	Representative Mechanisms	Dosage	Methods of Administration
Oleuropein[123]	Biogenesis	LKB1–PGC-1α–TFAM	Nonalcoholic fatty liver disease	Inhibits lipid production and enhances mitochondrial volume	80 μM/L (in vitro), 0.6% Oleuropein in HFD	Cell treatment, dietary supplementation
Astragaloside IV[124]	Biogenesis	AMPK–PGC-1α	Hepatocellular injury model	Improves hepatocyte energy metabolism	2.5, 5 and 10 μM/L	Cell treatment
Nicotinamide riboside[125,126]	Proteostasis	ATF5–ClpP/HSP60	Ethanol-induced hepatocellular damage	Restores mitochondrial protein homeostasis	1 mM/L	Cell treatment
α-Lipoic acid[99]	Proteostasis	UPR^{mt} modulation	FFA-induced hepatocyte model	Alleviates lipotoxicity-related protein stress	1 and 5 μM/L	Cell treatment

Punicalagin intervention significantly increased the expression of Pink1, Parkin, Bnip3, LC3b, and P62 in the liver, and significantly increased MMP. It reduced oxidative stress in the liver by upregulating mitophagy and antioxidant enzyme activity, thereby exerting a protective effect against diabetic liver injury.[115] These findings expand the field beyond PINK1/Parkin by showing that natural products can also modulate BNIP3, FUNDC1, and inflammasome–mitochondria crosstalk.

AMPK acts as a metabolic rheostat coupling nutrient signals with MQC. Several compounds stimulate mitophagy by rewiring hepatocellular energy sensing. Quercetin reduces intracellular lipids and ROS/DHE, upregulates PINK1/Parkin signaling, clears damaged mitochondria, and improves hepatic lipid metabolism, thus preventing NAFLD through AMPK-mediated mitophagy.[113] Cajaninstilbene Acid increased the expression of PGC-1α, TFAM, LC3-II, PINK1, and mitochondrial Parkin, and decreased p62 expression. It alleviated APAP-induced oxidative stress and enhanced mitochondrial quality control by activating Sestrin2/AMPK.[133]

Some natural products act upstream by strengthening antioxidant defenses or deacetylation networks, creating a cellular environment permissive for efficient mitophagy. Resveratrol has anti-inflammatory, antioxidant, and detoxifying properties. It upregulates PINK1, Parkin, Beclin-1, LC3B, and ATG5, while lowering p62.[117] Resveratrol also restores Parkin-mediated mitophagy in acute CCl_4 injury by elevating PINK1, Parkin, and LC3-II, reducing p62, and limiting lipid peroxidation and apoptosis.[118] In fish hepatocytes, resveratrol activates SIRT1/PGC-1α and PINK1/Parkin pathways, reduces ROS, and suppresses NF-κB, thereby promoting mitochondrial clearance and biogenesis.[119] Polydatin activates SIRT3-FOXO3-BNIP3 and PINK1-PRKN pathways. It enhances mitochondrial autophagy, improves mitochondrial biogenesis, and corrects hepatic injury and steatosis in NAFLD mice and hepatocytes.[121] Korean Red Ginseng increases PINK1 and Parkin expression, enhances mitophagy, improves insulin signaling, and reduces oxidative stress in hepatocytes under metabolic stress.[134] Salidroside increases PINK1, Parkin, and LC3-II, and decreases Bax/Bcl-2 and p62. These changes maintain mitochondrial function and prevent hepatocyte injury.[135]

Collectively, these compounds converge on a unifying mechanism: restoring the mitophagy–biogenesis equilibrium as a foundational strategy to correct lipotoxicity, oxidative stress, and hepatocellular dysfunction in MASLD (Table 2).

Natural Products Promoting Mitochondrial Biogenesis and NAD^+ Metabolism

Mitochondrial biogenesis is crucial for maintaining MQC and energy homeostasis. PGC-1α acts as a master transcriptional coactivator, driving mtDNA replication and mitochondrial protein expression. Several natural products have been reported to promote mitochondrial biogenesis through various upstream signaling pathways.

Several compounds act primarily by coupling AMPK/PGC-1α, reactivating the canonical metabolic stress response. Luteolin stimulates mitochondrial biogenesis via the AMPK/PGC-1α pathway, increasing mitochondrial mass and ATP production in hepatocytes.[122] Picrorhiza kurroa upregulates PGC-1α, TFAM, and Nrf2, promoting mitochondrial biogenesis while exerting anti-inflammatory and anti-fibrotic effects.[136] Resveratrol enhances the PGC-1α/PPARγ axis, increases mtDNA copy number and biogenesis-related proteins, and restores hepatocyte energy metabolism.[120] Oleuropein increases LKB1/PGC-1α promoter binding, upregulates PGC-1α and TFAM expression, and suppresses hepatic lipogenesis, linking mitochondrial biogenesis to improved lipid metabolism.[123] These findings suggest that natural compounds can simultaneously enhance mitochondrial function and combat steatosis by activating AMPK.

SIRT1, a NAD^+-dependent deacetylase, a growing cluster of natural products restores mitochondrial biogenesis by re-establishing NAD^+ metabolism and SIRT1/3 activity. Lycium ruthenicum polysaccharides activate SIRT1/PGC-1α signaling, maintaining mitochondrial structure and function, improving ATP levels, and reducing oxidative stress in liver injury models.[137] Astragaloside IV activates PGC-1α, AMPK, and SIRT3 in AML12 hepatocytes, promoting mitochondrial biogenesis and exerting antioxidative effects.[124] Curcumin activates SIRT3, increases mtDNA copy number and superoxide dismutase activity, and improves mitochondrial respiration in fatty hepatocytes.[138] Bergenin upregulates SIRT1 and activates the AMPK/SIRT1 axis, stimulating hepatic mitochondrial biogenesis.[139] Baicalein regulates the AMPK/SIRT1/PGC-1α pathway, modulating mitochondrial biogenesis and dynamics, and attenuates macrophage M1 hyperpolarization and hepatocyte pyroptosis via NF-κB inhibition.[140] Restoring NAD^+ sirtuin tone is a prerequisite for sustained mitochondrial biogenesis in metabolic liver diseases.

Several agents enhance mitochondrial biogenesis indirectly by remodeling autophagy–lysosome signaling, expanding the mechanistic diversity of natural-product interventions. The rhizome of Gentiana kurroo is dominated by secoiridoid glycosides, supported by xanthones, flavonoids, and phenolics.[141] Gentiana kurroo rhizome improves hepatic ADH, SREBP1c, and mitochondrial biogenesis gene expression, reduces lipid peroxidation, and enhances antioxidant enzyme activities.[142] Hyperoside inhibits mTORC1, activating the TFEB-mediated autophagy-lysosome pathway and mitochondrial biogenesis, alleviating palmitic acid-induced liver injury.[143]

Some natural products activate both mitochondrial biogenesis and mitophagy. Lycium barbarum polysaccharide (LBP) administration reduces oxidative stress, restores mitochondrial structure and function, and prevents mitochondrial dysfunction, thereby mitigating hepatic fibrosis.[144] Another study demonstrated that LBP enhances mitochondrial respiration, increases tissue ATP levels, and reactivates respiratory chain complexes I–V, alleviating mitochondrial damage and boosting hepatic antioxidant capacity.[145] Cordycepin promotes Parkin-dependent mitophagy and mitochondrial biogenesis, restoring mitochondrial homeostasis and reducing oxidative stress, thereby alleviating MASLD.[146] Pseudolaric Acid B upregulates PPARα downstream genes involved in lipid metabolism and mitochondrial biogenesis, reduces lipid accumulation, improves liver injury, and enhances mitochondrial biogenesis.[147]

In summary, Natural products do not merely increase mitochondrial number; they reprogram mitochondrial quality, redox homeostasis, and metabolic signaling through convergent activation of PGC-1α, sirtuins, and nuclear transcription factors. This mechanistic convergence highlights mitochondrial biogenesis, not as an isolated compensatory response, but as a central therapeutic axis that integrates lipid metabolism, inflammation, autophagy, and NAD^+ biology (Table 2).

Natural Products Improving Mitochondrial Proteostasis and UPR^{mt}

Direct evidence that natural products modulate canonical UPR^{mt} components in liver disease models remains sparse but is emerging. Hesperidin has a potential binding site for SIRT3, thereby activating the SIRT3-FOXO3A signaling pathway and leading to a significant decrease in the expression levels of UPR^{mt}-related proteins and genes.[148] Nicotinamide riboside can alleviate ethanol-induced oxidative stress, inflammation, and mitochondrial dysfunction, and regulate the

ATF5-dependent UPR^{mt} pathway in ImKCs.[125] Nicotinamide riboside also increases the expression of UPR^{mt} markers, including ClpP and HSP60, and restores mitochondrial protein homeostasis and function in preclinical studies, providing a feasibility for drug-induced UPR^{mt}.[126] Lipoic acid can regulate UPR^{mt} and alleviate oxidative stress, reducing UPRmt activation induced by a FFA mixture in HepG2 cells while improving mitochondrial function.[99] Despite mechanistic plausibility and a few promising reports, several critical gaps remain. Few liver studies measure the full UPR^{mt} signature after natural-product treatment. How UPR^{mt} interacts temporally with mitophagy, fusion/fission, and biogenesis under natural-product treatment remains largely untested (Table 2).

Multi-Target MQC Modulation by Traditional Chinese Medicine Formulas

Unlike single-target small molecules, TCM formulas frequently act on coordinated mitochondrial modules, enabling integrated remodeling of hepatocellular metabolism. Several formulas simultaneously promote mitochondrial biogenesis and stabilize mitochondrial structure. Jianpi Shengqing Huazhuo Formula promotes liver mitochondrial biosynthesis, improves glucose and lipid metabolism, and regulates the mitochondrial-dependent apoptosis marker Bcl-2/Bax to alleviate liver damage.[149] The modified Rougan decoction upregulates the SIRT1/PGC-1α pathway to promote mitochondrial biosynthesis, maintain mitochondrial structure and function, and thus reduce hepatocyte apoptosis.[150] TCM formulas frequently modulate mitochondrial dynamics and their coupling to mitophagy. Sheng Mai San regulates glycolysis and the tricarboxylic acid cycle to support energy metabolism, promotes AMPK phosphorylation, and maintains mitochondrial homeostasis, thereby alleviating liver damage through Drp1-dependent mitophagy.[151] GerGen-ChynLian-Tang promotes Parkin-dependent, non-disintegrative mitophagy through mitochondrial fusion rather than fission.[152]

Activation of mitophagy is a central and conserved signature across numerous formulas. Lipi Jiangzhuo Decoction increases the expression of PINK1 and Parkin proteins, increases the number of mitophagosomes, and restores mitochondrial membrane potential to activate mitophagy, reduces PERK expression to inhibit endoplasmic reticulum stress, improves liver function, and reduces liver lipid droplet accumulation.[153] S100A9/RAGE pathway activation impairs mitophagy, and the expression of Pink1, Parkin, and LC3B decreases. JianPi LiShi YangGan Formula increases the expression levels of Pink1, Parkin, and LC3B and enhances mitophagy, while inhibiting the activation of the S100A9/RAGE signaling pathway.[154] YangGan-JiangMei formula promotes PINK1/Parkin-mediated mitophagy and inhibits NLRP3 inflammasome activation, leading to recovery of mitochondrial function and reducing liver damage and lipid deposition.[155] Qidan Tiaozhi capsule activates AMPK/PINK1-Parkin-mediated mitophagy, thereby inhibiting oxidative stress and reducing intracellular lipid accumulation, as well as TC, TG, MDA, and ROS levels, and increasing SOD levels and mitochondrial membrane potential.[156]

Traditional Chinese medicine formulas demonstrate their multi-component, multi-pathway pharmacological effects by systematically regulating multiple MQC levels, including mitochondrial dynamics, biosynthesis, mitophagy, and protein homeostasis (Table 3).

Toxicology, Safety, and Translational Perspectives

Natural products can simultaneously activate mitophagy, stabilize mitochondrial dynamics, and enhance biosynthesis, making them useful for treating MASLD. However, their toxicological risks are often overlooked, as many drugs can impair mitochondrial function and lipid homeostasis.[158,159] Many traditional Chinese medicines and their active ingredients exhibit hepatotoxicity and nephrotoxicity under specific conditions. These toxicities are triggered by mechanisms such as ETC inhibition, ROS amplification, or membrane uncoupling, posing a significant obstacle to their translational application.[160] MASLD hepatocytes are characterized by redox overload and impaired MQC buffering capacity, which exacerbates their susceptibility to toxic metabolites and membrane depolarization.[161] The toxic components of Evodiae Fructus and Polygonum multiflorum or their metabolic intermediates can induce excessive mitochondrial ROS production, disrupt mitochondrial membrane potential, and inhibit oxidative phosphorylation, leading to insufficient ATP synthesis, activation of mitochondrial permeability transition and cell death pathways, and exacerbating hepatocyte damage.[162,163] Furthermore, many natural products, such as Emodin, have low bioavailability,[164] complex metabolic activation, and inter-individual

Table 3 Traditional Chinese Medicines for MASLD Mitochondrial Quality Control

Traditional Chinese Medicine	Representative Compounds	Major Bioactive Constituents	Experimental Evidence	Experimental Models	Molecular Mechanism	Pharmacological Effects
Jianpi Shengqing Huazhuo Formula[149]	*Astragalus mongholicus* Bunge (20g), *Dioscorea opposita* Thunb (20g), *Atractylodes macrocephala* Koidz (15g), *Pseudostellaria heterophylla* (Miq.) Pax (15g), *Pueraria lobata* (Willd.) Ohwi (15g), and *Gallus domesticus* Brisson (15g)	Calycosin-7-glucoside, Allantoin, Puerarin (Pueraria lobata (Willd.) Ohwi) and Atractylenolide II (Atractylodes macrocephala Koidz)	Clinical trials and in vivo	Obesity/ Metabolic Disorder Model	Increased SIRT1/PGC-1α ratio, and promotes mitochondrial biogenesis	Improve glucose and lipid metabolism and reduce obesity-related metabolic abnormalities
The modified rougan decoction[150]	*Hypericum japonicum, Alisma orientalis, Paeonia lactiflora, Poria, Glycyrrhizae radix, Schisandra Chinensis fruit*, and *Magnolia officinalis*	Flavonoids, polysaccharides, polyphenols, terpenoids, sterols, vitamins[157]	In vivo and in vitro	Liver oxidative damage model	Upregulation of the SIRT1/PGC-1α signaling pathway promotes mitochondrial biosynthetic capacity.	In vivo and in vitro amelioration of hepatocyte apoptosis
Sheng Mai San[151]	*Panax ginseng* C.A. Mey., *Ophiopogon japonicas*, Ker-Gawl and *Schisandra chinensis*	Ginsenoside Rb1, ginsenoside Rh1, ginsenoside Rg3, ophiopogonin D, ruscogenin and schisandrin A	In vivo	Heat stress liver injury model	AMPK/Drp1 regulates autophagy and improves energy metabolism	Reduce liver damage and improve mitochondrial function
GerGen ChynLian Tang[152]	*Puerariae Radix, Scutellariae Radix, Coptidis Rhizoma*, and *Glycyrrhizae Radix*	Puerarin, baicalin, berberine, baicalein, glycyrrhizic acid, and wogonin	In vivo	NAFLD mouse model	Promotes mitochondrial biogenesis and regulates mitophagy	Improves lipotoxicity and inhibits inflammation
Lipi Jiangzhuo Decoction[153]	*Polygonatum sibiricum* F. Delaroche (15g), *Pueraria alopecuroides* Craib (30g), *Panax ginseng* C. A. Mey (6g), *Atractylodes lancea* (Thunb.) DC. (15g), *Crataegus pinnatifida* Bunge (15g) and *Alisma plantago-aquatica* L (30g).	Quercetin, arginine, naringenin, and berberine	In vivo and in vitro	MASH model	Regulates ferroptosis and mitochondrial function through the PERK/PINK1/ GPx4 pathway	Improves fatty liver disease and inhibiting oxidative stress.

(*Continued*)

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Table 3 (Continued).

Traditional Chinese Medicine	Representative Compounds	Major Bioactive Constituents	Experimental Evidence	Experimental Models	Molecular Mechanism	Pharmacological Effects
JianPi LiShi YangGan Formula[154]	*Herba Artemisiae Scopariae* (30g), *Astragalus membranaceus* (20g), *Rhizoma Dioscoreae* (15g), *Cornus officinalis* Sieb. (10g), *Amomum tsao-ko* Crevost et Lemarié (10g), *Herba Hyperici Japonici* (20g), *Crataegi Fructus* (15g), *Amomum aurantiacum* (5g) and *Rhizoma Cyperi* (10g).	Chlorogenic acid, rutin, quercetin, and catechin	In vivo and in vitro	Liver failure model	Regulates mitophagy via the S100A9/ RAGE pathway	Inhibits inflammation and reducing hepatocellular damage
YangGan-JiangMei formula[155]	*Ligustrum lucidum* Ait (15g), *Ophiopogon japonicus* (Linn.f.) Ker-Gawl (15g), *Lycium barbarum* L (12g), *Forsythia suspensa* (Thunb.) Vahl (15g), *Atractylodes macrocephala* Koidz (10g) and *Glycyrrhiza uralensis* Fisch (6g)	/	In vivo	NASH model	Inhibites NLRP3 inflammasomes promotes mitophagy	Anti-inflammatory and improves fatty liver disease
Qidan Tiaozhi capsule[156]	*Astragalus membranaceus* (Fisch.) Ege., *Salvia miltiorrhiza* Bge., *Laminaria japonica* Aresch., and *Cassia obtusifolia* L.,	/	In vivo and in vitro	Metabolic syndrome mode	AMPK/PINK1-Parkin-mediated mitophagy	Improves metabolic syndrome and regulates lipid metabolism

variability in metabolism influenced by the gut microbiota,[165,166] further complicating their translational applications. Advanced formulations (nanoparticles, liposomes) improve exposure but may alter subcellular targeting and mitochondrial distribution, creating new uncertainties.[167] In summary, natural products possess significant potential to modulate the MQC network in MASLD. To drive the clinical translation of MQC-targeted natural products, key research areas include subcellular pharmacokinetics, standardized mitophagy and respiratory flux assays, and the development of MQC-related biomarkers. Formulation innovation should focus on targeted delivery systems to minimize systemic toxicity.

Conclusions and Perspectives

MASLD is a disease characterized by hepatic lipid metabolism imbalance, driven not only by metabolic overload but also by mitochondrial quality-control failure. MASLD is not a single "mitochondrial dysfunction," but rather is characterized by selective and progressive damage to different MQC modules, including excessive cell division, defective mitophagy, insufficient biosynthesis, and dysregulation of protein homeostasis. These defects collectively

impair hepatocytes' resistance to chronic nutritional stress. Importantly, these mitochondrial defects exhibit a spatial distribution within liver lobules and spread beyond hepatocytes via the inflammatory and fibrotic signaling pathways, mediated by mitochondrial DAMP.

Natural products, as a unique class of drugs, can target this multifaceted MQC network. Unlike single-pathway drugs, many natural compounds and traditional Chinese medicine formulas can simultaneously activate the AMPK-SIRT-PGC-1α-driven biosynthetic pathway, restore PINK1/Parkin-dependent mitophagy, rebalance mitochondrial dynamics, and regulate the UPR^{mt} signaling pathway, thereby reprogramming mitochondrial quality rather than simply increasing mitochondrial quantity. This systemic regulation is closely related to the complex multi-hit pathogenesis of MASLD.

However, clinical translation still faces many challenges. The hepatotoxicity, limited bioavailability, and context-dependent effects of natural products on mitochondria necessitate rigorous toxicological assessments, subcellular pharmacokinetic analyses, and standardized MQC biomarker assays. These advances will make mitochondrial quality control an actionable and drug-targetable axis in the precision treatment of MASLD.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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References

1. Younossi ZM, Kalligeros M, Henry L. Epidemiology of metabolic dysfunction-associated steatotic liver disease. *Clin Mol Hepatol*. 2025;31 Suppl:S32–50. doi:10.3350/cmh.2024.0431
2. Girish V, John S. Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2025.
3. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). 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
4. Rinella ME, Lazarus JV, Ratziu V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *J Hepatol*. 2023;79:1542–1556. doi:10.1016/j.jhep.2023.06.003
5. Stefan N, Yki-Järvinen H, Neuschwander-Tetri BA. Metabolic dysfunction-associated steatotic liver disease: heterogeneous pathomechanisms and effectiveness of metabolism-based treatment. *Lancet Diabetes Endocrinol*. 2025;13:134–148. doi:10.1016/S2213-8587(24)00318-8
6. Zheng Y, Wang S, Wu J, Wang Y. Mitochondrial metabolic dysfunction and non-alcoholic fatty liver disease: new insights from pathogenic mechanisms to clinically targeted therapy. *J Transl Med*. 2023;21:510. doi:10.1186/s12967-023-04367-1
7. Ramanathan R, Ali AH, Ibdah JA. Mitochondrial dysfunction plays central role in nonalcoholic fatty liver disease. *Int J Mol Sci*. 2022;23:7280. doi:10.3390/ijms23137280
8. Hernández-Alvarez MI, Sebastián D, Vives S, et al. Deficient endoplasmic reticulum-mitochondrial phosphatidylserine transfer causes liver disease. *Cell*. 2019;177:881–895. doi:10.1016/j.cell.2019.04.010
9. Undamatla R, Fagunloye OG, Chen J, et al. Reduced mitophagy is an early feature of NAFLD and liver-specific PARKIN knockout hastens the onset of steatosis, inflammation and fibrosis. *Sci Rep*. 2023;13:7575. doi:10.1038/s41598-023-34710-x
10. Keam SJ. Resmetirom: first approval. *Drugs*. 2024;84:729–735. doi:10.1007/s40265-024-02045-0

11. Xu J, Shen J, Yuan R, et al. Mitochondrial targeting therapeutics: promising role of natural products in non-alcoholic fatty liver disease. *Front Pharmacol*. 2021;12:796207. doi:10.3389/fphar.2021.796207
12. Zhang X, Fan Y, Tan K. A bird's eye view of mitochondrial unfolded protein response in cancer: mechanisms, progression and further applications. *Cell Death Dis*. 2024;15:667. doi:10.1038/s41419-024-07049-y
13. Dabravolski SA, Bezsonov EE, Orekhov AN. The role of mitochondria dysfunction and hepatic senescence in NAFLD development and progression. *Biomed Pharmacother*. 2021;142:112041. doi:10.1016/j.biopha.2021.112041
14. Cai J, Huang J, Yang J, et al. The protective effect of selenoprotein M on non-alcoholic fatty liver disease: the role of the AMPKα1-MFN2 pathway and Parkin mitophagy. *Cell Mol Life Sci*. 2022;79:354. doi:10.1007/s00018-022-04385-0
15. Kamfar S, Alavian SM, Houshmand M, et al. Liver mitochondrial DNA copy number and deletion levels may contribute to nonalcoholic fatty liver disease susceptibility. *Hepat Mon*. 2016;16:e40774. doi:10.5812/hepatmon.40774
16. Aharoni-Simon M, Hann-Obercyger M, Pen S, Madar Z, Tirosh O. Fatty liver is associated with impaired activity of PPARγ-coactivator 1α (PGC1α) and mitochondrial biogenesis in mice. *Lab Investig*. 2011;91:1018–1028. doi:10.1038/labinvest.2011.55
17. Sasse D, Spornitz UM, Maly IP. Liver architecture. *Enzyme*. 1992;46:8–32. doi:10.1159/000468776
18. Braet F, Wisse E. Structural and functional aspects of liver sinusoidal endothelial cell fenestrae: a review. *Comp Hepatol*. 2002;1:1. doi:10.1186/1476-5926-1-1
19. Kang SWS, Cunningham RP, Miller CB, et al. A spatial map of hepatic mitochondria uncovers functional heterogeneity shaped by nutrient-sensing signaling. *Nat Commun*. 2024;15:1799. doi:10.1038/s41467-024-45751-9
20. Parlakgül G, Pang S, Artico LL, et al. Spatial mapping of hepatic ER and mitochondria architecture reveals zonated remodeling in fasting and obesity. *Nat Commun*. 2024;15:3982. doi:10.1038/s41467-024-48272-7
21. Kietzmann T. Metabolic zonation of the liver: the oxygen gradient revisited. *Redox Biol*. 2017;11:622–630. doi:10.1016/j.redox.2017.01.012
22. Seubnooch P, Montani M, Dufour J-F, Masoodi M. Spatial lipidomics reveals zone-specific hepatic lipid alteration and remodeling in metabolic dysfunction-associated steatohepatitis. *J Lipid Res*. 2024;65:100599. doi:10.1016/j.jlr.2024.100599
23. Otkur W, Zhang Y, Li Y, et al. Spatial multi-omics characterizes GPR35-relevant lipid metabolism signatures across liver zonation in MASLD. *Life Metab*. 2024;3:loae021. doi:10.1093/lifemeta/loae021
24. Zhang X, Wu X, Hu Q, et al. Mitochondrial DNA in liver inflammation and oxidative stress. *Life Sci*. 2019;236:116464. doi:10.1016/j.lfs.2019.05.020
25. Yu Y, Liu Y, An W, Song J, Zhang Y, Zhao X. STING-mediated inflammation in Kupffer cells contributes to progression of nonalcoholic steatohepatitis. *J Clin Invest*. 2019;129:546–555. doi:10.1172/JCI121842
26. Chen R, Du J, Zhu H, Ling Q. The role of cGAS-STING signalling in liver diseases. *JHEP Rep Innov Hepatol*. 2021;3:100324. doi:10.1016/j.jhepr.2021.100324
27. An P, Wei -L-L, Zhao S, et al. Hepatocyte mitochondria-derived danger signals directly activate hepatic stellate cells and drive progression of liver fibrosis. *Nat Commun*. 2020;11:2362. doi:10.1038/s41467-020-16092-0
28. Liu W, Chen ZZ, Yang C, et al. Update on the STING signaling pathway in developing nonalcoholic fatty liver disease. *J Clin Transl Hepatol*. 2024;12:91–99. doi:10.14218/JCTH.2023.00197
29. Bazzani V, Equisoain Redin M, McHale J, Perrone L, Vascotto C. Mitochondrial DNA repair in neurodegenerative diseases and ageing. *Int J Mol Sci*. 2022;23:11391. doi:10.3390/ijms231911391
30. Detmer SA, Chan DC. Functions and dysfunctions of mitochondrial dynamics. *Nat Rev Mol Cell Biol*. 2007;8:870–879. doi:10.1038/nrm2275
31. Santos RX, Correia SC, Zhu X, et al. Mitochondrial DNA oxidative damage and repair in aging and Alzheimer's disease. *Antioxid Redox Signal*. 2013;18:2444–2457. doi:10.1089/ars.2012.5039
32. Bohr VA, Stevnsner T, de Souza-Pinto NC. Mitochondrial DNA repair of oxidative damage in mammalian cells. *Gene*. 2002;286:127–134. doi:10.1016/s0378-1119(01)00813-7
33. de Souza-Pinto NC, Wilson DM, Stevnsner TV, Bohr VA. Mitochondrial DNA, base excision repair and neurodegeneration. *DNA Repair*. 2008;7:1098–1109. doi:10.1016/j.dnarep.2008.03.011
34. Qureshi K, Abrams GA. Metabolic liver disease of obesity and role of adipose tissue in the pathogenesis of nonalcoholic fatty liver disease. *World J Gastroenterol*. 2007;13:3540–3553. doi:10.3748/wjg.v13.i26.3540
35. Neeland IJ, Singh S, McGuire DK, et al. Relation of plasma ceramides to visceral adiposity, insulin resistance and the development of type 2 diabetes mellitus: the Dallas Heart Study. *Diabetologia*. 2018;61:2570–2579. doi:10.1007/s00125-018-4720-1
36. Yun H, Qi Q-B, Zong G, et al. Plasma sphingolipid profile in association with incident metabolic syndrome in a Chinese Population-Based Cohort Study. *Nutrients*. 2021;13:2263. doi:10.3390/nu13072263
37. Sanders FWB, Griffin JL. De novo lipogenesis in the liver in health and disease: more than just a shunting yard for glucose. *Biol Rev Camb Philos Soc*. 2016;91:452–468. doi:10.1111/brv.12178
38. Legaki A-I, Moustakas II, Sikorska M, Papadopoulos G, Velliou R-I, Chatzigeorgiou A. Hepatocyte mitochondrial dynamics and bioenergetics in obesity-related non-alcoholic fatty liver disease. *Curr Obes Rep*. 2022;11:126–143. doi:10.1007/s13679-022-00473-1
39. Malik AN, Simões ICM, Rosa HS, Khan S, Karkucinska-Wieckowska A, Wieckowski MR. A diet induced maladaptive increase in hepatic mitochondrial DNA Precedes OXPHOS defects and may contribute to non-alcoholic fatty liver disease. *Cells*. 2019;8:1222. doi:10.3390/cells8101222
40. Lee K, Haddad A, Osme A, et al. Hepatic mitochondrial defects in a nonalcoholic fatty liver disease mouse model are associated with increased degradation of oxidative phosphorylation subunits. *Mol Cell Proteomics*. 2018;17:2371–2386. doi:10.1074/mcp.RA118.000961
41. Pirola CJ, Garaycoechea M, Flichman D, Castaño GO, Sookoian S. Liver mitochondrial DNA damage and genetic variability of Cytochrome b - a key component of the respirasome - drive the severity of fatty liver disease. *J Intern Med*. 2021;289:84–96. doi:10.1111/joim.13147
42. Jakubek P, Kalinowski P, Karkucinska-Wieckowska A, et al. Oxidative stress in metabolic dysfunction-associated steatotic liver disease (MASLD): how does the animal model resemble human disease? *FASEB J*. 2024;38:e23466. doi:10.1096/fj.202302447R
43. Shimada K, Crother TR, Karlin J, et al. Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. *Immunity*. 2012;36:401–414. doi:10.1016/j.immuni.2012.01.009
44. Li X, Qu J, Zhang Y, Liu R. The dual function of cGAS-STING signaling axis in liver diseases. *Acta Pharmacol Sin*. 2024;45:1115–1129. doi:10.1038/s41401-023-01220-5

45. Sookoian S, Flichman D, Scian R, et al. Mitochondrial genome architecture in non-alcoholic fatty liver disease. *J Pathol*. 2016;240:437–449. doi:10.1002/path.4803
46. Sharma S, Le Guillou D, Chen JY. Cellular stress in the pathogenesis of nonalcoholic steatohepatitis and liver fibrosis. *Nat Rev Gastroenterol Hepatol*. 2023;20:662–678. doi:10.1038/s41575-023-00832-w
47. Luangmonkong T, Suriguga S, Mutsaers HAM, Groothuis GMM, Olinga P, Boersema M. Targeting Oxidative Stress for the Treatment of Liver Fibrosis. *Rev Physiol Biochem Pharmacol*. 2018;175:71–102. doi:10.1007/112_2018_10
48. Wang Q, Bu Q, Liu M, et al. XBP1-mediated activation of the STING signalling pathway in macrophages contributes to liver fibrosis progression. *JHEP Rep Innov Hepatol*. 2022;4:100555. doi:10.1016/j.jhepr.2022.100555
49. Perrone M, Patergnani S, Di Mambro T, et al. Calcium homeostasis in the control of mitophagy. *Antioxid Redox Signal*. 2023;38:581–598. doi:10.1089/ars.2022.0122
50. Arruda AP, Hotamisligil GS. Calcium homeostasis and organelle function in the pathogenesis of obesity and diabetes. *Cell Metab*. 2015;22:381–397. doi:10.1016/j.cmet.2015.06.010
51. Shi R, Zhang Y, Chen G, et al. Ageing-dependent thyroid hormone receptor α reduction activates IP3R1-meditated Ca^{2+} transfer in MAM and exacerbates skeletal muscle atrophy in mice. *Cell Prolif*. 2025:e70120. doi:10.1111/cpr.70120
52. Wang K, Wang Y, Liu H-Y, et al. Harpagide from radix scrophulariae attenuated ischemic stroke injury through calcium homeostasis regulation between mitochondria-associated membranes via the IP3R1/GRP75/VDAC1 complex. *J Ethnopharmacol*. 2025;351:120147. doi:10.1016/j.jep.2025.120147
53. Xiao C, Wang C, Wang J, et al. FMO2 prevents pathological cardiac hypertrophy by maintaining the ER-mitochondria association through interaction with IP3R2-Grp75-VDAC1. *Circulation*. 2025;151:1667–1685. doi:10.1161/CIRCULATIONAHA.124.072661
54. Garbincius JF, Elrod JW. Mitochondrial calcium exchange in physiology and disease. *Physiol Rev*. 2022;102:893–992. doi:10.1152/physrev.00041.2020
55. Xiao F, Zhang J, Zhang C, An W. Hepatic stimulator substance inhibits calcium overflow through the mitochondria-associated membrane compartment during nonalcoholic steatohepatitis. *Lab Investig*. 2017;97:289–301. doi:10.1038/labinvest.2016.139
56. Li F, Guan Z, Gao Y, et al. ER stress promotes mitochondrial calcium overload and activates the ROS/NLRP3 axis to mediate fatty liver ischemic injury. *Hepatol Commun*. 2024;8:e0399. doi:10.1097/HC9.0000000000000399
57. Mridha AR, Wree A, Robertson AAB, et al. NLRP3 inflammasome blockade reduces liver inflammation and fibrosis in experimental NASH in mice. *J Hepatol*. 2017;66:1037–1046. doi:10.1016/j.jhep.2017.01.022
58. Xu H-L, Wan S-R, An Y, et al. Targeting cell death in NAFLD: mechanisms and targeted therapies. *Cell Death Discov*. 2024;10:399. doi:10.1038/s41420-024-02168-z
59. Chen W, Zhao H, Li Y. Mitochondrial dynamics in health and disease: mechanisms and potential targets. *Signal Transduct Target Ther*. 2023;8:333. doi:10.1038/s41392-023-01547-9
60. Otera H, Mihara K. Discovery of the membrane receptor for mitochondrial fission GTPase Drp1. *Small GTPases*. 2011;2:167–172. doi:10.4161/sgtp.2.3.16486
61. Losón OC, Song Z, Chen H, Chan DC. Fis1, Mff, MiD49, and MiD51 mediate Drp1 recruitment in mitochondrial fission. *Mol Biol Cell*. 2013;24:659–667. doi:10.1091/mbc.E12-10-0721
62. Chan DC. Fusion and fission: interlinked processes critical for mitochondrial health. *Annu Rev Genet*. 2012;46:265–287. doi:10.1146/annurev-genet-110410-132529
63. Zou Y, Zhang S, Yang J, et al. Protective effects of astaxanthin on Ochratoxin A-induced liver injury: effects of endoplasmic reticulum stress and mitochondrial fission-fusion balance. *Toxins*. 2024;16:68. doi:10.3390/toxins16020068
64. Da Dalt L, Moregola A, Svecla M, et al. The inhibition of inner mitochondrial fusion in hepatocytes reduces non-alcoholic fatty liver and improves metabolic profile during obesity by modulating bile acid conjugation. *Cardiovasc Res*. 2024;119:2917–2929. doi:10.1093/cvr/cvad169
65. Yamada T, Murata D, Kleiner DE, et al. Prevention and regression of megamitochondria and steatosis by blocking mitochondrial fusion in the liver. *iScience*. 2022;25:103996. doi:10.1016/j.isci.2022.103996
66. Steffen J, Ngo J, Wang S-P, et al. The mitochondrial fission protein Drp1 in liver is required to mitigate NASH and prevents the activation of the mitochondrial ISR. *Mol Metab*. 2022;64:101566. doi:10.1016/j.molmet.2022.101566
67. Padelli M, Hamelin J, Desterke C, et al. Analysis of the mitochondrial dynamics in NAFLD: drp1 as a marker of inflammation and fibrosis. *Int J Mol Sci*. 2025;26:7373. doi:10.3390/ijms26157373
68. You Y, Ni H, Ma Q, et al. Ketogenic diet ameliorates MASLD via balancing mitochondrial dynamics and improving mitochondrial dysfunction. *Nutr Diabetes*. 2025;15:37. doi:10.1038/s41387-025-00391-w
69. Zhu S, Li M, Huo Y, et al. Proteomics and cytokine array jointly reveal the role of macrophage proinflammatory shift in liver fibrosis in dairy cows with ketosis. *J Anim Sci Biotechnol*. 2025;16:97. doi:10.1186/s40104-025-01219-4
70. Liu A, Kage F, Abdulkareem AF, et al. Fatty acyl-coenzyme A activates mitochondrial division through oligomerization of MiD49 and MiD51. *Nat Cell Biol*. 2024;26:731–744. doi:10.1038/s41556-024-01400-3
71. Elbadawy M, Tanabe K, Yamamoto H, et al. Evaluation of the efficacy of mitochondrial fission inhibitor (Mdivi-1) using non-alcoholic steatohepatitis (NASH) liver organoids. *Front Pharmacol*. 2023;14:1243258. doi:10.3389/fphar.2023.1243258
72. Lazarou M, Sliter DA, Kane LA, et al. The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy. *Nature*. 2015;524:309–314. doi:10.1038/nature14893
73. Narendra D, Tanaka A, Suen D-F, Youle RJ. Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. *J Cell Biol*. 2008;183:795–803. doi:10.1083/jcb.200809125
74. He H, Tang Y, Zhuang L, Zheng Y, Huang X. PINK1/Park2-mediated mitophagy relieve non-alcoholic fatty liver disease. *Physiol Res*. 2024;73:253–263. doi:10.33549/physiolres.934925
75. Tang Q-N, Tang L-Q, Liu L-T, et al. Efficacy of transnasal endoscopic fine-needle aspiration biopsy in diagnosing submucosal nasopharyngeal carcinoma. *Laryngoscope*. 2021;131:1798–1804. doi:10.1002/lary.29433
76. Wu W, Tian W, Hu Z, et al. ULK1 translocates to mitochondria and phosphorylates FUNDC1 to regulate mitophagy. *EMBO Rep*. 2014;15:566–575. doi:10.1002/embr.201438501

77. Chu CT, Ji J, Dagda RK, et al. Cardiolipin externalization to the outer mitochondrial membrane acts as an elimination signal for mitophagy in neuronal cells. *Nat Cell Biol*. 2013;15:1197–1205. doi:10.1038/ncb2837
78. Ma X, McKeen T, Zhang J, Ding W-X. Role and mechanisms of mitophagy in liver diseases. *Cells*. 2020;9:837. doi:10.3390/cells9040837
79. Giannakogeorgou A, Kahl S, Granata C, et al. Relationship of GDF15 with hepatic mitochondrial respiration is depending on the presence of fibrosis in obese individuals. *Metabolism*. 2025;173:156391. doi:10.1016/j.metabol.2025.156391
80. Mosca A, Braghini MR, Andolina G, et al. Levels of growth differentiation factor 15 correlated with metabolic dysfunction-associated steatotic liver disease in children. *Int J Mol Sci*. 2025;26:6486. doi:10.3390/ijms26136486
81. Rodgers JT, Lerin C, Haas W, Gygi SP, Spiegelman BM, Puigserver P. Nutrient control of glucose homeostasis through a complex of PGC-1alpha and SIRT1. *Nature*. 2005;434:113–118. doi:10.1038/nature03354
82. Rodgers JT, Lerin C, Gerhart-Hines Z, Puigserver P. Metabolic adaptations through the PGC-1α and SIRT1 pathways. *FEBS Lett*. 2008;582:46–53. doi:10.1016/j.febslet.2007.11.034
83. Gureev AP, Shaforostova EA, Popov VN. Regulation of mitochondrial biogenesis as a way for active longevity: interaction between the Nrf2 and PGC-1α signaling pathways. *Front Genet*. 2019;10:435. doi:10.3389/fgene.2019.00435
84. Morris EM, Meers GME, Booth FW, et al. PGC-1α overexpression results in increased hepatic fatty acid oxidation with reduced triacylglycerol accumulation and secretion. *Am J Physiol Gastrointest Liver Physiol*. 2012;303:G979–92. doi:10.1152/ajpgi.00169.2012
85. Vilà L, Elias I, Roca C, et al. AAV8-mediated Sirt1 gene transfer to the liver prevents high carbohydrate diet-induced nonalcoholic fatty liver disease. *Mol Ther Methods Clin Dev*. 2014;1:14039. doi:10.1038/mtm.2014.39
86. Wang X, Wang J, Ying C, Xing Y, Su X, Men K. Fenofibrate alleviates NAFLD by enhancing the PPARα/PGC-1α signaling pathway coupling mitochondrial function. *BMC Pharmacol Toxicol*. 2024;25:7. doi:10.1186/s40360-023-00730-6
87. Arconzo M, Piccinin E, Pasculli E, et al. Hepatic-specific Pgc-1α ablation drives fibrosis in a MASH model. *Liver Int*. 2024;44:2738–2752. doi:10.1111/liv.16052
88. Gomez-Llorente Y, Jebara F, Patra M, et al. Structural basis for active single and double ring complexes in human mitochondrial Hsp60-Hsp10 chaperonin. *Nat Commun*. 2020;11:1916. doi:10.1038/s41467-020-15698-8
89. Nouri K, Feng Y, Schimmer AD. Mitochondrial ClpP serine protease-biological function and emerging target for cancer therapy. *Cell Death Dis*. 2020;11:841. doi:10.1038/s41419-020-03062-z
90. Szczepanowska K, Trifunovic A. Mitochondrial matrix proteases: quality control and beyond. *FEBS J*. 2022;289:7128–7146. doi:10.1111/febs.15964
91. Huang S, Wang X, Yu J, et al. LonP1 regulates mitochondrial network remodeling through the PINK1/Parkin pathway during myoblast differentiation. *Am J Physiol Cell Physiol*. 2020;319:C1020–8. doi:10.1152/ajpcell.00589.2019
92. Weng S-W, Wu J-C, Shen F-C, et al. Chaperonin counteracts diet-induced non-alcoholic fatty liver disease by aiding sirtuin 3 in the control of fatty acid oxidation. *Diabetologia*. 2023;66:913–930. doi:10.1007/s00125-023-05869-9
93. Xu D, Zhang Z, Zhu Z, et al. Decreased LONP1 expression exacerbates MASH-induced liver fibrosis via elevated orotic acid levels. *J Hepatol*. 2026;84:165–180. doi:10.1016/j.jhep.2025.07.013
94. Zhang J, Jiang Y, Fan D, et al. Chemical activation of mitochondrial ClpP to modulate energy metabolism of CD4+ T cell for inflammatory bowel diseases treatment. *Cell Rep Med*. 2024;5:101840. doi:10.1016/j.xcrm.2024.101840
95. Shin C-S, Meng S, Garbis SD, et al. LONP1 and mtHSP70 cooperate to promote mitochondrial protein folding. *Nat Commun*. 2021;12:265. doi:10.1038/s41467-020-20597-z
96. Tian C, Min X, Zhao Y, et al. MRG15 aggravates non-alcoholic steatohepatitis progression by regulating the mitochondrial proteolytic degradation of TUFM. *J Hepatol*. 2022;77:1491–1503. doi:10.1016/j.jhep.2022.07.017
97. Uoselis L, Lindblom R, Lam WK, et al. Temporal landscape of mitochondrial proteostasis governed by the UPRmt. *Sci Adv*. 2023;9:eadh8228. doi:10.1126/sciadv.adh8228
98. Choi S-E, Hwang Y, Lee S-J, et al. Mitochondrial protease ClpP supplementation ameliorates diet-induced NASH in mice. *J Hepatol*. 2022;77:735–747. doi:10.1016/j.jhep.2022.03.034
99. Longhitano L, Distefano A, Musso N, et al. (+)-Lipoic acid reduces mitochondrial unfolded protein response and attenuates oxidative stress and aging in an in vitro model of non-alcoholic fatty liver disease. *J Transl Med*. 2024;22:82. doi:10.1186/s12967-024-04880-x
100. Yuan X, Sun W, Xu Y, et al. Altered mitochondrial unfolded protein response and FGF21 secretion in MASLD progression and the effect of exercise intervention. *Sci Rep*. 2025;15:3686. doi:10.1038/s41598-025-87190-6
101. Tang S, Borlak J. A comparative genomic study across 396 liver biopsies provides deep insight into FGF21 mode of action as a therapeutic agent in metabolic dysfunction-associated steatotic liver disease. *Clin Transl Med*. 2025;15:e70218. doi:10.1002/ctm2.70218
102. Wang L, Nomura S, Hasuzawa N, et al. Impact of Drp1 loss on organelle interaction, metabolism, and inflammation in mouse liver. *Cells*. 2025;14:679. doi:10.3390/cells14100679
103. Kai J, Yang X, Wang Z, et al. Oroxylin a promotes PGC-1α/Mfn2 signaling to attenuate hepatocyte pyroptosis via blocking mitochondrial ROS in alcoholic liver disease. *Free Radic Biol Med*. 2020;153:89–102. doi:10.1016/j.freeradbiomed.2020.03.031
104. Chen S, Lu H, Yin G, et al. Hesperitin prevents non-alcoholic steatohepatitis by modulating mitochondrial dynamics and mitophagy via the AMPKα-Drp1/PINK1-Parkin signaling pathway. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2025;1870:159570. doi:10.1016/j.bbalip.2024.159570
105. Yuan L, Jiang X, Ren Y, et al. Dihydromyricetin ameliorates lipopolysaccharide–induced hepatic injury in chickens by activating the Nrf2/Keap1 pathway and regulating mitochondrial dynamics. *Poult Sci*. 2025;104:105034. doi:10.1016/j.psj.2025.105034
106. Choi Y, Seo H, Cho M, et al. Rutin inhibits DRP1-mediated mitochondrial fission and prevents ethanol-induced hepatotoxicity in HepG2 cells and zebrafish. *Anim Cells Syst*. 2021;25:74–81. doi:10.1080/19768354.2021.1882565
107. Deshmukh H, Santos JM, Bender M, Dufour JM, Lovett J, Shen C-L. Peanut shell extract improves mitochondrial function in db/db mice via suppression of oxidative stress and inflammation. *Nutrients*. 2024;16:1977. doi:10.3390/nu16131977
108. Adhikari B, Dhungana SK, Waqas Ali M, Adhikari A, Kim I-D, Shin D-H. Antioxidant activities, polyphenol, flavonoid, and amino acid contents in peanut shell. *J Saudi Soc Agric Sci*. 2019;18:437–442. doi:10.1016/j.jssas.2018.02.004
109. Zhong Y, Li Z, Jin R, et al. Diosgenin Ameliorated Type II diabetes-associated nonalcoholic fatty liver disease through inhibiting de novo lipogenesis and improving fatty acid oxidation and mitochondrial function in rats. *Nutrients*. 2022;14:4994. doi:10.3390/nu14234994

110. Yang Y, Zhou W, Wang Y, et al. Bavachin induces liver injury and cell apoptosis by targeting Wnt/β-catenin/DRP1 signaling pathway mediated mitochondrial dysfunction. *Toxicol Lett*. 2023;387:1–13. doi:10.1016/j.toxlet.2023.09.006
111. Yu J, Fu R, Buhe A, Xu B. Quercetin attenuates lipopolysaccharide-induced hepatic inflammation by modulating autophagy and necroptosis. *Poult Sci*. 2024;103:103719. doi:10.1016/j.psj.2024.103719
112. Liu J, Chen H, Lin H, et al. Iron-frataxin involved in the protective effect of quercetin against alcohol-induced liver mitochondrial dysfunction. *J Nutr Biochem*. 2023;114:109258. doi:10.1016/j.jnutbio.2022.109258
113. Cao P, Wang Y, Zhang C, et al. Quercetin ameliorates nonalcoholic fatty liver disease (NAFLD) via the promotion of AMPK-mediated hepatic mitophagy. *J Nutr Biochem*. 2023;120:109414. doi:10.1016/j.jnutbio.2023.109414
114. He Q, Yin Z, Chen Y, et al. Cyanidin-3-O-glucoside alleviates ethanol-induced liver injury by promoting mitophagy in a Gao-binge mouse model of alcohol-associated liver disease. *Biochim Biophys Acta Mol Basis Dis*. 2024;1870:167259. doi:10.1016/j.bbadis.2024.167259
115. Zhang Y, Tan X, Cao Y, An X, Chen J, Yang L. Punicalagin protects against diabetic liver injury by upregulating mitophagy and antioxidant enzyme activities. *Nutrients*. 2022;14:2782. doi:10.3390/nu14142782
116. Zhang Q, Hu J, Mao A, Liu M, Guan S, Lu J. Ginsenoside Rb1 alleviated concanavalin A-induced hepatocyte pyroptosis by activating mitophagy. *Food Funct*. 2023;14:3793–3803. doi:10.1039/d2fo03130b
117. Wang X, Gao M, Lu X, et al. Resveratrol alleviates Mono-2-ethylhexyl phthalate-induced mitophagy, ferroptosis, and immunological dysfunction in grass carp hepatocytes by regulating the Nrf2 pathway. *J Environ Manage*. 2024;371:123235. doi:10.1016/j.jenvman.2024.123235
118. He S, Wen W, Li Y, Hu Z, Huang F, Xu H. Resveratrol ameliorates CCl4-induced acute liver injury by restoring Parkin-mediated mitophagy. *Mol Biol Rep*. 2025;53:56. doi:10.1007/s11033-025-11223-6
119. Wu L, Chen Q, Dong B, et al. Resveratrol alleviates lipopolysaccharide-induced liver injury by inducing SIRT1/P62-mediated mitophagy in gibel carp (Carassius gibelio). *Front Immunol*. 2023;14:1177140. doi:10.3389/fimmu.2023.1177140
120. Wang Y, Shan H, Wu H, et al. Resveratrol effectively promoted hepatocyte differentiation of hESCs by enhancing mitochondrial function through PGC-1α PPARγ pathway. *Biochem Biophys Res Commun*. 2025;777:152283. doi:10.1016/j.bbrc.2025.152283
121. He J, Qian Y-C, Yin Y-C, Kang J-R, Pan T-R. Polydatin: a potential NAFLD therapeutic drug that regulates mitochondrial autophagy through SIRT3-FOXO3-BNIP3 and PINK1-PRKN mechanisms - a network pharmacology and experimental investigation. *Chem Biol Interact*. 2024;398:111110. doi:10.1016/j.cbi.2024.111110
122. Wang T, Xu Q, Cao Y, et al. Luteolin ameliorates hepatic steatosis and enhances mitochondrial biogenesis via AMPK/PGC-1α pathway in western diet-fed mice. *J Nutr Sci Vitaminol*. 2023;69:259–267. doi:10.3177/jnsv.69.259
123. Hou Y, Zhao X, Wang Y, et al. Oleuropein-rich jasminum grandiflorum flower extract regulates the LKB1-PGC-1α axis related to the attenuation of hepatocellular lipid dysmetabolism. *Nutrients*. 2023;16:58. doi:10.3390/nu16010058
124. Tran Q-A, Tran GV, Velic S, et al. Effects of Astragaloside IV and formononetin on oxidative stress and mitochondrial biogenesis in hepatocytes. *Int J Mol Sci*. 2025;26:774. doi:10.3390/ijms26020774
125. Lee J, Woo H, Kang H, Park Y-K, Lee J-Y. Nicotinamide riboside targets mitochondrial unfolded protein response to reduce alcohol-induced damage in Kupffer cells. *J Pathol*. 2025;265:110–122. doi:10.1002/path.6372
126. Zhou Q, Zhu L, Qiu W, et al. Nicotinamide riboside enhances mitochondrial proteostasis and adult neurogenesis through activation of mitochondrial unfolded protein response signaling in the brain of ALS SOD1G93A mice. *Int J Biol Sci*. 2020;16:284–297. doi:10.7150/ijbs.38487
127. Zhang R, Chu K, Zhao N, et al. Corilagin alleviates nonalcoholic fatty liver disease in high-fat diet-induced C57BL/6 mice by ameliorating oxidative stress and restoring autophagic flux. *Front Pharmacol*. 2020;10:1693. doi:10.3389/fphar.2019.01693
128. Zhou H-Y, Li T, Lu Y-Q. Baicalin and its nanoliposome ameliorate diquat-induced liver injury by promoting PINK1/Parkin-dependent mitophagy. *Hepatobiliary Pancreat Dis Int*. 2025;24:527–534. doi:10.1016/j.hbpd.2025.06.008
129. Dong M, Zhang T, Liang X, et al. Sesamin alleviates lipid accumulation induced by oleic acid via PINK1/Parkin-mediated mitophagy in HepG2 cells. *Biochem Biophys Res Commun*. 2024;708:149815. doi:10.1016/j.bbrc.2024.149815
130. Yao Z, Li X, Wang W, et al. Corn peptides attenuate non-alcoholic fatty liver disease via PINK1/Parkin-mediated mitochondrial autophagy. *Food Nutr Res*. 2023;67:10–29219. doi:10.29219/fnr.v67.9547
131. Zhao J, He B, Zhang S, Huang W, Li X. Ginsenoside Rg1 alleviates acute liver injury through the induction of autophagy and suppressing NF-κB/NLRP3 inflammasome signaling pathway. *Int J Med Sci*. 2021;18:1382–1389. doi:10.7150/ijms.50919
132. Lin J, Qing Z, Huang H, Yang S, Zeng Z. Ginsenoside Rg1 alleviates rat liver ischemia-reperfusion ischemia through mitochondrial autophagy pathway. *Altern Ther Health Med*. 2023;29:16–25.
133. Yan M, Jin S, Liu Y, et al. Cajaninstilbene acid ameliorates acetaminophen-induced liver injury through enhancing Sestrin2/AMPK-mediated mitochondrial quality control. *Front Pharmacol*. 2022;13:824138. doi:10.3389/fphar.2022.824138
134. Rustamov N, Ma Y, Park J-S, et al. Korean red ginseng improves oxidative stress-induced hepatic insulin resistance via enhancing mitophagy. *Foods*. 2024;13:2137. doi:10.3390/foods13132137
135. Zhou Y, Wang J, Zhao Y, et al. Salidroside inhibits α-amanitin-induced AML-12 cell apoptosis via the regulation of PINK1/Parkin-mediated mitophagy and mitochondrial function. *Chem Res Toxicol*. 2024;37:1053–1061. doi:10.1021/acs.chemrestox.4c00139
136. Katoch S, Chhimwal J, Singh D, Kumar D, Patial V. Picrosides-rich fraction from Picrorhiza kurroa attenuates steatohepatitis in zebrafish and mice by modulating lipid metabolism and inflammation. *Phytomedicine*. 2025;137:156368. doi:10.1016/j.phymed.2025.156368
137. Wang W, Wu D, Liu J, Yang DA. Potential protective role of Lycium ruthenicum Murray polysaccharides against lipopolysaccharide-induced liver injury via mitochondrial biogenesis. *Int J Biol Macromol*. 2025;306(Pt 2):141365. doi:10.1016/j.ijbiomac.2025.141365
138. Du S, Zhu X, Zhou N, Zheng W, Zhou W, Li X. Curcumin alleviates hepatic steatosis by improving mitochondrial function in postnatal overfed rats and fatty L02 cells through the SIRT3 pathway. *Food Funct*. 2022;13:2155–2171. doi:10.1039/d1fo03752h
139. Nagara Y, Tsuji K, Kamei Y, Akagawa M. Bergenin promotes mitochondrial biogenesis via the AMPK/SIRT1 axis in hepatocytes. *J Med Investig*. 2025;72(1.2):66–75. doi:10.2152/jmi.72.66
140. Liu J, Zhang W, Li X, Xu S. New insights into Baicalein's effect on chlorpyrifos-induced liver injury in carp: involving macrophage polarization and pyroptosis. *J Agric Food Chem*. 2023;71:4132–4143. doi:10.1021/acs.jafc.2c08580
141. Skinder BM, Ganai BA, Wani AH. Scientific study of Gentiana kurroo Royle. *Medicines*. 2017;4:74. doi:10.3390/medicines4040074

142. Choubey P, Sharma V, Joshi R, Upadhyaya A, Kumar D, Patial V. Hydroethanolic extract of Gentiana kurroo Royle rhizome ameliorates ethanol-induced liver injury by reducing oxidative stress, inflammation and fibrogenesis in rats. *J Ethnopharmacol*. 2024;325:117866. doi:10.1016/j.jep.2024.117866
143. Xu J, Xiong A, Wang X, et al. Hyperoside attenuates pyrrolizidine alkaloids-induced liver injury by ameliorating TFEB-mediated mitochondrial dysfunction. *Arch Pharm Res*. 2023;46:694–712. doi:10.1007/s12272-023-01460-3
144. Song J, Luo X, Xiong L, et al. Lycium barbarum polysaccharide alleviate cadmium-induced mitochondrial dysfunction mediated pyroptosis in duck liver. *Int J Biol Macromol*. 2025;311(Pt 4):143989. doi:10.1016/j.ijbiomac.2025.143989
145. Huang J, Bai Y, Xie W, et al. Lyciumbarbarum polysaccharides ameliorate canine acute liver injury by reducing oxidative stress, protecting mitochondrial function, and regulating metabolic pathways. *J Zhejiang Univ Sci B*. 2023;24:157–171. doi:10.1631/jzus.B2200213
146. Tian H-Y, Yu D-J, Xie T, et al. Cordycepin alleviates metabolic dysfunction-associated liver disease by restoring mitochondrial homeostasis and reducing oxidative stress via Parkin-mediated mitophagy. *Biochem Pharmacol*. 2025;232:116750. doi:10.1016/j.bcp.2025.116750
147. Liu S-Y, Zhang X-W, Gao G, et al. Pseudolaric Acid B alleviates non-alcoholic fatty liver disease by targeting PPARα to regulate lipid metabolism and promote mitochondrial biogenesis. *Chin J Integr Med*. 2025;31:877–888. doi:10.1007/s11655-025-3832-y
148. Wu Y, Wang S, Huang H, et al. Hesperidin mitigates copper nanoparticle exposure-induced mitochondrial unfolded protein response through the SIRT3-FOXO3A signaling pathway. *Int J Biol Macromol*. 2025;320(Pt 1):145750. doi:10.1016/j.ijbiomac.2025.145750
149. Wang W, Chen S, Xu S, et al. Jianpi Shengqing Huazhuo Formula improves abnormal glucose and lipid metabolism in obesity by regulating mitochondrial biogenesis. *J Ethnopharmacol*. 2024;319(Pt 1):117102. doi:10.1016/j.jep.2023.117102
150. Wang W, Wu D, Ding J, et al. Modified rougan decoction attenuates hepatocyte apoptosis through ameliorating mitochondrial dysfunction by upregulated SIRT1/PGC-1α signaling pathway. *Poult Sci*. 2023;102:102992. doi:10.1016/j.psj.2023.102992
151. Zhang X, Jia Y, Yuan Z, et al. Sheng Mai San ameliorated heat stress-induced liver injury via regulating energy metabolism and AMPK/Drp1-dependent autophagy process. *Phytomedicine*. 2022;97:153920. doi:10.1016/j.phymed.2021.153920
152. Wang C-H, Liu H-M, Chang Z-Y, Lee M-C, Hsu C-H, Lee T-Y. Antioxidants rich herbal formula Ger-Gen-Chyn-Lian-Tang protects lipotoxicity and ameliorates inflammation signaling through regulation of mitochondrial biogenesis and mitophagy in nonalcoholic fatty liver disease mice. *Front Biosci*. 2022;27:242. doi:10.31083/j.fbl2708242
153. Pan L, Liu J, Pang G, Liu G, Tian Y. Mechanism of Lipi Jiangzhuo decoction in improving metabolic dysfunction-associated steatohepatitis through the PERK/PINK1/GPx4 pathway. *J Inflamm Res*. 2025;18:10969–10994. doi:10.2147/JIR.S532630
154. Li J, Hu R, Liu X, et al. S100A9/RAGE pathway regulation of mitophagy and the effect of JianPi LiShi YangGan formula in acute-on-chronic liver failure. *J Ethnopharmacol*. 2025;348:119887. doi:10.1016/j.jep.2025.119887
155. Wu Y, Kuang Y, Wu Y, et al. Yang-Gan-Jiang-Mei formula alleviates non-alcoholic steatohepatitis by inhibiting NLRP3 inflammasome through mitophagy. *Biotechnol Genet Eng Rev*. 2024;40:1314–1333. doi:10.1080/02648725.2023.2193482
156. Su Z, Li H, Ye Z, et al. Qidan Tiaozhi capsule attenuates metabolic syndrome via activating AMPK/PINK1-Parkin-mediated mitophagy. *J Ethnopharmacol*. 2023;307:116091. doi:10.1016/j.jep.2022.116091
157. Wang W, Shi Y, Qiu T, et al. Modified rougan decoction alleviates lipopolysaccharide-enrofloxacin-induced hepatotoxicity via activating the Nrf2/ARE pathway in chicken. *Poult Sci*. 2022;102:102404. doi:10.1016/j.psj.2022.102404
158. Wallace KB. Mitochondrial off targets of drug therapy. *Trends Pharmacol Sci*. 2008;29:361–366. doi:10.1016/j.tips.2008.04.001
159. Begriche K, Massart J, Robin M-A, Bonnet F, Fromenty B. Mitochondrial adaptations and dysfunctions in nonalcoholic fatty liver disease. *Hepatology*. 2013;58:1497–1507. doi:10.1002/hep.26226
160. Łupina K, Nowak A, Jabłońska A, et al. Herb-induced liver injury. *Livers*. 2025;5:55. doi:10.3390/livers5040055
161. Li R, Toan S, Zhou H. Role of mitochondrial quality control in the pathogenesis of nonalcoholic fatty liver disease. *Aging*. 2020;12:6467–6485. doi:10.18632/aging.102972
162. Yan C, Peng T, Zhang T, et al. Molecular mechanisms of hepatotoxicity induced by compounds occurring in Evodiae Fructus. *Drug Metab Rev*. 2023;55:75–93. doi:10.1080/03602532.2023.2180027
163. Teka T, Wang L, Gao J, et al. Polygonum multiflorum: recent updates on newly isolated compounds, potential hepatotoxic compounds and their mechanisms. *J Ethnopharmacol*. 2021;271:113864. doi:10.1016/j.jep.2021.113864
164. Dong X, Fu J, Yin X, et al. Emodin: a review of its pharmacology, toxicity and pharmacokinetics. *Phytother Res*. 2016;30:1207–1218. doi:10.1002/ptr.5631
165. Dey P. Gut microbiota in phytopharmacology: a comprehensive overview of concepts, reciprocal interactions, biotransformations and mode of actions. *Pharmacol Res*. 2019;147:104367. doi:10.1016/j.phrs.2019.104367
166. Woo SM, Davis WD, Aggarwal S, Clinton JW, Kiparizoska S, Lewis JH. Herbal and dietary supplement induced liver injury: highlights from the recent literature. *World J Hepatol*. 2021;13:1019–1041. doi:10.4254/wjh.v13.i9.1019
167. Geng J, Wang J, Wang H. Emerging landscape of cell-penetrating peptide-mediated organelle restoration and replacement. *ACS Pharmacol Transl Sci*. 2023;6:229–244. doi:10.1021/acsptsci.2c00229