ABCResearch

Arch Basic Clin Res 2026;8(2):212-221
**DOI:** 10.4274/ABCR.2026.26417

Review

# Pharmacological Modulation of Mitochondrial Dysfunction in Experimental Models of Hepatic Injury

Aslı Özbek Bilgin

Department of Pharmacology, Erzincan Binali Yıldırım University Faculty of Medicine, Erzincan Türkiye

**Cite this article as:** Özbek Bilgin A. Pharmacological modulation of mitochondrial dysfunction in experimental models of hepatic injury. *Arch Basic Clin Res*. 2026;8(2):212-221.

**ORCID IDs of the authors:** A.Ö.B. 0000-0001-9027-4299.

## ABSTRACT

Mitochondrial dysfunction plays a central role in the pathogenesis of various liver diseases, ranging from drug-induced liver damage to steatotic liver disease associated with metabolic dysfunction. This review synthesizes recent advances in pharmacological strategies targeting mitochondrial quality control mechanisms. The shift from non-specific antioxidants to mitochondria-targeted agents is highlighted, as are the emerging roles of cardiolipin stabilizers (SS-31), next-generation cyclophilin inhibitors (Rencofilstat, C105SR), and modulation of immunometabolic pathways such as cGAS-STING and NLRP3. The transition of these promising experimental agents to clinical applications is also presented.

**Keywords:** Hepatic injury, mitochondria, mitochondrial dysfunction, mitochondrial permeability transition pore, pharmacological modulation

## INTRODUCTION

Hepatic injury is a major global health problem contributing to acute liver failure, chronic liver disease, and liver-related mortality. Diverse insults, including drug toxicity, ischemia-reperfusion, alcohol, viral infections, and metabolic stress, disrupt hepatocellular homeostasis and promote progressive liver damage. Despite advances in supportive care and transplantation, effective pharmacological strategies targeting the core cellular mechanisms of hepatic injury remain limited.

In recent years, increasing evidence has identified mitochondrial dysfunction as a central and unifying event in both acute and chronic liver injury. Hepatocytes are highly dependent on mitochondrial oxidative phosphorylation (OXPHOS) to meet their substantial energy demands, rendering them particularly vulnerable to mitochondrial insults. Experimental models of hepatic injury consistently demonstrate that mitochondrial abnormalities, including excessive reactive oxygen species (ROS) production, impairment of the electron transport chain (ETC), loss of mitochondrial membrane potential ($\Delta\Psi m$), mitochondrial DNA (mtDNA) damage, and dysregulated mitochondrial quality control, precede and drive hepatocellular death.[1-5] Importantly, mitochondria are no longer regarded as passive victims of cellular stress but rather as active regulators of cell fate decisions, inflammation, and tissue repair. This conceptual shift has transformed the therapeutic paradigm from merely counteracting downstream oxidative injury to directly targeting mitochondrial signaling, permeability transition, biogenesis, and quality-control pathways.

Among the various pathogenic mechanisms, mitochondrial oxidative stress has emerged as a key trigger of hepatocellular injury.[6] Excessive generation of mitochondrial ROS and reactive nitrogen species (RNS) disrupts redox homeostasis, promotes lipid peroxidation, and impairs mitochondrial enzymes critical for energy production. These mitochondrial disturbances converge on oxidative stress, permeability transition, bioenergetic failure, and defective quality control, all of which contribute to hepatocyte death and impaired tissue recovery.

Experimental models such as $CCl_4$, TAA, APAP, methotrexate (MTX), and ischemia-reperfusion injury have been instrumental in defining how mitochondrial dysfunction initiates and amplifies hepatic damage and have enabled the evaluation of mitochondria-targeted pharmacological interventions.[7,8]

**Corresponding author:** Aslı Özbek Bilgin, **E-mail:** asli.bilgin@erzincan.edu.tr

**Received:** February 19, 2026
**Revision Requested:** March 27, 2026 **Accepted:** May 25, 2026 **Publication Date:** July, 14, 2026

Copyright© 2026 The Author(s). Published by Galenos Publishing House on behalf of Erzincan Binali Yıldırım University.
This is an open access article under the Creative Commons AttributionNonCommercial 4.0 International (CC BY-NC 4.0) License.

In addition to acute mitochondrial injury, adaptive responses such as mitochondrial biogenesis and mitophagy have emerged as critical determinants of hepatocyte survival and recovery. Accordingly, this review examines mitochondrial dysfunction as a central pathogenic driver in experimental hepatic injury and discusses current pharmacological strategies targeting oxidative stress, modulators of the mitochondrial permeability transition pore (mPTP) regulation, mitochondrial biogenesis, mitophagy, and organelle crosstalk.

## MATERIALS AND METHODS

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. PubMed, Scopus, and Web of Science were searched for studies published between 2020 and 2025 using combinations of the terms "hepatic injury," "mitochondrial dysfunction," "oxidative stress," "mPTP," "mitophagy," and "experimental model." Titles and abstracts were screened for relevance, followed by full-text evaluation of potentially eligible articles. The primary focus was on peer-reviewed original experimental studies that used in vivo or in vitro models of hepatic injury and addressed mitochondrial pathways and their pharmacological modulation. To provide mechanistic context and clinical perspective, selected review articles and a limited number of foundational studies published before 2020 were also included, where directly relevant.

### Molecular Mechanisms and Pharmacological Modulation of Mitochondrial Dysfunction in Hepatic Injury

An overview of mitochondria-targeted pharmacological agents and their mechanisms of action is presented in this chapter and summarized in Table 1.

#### Oxidative/Nitrosative Stress and Antioxidants-ROS Scavengers

Mitochondria, while essential for OXPHOS, are also a major intracellular source of ROS and RNS. Under physiological conditions, low levels of ROS are involved in redox signaling and cellular homeostasis. However, excessive ROS/RNS generation during hepatic injury leads to oxidative modification of lipids, proteins, and mtDNA, culminating in mitochondrial dysfunction and bioenergetic collapse.

### MAIN POINTS

- Mitochondrial dysfunction is a key driver of hepatic injury across experimental models, integrating oxidative stress, energy failure, and cell death.
- Experimental evidence shows that mitochondria actively shape liver injury outcomes, rather than serving as passive targets of damage.
- Mitochondria-targeted pharmacological interventions provide mechanistic advantages over conventional antioxidant strategies in hepatoprotection.
- Restoring mitochondrial quality control and adaptive responses represents a promising translational approach to the treatment of liver injury.

Mitochondrial oxidative stress in hepatocytes is primarily driven by the activation of cytochrome P450 2E1, NADPH oxidase, and nitric oxide synthase isoforms, which together amplify the redox imbalance. ROS overproduction induces lipid peroxidation and membrane depolarization, while RNS, particularly peroxynitrite, promote tyrosine nitration and S-nitrosylation of mitochondrial proteins such as ATP synthase, aconitase, and complex I subunits. These post-translational modifications impair electron transfer efficiency, reduce adenosine triphosphate (ATP) production, and activate redox-sensitive signaling pathways, including NF-κB, JNK, and Nrf2.

In hepatic IR models, characterized by 60 min of ischemia followed by reperfusion of 120 min or longer, increased levels of 3-nitrotyrosine and 4-hydroxynonenal are consistently reported, accompanied by mitochondrial depolarization and enhanced expression of thioredoxin-1, indicating a compensatory redox response to nitrosative stress.[9] Similarly, in APAP-induced hepatotoxicity, typically produced by single oral doses ranging from 200 mg/kg to 3 g/kg, the generation of mitochondrial ROS and peroxynitrite triggers mtDNA fragmentation, ATP depletion, and mPTP opening. The ensuing collapse of the ΔΨm leads to the release of cytochrome c and the activation of caspase-dependent cell death cascades. Recent studies emphasize that nitro-oxidative stress is not merely a byproduct of hepatic injury but a primary initiator of mitochondrial dysfunction. Persistent oxidation of cardiolipin, an inner mitochondrial membrane phospholipid, disrupts the integrity of the ETC and sensitizes mitochondria to permeability transition. Moreover, chronic redox imbalance activates nuclear transcriptional responses mediated by p53, SIRT3, and proliferator-activated receptor gamma coactivator-1α (PGC-1α), which link mitochondrial stress to inflammation and apoptosis.[10]

Based on these mechanisms, pharmacological approaches that directly target mitochondrial oxidative stress have been explored to prevent or reverse hepatic injury. These include both conventional antioxidants (e.g., N-acetylcysteine) and mitochondria-targeted molecules such as MitoQ, SkQ1, and MitoTEMPO, which neutralize ROS within the mitochondrial matrix.

Conventional antioxidants, including N-acetylcysteine (NAC), vitamin E, and silymarin, have been shown to protect hepatocytes by replenishing glutathione (GSH) pools and neutralizing cytosolic ROS. However, their limited ability to penetrate mitochondria restricts their efficacy against mitochondrial oxidative damage. NAC remains the standard treatment for APAP-induced hepatotoxicity, but incomplete protection underscores the need for mitochondria-targeted strategies.

The development of mitochondria-targeted antioxidants represents a major advancement in the pharmacological management of oxidative stress–related liver injury. Unlike conventional antioxidants, which often fail to reach sufficient intramitochondrial concentrations, these agents are chemically engineered to accumulate specifically within the mitochondrial matrix using lipophilic cationic carriers, typically triphenylphosphonium ($TPP^+$). Because the mitochondrial inner

**Table 1.** Mitochondria-targeted pharmacological agents and their mechanisms of action

| Agent/strategy | Main mitochondrial target | Mechanism of action | Outcomes |
|---|---|---|---|
| **MitoQ** | Mitochondrial ROS | $TPP^+$-mediated accumulation in mitochondria; scavenges mitochondrial ROS and prevents lipid peroxidation | Reduced oxidative stress, preserved ΔΨm, decreased hepatocyte necrosis |
| **Mito-TEMPO** | Mitochondrial superoxide | SOD mimetic nitroxide conjugated to $TPP^+$; selectively dismutates mitochondrial superoxide | Reduced mitochondrial ROS, improved ATP levels, attenuated liver injury |
| **SS-31 (elamipretide)** | Cardiolipin-ETC interaction | Stabilizes cardiolipin and ETC complexes, improves electron transfer efficiency | Preserved mitochondrial respiration, reduced necrosis |
| **Cyclosporin A** | Cyclophilin D/mPTP | Inhibits cyclophilin D, preventing sustained mPTP opening | Reduced mitochondrial swelling, decreased necrotic cell death |
| **NIM811/alisporivir** | Cyclophilin D/mPTP | Non-immunosuppressive inhibition of mPTP opening | Preserved ΔΨm, reduced oxidative stress |
| **Metformin** | AMPK pathway | Activates AMPK, enhances mitochondrial biogenesis and energy homeostasis | Improved mitochondrial biogenesis, reduced oxidative stress |
| **Resveratrol** | SIRT1-PGC-1α axis | Activates SIRT1, promotes mitochondrial biogenesis and antioxidant defense | Enhanced mitochondrial adaptation, hepatoprotection |
| **Urolithin A** | Mitophagy machinery | Induces mitophagy, improves mitochondrial quality control | Reduced accumulation of dysfunctional mitochondria |
| **Spermidine** | Autophagy/mitophagy pathways | Enhances autophagic flux and mitochondrial turnover | Improved mitochondrial quality, reduced injury |
| **YAQ-005 (TAK-242)** | TLR4-mitochondrial necroptosis axis | Inhibits TLR4 signaling, reduces RIPK1/RIPK3-mediated mitochondrial damage and hyperammonemia | Preserved mitochondrial integrity, reduced cell death |
| **Mitochondrial transplantation** | Mitochondrial bioenergetics | Delivery of functional mitochondria to injured liver tissue | Increased ATP production, reduced necrosis |
| **Nanoparticle-based delivery systems** | Mitochondrial matrix | Targeted delivery of drugs via biomimetic or $TPP^+$-modified nanoparticles | Enhanced mitochondrial targeting, reduced off-target toxicity |

$TPP^+$: Triphenylphosphonium, ΔΨm: Mitochondrial membrane potential, ATP: Adenosine triphosphate, ETC: Electron transport chain, mPTP: Mitochondrial permeability transition pore, AMPK: Adenosine monophosphate-activated protein kinase, SIRT1: Sirtuin 1.

membrane is highly negatively charged, the positively charged $TPP^+$ fragment drives these molecules into mitochondria via electrophoretic accumulation, reaching concentrations up to 1000-fold higher in mitochondria than in the cytosol.

MitoQ is obtained by conjugating ubiquinone (the active part of Coenzyme Q10), an endogenous antioxidant, with $TPP^+$, a lipophilic cation. Thanks to its $TPP^+$ charge, it is attracted to the negative membrane potential and accumulates in the mitochondrial matrix at concentrations hundreds of times higher than in the cytosol.[11] MitoQ is reduced to ubiquinol by the ETC complex II and detoxifies lipid peroxyl radicals and peroxynitrite. In studies, MitoQ has generally been administered at 10 mg/kg by oral or intraperitoneal routes and is the most extensively studied mitochondria-targeted antioxidant in hepatic models. Experimental studies of $CCl_4$, TAA-, and APAP-induced hepatotoxicity have shown that MitoQ reduces lipid peroxidation, restores ATP production, and inhibits mPTP opening, thereby attenuating hepatocellular necrosis.[12]

In APAP hepatotoxicity, MitoQ inhibits JNK activation and subsequent activation of mPTP by scavenging mitochondrial ROS. A key finding is that MitoQ prevents necrosis despite not preventing GSH depletion; this suggests that the main driver of damage is mitochondrial redox collapse rather than GSH deficiency. However, MitoQ has a narrow therapeutic window, as it can suppress respiration at high doses and can exhibit a "pro-oxidant" effect.[13]

In $CCl_4$-induced fibrosis models, MitoQ has been shown to suppress pro-fibrotic TGF-β /smad signaling and reduce hepatic stellate cell activation. It also enhances mitophagy (the clearance of damaged mitochondria) by stabilizing the PINK1/Parkin pathway, thereby inhibiting NLRP3 activation.[14] In high-fat diet (HFD) models, MitoQ reduces hepatic steatosis and insulin resistance. Mechanistically, it increases fatty acid oxidation while and alleviates ER stress associated with lipotoxicity.[13] In a Phase II study (NCT00433108) in patients with chronic hepatitis C, MitoQ was shown to reduce alanin aminotransferaz levels (indicating a reduction in necrosis) but not to alter viral load. Ongoing research is exploring its potential to improve endothelial function in metabolic dysfunction-associated steatohepatitis (MASH) and in diabetic liver damage.

Mito-TEMPO, a mitochondria-targeted antioxidant, is a hybrid molecule composed of two functional moieties. TEMPO, a piperidine nitroxide that acts as a superoxide dismutase mimetic, and $TPP^+$, a lipophilic cation that enables selective accumulation within mitochondria driven by the negative ΔΨm, are two compounds. TEMPO catalyzes the dismutation of superoxide anions ($O_2$-) into less reactive species, thereby limiting mitochondrial oxidative stress. Conjugation with $TPP^+$ allows Mito-TEMPO to accumulate in the mitochondrial

matrix to concentrations several hundred-fold higher than in the cytosol, making it markedly more effective than non-targeted antioxidants at scavenging mitochondrial superoxide. Mito-TEMPO has demonstrated protective effects in multiple experimental models characterized by mitochondrial oxidative stress, including endotoxin-induced liver injury**,** sepsis-associated acute kidney injury**,** hypertension**,** and experimental colitis. These studies consistently show reductions in mitochondrial ROS production, preservation of ΔΨm, and attenuation of tissue injury. Mito-TEMPO has been evaluated as a potential hepatoprotective agent in APAP overdose models. Experimental findings indicate that Mito-TEMPO alleviates mitochondrial oxidative stress and dysfunction, thereby limiting liver injury. Its therapeutic efficacy has also been compared with NAC, highlighting the potential of mitochondria-targeted antioxidants as complementary or alternative strategies.[15] The evidence supporting hepatoprotection remains preclinical, and further standardized dose–response studies are required to define its translational relevance.

SkQ1 (visomitin) is a $TPP^+$ derivative of plastoquinone that effectively modulates ROS production in mitochondria (particularly during reverse electron transport at Complex I). Adding SkQ1 to the cold storage solutions used for the organ during liver transplantation has been shown to minimize damage during reperfusion. SkQ1 improves sinusoidal microcirculation by protecting endothelial cells and preserves ATP stores in hepatocytes. In hemorrhagic shock models, SkQ1 prevents the release of mtDNA from the liver into the systemic circulation, thereby preventing the spread of liver damage to distant organs, such as the lungs and kidneys.[16] SkQ1 (visomitin) preserves the ΔΨm and limits cytochrome c release during hepatic IR injury.[17]

The mitochondria-targeted peptide SS-31 (elamipretide) binds to cardiolipin, stabilizes the inner mitochondrial membrane, and reduces ROS generation and fibrotic activation in $CCl_4$-induced fibrosis. SS-31 is a potent agent that may treat liver fibrosis by blocking mitochondrial ROS and suppressing the NLRP3 pathway.[18]

**Loss of ΔΨm and Modulators of the mPTP Opening**

As discussed in the oxidative stress section, mitochondrial ROS generation and calcium overload are major upstream triggers of mPTP opening. The ΔΨm is a critical electrochemical gradient that drives ATP synthesis and maintains ion homeostasis. Loss of ΔΨm typically results from oxidative damage to mitochondrial membranes, calcium overload, and the opening of the mPTP. The mPTP is a multiprotein complex composed primarily of ANT, the voltage-dependent anion channel, and cyclophilin D (CypD). Under oxidative or calcium overload conditions, conformational changes in these proteins trigger pore opening, leading to ΔΨm dissipation and cytochrome c release.[3] Under physiological conditions, transient pore flickering may serve adaptive roles; however, sustained mPTP opening results in irreversible mitochondrial dysfunction characterized by loss of ΔΨm, cessation of ATP synthesis, osmotic swelling of the mitochondrial matrix, and rupture of the outer mitochondrial membrane, ultimately leading to necrotic cell death.

In $CCl_4$-induced acute liver injury, reactive trichloromethyl radicals ($CCl_3$) are formed that attack cardiolipin, a phospholipid essential for maintaining ΔΨm. Six-12 hours after dosing, mitochondria display significant depolarization, decreased ATP levels, and increased expression of CypD and Bax, indicating mPTP-mediated apoptotic priming.[19]

In APAP-induced hepatotoxicity, overdoses (250-500 mg/kg) cause formation of mitochondrial protein adducts, oxidative and nitrosative stress, and opening of the mitochondrial mPTP, leading to ATP depletion and necrosis.[20]

IR injury represents another prototypical model in which ΔΨm collapse plays a central role. During the reperfusion phase, a burst of ROS at Complex I sites triggers mPTP opening via CypD activation. Hepatocytes display massive mitochondrial swelling, loss of cristae, and rapid ATP depletion within 30 minutes of reperfusion onset.[21]

Chronic models, such as TAA-induced fibrosis (200 mg/kg i.p., three times weekly for 8-12 weeks), also exhibit a progressive reduction in ΔΨm, albeit in a slower, cumulative fashion. Long-term oxidative stress and depletion of cardiolipin result in sustained low-grade mPTP opening, driving hepatocyte apoptosis and fibrogenic signaling through TGF-β/Smad.[22] Similarly, during chronic $CCl_4$ exposure (0.5 mL/kg i.p., twice weekly for 6–8 weeks), prolonged mPTP activation leads to mitochondrial fragmentation and impaired autophagic clearance of damaged organelles, resulting in persistent hepatocyte injury.[23]

Among the regulatory components of the mPTP, CypD is the best-characterized and most widely accepted molecular modulator. Genetic ablation of CypD or its pharmacological inhibition has been shown to confer significant protection against mitochondrial dysfunction and hepatocellular necrosis in experimental liver injury models. Advances in this field have been accelerated by the discovery of new-generation, non-immunosuppressive cyclophilin inhibitors (targeting CypD, A, and B, known as "pan-cyclophilin" inhibitors).

Cyclosporin A (CsA) is the prototypical mPTP inhibitor that binds to CypD and prevents pore opening. Experimental studies have demonstrated that CsA attenuates mitochondrial swelling, preserves ΔΨm, and reduces hepatocellular necrosis in hepatic IR and APAP-induced liver injury models. However, its clinical use is limited by calcineurin inhibition mediated by cytosolic cyclophilin A (CypA) and by immunosuppressive effects that increase the risk of infection.[24] To circumvent these limitations, non-immunosuppressive CypD inhibitors have been developed.

Alisporivir (Debio-025) is a clinically advanced non-immunosuppressive cyclophilin inhibitor. It has been shown to prevent mPTP activation and cell death by inhibiting CypD, and to inhibit Hepatitis C virus replication by inhibiting CypA (an antiviral effect). Recent studies report that Alisporivir reduces mitochondrial fission (Drp1-mediated) and stabilizes mitochondrial fusion (Mfn2-mediated) in diabetic conditions and metabolic liver damage.[25]

Although the majority of evidence regarding CypD inhibition originates from hepatic models, supportive data from

extrahepatic tissues further underscore the central role of mPTP modulation under metabolic stress. In a HFD/streptozotocin-induced diabetes model, alisporivir (Debio-025) significantly alleviated mitochondrial dysfunction in skeletal muscle by preserving ΔΨm, restoring OXPHOS, and reducing mitochondrial ROS production.[25] These findings demonstrate that CypD-dependent mPTP opening represents a common pathogenic mechanism across metabolically active tissues. Given the shared susceptibility of hepatocytes to oxidative stress and mitochondrial calcium overload, inhibition of CypD by alisporivir may represent a translationally relevant strategy for mitigating mitochondrial dysfunction in liver injury, particularly in metabolic and IR contexts.

Rencofilstat is a macrocyclic pan-cyclophilin inhibitor with activity against CypD, A, and B, thereby linking mitochondrial protection to anti-inflammatory and antifibrotic effects. CypD inhibition prevents mitochondrial swelling and necrotic cell death (hepatoprotection); CypA inhibition suppresses inflammatory signaling. CypB, located in the ER, is a chaperone (a prolyl isomerase) necessary for collagen synthesis. Rencofilstat inhibits CypB, thereby disrupting the correct folding and secretion of procollagen. This not only prevents cell death but also directly halts fibrotic scar formation.[26] It has been investigated in preclinical liver fibrosis and NASH-related models, and clinical evaluations in Phase IIa and IIb (AMBITION, ALTITUDE) studies have also been reported in patients with F2/F3 NASH.[27] While these findings suggest that rencofilstat is a promising candidate for liver diseases, it is not yet an established mitochondria-targeted therapy.

Similarly**,** Sanglifehrin A, another CypD ligand, stabilizes mitochondrial integrity and limits necrotic hepatocyte death by preventing prolonged mPTP opening. Sanglifehrin A is a cyclophilin inhibitor that is structurally distinct from CsA. Its derivative, NV556, is particularly effective in liver fibrosis models.[28] Its mechanism of action, similar to that of rencofilstat, focuses on reducing collagen cross-linking and secretion via inhibition of CypB.[29]

The newly identified C105SR is smaller than large macrocyclic structures (CsA, alisporivir). It exhibits nanomolar-level affinity by binding to both the catalytic pocket (S1) and the "gatekeeper" pocket (S2) of

CypD. It has been reported to reduce liver necrosis and apoptosis more effectively than other inhibitors when administered via osmotic pump in mouse ischemia-reperfusion models.[24]

**Modulators of Mitochondrial Biogenesis and Energy-Sensing Pathways (AMPK–SIRT–PGC-1α)**

Beyond acute oxidative and permeability-related injury, hepatocytes activate adaptive pathways aimed at restoring mitochondrial mass and function. Mitochondrial ETC complexes (I-V) are responsible for the transfer of electrons from NADH and $FADH_2$ to molecular oxygen, generating ATP through OXPHOS. Under physiological conditions, this process is tightly regulated to ensure efficient ATP production and minimal ROS leakage. However, in hepatocellular injury, disruption of ETC activity is a key mechanism contributing to mitochondrial dysfunction and cellular energy failure. Experimental and clinical studies consistently demonstrate that hepatic toxins such as $CCl_4$, TAA, and APAP inhibit ETC activity, particularly at complex I (NADH: ubiquinone oxidoreductase) and complex III (cytochrome $bc_1$ complex). This inhibition results in excessive electron leakage and $O_2$- formation, leading to secondary oxidative stress and lipid peroxidation of mitochondrial membranes.

In $CCl_4$-induced hepatotoxicity, reactive $CCl_3$ and trichloromethyl peroxy radicals directly attack mitochondrial membranes and ETC proteins. Within 24 hours of exposure to a single intraperitoneal dose (1-1.5 mL/kg, 1:1 in olive oil), the activities of complexes I and III are markedly reduced, whereas the activity of complex II remains partially preserved. This imbalance increases superoxide release and diminishes the respiratory control ratio, reflecting uncoupling between electron transport and ATP synthesis.[19] In the TAA-induced chronic fibrosis model, mitochondrial respiration is progressively impaired by thioacetamide S-oxide and its reactive intermediates. Animals receiving TAA (200 mg/kg, i.p., three times per week for 8-12 weeks) show a significant reduction in the enzymatic activities of complexes I-III, coupled with a 50-60% decline in the ATP/ADP ratio. The ensuing redox imbalance triggers the accumulation of NADH and reduced coenzyme Q and the subsequent production of ROS at the $Q_0$ site of complex III. This defective electron transfer promotes hepatocyte apoptosis and the progression of fibrosis.[22]

Similarly, APAP-induced hepatotoxicity, resulting from single oral doses ranging from 200 mg/kg to 3 g/kg, causes accumulation of N-acetyl-p-benzoquinone imine (NAPQI), which binds to mitochondrial proteins, particularly complexes I and IV. This adduct formation interferes with electron flow, resulting in ATP depletion, membrane depolarization, and mitochondrial swelling. A reduced oxygen consumption rate and an elevated NADH/$NAD^+$ ratio indicate a shift from oxidative to anaerobic metabolism, which is characteristic of mitochondrial bioenergetic collapse. In the MTX-induced hepatotoxicity model, a single intraperitoneal dose of 20 mg/kg MTX results in transcriptional repression of mtDNA-encoded subunits such as ND1, ND6, and COX1, which encode essential components of complexes I and IV. This downregulation correlates with decreases in the oxygen consumption rate and ATP generation, and is accompanied by upregulation of apoptotic markers (Bax, cytochrome c).[30]

In hepatic IR injury**,** transient oxygen deprivation followed by reperfusion results in reverse electron transport at complex I, driven by succinate oxidation. This generates a burst of superoxide at the flavin mononucleotide site, causing damage to complex I, opening of the mPTP, and subsequent ATP depletion.[31]

mtDNA encodes 13 essential subunits of the ETC and components of the OXPHOS machinery. Owing to its close proximity to the inner mitochondrial membrane and the absence of protective histones, mtDNA is highly vulnerable to oxidative and nitrosative damage. In hepatic injury, sustained exposure to ROS/RNS leads to oxidative base modifications (particularly 8-hydroxy-2′-deoxyguanosine, 8-OHdG), strand breaks, and deletions, compromising ETC integrity and mitochondrial gene expression.[19]

In APAP-induced acute hepatotoxicity, single oral doses (300-500 mg/kg) induce mtDNA adduct formation due to NAPQI binding to mitochondrial proteins and nucleic acids. APAP-induced hepatotoxicity results in extensive mtDNA oxidation and fragmentation. This leads to decreased transcription of key OXPHOS genes such as ND1, ND6, and COX1, impairing the activities of complexes I and IV and exacerbating ATP depletion. These events have been confirmed in experimental contexts.[1] Simultaneously, depletion of mitochondrial transcription factor A (TFAM) and POLG (DNA polymerase gamma) limits mtDNA repair, leading to further bioenergetic failure.

TAA-induced fibrosis (200 mg/kg, i.p., 8-12 weeks) and chronic $CCl_4$ exposure (0.5 mL/kg, twice weekly, 6-8 weeks) lead to cumulative mtDNA damage and repression of biogenic transcriptional regulators. Persistent oxidative stress reduces PGC-1α, SIRT3, and NRF1 levels, impairing mitochondrial replication and turnover. This sustained biogenic failure is associated with increased collagen deposition and hepatocyte apoptosis.[22,23]

In hepatic IR injury, mtDNA degradation occurs rapidly after reperfusion due to enhanced oxidative stress and mitochondrial permeability transition. The cytosolic release of mtDNA activates the cGAS-STING-TBK1-IRF3 signaling cascade, promoting pro-inflammatory cytokine production and amplifying hepatocellular injury.[32]

Hepatocytes require adaptive responses to restore mitochondrial mass and function under toxic, metabolic, and ischemic stress. Central to these adaptive processes is the AMPK-SIRT-PGC-1α signaling axis, which coordinates cellular energy status with mitochondrial biogenesis and oxidative metabolism.[8] AMP-activated protein kinase (AMPK) is the primary cellular energy sensor activated by increases in the AMP/ATP ratio during mitochondrial dysfunction, ischemia, and toxic liver injury. When the ATP/AMP ratio decreases, it is activated and triggers energy-producing pathways. Downstream of AMPK, sirtuins, particularly sirtuin 1 (SIRT1) and SIRT3, play critical roles in regulating mitochondrial function through $NAD^+$-dependent deacetylation. SIRT1 activates peroxisome PGC-1α, the master transcriptional regulator of mitochondrial biogenesis. Activation of the AMPK–SIRT1–PGC-1α axis enhances transcription of nuclear-encoded mitochondrial genes, improves OXPHOS efficiency, and strengthens antioxidant defenses in hepatocytes.[8]

**AMPK Activators**

Metformin is the most commonly used antidiabetic drug. It activates AMPK in the liver, increasing insulin sensitivity and reducing fat accumulation (steatosis). In mouse models, 4 weeks of metformin treatment has been shown to improve liver function by restoring contact points between mitochondria and the endoplasmic reticulum (ER).[33]

Berberine is a naturally occurring isoquinoline alkaloid. In experimental models, it promotes fatty acid oxidation by increasing activation of peroxisome PGC-1α. It has also been shown to regulate liver microfibers and to alleviate fibrosis by acting through the gut flora.[34]

**SIRT1 and PGC-1α Modulators**

SIRT1 is an NAD+-dependent deacetylase that activates PGC-1α, the main regulator of mitochondrial biogenesis.

Resveratrol is a potent SIRT1 activator. It reduces oxidative stress in liver damage models while stimulating mitochondrial biogenesis via PGC-1α.[35]

In APAP-induced liver damage models, MI administration has been shown to significantly increase expression of SIRT1, PGC-1beta, NRF-1, and TFAM, promoting biogenesis and preventing hepatocyte necrosis.[36]

Formoterol is a beta2-adrenergic agonist. In mouse models of liver resection and sepsis, PGC-1α levels have been observed to increase mitochondrial ATP production capacity and to accelerate liver regeneration.[37]

**Other Compounds Affecting Energy Pathways**

Resmetirom (THR-beta agonist) stimulates thyroid hormone receptor-beta in a liver-specific manner. It reduces liver steatosis and inflammation by directly increasing mitochondrial fatty acid beta-oxidation. While Phase 3 clinical trials, such as MAESTRO-NASH, have shown clinically significant benefit in steatotic liver disease,[38] this review primarily evaluates it within the context of mitochondrial metabolic modulation; further research is still needed to consider it a widely accepted hepatoprotective treatment in all experimental liver damage models.

Astaxanthin coordinates the Nrf2–PGC-1α axis in stressed cells, increasing both antioxidant defense and mitochondrial content.[39]

Quercetin has been shown in animal models to alleviate HFD-induced liver damage by enhancing PINK1/Parkin-dependent mitophagy.[40]

**Modulators of Mitophagy and Mitochondrial Quality Control**

In addition to antioxidant defense and mPTP modulation, mitochondrial quality control through mitophagy is a major determinant of hepatocyte survival. Mitophagy, a specialized form of autophagy, is a key mitochondrial quality control mechanism that eliminates damaged or dysfunctional mitochondria to preserve cellular homeostasis. In hepatocytes, this process plays a critical role in limiting oxidative stress, preventing excessive inflammation, and maintaining ATP production (Figure 1). The mitophagy pathway is mainly regulated by the PINK1/Parkin, BNIP3/NIX, and FUNDC1 signaling axes, which target depolarized mitochondria for lysosomal degradation.[2] Under physiological conditions, PINK1 is rapidly degraded in healthy mitochondria. However, loss of ΔΨm leads to PINK1 stabilization on the outer mitochondrial membrane, recruitment of the E3 ubiquitin ligase Parkin, and ubiquitination of mitochondrial proteins, thereby initiating mitophagic clearance. Experimental studies in drug-induced and ischemic liver injury models have demonstrated that activation of the PINK1/Parkin pathway limits mitochondrial ROS accumulation, preserves ATP production, and attenuates hepatocellular injury. In contrast, defective or excessive mitophagy may become

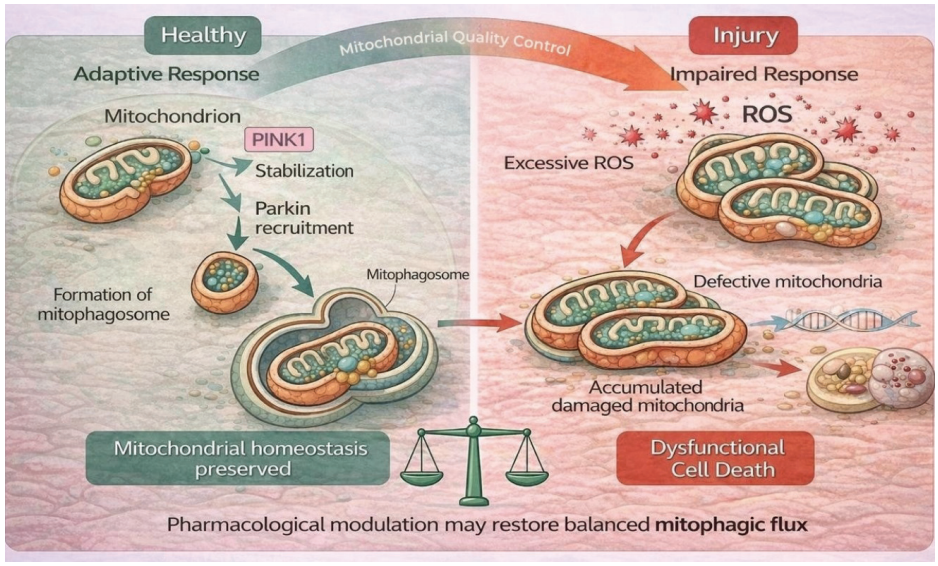



**Figure 1.** Mitophagy and mitochondrial quality control in experimental hepatic injury.

maladaptive. Insufficient mitophagy promotes accumulation of dysfunctional mitochondria, amplifying oxidative stress and inflammatory signaling, whereas excessive mitophagy can lead to mitochondrial depletion and bioenergetic failure. This dual role highlights the necessity for tightly regulated mitophagic flux in hepatocytes. In hepatic injury, disruption of this process aggravates the accumulation of dysfunctional mitochondria and ROS, exacerbates ATP depletion, and promotes hepatocyte death.

Experimental evidence supports the view that the PINK1/Parkin-mediated mitophagy pathway is a central mechanism of mitochondrial turnover in both acute and chronic liver injury. In APAP-induced hepatotoxicity, excessive mitochondrial ROS production leads to depolarization of ΔΨm, accumulation of PINK1 on the outer mitochondrial membrane, and recruitment of Parkin to initiate mitophagy. Experimental inhibition of PINK1 or Parkin amplifies APAP-induced hepatocellular necrosis, confirming the cytoprotective role of mitophagy.[2,7]

Similarly, during IR injury, transient activation of mitophagy limits mitochondrial ROS buildup, while prolonged or defective mitophagy exacerbates inflammation and necrosis. Enhancing mitophagic flux via AMPK or SIRT3 activation has been shown to protect against IR-induced oxidative damage.[4] In hepatic IR models, PINK1/Parkin-mediated mitophagy is transiently activated during early reperfusion, coinciding with mild restoration of ΔΨm. However, prolonged ischemia leads to suppression of mitophagy through mPTP opening and ATP depletion, resulting in accumulation of damaged mitochondria and exacerbation of oxidative injury.[2,4]

In chronic liver injury models, including non-alcoholic fatty liver disease and $CCl_4$- and TAA-induced fibrosis, persistent oxidative stress suppresses Parkin translocation, leading to mitophagy failure and contributing to hepatocyte apoptosis and fibrogenesis. The impaired mitophagy, resulting in mitochondrial accumulation, aggravates lipid peroxidation, stellate cell activation, and fibrogenesis. Experimental activation of PINK1/Parkin or SIRT1–SIRT3 pathways restores mitophagy and reduces fibrotic progression.[41] Similarly, decreased expression of PINK1, Parkin, and FUNDC1, along with elevated p62/SQSTM1 accumulation, indicates disrupted autophagic flux. This failure in mitochondrial turnover promotes NLRP3 inflammasome activation and TGF-β1/Smad3-driven fibrosis.[4]

Pharmacological modulation of mitophagy has therefore emerged as a promising therapeutic strategy. Urolithin A, a gut microbiota–derived metabolite, has been shown to enhance mitophagy and improve mitochondrial function in experimental liver injury models by restoring mitochondrial quality control and reducing oxidative stress.[42] These mitochondrial effects are associated with improvement in hepatocellular resilience and attenuation of liver injury. However, its evidence base in hepatic disease remains largely experimental, and its translational potential requires further validation. Similarly, spermidine, a natural polyamine, induces mitophagy through autophagy-related pathways and confers hepatoprotection in models of toxic and metabolic liver injury.[43] It is known to support mitochondrial turnover and preserve mitochondrial quality, thereby limiting the accumulation of dysfunctional organelles in these experimental models. These actions are associated with reduced tissue injury and improved hepatocellular adaptation. Its role should be considered supportive and preclinical, rather than clinically established.

In addition, modulation of mitochondrial dynamics, such as fusion and fission, plays an integral role in the regulation of mitophagy. Excessive mitochondrial fission mediated by dynamin-related protein 1 (Drp1) has been associated with aggravated liver injury, whereas pharmacological inhibition of Drp1 preserves mitochondrial morphology and limits hepatocellular damage.[44] Together, these findings indicate that targeting mitophagy and mitochondrial quality control represents a complementary approach to preserve mitochondrial integrity beyond acute injury prevention.

**Mitochondria-Nucleus Crosstalk and Inflammatory Signaling**

Inter-organelle communication among mitochondria, the ER, and the nucleus is a key determinant of cellular homeostasis, particularly under hepatic stress conditions, such as toxic injury and IR. The ER and mitochondria are physically connected at specialized regions known as mitochondria-ER contact sites or mitochondria-associated ER membranes (MAMs), which regulate calcium signaling, lipid transfer, and stress responses. Malfunction of these contact sites contributes to mitochondrial dysfunction, ER stress, and aberrant gene expression in liver diseases.[5]

Mitochondria-ER Contacts and Calcium Transfer: Mitochondria and the ER interact at MAMs, facilitating $Ca_2^+$ transfer between the two organelles. These contact sites help coordinate metabolic and signaling responses. Disruption of MAMs can impair calcium homeostasis and promote mitochondrial calcium overload, which worsens oxidative stress and triggers mPTP opening, a key event in hepatocellular injury.[5] Recent studies show that MAMs not only mediate calcium exchange but also regulate lipid and glucose homeostasis. In hepatocytes, MAMs contribute to neutral lipid metabolism and may influence lipid droplet dynamics and steatosis in fatty liver disease.[45]

ER Stress and the Unfolded Protein Response (UPR): Accumulation of unfolded or misfolded proteins in the ER lumen activates the UPR, a highly conserved stress pathway. UPR initially aims to restore protein folding capacity by upregulating chaperones (e.g., GRP78/BiP) and decreasing general protein translation. However, when ER stress persists, UPR signaling can shift toward pro-apoptotic pathways involving factors such as CHOP and JNK, which also impact mitochondrial function and can exacerbate liver injury.[5] Importantly, prolonged ER stress promotes mitochondrial dysfunction by enhancing ROS production and calcium imbalance, thereby amplifying hepatocellular damage.[46]

**cGAS-STING Pathway and mtDNA Signaling:** In models of hepatic IR injury, mitochondrial damage leads to the release of mtDNA into the cytosol. Cytosolic mtDNA, which acts as a danger-associated molecular pattern**,** can activate the cGAS-STING cytosolic DNA-sensing pathway, linking mitochondrial dysfunction to innate immune activation and inflammation. Targeting this pathway has been proposed to mitigate sterile inflammation in IRI.[47] Although most studies on the cGAS-STING pathway have been performed in models of systemic inflammation or organ transplantation, similar mechanisms are now recognized in hepatic injury. The resulting inflammatory response exacerbates oxidative stress and further impairs the function of mitochondria and the ER, ultimately promoting hepatocyte death.[47] Recent studies indicate that Dimethyl Fumarate directly targets STING, preventing recruitment of TBK1 and IRF3 and thereby suppressing production of pro-inflammatory cytokines in models of hepatic ischemia-reperfusion.

**Modulation of Organelle Crosstalk:** Understanding organelle crosstalk reveals therapeutic opportunities. Agents that stabilize MAMs and improve calcium handling or modulators that attenuate ER stress (e.g., chemical chaperones targeting UPR) may help preserve mitochondria and restore homeostasis. Similarly, interventions that dampen cGAS–STING signaling could reduce inflammation triggered by organellar danger-associated molecular patterns. These strategies are being explored in preclinical models of hepatic injury and represent promising directions for translational research.[47]

**Emerging Therapeutic Strategies**

**Ammonia-Targeted Mitoprotection YAQ-005:** Data published in 2025 showed that hyperammonemia causes mitochondrial damage and cell death by increasing RIPK1 and RIPK3 protein levels. The drug YAQ-005 (TAK-242) protects mitochondria by blocking the TLR4 pathway and facilitating ammonia removal via the urea cycle. The drug has been proposed for further clinical evaluation in mid-2025.[48]

Mitochondrial transplantation, the transfer of healthy mitochondria (usually isolated from skeletal muscle) directly via the portal vein or spleen, has emerged as an experimental and highly innovative approach in MASH and ischemia-reperfusion injury. Transplanted mitochondria are rapidly internalized by Kupffer cells and can reduce necrosis by more than 20% through increasing ATP production. Ethical and genetic risks, such as immune rejection and incompatibility between the nuclear and mitochondrial genomes in allogeneic transplants, remain under investigation.[49]

**Nanomedicine as a Future Perspective:** Nanotechnology enables the delivery of drugs to the liver and directly to the mitochondrial matrix. Biomimetic (cell membrane-coated) nanoparticles optimize the targeted distribution of the drug to the space of Disse and to hepatocytes by evading the immune system.[50]

## CONCLUSION

Mitochondrial dysfunction has emerged as a central pathogenic hub in experimental models of hepatic injury, integrating oxidative stress, bioenergetic failure, dysregulated cell death, and impaired cellular adaptation. Accumulating experimental evidence demonstrates that mitochondria are not merely secondary targets of hepatocellular damage but active regulators of injury severity and disease progression. Accordingly, pharmacological strategies that directly target mitochondrial pathways, ranging from mitochondria-targeted antioxidants and mPTP modulators to regulators of energy sensing, biogenesis, and mitophagy, offer mechanistically grounded advantages over conventional, non-specific hepatoprotective approaches. In addition to established mitochondria-targeted pharmacological approaches, emerging therapeutic strategies further expand the translational potential of mitochondrial modulation in hepatic injury. Novel concepts such as ammonia-targeted mitoprotection, mitochondrial transplantation, and nanotechnology-based drug delivery highlight innovative directions aimed at preserving mitochondrial integrity and improving hepatocellular resilience. Although these approaches remain at early experimental or clinical stages, they underscore the growing recognition of mitochondria as dynamic and druggable targets in liver disease prevention and therapy. Nevertheless, the current evidence

remains predominantly preclinical, and important uncertainties persist regarding optimal dosing, tissue selectivity, long-term safety, and translatability to human liver disease. Future therapeutic success will likely depend on integrated strategies that combine acute mitochondrial protection with restoration of mitochondrial quality control and adaptive recovery mechanisms. In this context, targeting mitochondrial dysfunction is a promising and evolving avenue for developing more effective treatments for drug-induced liver injury, IR damage, and chronic liver disease.

### Ethics

**Informed Consent:** N/A.

### Footnotes

**Funding:** The author declare that this study has received no financial support.

**Declaration of Interests:** The author declare no conflict of interest regarding the publication of this paper.

## REFERENCES

1. Fromenty B. Alteration of mitochondrial DNA homeostasis in drug-induced liver injury. *Food and Chemical Toxicology*. 2020;135: 110916 [CrossRef]
2. Ma X, McKeen T, Zhang J, Ding WX. Role and mechanisms of mitophagy in liver diseases. *Cells*. 2020;9(4):837. [CrossRef]
3. Baburina Y, Odinokova I, Krestinina O. The effects of pk11195 and protoporphyrin ix can modulate chronic alcohol intoxication in rat liver mitochondria under the opening of the mitochondrial permeability transition pore. *Cells*. 2020;9(8):1774. [CrossRef]
4. Liu S, Wang L, Zhu L, et al. Mechanism and regulation of mitophagy in liver diseases: a review. *Front Cell Dev Biol*. 2025;13:1-18. [CrossRef]
5. Guo M, Liu R, Zhang F, Qu J, Yang Y, Li X. A new perspective on liver diseases: focusing on the mitochondria-associated endoplasmic reticulum membranes. *Pharmacol Res*. 2024;208: 107409. [CrossRef]
6. Şenbil DC, Aydın S. Coronavirus disease 2019-related liver ınjury: ımaging aspects. *Arch Basic Clin Res*. 2024;6(1):69-72. [CrossRef]
7. Wang H, Ni HM, Chao X, et al. Double deletion of PINK1 and Parkin impairs hepatic mitophagy and exacerbates acetaminophen-induced liver injury in mice. *Redox Biol*. 2019;22:101148. [CrossRef]
8. Chen J, Liu B, Yao X, et al. AMPK/SIRT1/PGC-1α Signaling pathway: molecular mechanisms and targeted strategies from energy homeostasis regulation to disease therapy. *CNS Neurosci Ther*. 2025;31(11):1-23. [CrossRef]
9. Samuvel DJ, Krishnasamy Y, Li L, Lemasters JJ, Chou CJ, Zhong Z. LP342, a novel histone deacetylase inhibitor, decreases nitro-oxidative stress, mitochondrial dysfunction and hepatic ischaemia/reperfusion injury in mice. *RPS Pharm Pharmacol Rep*. 2023;2(2):1-13. [CrossRef]
10. LeFort KR, Rungratanawanich W, Song BJ. Contributing roles of mitochondrial dysfunction and hepatocyte apoptosis in liver diseases through oxidative stress, post-translational modifications, inflammation, and intestinal barrier dysfunction. *Cellular and Mol Life Sci*. 2024;81(1):34. [CrossRef]
11. Franczyk B, Bojdo K, Chłądzyński J, et al. Rational design of mitochondria-targeted antioxidants: from molecular determinants to clinical perspectives. *Drugs and Drug Candidates*. 2026;5(1):9. [CrossRef]
12. Dhiman A, Shah Y, Chaudhary U, Garkhal K. Reactive oxygen species-mediated mitochondrial-targeted therapeutics in hepatic disorders: current progress and future opportunities. *Mol Pharm*. 2025;22(10):5715-5737. [CrossRef]
13. Pang M, Wang S, Shi T, Chen J. Overview of MitoQ on prevention and management of cardiometabolic diseases: a scoping review. *Front Cardiovasc Med*. 2025;12:1506460. [CrossRef]
14. Dou SD, Zhang JN, Xie XL, et al. MitoQ inhibits hepatic stellate cell activation and liver fibrosis by enhancing PINK1/parkin-mediated mitophagy. *Open Medicine* (*Poland*). 2021;16(1):1718-1727. [CrossRef]
15. Jamshidi HR, Saadati M, Saghafi F. The protective effects of Mito-TEMPO on acetaminophen-induced hepatotoxicity: a systematic review. journal of current toxicology and venomics. 2024;04: E26661217306815. [CrossRef]
16. Rogov AG, Goleva TN, Aliverdieva DA, Zvyagilskaya RA. SkQ3 Exhibits the most pronounced antioxidant effect on ısolated rat liver mitochondria and yeast cells. *Int J Mol Sci*. 2024;25(2):1107. [CrossRef]
17. Teodoro JS, Da Silva RT, Machado IF, et al. Shaping of hepatic ıschemia/reperfusion events: the crucial role of mitochondria. *Cells*. 2022;11(4):688. [CrossRef]
18. Liu L, Wei YF, Xie NS, Cai H, Lin Y. Mitochondria-targeted reactive oxygen species blockor SS-31 blocks hepatic stellate cell activation and alleviates hepatic fibrosis by regulating NLRP3 inflammasomes. *Cell Mol Biol*. 2024;70(2):183-188. [CrossRef]
19. Chen P, Yao L, Yuan M, et al. Mitochondrial dysfunction: a promising therapeutic target for liver diseases. *Genes Dis*. 2024;11(3):101115. [CrossRef]
20. Ramachandran A, Jaeschke H. A mitochondrial journey through acetaminophen hepatotoxicity. *Food and Chemical Toxicology*. 2020;140:111282. [CrossRef]
21. Shi S, Wang L, Van der Laan LJW, Pan Q, Verstegen MMA. Mitochondrial dysfunction and oxidative stress in liver transplantation and underlying diseases: new insights and therapeutics. *Transplantation*. 2021;105(11):2362-2373. [CrossRef]
22. Ezhilarasan D. Molecular mechanisms in thioacetamide-induced acute and chronic liver injury models. *Environ Toxicol Pharmacol*. 2023;99:104093. [CrossRef]
23. Grabeklis SA, Mikhaleva LM, Dygai AM, Kozlova MA, Chernikov VP, Areshidze DA. Effect of exogenous melatonin on the ultrastructure of hepatocytes in rats with experimental toxic liver injury. *Morphology*. 2025;163(3):210-219. [CrossRef]
24. Kheyar A, Ahnou N, Ahmed-Belkacem A, et al. The novel cyclophilin inhibitor C105SR reduces hepatic ischaemia–reperfusion injury via mitoprotection. *JHEP Reports*. 2023;5(11):100876. [CrossRef]
25. Belosludtsev KN, Starinets VS, Talanov EY, Mikheeva IB, Dubinin M V., Belosludtseva N V. Alisporivir treatment alleviates mitochondrial dysfunction in the skeletal muscles of C57BL/6NCrl mice with high-fat diet/streptozotocin-induced diabetes mellitus. *Int J Mol Sci*. 2021;22(17):9524. [CrossRef]
26. Ure D, Stauffer W, Variya B, et al. Cyclophilin inhibition with rencofilstat shifts the liver transcriptome and lipidome in preclinical models toward resolution of non-alcoholic steatohepatitis. J Hepatol. 2023;78:770. [CrossRef]

27. Harrison SA, Mayo PR, Hobbs TM, et al. Rencofilstat, a cyclophilin inhibitor: a phase 2a, multicenter, single-blind, placebo-controlled study in F2/F3 NASH. *Hepatol Commun*. 2022;6(12):3379-3392. [CrossRef]

28. Serrano SS, Grönberg A, Longato L, et al. Evaluation of NV556, a novel cyclophilin inhibitor, as a potential antifibrotic compound for liver fibrosis. Cells. 2019;8(11):1409. [CrossRef]

29. Flaxman HA, Chrysovergi MA, Han H, et al. Sanglifehrin a mitigates multi-organ fibrosis in vivo by inducing secretion of the collagen chaperone cyclophilin B. *bioRxiv*. Published online 2023;03: 531890. [CrossRef]

30. Schmidt S, Messner CJ, Gaiser C, Hämmerli C, Suter-Dick L. Methotrexate-ınduced liver ınjury ıs associated with oxidative stress, impaired mitochondrial respiration, and endoplasmic reticulum stress ın vitro. *Int J Mol Sci*. 2022;23(23):15116. [CrossRef]

31. Zhou M, Lv J, Chen X, Shi Y, Chao G, Zhang S. From gut to liver: Exploring the crosstalk between gut-liver axis and oxidative stress in metabolic dysfunction-associated steatotic liver disease. *Ann Hepatol*. 2025;30(1):101777. [CrossRef]

32. Xiong Y, Chen J, Liang W, et al. Blockade of the mitochondrial DNA release ameliorates hepatic ischemia-reperfusion injury through avoiding the activation of cGAS-Sting pathway. *J Transl Med*. 2024;22(1):796. [CrossRef]

33. Hasanvand A. The role of AMPK-dependent pathways in cellular and molecular mechanisms of metformin: a new perspective for treatment and prevention of diseases. *Inflammopharmacology*. 2022;30(3:775-788. [CrossRef]

34. Ionita-Radu F, Patoni C, Nancoff AS, et al. Berberine effects in pre-fibrotic stages of non-alcoholic fatty liver disease—clinical and pre-clinical overview and systematic review of the literature. *Int J Mol Sci*. 2024;25(8):4201. [CrossRef]

35. Shamardl HAMA, Ibrahim NA, Merzeban DH, Elamir AM, Golam RM, Elsayed AM. Resveratrol and Dulaglutide ameliorate adiposity and liver dysfunction in rats with diet-induced metabolic syndrome: Role of SIRT-1 / adipokines / PPARγ and IGF-1. Daru. 2023;31(1):13-27. [CrossRef]

36. Xia S, Hu ZY, Cao R, et al. Magnesium isoglycyrrhizinate prevented the liver injury of acetaminophen by promoting mitochondrial biogenesis. *Toxicol Res (Camb)*. 2025;14(2). [CrossRef]

37. Richardson AK. Formoterol promotes mitochondrial biogenesis, improves liver regeneration, and suppresses liver injury and inflammation after liver resection in mice with endotoxemia. *Int J Physiol Pathophysiol Pharmacol*. 2025;17(4):131. [CrossRef]

38. Brennan PN, Kopka CJ, Agirre-Garrido L, et al. Reviewing MAESTRO-NASH and the implications for hepatology and health systems in implementation/accessibility of Resmetirom. npj Gut and Liver. 2025;2(1):3. [CrossRef]

39. Li J, Guo C, Wu J. Astaxanthin in liver health and disease: a potential therapeutic agent. *Drug Des* Devel Ther. 2020;14:2275-2285. [CrossRef]

40. Cao P, Wang Y, Zhang C, et al. Quercetin ameliorates nonalcoholic fatty liver disease (NAFLD) via the promotion of AMPK-mediated hepatic mitophagy. Journal of Nutritional Biochemistry. 2023;120: 109414. [CrossRef]

41. He H, Tang Y, Zhuang L, Zheng Y, Huang X. PINK1/Park2-mediated mitophagy relieve non-alcoholic fatty liver disease. Physiol Res. 2024;73(2):934925. [CrossRef]

42. Alrawili HM, Elshal M, Serrya MS, El-Agamy DS. The gut microbiota metabolite urolithin b mitigates cholestatic liver ınjury in mice via modulating the crosstalk between PPARα, Nrf2, and NF-κB signaling pathways. *J Xenobiot*. 2025;15(4):128. [CrossRef]

43. Liu H, Dong J, Song S, et al. Spermidine ameliorates liver ischaemia-reperfusion injury through the regulation of autophagy by the AMPK-mTOR-ULK1 signalling pathway. *Biochem Biophys Res Commun*. 2019;519(2):227-233. [CrossRef]

44. Zhou H, Zhu P, Wang J, Toan S, Ren J. DNA-PKcs promotes alcohol-related liver disease by activating drp1-related mitochondrial fission and repressing FUNDC1-required mitophagy. *Signal Transduct Target Ther*. 2019;4(1):56. [CrossRef]

45. Dong J, Chen L, Ye F, et al. Mic19 depletion impairs endoplasmic reticulum-mitochondrial contacts and mitochondrial lipid metabolism and triggers liver disease. *Nat Commun*. 2024;15(1):168. [CrossRef]

46. Pu S, Pan Y, Zhang Q, et al. Endoplasmic reticulum stress and mitochondrial stress in drug-ınduced liver ınjury. *Molecules*. 2023;28(7):3160. [CrossRef]

47. Chen Z, Liu Y, Lin Z, Huang W. cGAS–STING pathway in ischemia-reperfusion injury: a potential target to improve transplantation outcomes. *Front Immunol*. 2023;14:1231057. [CrossRef]

48. Kerbert AJC, Engelmann C, Habtesion A, et al. Hyperammonemia induces programmed liver cell death. *Science Advances*. 2025;11(10):1648. [CrossRef]

49. Chen Y, Yang F, Chu Y, Yun Z, Yan Y, Jin J. Mitochondrial transplantation: opportunities and challenges in the treatment of obesity, diabetes, and nonalcoholic fatty liver disease. *J Transl Med*. 2022;20(1):483. [CrossRef]

50. Peng M, Fang F, Wang B. Nanoparticle technologies for liver targeting and their applications in liver diseases. *Front Bioeng Biotechnol*. 2025;13:1661872. [CrossRef]