*Journal of Zhejiang University-SCIENCE B 2025 26(10):972-994*
www.jzus.zju.edu.cn; www.springer.com/journal/11585
E-mail: jzus_b@zju.edu.cn

**Review**

https://doi.org/10.1631/jzus.B2400053

# Roles of the Keap1/Nrf2 pathway and mitophagy in liver diseases

Qihui ZHOU[1], Panpan CEN[1], Zhi CHEN[2]✉, Jie JIN[1]✉

*[1]Department of Infectious Diseases, Affiliated Hangzhou First People's Hospital, School of Medicine, Westlake University, Hangzhou 310006, China*
*[2]Department of Infectious Diseases, State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, National Clinical Research Center for Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310003, China*

**Abstract:** Nuclear factor erythroid 2-related factor 2 (Nrf2) is an intracellular transcription factor that helps protect against oxidative stress in different types of cells under pathological conditions. Mitochondria are vital organelles that function in diverse metabolic processes in the body, including redox reactions, lipid metabolism, and cell death. Mitophagy, a specific form of autophagy for damaged mitochondria, plays a critical role in the pathophysiology of liver diseases. In this review, we explain in detail the roles of the Nrf2 signaling pathway and mitophagy, and the relationship between them, in various hepatic diseases (nonalcoholic fatty liver disease, viral hepatitis, alcoholic liver disease, drug-induced liver injury, autoimmune hepatitis, hepatic ischemia–reperfusion injury, and liver cancer). We also offer some potential insights and treatments relevant to clinical applications.

**Key words:** Nrf2 signaling pathway; Mitophagy; Liver disease

## 1 Introduction

The liver is the most important metabolic organ and plays roles in synthesis, metabolism, and detoxification. Liver diseases, injury, inflammation, and apoptosis are caused by exogenous inflammation and oxidative stress, mitochondrial respiratory chain failure, and other mechanisms (Solano-Urrusquieta et al., 2020).

Several cellular pathways participate in maintaining internal homeostasis. Nuclear factor erythroid 2-related factor 2 (Nrf2) is an important factor responsible for detoxification, antioxidation, anti-inflammation, proteostasis, xenobiotic/drug metabolism, iron metabolism, and apoptosis. It is a nuclear transcription factor attached to the cytoskeleton and other proteins, especially Kelch-like ECH-associated protein 1 (Keap1), in the cytoplasm. Under homeostatic conditions, Nrf2 is rigorously regulated by Keap1 for ubiquitination and proteasome-dependent degradation, thus keeping its expression and that of downstream genes at low levels. Upon exposure to oxidative stress or inflammation, mainly reactive oxygen species (ROS), Nrf2 is released from Keap1 and translocates into the nucleus to regulate the transcription of antioxidant response elements (AREs), including heme oxygenase-1 (HO-1), glutathione, and thioredoxin (Trx)-dependent enzymes involved in DNA repair, antioxidation, anti-apoptosis, and maintenance of homeostasis (Solano-Urrusquieta et al., 2020). Nrf2 exerts protection through several mechanisms. It downregulates the level of mitochondrial ROS and impacts mitochondrial biogenesis by promoting the peroxisome proliferator-activated receptor-γ (PPAR-γ) coactivator-1α (PGC-1α) level. Pharmacologically targeting Nrf2 can mediate several diseases through ferroptosis in some manner (Dodson et al., 2019). Nrf2 increases the level of nicotinamide adenine dinucleotide phosphate (NADPH) by upregulating the genes responsible for NADPH. In cancers with activated Nrf2, glutamates are recruited into glutathione biosynthesis or exported through the cystine/glutamate antiporter (system $xc^-$). This results in the depletion of intracellular glutamate and the restriction of its use in the synthesis of non-essential amino acids (NEAAs), limiting tumor growth (Leboeuf et al.,

---

✉ Jie JIN, jinjie0429@163.com
Zhi CHEN, zjuchenzhi@zju.edu.cn
Jie JIN, https://orcid.org/0000-0001-9512-859X
Zhi CHEN, https://orcid.org/0000-0002-0848-1502
Qihui ZHOU, https://orcid.org/0000-0001-5369-3320

Received Feb. 26, 2024; Revision accepted June 5, 2024;
Crosschecked Aug. 8, 2025; Published online Aug. 28, 2025

2020). The expression of Nrf2 is inversely correlated with that of inflammatory cytokines, including interleukin-1β (IL-1β) and IL-6 (Solano-Urrusquieta et al., 2020). Thimmulappa et al. (2006) revealed that Nrf2 improved the survival rate by downregulating the pro-inflammatory signaling pathway. Regulatory T cells (Tregs) are closely related to the occurrence of autoimmune diseases. However, even when Tregs are absent, Nrf2 can exert anti-inflammatory effects by inhibiting effector T cell activity (Suzuki et al., 2017). In addition, Nrf2 promotes the differentiation of cluster of differentiation 4-positive ($CD4^+$) T cells into T helper type 2 (Th2) cells by producing the cytokines IL-4 and IL-5 and inhibiting interferon-γ (IFN-γ) (Rockwell et al., 2012). However, in *Pten*::*Keap1* and *Keap1*::*Atg7* double knockout mouse models of hepatic disease, Baird et al. (2023) suggested that Nrf2 induces the expression of senescence-associated secretory phenotype genes, thus recruiting immune effector cells, including chemokine C-C-motif receptor 2-positive ($CCR2^+$) classical monocytes, to suppress early-stage tumors. They also found that not only monocytes but also activated natural killer (NK) cells and γδ T cells were enriched in tumors with the activating mutated gene *NRF2* (specifically the $\mathit{NFE2L2}^{\mathrm{E82D}}$ mutation) (Baird and Yamamoto, 2023). In addition, more pro-inflammatory immune cells and cytokines, such as macrophages, neutrophils, chemokine C-C motif ligand 2 (CCL2), and IL-1β, were enriched in the livers of $\mathrm{NEMO}^{\Delta\mathrm{hepa}}$/$\mathrm{KEAP1}^{\Delta\mathrm{hepa}}$ mice with consecutive NRF2 activation (Mohs et al., 2021). The potential mechanisms might involve the inactivation of nuclear factor-κB (NF-κB) signaling and massive infiltration of myeloid cells.

Autophagy is the process by which autophagosomes bring cargo to lysosomes to exert enzymatic effects to remove damaged organelles. Autophagy can be broadly classified into three categories: macroautophagy, microautophagy, and chaperone-mediated autophagy. The major category, macroautophagy, refers to the process of the fusion of autophagosomes and lysosomes to degrade the materials. Microautophagy represents the process in which the lysosome itself invaginates the membrane to swallow the components. The third category manifests as the translocation of the lysosomal membrane formed by oligomerization of the heat-shock cognate protein HSPA8/HSC70. Conserved genes, known as autophagy-related genes (*ATG*), take part in different stages of autophagy, including phagophore initiation, fusion of autophagosomes with lysosomes, and degradation. Under normal conditions, autophagy varies with the body's nutrient status. For example, proteasomes generate mainly amino acids. Under nutrient starvation, hepatic autophagy is enhanced to provide cells with different nutrients (Schneider and Cuervo, 2014). A portion of proteins, including vacuolar/lysosomal enzymes, respiratory chain proteins, antioxidant enzymes, and proteins related to amino acid synthesis, are produced during starvation (Mizushima and Komatsu, 2011). During an adequate supply of nutrients, a tiny percentage of proteins are metabolized through selective and nonselective degradation. Selective degradation commonly occurs.

Mitochondria are involved in several physical processes, including cellular redox, supplemental energy through the tricarboxylic acid cycle and oxidative phosphorylation (OXPHOS), participation in fatty acid oxidation, calcium buffering, amino acid synthesis, heme biosynthesis, iron–sulfur cluster formation, and cell death (Ma et al., 2020; Innokentev and Kanki, 2021). It is estimated that more than 2000 mitochondria are involved in each hepatocyte, implying their critical roles in liver diseases (Chen et al., 2015). Diverse liver diseases are associated with selective autophagy, mainly mitophagy (autophagy of mitochondria), which normally ensures mitochondrial quality and normal liver function. Mitophagy is realized through the ubiquitin-independent or -dependent pathway, involving mammalian Atg8 family members including microtubule-associated protein light chain 3 (LC3) and γ-aminobutyric acid receptor-associated protein (GABARAP), especially the LC3-interacting region (LIR)-domain receptor pathway or phosphatase and tensin homolog (PTEN)-induced putative kinase 1 (PINK1)/Parkin pathway, respectively (Wang and Wang, 2023). The LIR-domain receptor pathway involves outer mitochondrial membrane (OMM) receptors such as B-cell lymphoma 2 (Bcl-2)/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3), BNIP3-like (BNIP3L) (also known as NIP3-like protein X (NIX)), FUN14 domain-containing protein 1 (FUNDC1), and Bcl-2-like protein 13 (BCL2L13). These receptors interact with LC3, which promotes mitophagy. It is reported that BNIP3 and NIX also play a part in the PINK1/Parkin pathway. For example, BNIP3 interacts with PINK1, which leads to the accumulation of PINK1 and Parkin at the OMM.

NIX can be ubiquitinated by Parkin to promote mitophagy. FUNDC1 is integrated into the OMM and acts with LC3 under hypoxic conditions. The overexpression of BCL2L13 promotes mitochondrial fragmentation and its interaction with Unc-51-like kinase 1 (ULK1) initiates mitophagy. The PINK1/Parkin pathway can be summarized as follows: PINK1 is autophosphorylated in response to decreased mitochondrial membrane potential, which recruits and activates the Parkin E3 ubiquitin ligase. Parkin ubiquitinates the substrates at the OMM, and the ubiquitinated proteins bind to adaptors including p62, optineurin (OPTN), and nuclear dot protein 52 (NDP52), which interact with the Atg8 family to promote mitophagy. The accumulation of p62 and polyubiquitinated proteins often indicates a deficiency of autophagy (Fig. 1).

Nrf2 interacts with PGC-1α in mitochondrial biogenesis. The activation of Nrf2 upregulates the mitochondrial membrane potential and the level of adenosine triphosphate (ATP), directly impacting energy metabolism (Holmström et al., 2013). There is positive feedback between Nrf2 and mitophagy. Under oxidative conditions, Nrf2 elevates the expression of p62 and PINK1, leading to mitophagy. Phosphorylated p62 binds to Keap1 and releases Nrf2, leading to activation of downstream antioxidant proteins.

Dysfunction of the Nrf2 signaling pathway and mitophagy are closely correlated with diverse hepatic diseases. The possible relationship between them in terms of their antioxidative response has received great attention recently. Here, we explain the roles of the Nrf2 signaling pathway and mitophagy in hepatic diseases, as well as the relationships between them (Table 1).

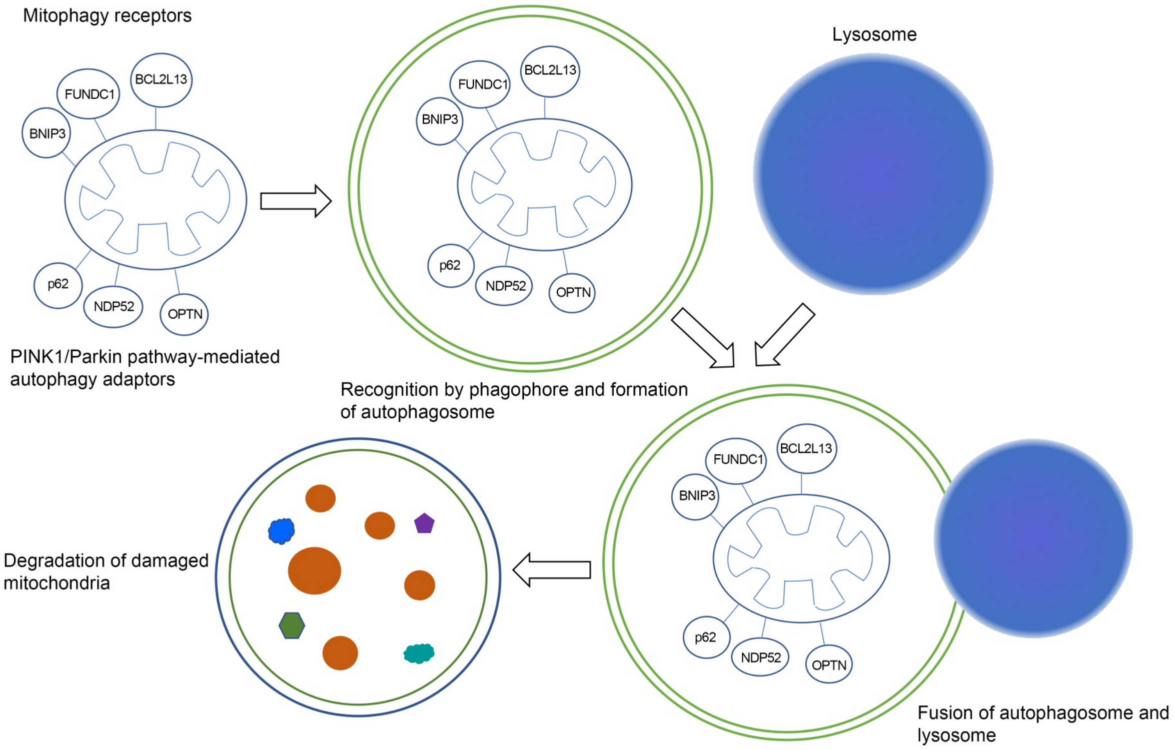

**Fig. 1 Main process of mitophagy. Under stress conditions (the presence of ROS, nutrient deficiency, cell aging, and other external stimuli), damaged mitochondria depolarize and lose their membrane potential. The damaged mitochondria are then wrapped by autophagosomes and form mitochondrial autophagosomes. These fuse with lysosomes and subsequently the mitochondria are degraded by lysosomes. Mitophagy is usually divided into ubiquitin-dependent and -independent pathways. In the ubiquitin-dependent mechanism, the PINK1/Parkin pathway is located on the same pathway to protect mitochondria. In the ubiquitin-independent mechanism, many receptors, including BNIP3, NIX/BNIP3L, and FUNDC1, bind directly to LC3 without ubiquitination. BCL2L13: B-cell lymphoma 2 (Bcl-2)-like protein 13; BNIP3: Bcl-2/adenovirus E1B 19 kDa protein-interacting protein 3; FUNDC1: FUN14 domain-containing protein 1; LC3: light chain 3; NDP52: nuclear dot protein 52; OPTN: optineurin; PINK1: phosphatase and tensin homolog (PTEN)-induced putative kinase 1; ROS: reactive oxygen species.**

**Table 1 Roles of the Nrf2 signaling pathway and mitophagy in diverse liver diseases**

| Liver disease | Roles of Nrf2 signaling pathway | Roles of mitophagy |
|---|---|---|
| Metabolic dysfunction-associated steatotic liver disease (MASLD) | Nrf2 is upregulated to repress obesity and hepatic lipidoses and enhance antioxidative capacity. | Either defective or excessive mitophagy aggravates MASLD. |
| Viral hepatitis | Nrf2 inhibits HBV and HCV replication. | Mitophagy promotes HBV replication, thus accelerating HBV-related liver cancer; mitophagy may also suppress HBV replication. Mitophagy supports HCV replication, maturation, and release. |
| Alcoholic liver disease (ALD) | Nrf2 is activated to attenuate oxidative stress in ALD; Nrf2 is also inhibited in several alcohol-feeding modes. | Mitophagy accelerates alcohol metabolism and prevents liver damage. |
| Drug-induced liver injury (DILI) | Nrf2 is upregulated to fight against DILI. | Mitophagy protects the liver from APAP injury through the suppression of NF-κB, NLRP3 inflammasome, and IL-1β; *Parkin*-knockout mitophagy protects against APAP injury. |
| Hepatic ischemia-reperfusion injury (IRI) | Nrf2 is suppressed to aggravate hepatic IRI; however, Nrf2 is also elevated to improve hepatic IRI. | Mitophagy attenuates hepatic IRI. |
| Liver carcinoma | Nrf2 prevents carcinogenesis in normal cells and promotes tumor cells in cancer tissues. | Mitophagy suppresses liver cancer in the initial stage, while it supports the development of liver cancer in the formed tumors. |

APAP: acetaminophen; HBV: hepatitis B virus; HCV: hepatitis C virus; IL-1β: interleukin-1β; NF-κB: nuclear factor-κB; NLRP3: NOD-like receptor family, pyrin domain-containing protein 3; Nrf2: nuclear factor erythroid 2-related factor 2.

## 2 Metabolic dysfunction-associated steatotic liver disease

Metabolic dysfunction-associated fatty liver disease (MAFLD), introduced in 2020, is distinguished from non-alcoholic fatty liver disease (NAFLD) by its stricter metabolic criteria. Metabolic dysfunction-associated steatotic liver disease (MASLD), proposed by international expert groups in June 2023, is a "multisystem disease." It is more objective in some controversial aspects and includes one of the five cardiovascular risk factors, insulin resistance and metabolic syndrome (Rinella et al., 2023; Targher et al., 2024). MASLD may be attributed to the following mechanisms: (1) insulin resistance-induced intracellular triglyceride accumulation; (2) oxidative stress, such as an increase in ROS; and (3) oxidative stress-triggered hepatocellular necrosis and toxicity (Ezhilarasan and Lakshmi, 2022). Increasing evidence suggests that MASLD almost conforms to NAFLD. MASLD includes metabolic dysfunction-associated steatohepatitis (MASH), previously known as non-alcoholic steatohepatitis (NASH).

Intrahepatic Nrf2 appears to regulate lipid metabolism. In rats fed a high-fat diet (HFD), *Lactobacillus mali* APS1 from sugary kefir decreased body weight and hepatic lipidoses and enhanced antioxidative capacity by regulating the Sirtuin-1 (SIRT1)/Nrf2/HO-1 pathway (Chen et al., 2018). Nrf2 and sterol regulatory element-binding protein-1 (SREBP-1) were increased in palmitic acid-treated HepG2 cells, and Nrf2 was significantly upregulated when the cells were cotreated with fermented soymilk and palmitic acid, indicating a protective role of fermented soymilk in the NAFLD model (Ahn et al., 2018). Receptor-interacting serine/threonine-protein kinase-3 (RIP3) increased in HFD-fed mice and regulated programmed necrosis as well as inflammatory responses by producing ROS. Nevertheless, diminished hepatic lipid accumulation, oxidative stress, and the NF-κB signaling pathway were all observed by downregulating Keap1 and activating Nrf2 expression in *RIP3*$^{-/-}$ mice (Ge et al., 2019). Agonists of intrahepatic Nrf2, regardless of the genes or agents (e.g., 1-[2-cyano-3,12-dioxooleana-1,9(11)-dien-28oyl] imidazole (CDDO-Im)), repressed HFD-induced obesity, diabetes, and cancers (Yates et al., 2009). Nrf2 retarded lipid accumulation and peroxidation in Nrf2-null and Keap1-knockout (KO) mice (Zhang et al., 2010). A few compounds, including phenolic antioxidants, dithiolethione, isothiocyanate, triterpenoid, pioglitazone, vitamin E, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and resveratrol, were reported to promote the expression of Nrf2 (Solano-Urrusquieta et al., 2020). Silybin restrained oxidative stress by activating Nrf2-associated genes and inhibiting the NF-κB signaling pathway in the NASH liver (Ou et al., 2018). Liraglutide was shown to enhance antioxidative capacity and decrease liver apoptosis in Zucker diabetic fatty (ZDF) rats by increasing the Nrf2 signaling pathway (Guo et al., 2018). Terpenoids, including geniposide, aucubin, gentiopicroside, and ginkgolide B, improve lipid metabolism, suppress oxidative stress, and eventually prevent liver fibrosis by activating the Nrf2 and adenosine monophosphate-activated protein kinase (AMPK) signaling pathways (Yao and Liu, 2022). Another experiment confirmed that *Nrf2*$^{-/-}$ mice fed a methionine- and choline-deficient (MCD) diet endured more severe steatosis and oxidative stress (Chowdhry et al., 2010). Resveratrol, a polyphenol and antioxidant derived from plants, suppressed Nrf2 promoter methylation and ROS levels in vitro to mitigate the progression of NAFLD (Ezhilarasan and Lakshmi, 2022). In clinical use, resveratrol combined with a healthy lifestyle can alleviate liver inflammation and fibrosis (Faghihzadeh et al., 2014). As previously demonstrated, zinc, participating in the reduction reaction, plays a key role in type 1 and type 2 diabetes-induced liver injuries. Nrf2 bridges zinc supplementation and metallothionein expression to exert antioxidative effects on diabetes-induced liver injury (Yu et al., 2021). Han et al. (2016) showed that the expression of Nrf2 and ARE was increased in mice fed a high-fructose diet, which mimicked the NAFLD model, but was downregulated in those fed hawthorn fruit peel and flesh at the same time, which exerted antioxidative effects on injured livers. The phosphoglycerate mutase family member 5 (*Pgam5*)-knockout mice fed with a high-fat high-fructose diet showed reduced hepatic steatosis and inflammation by upregulating antioxidant genes and proteins including glutathione peroxidase-6 (*GPX6*) and HO-1 (Li L et al., 2023). Bioactive dipeptides tyrosine (Tyr) and phenylalanine (Phe) dose-dependently exert antioxidant effects and protect against HFD and high fructose corn syrup-induced MAFLD, mainly through activation of the Nrf2 signaling pathway and adiponectin secretion and downregulation of 4-hydroxynonenal (Wayal and Hsieh, 2023). It was reported that silica nanoparticles (SiNPs), one of the most common nanomaterials, aggravate MAFLD by enhancing lipid accumulation and suppressing fatty acid β-oxidation and lipid efflux, mainly by down-regulating Nrf2 signaling (Abulikemu et al., 2023). S217879 alleviates diet-induced steatosis, inflammation, and fibrosis in patients with MAFLD by pharmacologically activating Nrf2 and suppressing transforming growth factor-β 1 (TGF-β1) signaling (Hammoutene et al., 2023). Linalool, a kind of monoterpene in a variety of aromatic plants, also protects against HFD-induced MASLD through activating the Nrf2 signaling and SIRT1/protein kinase B (Akt)/peroxisome proliferator-activated receptor-α (PPRA-α)/AMPK pathways to attenuate liver steatosis and oxidative stress (Tamilmani et al., 2023). Baicalin, a traditional Chinese medicine, exerts its strong antioxidant and anti-inflammatory capacities through upregulating the p62/Keap1/Nrf2 pathway in the liver of MAFLD mice (Liu et al., 2025). Puerarin, another advantageous Chinese medicine, improves MAFLD by inhibiting ferroptosis and inflammation, mainly by activating the SIRT1/Nrf2 signaling pathway (Yang MM et al., 2023). However, Kumar et al. (2019) showed that the expression of Nrf2 and HO-1 was significantly decreased in HFD- and ethanol-fed rats. Liu PF et al. (2023) showed that the mechanism underlying NAFLD linked to an HFD involved decreased autophagosome biogenesis and Nrf2 levels, which contributed to enhanced lipid peroxidation and ferroptosis.

Defective mitophagy was also observed in HFD models with several impaired signaling pathways, including: (1) upregulated expression of acyl-coenzyme A (acyl-CoA):lysocardiolipin acyltransferase 1 (ALCAT1), the removal of which could recover mitophagy; (2) genetic removal of macrophage stimulating 1 (Mst1), which remits injuries through activation of mitophagy; and (3) BNIP3, the knockout of which promotes lipid accumulation (Wang et al., 2015; Ma et al., 2020). Increased *S*-nitrosylation of hepatic lysosomal proteins and impaired mitophagy, especially the level of Atg7, were observed in obesity groups (Yang et al., 2010; Qian et al., 2018). Megamitochondria in NAFLD blocked Parkin-independent mitophagy, leading to liver damage in an NAFLD mouse model, while an *Opa1* knockout rescued liver damage (Yamada et al., 2018). A high degree of phosphorylation of protein kinase R-like endoplasmic reticulum kinase (PERK), dysregulated association between the endoplasmic reticulum (ER) and mitochondria, and mitochondrial dysfunction and mitofusin 2 (Mfn2) deficiency are related to the development of the NAFLD model (Mao et al., 2022). An increased level of mortality factor 4-like protein 1 (MORF4L1, also called MRG15) in fatty liver models is associated with mitochondrial Tu translation elongation factor (TUFM), resulting in defective mitophagy, excessive oxidative stress, and NOD-like receptor family, pyrin domain-containing protein 3 (NLRP3) inflammasome activation (Tian et al., 2022). Restoration of hepatic autophagy alleviates ER stress and enhances insulin action (Yang et al., 2010). Double knockout of Akt and AMPK amplifies Parkin-mediated mitophagy and protects against hepatic steatosis in NAFLD (Wang SY et al., 2021). The mitophagy inducer cyanidin-3-*O*-glucoside enhances PINK1-mediated mitophagy, which is blunted in NAFLD, and alleviates hepatic oxidative stress (Li XW et al., 2020). Exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist, is used to regulate glycemia and serum lipids, improve β-cell function, control weight, enhance mitophagy, and inhibit NLRP3 inflammasome activation to suppress hepatic inflammation in NAFLD (Shao et al., 2018). SIRT3, which protects mitochondria under several kinds of stress, promotes BNIP3-mediated mitophagy and protects the liver in NAFLD via activation of the extracellular signal-regulated kinase (ERK)-cAMP response element-binding protein (CREB) signaling pathway (Li et al., 2018). The lysosomal–autophagic pathway plays an important role in the translocation of transcription factor EB (TFEB) to the liver to control weight gain and metabolic syndromes such as NAFLD (Settembre et al., 2013). Ampawong et al. (2017) demonstrated that liver Nrf2 expression is negatively correlated with the percentage of dysmorphic mitochondria, especially the fission marker dynamin-related protein 1 (Drp1), in a high-cholesterol-challenged rat model with or without sericin pretreatment. However, it was also reported that a deficiency of the adipose-specific mitochondrial antioxidant Trx2 increases hepatic insulin resistance and steatosis through excessive mitophagy and inflammation (He et al., 2021). Petersen et al. (2018) showed that Nrf2 and autophagic markers, including p62 and LC3-II, are simultaneously increased in liver-specific PTEN-deletion mice, which mimics NASH-like conditions, indicating the activation of both the antioxidant response and mitophagy. Bae et al. (2013) demonstrated that Nrf2 activation induced by Sestrin2 (Sesn2) is beneficial to liver oxidative injury triggered by the acute lipogenic stimulus through the p62-dependent degradation of Keap1. In a mouse model of partial hepatectomy or HFD-induced hepatic steatosis, the suppression of p62 and antioxidant molecules through the inhibition of Nrf2, the overexpression of Fas/Fas ligand (FasL), and the hyporesponsiveness of Akt jointly accelerated liver injury and retarded liver regeneration (Haga et al., 2014).

## 3 Viral hepatitis

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are often regarded as the most common causes of viral hepatitis and are related to the progression of liver fibrosis to liver cancer (Zhou et al., 2021).

Accumulating evidence supports that the induction of Nrf2 inhibits HBV replication. Bardoxolone methyl, an activator of Nrf2, inhibits HBV pregenomic RNA (pgRNA) and DNA, as well as the HCV genome, in an Nrf2-dependent manner (Nio et al., 2019). Hemin, an HO-1 inducer, markedly suppresses the levels of hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg), as well as HBV-DNA, in a dose- and time-dependent manner (Shen et al., 2015). The underlying mechanism might be the downregulated stability of the HBV core protein at the posttranscriptional stage, which leads to a blockade of nuclear HBV covalently closed circular DNA (cccDNA) (Protzer et al., 2007). In addition, Keap1-recognized HBV X protein (HBx) leads to Nrf2/ARE pathway activation, which enhances the interaction between Nrf2 and the HBV core promoter, thereby reducing the core promoter's ability and HBV replication (Ariffianto et al., 2023). The anti-HCV activity of 3-amino-2-hydroxypropoxy isoflavone derivatives, natural isoflavonoids with anticancer, antiviral, and anti-inflammatory effects, relies on Keap1/Nrf2/HO-1 pathway induction (Lee JC et al., 2018). Lucidone, isolated from the fruits of *Lindera erythrocarpa* Makino, also significantly lowers HCV RNA levels and viral protease activity through Nrf2/HO-1 activation (Chen et al., 2013). HO-1 overexpression is correlated with decreased HCV replication and prooxidant levels in both full-length and nonstructural replicons, which might protect the liver from cytotoxicity (Zhu et al., 2008). The microRNA let-7, used to fight against liver fibrosis and liver cancer, exerts anti-HCV activity through interaction with BTB and CNC homolog 1 (Bach1) and induction of HO-1 (Chen WC et al., 2019). A study conducted on the anti-HCV effect of caffeic acid demonstrated that the Keap1/Nrf2/HO-1 interaction and an underlying increase in p62 elicited IFN-α antiviral activity (Shen et al., 2018). In addition to HO-1, biliverdin, the oxidative product of HO-1, has anti-HCV activity through the interferon response (Zhu et al., 2010). Abdalla et al. (2004) showed that the level of HO-1 in hepatocytes from HCV-infected patients or cell lines that expressed HCV core protein was all downregulated. The reason behind this might be siderosis present in the liver biopsy samples. The amino acid substitutions of R70Q/H or L91M in the HCV core region affect hepatocellular carcinoma (HCC) progression via impaired nuclear Nrf2 translocation and enhanced oxidative stress (Chida et al., 2024). In Huh7 cells, Smirnova et al. (2023) showed that the expression of hepatitis delta virus (HDV) antigen provoked the antioxidant Nrf2/ARE pathway, ER stress, and an unfolded protein response (UPR).

HBx is involved in the chronic process of HCC and mitochondrial damage. HBV upregulates autophagy in cell culture and natural infection in a manner dependent on HBx, thus enhancing viral replication (Sir et al., 2010). HBx induces BNIP3L-mediated mitophagy in liver cancer stem cells and upregulates glycolysis, thereby accelerating HCC development, indicating a potential role of anti-HBx monoclonal antibodies in delaying HBV infection progression (Chen et al., 2020). HBx-induced arrestin β1 (ARBB1) overexpression promotes carcinogenesis in an autophagy-dependent manner, indicating that autophagy may be a clinical therapeutic target in treating liver cancer (Lei et al., 2021). Decreased total serum $T_3$ levels in patients with HBV-related liver cirrhosis were observed in a previous study. Chi et al. (2017) explored the underlying mechanism. The hepatoprotective role of thyroid hormone-induced PINK1/Parkin-dependent mitophagy might provide a potential therapy for preventing HBx-related carcinogenesis. Tunicamycin-induced ER stress and mitophagy enhance HBV replication and release subviral particles in the early stage of autophagy. However, in chronic hepatitis B (CHB)-infected patients, mitophagy is inhibited, and conflicting phenomena were observed, suggesting that mitophagy suppresses HBV replication (Wang et al., 2022b). Miyakawa et al. (2022a, 2022b) demonstrated that galectin 9 worked together with radical *S*-adenosyl methionine domain-containing protein 2 (RSAD2)/viperin, RING finger protein 13 (RNF13), and p62 to form autophagosomes to selectively degrade hepatitis B core (HBc) in HBV-infected hepatocytes, thereby contributing to intracellular antiviral immunity. Coiled-coil domain containing 88A (CCDC88A/GIV) promotes HBV replication by reducing the autophagic degradation of HBV antigens (Wang et al., 2022a). HBx-induced deficient autophagy leads to endonuclease G (ENDOG) translocation to nuclei in a mitochondrial permeability-dependent manner, thereby promoting HBV-related liver cancer development (Chao et al., 2021). In a study conducted on glucosamine in patients with chronic viral infection, suppressed lysosomal acidification and autophagic degradation of HBV virions accelerated HBV replication (Lin et al., 2020). Autophagy serves as a protective mechanism in eliminating some intracellular pathogens but may be used by some kinds of viruses, such as HCV, to support their replication through multiple mechanisms, including activation of ER stress and the UPR, as well as the induction of oxidative stress (Chu and Ou, 2021). HCV, regardless of genotype, can induce ER stress and the accumulation of autophagosomes in host cells, while autophagic protein degradation is inefficient, which indicates that enhanced autophagy plays an important role in HCV replication (Sir et al., 2008a, 2008b). Mechanistically, HCV-induced autophagy is not dependent on the Class III phosphatidylinositol 3-kinase (PI3K) pathway, and HCV replicates on autophagosomal membranes (Sir et al., 2012). However, Twu et al. (2021) demonstrated that autophagosome biogenesis components such as the Class III PI3K complex and double FYVE-containing protein 1 (DFCP1) are important in HCV replication by double-membrane vesicles, although the ATG5-12/16L1 complex was also important. Autophagy not only facilitates HCV replication but also promotes HCV maturation and release. It has been demonstrated that HCV infection is often correlated with elevated levels of oxidative stress and autophagy, thus facilitating the release of HCV particles. Diminishing ROS could lower the activities of autophagy and reduce the particles (Medvedev et al., 2017). Apolipoprotein E (ApoE), associated with HCV virion infectivity, is degraded by autophagy. The inhibition of autophagy leads to colocalization of ApoE and the HCV E2 envelope protein and elevated progeny viral titers (Kim and Ou, 2018).

## 4 Alcoholic liver disease

Alcoholic liver disease (ALD) due to excessive alcohol consumption covers a series of disorders, including steatosis, alcoholic hepatitis, alcoholic cirrhosis, and ultimately HCC. Chronic alcohol abuse promotes lipid peroxidation and oxidative stress, along with impaired antioxidant enzymes, including glutathione and superoxide dismutase (SOD) (Zhu et al., 2012).

Nrf2, in turn, is activated as an early compensatory mechanism to attenuate inflammation and oxidative injury in ALD (Zhu et al., 2012). Kupffer cells and human monocytic Tohoku hospital pediatrics-1 (THP-1) cells treated with ethanol show increased messenger RNA (mRNA) levels of *HO-1*, quinone oxidoreductase 1 (*NQO1*), and hypoxia-inducible factor-1 (*HIF-1*) (Yeligar et al., 2010). Wu et al. (2012) showed that in different genetic experimental groups, including *Nrf2*-null mice, wild-type mice, *Keap1*-knockout mice with enhanced Nrf2, and *Keap1*-hepatocyte-knockout mice with maximum Nrf2 activation, Nrf2 activation prevented ethanol-induced liver oxidative stress and steatosis by upregulating the expression of antioxidant enzymes and downregulating the SREBP-1 signaling pathway. AHPN80, a polysaccharide from Alhagi honey, reduces the oxidative stress in ALD by upregulating the Nrf2 pathway and inhibiting the lipopolysaccharide (LPS)/Toll-like receptor 4 (TLR4)/MAPK pathway, which repairs the intestinal barrier (Song et al., 2024). Asiatic acid extracted from *Potentilla chinensis* relieves alcoholic hepatitis by upregulating the Nrf2 signaling pathway, downregulating the NF-κB pathway, and ameliorating lipid metabolic disturbance (Chen et al., 2022). *Dracocephalum tanguticum* Maxim. ethyl acetate extract, a traditional Tibetan medicine, protects the liver against alcohol in vitro and in vivo through activation of the Nrf2 signaling and inhibition of the p65/NF-κB signaling pathway (Guo et al., 2022). A supplement of a peptide from sea cucumber attenuates hepatitis, lipid accumulation, and hepatocyte apoptosis, and enhances antioxidant enzyme activity in ALD by activating the Nrf2 pathway and mitochondrial dynamics (Zhu et al., 2022). Alcohol induces a high expression of miR-138-5p, a low expression of deacetylase SIRT1, and decreased farnesoid X receptor (FXR) activity. Downregulation of miR-138-5p by kaempferol and nicotiflorin treatment upregulates the level of SIRT1, thereby strengthening FXR activity and phosphorylated Nrf2 level, and suppressing oxidative stress (Ge et al., 2024). Various antioxidants, also known as Nrf2 activators, including *N*-acetyl cysteine (NAC), resveratrol, silymarin, quercetin, sulforaphane, curcumin, and diallyl disulfide, have been used to relieve liver injury in ALD (Zhao N et al., 2018). However, contradictory results indicated that ethanol consumption suppressed the intrahepatic levels of Nrf2, HO-1, and NQO1 in mice (Choi et al., 2015; Lu et al., 2016; Huang et al., 2017; Meng et al., 2019; Abdelhamid et al., 2021). Alcoholics with nutritional deficiency usually present with increased prooxidant production and low levels of antioxidants such as Nrf2 (Namachivayam and Valsala Gopalakrishnan, 2021). Abdelhamid et al. (2021) showed that the binding capacities of PPAR-γ and Nrf2 were decreased in alcohol-fed mice. Patel et al. (2021) demonstrated that the expression of Nrf2 and HO-1 declined in an ethanol-only treated group compared to groups in which metformin and probiotics were added. Xie et al. (2022) observed decreased levels of Nrf2 and HO-1 in mice fed only alcohol compared to those in mice administered alcohol and a modified Lvdou Gancao decoction. Yi et al. (2020) also showed that the gene expression of Nrf2 and HO-1 was downregulated in alcohol-fed mice compared to vehicle-fed mice, while the trends were reversed by treatment with Antrodin A. PPAR-γ/Nrf2 crosstalk is inhibited in alcohol-fed mice compared to normal mice, whereas the expression of PPAR-γ and Nrf2 is enhanced by telmisartan (Abdelhamid et al., 2021). In alcohol-damaged mice, the observed downregulation of the Nrf2 signaling pathway and an increased level of Keap1 can be reversed by the antioxidant and anti-inflammatory fruiting body of *Morchella esculenta* (Meng et al., 2019). Ginsenoside Rc, isolated from *Panax ginseng*, alleviates the hepatic inflammation and oxidative stress in ALD by activating SIRT6, which deacetylates and boosts Nrf2 (Pan et al., 2022). These different phenomena might be attributable to the mode and duration of alcohol feeding.

It was reported that ethanol inhibited the synthesis of mitochondrial DNA (mtDNA) encoding mitochondrial respiratory complex proteins, implying the targeting of mtDNA by ethanol, manifesting as mtDNA strand breakage and integrity damage (Ding et al., 2011; Axley et al., 2019). Mitophagy works as a compensatory mechanism to accelerate ethanol metabolism and prevent liver injury. However, accumulating evidence has shown that mitophagy is impaired and decompensatory during both acute and chronic ALD (Ma et al., 2020). Ethanol-treated autophagy-related gene expression is suppressed when the negative form of Forkhead box O3a (FoxO3a) is overexpressed or in *FoxO3a*$^{-/-}$ mice (Ni et al., 2013). Decreased mitophagy, β-oxidation, mitochondrial respiration, and cytochrome *c* oxidase activity were observed in *Parkin*-knockout alcohol-treated mice compared to wild-type mice (Williams et al., 2015b). FUNDC1-mediated mitophagy is suppressed by the activation of the orphan nuclear receptor subfamily 4 group A member 1 (NR4A1)/DNA-dependent protein kinase catalytic subunit (DNA-PKcs)/p53 pathway in the livers of alcohol-treated mice, an effect related to hepatic injury (Zhou et al., 2019). Acute ethanol-induced autophagy is related to a higher nuclear TFEB content, while chronic ethanol gavage exhibits the reverse trend (Thomes et al., 2015). Autophagy negatively regulates the Nrf2/Keap 1 pathway, as shown in a study in which autophagy deficiency activated the Nrf2/Keap 1 pathway (Lau et al., 2010). Xie et al. (2018) demonstrated that autophagy restraint characterized by less p62 and an increased LC3II/LC3I ratio played a part in HSC inhibition and fibrogenesis in mice with ALD through Nrf2 activation and subsequent α-smooth muscle actin (α-SMA) or α1 type I collagen (COL1A1) downregulation. This suggests an antifibrotic relationship between autophagy blockade and Nrf2 activation. However, Lu et al. (2021) suggested that AMPK upregulated ubiquinol-cytochrome *c* reductase core protein 2 (*UQCRC2*) gene transcription by activating Nrf2 to enhance mitophagy, thereby attenuating the liver injury induced by alcohol.

## 5 Drug-induced liver injury

Acetaminophen (APAP), an antipyretic and analgesic drug, has been widely used in the clinic. Overdosage of APAP is currently the main cause of liver failure in developed countries, which may be due to the overproduction of ROS and dysfunction of mitochondria.

It was suggested that rats exhibit a higher activation of Nrf2-associated response and greater autophagic capacities to an equivalent *N*-acetyl-*p*-benzoquinone imine (NAPQI) insult than mice and humans (Russomanno et al., 2023). Several studies on new medicines or treatments have implied a protective role of Nrf2 in drug-induced liver diseases. Sea buckthorn polysaccharide exerts antioxidant and hepatoprotective effects against APAP-induced hepatotoxicity mainly by downregulating the expression of Keap1 and activating the Nrf2/HO-1-SOD-2 signaling pathway, as well as suppressing the phosphorylation of c-Jun N-terminal kinase (JNK) (Wang et al., 2018). Hyperoside protects the liver against APAP through Nrf2 and a series of phase II enzymes in a dose-dependent manner (Xie et al., 2016). The activation of the Nrf2/Mn-SOD pathway might account for the antioxidative roles of berberine in APAP-triggered hepatotoxicity (Zhao Z et al., 2018). Aliyu et al. (2018) suggested that the expression of Nrf2 and its upstream kinases, including Akt1, PI3K, and protein kinase C (PKC), was greatly upregulated in APAP-induced mice pretreated with lophirones B and C, which halted liver injury. The traditional Chinese medicine *Schisandra chinensis* treatment significantly upregulated the hepatic expression of Nrf2 and HO-1 when compared to an APAP-treated group in which both were decreased (Che et al., 2019). Sarmentosin, extracted from traditional Chinese medicine, protects against APAP-induced liver injury through the ubiquitin-specific protease 17 (USP17)-mediated Nrf2 pathway and PINK1-related mitophagy (Jiang et al., 2022). When USP25 is genetically or pharmacologically blocked, the level of Keap1 is downregulated and Nrf2 increases, which effectively protects hepatocytes from APAP-induced oxidative stress (Cai et al., 2023). Cai et al. (2022) indicated that astaxanthin fights against liver injury induced by APAP mainly through the activation of the Nrf2 pathway and autophagy, as well as the inhibition of ferroptosis and the NF-κB pathway. Based on these observations, they were the first to develop astaxanthin-loaded hollow mesoporous SiNPs with biodegradability and biocompatibility to target liver diseases. Similarly, daidzein released by *Lactobacillus vaginalis* β-galactosidase alleviates APAP toxicity to hepatocytes by inhibiting farnesyl diphosphate synthase-mediated ferroptosis mainly through the activation of Akt-glycogen synthase kinase-3β (GSK3β)-Nrf2 signaling (Zeng et al., 2023). Pectolinarigenin ameliorates APAP-induced oxidative stress by upregulating Nrf2 and PPAR-α signaling, as well as phase II detoxification enzymes (Li Q et al., 2023). Blockout of macrophage phosphatase and deletion of a tensin homolog on chromosome 10 attenuate APAP-induced hepatic sterile inflammation through enhancement of PI3K/Akt and the Notch intracellular domain (NICD)/Nrf2 pathway, and suppression of the stimulator of interferon genes (STING)-TANK-binding kinase 1 (TBK1) signaling in innate immune responses (Yang T et al., 2023). The ablation of PAPS synthase 2 protects against APAP-mediated hepatotoxicity mainly through activation of the p53-p21-Nrf2 signaling pathway (Xu et al., 2022). Turnip and radish extracts reverse the downward trend of the Nrf2/HO-1 pathway in APAP-treated mice, thereby strengthening the capacities of antioxidant enzymes (Hwang et al., 2022). Tauroursodeoxycholic acid (TUDCA) relieves HepG2 cell injury induced by rifampicin primarily by promoting the Nrf2-mediated adaptive response and then positively regulating the expression of bile acid transporters, including the bile salt export pump (BSEP) and multidrug resistance protein 1 (MDR1) (Zhang et al., 2017). Meanwhile, during methotrexate-triggered liver injury, the phosphorylated cAMP response element-binding protein (pCREB)/Nrf2 pathway is downregulated, while this trend is reversed by liraglutide (Abdelaziz et al., 2019). Similarly, the expression of Nrf2 was higher in a carbon tetrachloride ($CCl_4$) and ellagic acid-treated group than in a $CCl_4$-treated group, demonstrating the antioxidant property of ellagic acid (Aslan et al., 2018). *Vitis vinifera* L. and *Centella asiatica* synergistically exert anti-inflammatory and antioxidant effects against $CCl_4$-induced acute liver injury through activation of the Nrf2 pathway (Munakarmi et al., 2023). In addition, Nrf2 is downregulated in 1,3-dichloro-2-propanol-treated rats compared to those gavaged with caffeic acid (Ajiboye et al., 2019). Ibitoye and Ajiboye (2020) showed that Nrf2 was not altered when mice were treated with hepatotoxic menadione; nevertheless, Nrf2 played a crucial role in the mitigative effect of PA on menadione-induced hepatotoxicity. However, Urrunaga et al. (2015) demonstrated that the expression of Nrf2 and its downstream cytoprotective gene glutamate-cysteine ligase catalytic subunit (*GCLC*) was higher at 4 h after APAP injection than at the peak of liver injury at about 16 h in wild-type mice, which suggested glutathione recovery at 4 h, especially in M1 muscarinic receptor-deficient mice.

Several studies have demonstrated that APAP promotes mitophagy induction in the mouse liver, which protects the liver from APAP injuries (Chao et al., 2018; Ma et al., 2020). Adiponectin protects the liver from APAP injury through the activation of mitophagy (Lin et al., 2014). APAP adducts in hepatocytes are removed by the induction of mitophagy (Ni et al., 2016). Mice treated with the mitophagy inducer rapamycin are protected from drug-induced liver injury (DILI) through suppression of NF-κB, NLRP3 inflammasome, and IL-1β, while mice treated with the mitophagy inhibitor chloroquine suffered from DILI through the activation of the NLRP3 inflammasome (Shan et al., 2019). Acid sphingomyelinase (ASMase) deficiency-induced lysosomal cholesterol accumulation triggers hepatotoxicity in mice by hampering mitophagy. Likewise, human hepatocytes treated with amitriptyline, a kind of ASMase inhibitor, are more prone to APAP injury through impaired mitophagy (Baulies et al., 2015). In a study conducted in mouse livers and cultured hepatocytes treated with APAP, the fusion protein Mfn1/2 was decreased, while the fission protein Drp1 was increased (Gao et al., 2017). In APAP-treated mice and L02 cells, the autophagic gene *LC3II*/*LC3I*, autophagic flux marker p62 and mitochondrial fission protein Drp1 were significantly elevated, and mitophagy proteins, including OPTN and Parkin, were significantly decreased compared to vehicle control mice, showing dysregulated microstructure organization in APAP-challenged mice and L02 cells (Gao et al., 2022). It was speculated that chronic or acute deletion of Parkin also plays a role in the APAP-treated mouse model. Mitophagy can still be observed in chronic *Parkin*-knockout mice with hepatoprotective effects. Mitophagy was reduced in the acute knockdown of *Parkin* in mouse livers using adenovirus short hairpin RNA (shRNA), which showed exacerbated liver injury (Williams et al., 2015a). Chao et al. (2018) also found that *Parkin*-knockout mice were protected from APAP injury. The compensatory reasons were explained as follows: (1) PINK1-mediated mitophagy still occurred; (2) mitophagy receptor proteins and ubiquitin E3 ligases were involved in mitophagy independent of the PINK1/Parkin pathway; (3) mitochondrial spheroids were formed to substitute for the autophagosome-lysosome structure; and (4) myeloid leukemia cell differentiation proteins and hepatocytes were increased. The compensatory mechanism cannot be established in a short period of APAP treatment. Wang et al. (2019) observed a similar phenomenon in which *PINK1* or *Parkin* single knockout mice showed mild defects in mitophagy and an improved survival rate. However, *PINK1* and *Parkin* double knockout mice had more severe liver injury and increased mortality. In addition, due to the positive feedback loop of p62-Keap1-Nrf2-HO-1, the Nrf2 signaling pathway also plays a part in liver protection against APAP treatment. Sequestosome-1 (p62/SQSTM1) bridges the Nrf2 pathway and autophagy, thus activating Nrf2 by hindering its combination with Keap1. Meanwhile, SQSTM1 is also transcriptionally regulated by Nrf2, forming a loop between the Nrf2 pathway and p62 (Russomanno et al., 2023). The researchers also concluded that mitophagy is not the only compensatory mechanism of urolithin A against APAP overdose, which worked together with the Nrf2/ARE pathway (Gao et al., 2022). Persistent activation of Nrf2 and subsequent recovery of hepatic glutathione attenuates APAP-induced liver injury in *Atg5* liver-specific knockout mice (Ni et al., 2012). Additionally, carbon monoxide (CO), an end-product of HO-1 activity, induces hepatic Parkin expression and alleviates APAP-induced injury by reducing enhancer-binding protein homologous protein (Chen YQ et al., 2019).

## 6 Hepatic ischemia-reperfusion injury

Hepatic ischemia-reperfusion injury (IRI) is related to liver surgeries and hemorrhagic shock in clinical practice. A great amount of proinflammatory cytokines and ROS are generated, causing lipid peroxidation, mitochondrial dysfunction, and DNA damage, while Kupffer cells and neutrophils infiltrate during hepatic IRI, in which acute liver failure occurs (Kudoh et al., 2014; Ali et al., 2021).

In studies investigating the effects of various kinds of treatment in hepatic IRI, the Nrf2 pathway was found to play an important role. Du et al. (2022) showed that the Nrf2/HO-1 pathway is suppressed during hepatic IRI, while curculigoside alleviates the injury through reversing Nrf2/HO-1 signaling. Ali et al. (2021) hinted that there are marked declines in the expression of Nrf2/HO-1, cytochrome *c* oxidase subunit 4 (COX-4), and cytoglobin during hepatic IRI, while treatment with royal jelly protects the liver against IRI through significant upregulation of Nrf2/HO-1/COX-4 and cytoglobin. Rabie et al. (2019) showed that pS40-Nrf2 protein expression was significantly decreased, reaching 13% of a sham-operated control rat group, while it reached 506% in a telluric acid-treated group compared to the IRI group. Nrf2 and its downstream targets, including HO-1, GCLC, and NQO1, were markedly reduced in the rat hepatic IRI model, while their levels were significantly elevated when the rats were pretreated with umbelliferone, which indicated a protective role of umbelliferone through activation of the Keap-1/Nrf2/ARE signaling pathway (Hassanein et al., 2021). Soto et al. (2020) showed that nuclear Nrf2 expression was decreased in the rat hepatic IRI model but upregulated in rats pretreated with Maresin-1, which exerted anti-inflammatory and antioxidant effects, as well as stimulating cell division. Nrf2, FoxO3, and SIRT1 were decreased in IRI rats compared to the sham group, while the levels were upregulated when the rats were pretreated with coenzyme Q10, revealing an antioxidant role of coenzyme Q10 (Mahmoud et al., 2019). Liver function injury, hepatic oncotic necrosis, oxidative stress, and induction of inflammatory cytokines were exacerbated, and the antioxidant genes as well as PPAR-γ were reduced in the *Nrf2*$^{-/-}$ mice that underwent IRI compared to those in *Nrf2*$^{+/+}$ mice. This suggests that Nrf2 is the essential transcription factor in hepatoprotection and that overactivation of Nrf2 might provide new insights into liver injury during hepatic IRI (Kudoh et al., 2014; Lee et al., 2016). HO-1 was not significantly different between the cilostazol-treated and -untreated groups in primary cells isolated from *Nrf2*$^{-/-}$ mice challenged with $H_2O_2$, while mitochondrial genes, antioxidant enzymes, and the level of liver damage were not significantly different between the cilostazol-treated and -untreated groups in *Nrf2*$^{-/-}$ mice subjected to IRI. These phenomena were reversed in the *Nrf2*$^{+/+}$ mice. These results confirmed that mitochondrial biogenesis and functions, as well as hepatoprotective and antioxidative effects stimulated by cilostazol in hepatic IRI, are mediated by an Nrf2- and HO-1-dependent pathway (Joe et al., 2015). Pectolinarigenin, which helps prevent DILI, is also protective against hepatic IRI through activation of the PI3K/Akt/Nrf2 pathway (Li H et al., 2023). Zhang et al. (2023) elucidated that dexmedetomidine, an anesthetic adjuvant, attenuates ferroptosis and ameliorates hepatic IRI by activation of the Nrf2/GPX4 signaling pathway. Qi et al. (2023) also demonstrated that dimethyl fumarate-induced ferroptosis inhibition protects against hepatic IRI by upregulating the Nrf2/solute carrier family 7 member 11 (SLC7A11)/HO-1 axis. The overexpression of fibroblast growth factor 18 exerts protection against hepatic IRI mainly through the reduction of ubiquitin carboxyl-terminal hydrolase 16 (USP16) and the subsequent upregulation of Keap1 ubiquitination, thereby activating Nrf2 signaling (Tong et al., 2023). Paeonol suppresses liver oxidative stress, inflammation, and apoptosis during hepatic IRI through activation of Nrf2/ARE and inhibition of the NF-κB and Bcl-2-associated X protein (Bax)/Bcl-2 signaling pathways (Morsy et al., 2022). To our knowledge, thioredoxin-interacting protein (TXNIP), phosphorylated stimulator of interferon genes (p-STING), and phosphorylated TBK1 (p-TBK1) are increased during hepatic IRI. Myeloid-specific deficiency of TXNIP enhances the cylindromatosis-Nrf2-oligoadenylate synthetase-like 1 axis, thus reducing TBK1-mediated inflammation and promoting the antioxidant capacity in hepatic IRI (Zhan et al., 2022). Oxidative stress is commonly seen in the acute cellular rejection occurring in recipients following liver transplantation, while the expression of the Nrf2 signaling pathway is decreased due to the corticosteroid therapy, indicating a reduced antioxidant capacity (Tomulic Brusich et al., 2023). Meanwhile, Kojima et al. (2023) demonstrated that $CD4^+$ T cell-specific Nrf2 signaling mitigates hepatic injury in mouse orthotopic liver transplantation models, and promotes $CD4^+$ T cell differentiation into Th2/$CD4^+CD25^+Foxp3^+$ Tregs cells while inhibiting differentiation into the pro-inflammatory phenotype Th1/Th17 cells in vitro, which is beneficial to IRI stress. However, several studies have reported the opposite phenomenon. Nrf2 and HO-1 were elevated in a rat IRI group compared to the normal or sham group, indicating that there might be a defense mechanism against hepatic IRI (Hui et al., 2022). Not only Nrf2 but also its downstream target genes *HO-1*, *NQO-1*, and cyclooxygenase-2 (*COX-2*) were activated in IRI groups compared to the sham group (Chen et al., 2021). Nrf2/ARE signaling was significantly activated in senkyunolide I-treated HuCCT1 cells previously challenged by $H_2O_2$ to mimic oxidative stress (Yang et al., 2021).

Starvation stimulates autophagy and complete exhaustion of ATP during long-term hepatic ischemia hampers mitophagy (Ma et al., 2020), although enhanced mitophagy was observed in the early stage of hepatic IRI (Hong et al., 2016; Bhogal et al., 2018; Ning et al., 2018). Impaired mitophagy in aged macrophages triggers the release of mtDNA into the cytosol, leading to STING activation and sterile inflammation, including hepatic IRI (Zhong et al., 2022). The downregulation of hepatic DJ-1, which participates in the pathogenesis of different liver diseases, ameliorates liver IRI through augmented mitophagy (Xu et al., 2021). Umbilical cord-derived mesenchymal stem cells (UC-MSCs) attenuate hepatic IRI through the activation of AMPKα and consequently augmented mitophagy (Zheng et al., 2020). A defective capacity of autophagy can be reversed by HO-1, which indicates its important role (Yun et al., 2014).

## 7 Hepatocellular carcinoma

HCC is the third leading cause of tumor-related mortality related to chronic liver pathologies, including inflammation, stromal activation, fibrosis, regeneration, and cirrhosis.

Nrf2 works as a double-edged sword in HCC, sometimes suppressing but sometimes contributing to HCC (Aslaminabad et al., 2022). Nrf2 has long been considered a tumor suppressor. The synergistic induction of SLC7A11 by activating transcription factor 4 (ATF4) (a kind of stress-related transcription factor) and Nrf2 inhibits ferroptosis and concomitant HCC progression (He et al., 2023). There are diverse potential compounds for the treatment of HCC through the Nrf2 pathway. A study conducted on the cytotoxic effect of compound 5h2c on HCC indicated that the expression of Nrf2, HO-1, and catalase was enhanced, leading to hepatic cancer cell apoptosis (Zhang et al., 2018). A study investigating the cytotoxic potential of β-sitosterol-assisted silver nanoparticles (BSS-SNPs) in HepG2 cells also showed that Nrf2 expression was high after 24 h of BSS-SNP treatment due to an increase in ROS (Kathiswar Raj et al., 2020). Another study dedicated to the role of saponins in HepG2 cells showed that the expression of Nrf2 increased dose-dependently with saponins, demonstrating reduced oxidative stress and elimination of ROS (Khan et al., 2022). However, the unregulated provocation of Nrf2 seemed to contribute to tumor growth, metastasis, and resistance to antitumor drugs, which indicated poor prognosis in the clinic (Kalantari et al., 2023). Hepatoma cells survive glucose deprivation through decreasing $N^6$-methyladenosine (m$^6$A) and upregulating FOS-like antigen 1 (FOSL1), thus inhibiting ATF3 and activating Nrf2 signaling, which protects hepatoma cells from necrosis (Wang et al., 2024). Under the oxidant stress tumor condition, self-renewing cancer stem cells maintain long-term clonal capacity with the help of the higher expression of Nrf2, which may also lead to multidrug resistance (Kalantari et al., 2023). Baird and Yamamoto (2023) put forward the theory that highly immunoedited Nrf2-activated cells in the later stage of human cancer can escape immune surveillance and are resistant to immune checkpoint inhibitor therapies through reducing antigen presentation by the major histocompatibility class I (MHC-I) complex and diminishing the ligands for NK cells. This may provide a novel strategy based on immune cell infiltration and inflammatory cytokines for treating Nrf2-activated tumors. The Nrf2 signaling pathway mediates resistance to sorafenib through protecting HCC cells against ferroptosis. The combination therapy of metformin and sorafenib suppresses HCC growth by blocking the p62-Keap1-Nrf2 pathway and inducing ferroptosis (Tang et al., 2022). Nrf2 is abundantly expressed, which negatively regulates the expression of microRNA-1 and then promotes the overexpression of programmed death-ligand 1 (PD-L1), leading to migration, invasion, clone formation, and tumorigenicity of sorafenib-resistant hepatoma cells (Li D et al., 2020). Sun et al. (2015) showed that isoliquiritigenin enhances the radiosensitivity of liver cancer cells both in vivo and in vitro by inhibiting the Nrf2 antioxidant pathway and increasing the level of Keap1, which shows that disturbance of redox status might be a potential method for radiosensitization. Liu YQ et al. (2023) found that *Nrf2* gene *rs6721961* variation is a potential marker for HBV-associated HCC. Autophagy is correlated with the pathogenesis of Nrf2 in the development of HCC. Inami et al. (2011) showed that prolonged activation of Nrf2 due to the accumulation of p62 led to the occurrence of HCC in Atg7-deficient mice. Ni et al. (2014) also observed that persistent activation of Nrf2 and a high level of p62 were closely related to liver dysregulation, including inflammation, fibrosis, and tumorigenesis, in autophagy-deficient mice, implying that autophagy inducers might be beneficial to the treatment of HCC. It was revealed that the upregulated expression of p62 and the concomitant boost in Nrf2 facilitate the growth of HCC cells (Hallis et al., 2023). Chao et al. (2022) revealed that the antitumorigenic effect of p62 in hepatocytes is achieved via activation of the mechanistic target of rapamycin complex 1 (mTORC1) and defective autophagy, which is opposite to the pro-tumorigenic role of p62 indicated by previous findings.

It is generally acknowledged that mitophagy suppresses tumors. Enhanced oxidative stress and impaired mitophagy are observed in $CCl_4$-induced liver fibrosis (di Paola et al., 2022). Several experiments have demonstrated that depletion of *Beclin1*, an autophagy-related gene, accelerates tumorigenesis (Aita et al., 1999; Qu et al., 2003). The expression of DEAD box protein 5 (DDX5) is inversely correlated with that of p62, promotes autophagy, and reduces HCC proliferation and tumorigenesis, which is valuable in treating HCC (Zhang et al., 2019). Icaritin activates mitophagy to strengthen doxorubicin-induced immunogenic cell death, thus exerting an anti-HCC effect (Yu et al., 2020). Ketoconazole works with sorafenib to fight against HCC by downregulating COX-2 and inducing mitophagy (Chen Y et al., 2019). Other studies focusing on the depletion of hepatic Atg5 and Atg7 also showed hepatic carcinoma development (Takamura et al., 2011; Ni et al., 2014). Studies showed that defective autophagy characterized by the accumulation of p62 led to prolonged Nrf2 activation, which promoted tissue injury and cancers. The levels of p62 and Nrf2 were positively correlated, while Keap1 was a negative regulator of Nrf2. The overexpression of Nrf2 accelerates liver diseases, including inflammation, cirrhosis, and carcinogenesis (Komatsu et al., 2010; Inami et al., 2011; Taguchi et al., 2012; Bae et al., 2013; Ni et al., 2014; Jiang et al., 2015). Yang et al. (2015) showed that autophagy induced by loss of protein targeting glycogen promoted hepatocellular toxicity and death. Another experiment demonstrated that Nrf2 activation triggered liver injury even in the absence of p62. However, p62 accumulation in the absence of Nrf2 alone did not cause liver abnormalities, which showed that Nrf2 was the dominant factor in liver injury in autophagy-deficient mice (Taguchi et al., 2012). Apart from Nrf2, the autophagy-dependent degradation of Yap and the control of high mobility group box-1 protein (HMGB1) release also play important roles in suppressing inflammation, fibrosis, and hepatocarcinogenesis (Khambu et al., 2018; Lee YA et al., 2018). However, a few studies have demonstrated that autophagy may support the development of tumor cells in formed tumors, which indicates that autophagy works as a double-edged sword in carcinogenesis, depending on the stage of the cancer (Guo et al., 2011; White et al., 2015). It was reported that deletion of some genes (for example, *Ambra1*, *Atg5*, and *Atg7*) that block autophagy promoted tumor progression. This phenomenon was more frequently observed in high-grade tumors or malignancies. As in the development of liver fibrosis and cirrhosis, the T-cell immunoglobulin domain and mucin domain-containing protein-4 (TIM-4) mediates the production of $H_2O_2$ via the Akt1 pathway, thus upregulating mitophagy in Kupffer cells (Wu et al., 2020b). FUNDC1–GPx4 interaction accelerates GPx4 mitophagy and triggers ferroptosis in $CCl_4$-related liver cirrhosis, indicating that targeting FUNDC1 or mitophagy might be a potential treatment (Bi et al., 2024). Mitophagy downregulates PINK1-mediated p53 and promotes the expression of Nanog homeobox (NANOG), a critical transcription factor that promotes the self-renewal ability of liver cancer stem cells (LCSCs), to maintain the LCSC population (Liu K et al., 2017). Mitophagy helps cancer cells survive drug treatment through mitochondrial dysfunction. Wu et al. (2020a) indicated that hypoxia-induced miR-210-5p suppressed the ATPase family AAA domain-containing 3A (ATAD3A) and hyperactivated mitophagy in sorafenib-resistant HCC. It has been implicated bioinformatically that the link between HCC heterogeneity and the degree of mitophagy, manifested as the higher mitophagy subtype, leads to a poorer prognosis (Wang Y et al., 2021). Another study using data from The Cancer Genome Atlas (TCGA) also demonstrated that mitophagy-related genes (*PGAM5*, *SQSTM1*, *ATG9A*, and *GABARAPL1*) of HCC contribute to the immune microenvironment, immune checkpoint-related gene expression, cancer stem cells, ferroptosis status, $m^6A$, prognosis, and HCC progression (Liu et al., 2022). The long intergenic nonprotein coding RNA p53-induced transcript 87aa (*PINT87aa*) was recognized as a key target for anti-HCC because of the downregulation of prohibitin 2 (PHB2) and resultant decreased mitophagy (Xiang et al., 2021). A study conducted on sesamol, a nutritional phenolic antioxidant compound, suggested its anticancer activity acted by inhibiting mitophagy through impeding the PI3K Class III/Belin-1 pathway (Liu ZG et al., 2017). Oroxylin, an inhibitor of cyclin-dependent kinase 9 (CDK9), blocks mitophagy through the SIRT1-FoxO3-BNIP3 pathway suppression, thus inhibiting HCC growth (Yao et al., 2022). Stomatin-like protein 2 (STOML2), which is highly expressed in HCC and transcriptionally regulated by HIF-1α, promotes HCC metastasis and reduces sensitivity to lenvatinib treatment by amplifying mitophagy (Zheng et al., 2021). Hence, the roles of mitophagy in HCC depend on the stage of liver cancer: mitophagy suppresses initiation while accelerating development.

## 8 Conclusions

The Keap1/Nrf2 antioxidant pathway and mitophagy are crucial to the homeostasis of the internal environment. The opposite statuses of the Keap1/Nrf2 signaling pathway and mitophagy, whether inactivated or hyperactivated, might be beneficial or deleterious to the body. These two mechanisms are already potential targets of treatments for different liver diseases. We hope that more novel drugs aimed at the Keap1/Nrf2 pathway and mitophagy will soon be developed for application in the clinic.

### Acknowledgments

This study was supported by the Medical Science and Technology Project of Zhejiang Province (No. 2018KY566). All authors were thankful to the Key Laboratory of Integrated Oncology and Intelligent Medicine of Zhejiang Province for their contributions.

### Author contributions

Qihui ZHOU: conceptualization and writing the original draft. Panpan CEN: formal analysis and investigation. Zhi CHEN: supervision. Jie JIN: supervision and project administration. All Authors have read and approved the final manuscript.

### Compliance with ethics guidelines

Zhi CHEN is an Editorial Board Member for *Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)* and was not involved in the editorial review or the decision to publish this article. Qihui ZHOU, Panpan CEN, Zhi CHEN, and Jie JIN declare that they have no conflicts of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

## References

Abdalla MY, Britigan BE, Wen F, et al., 2004. Down-regulation of heme oxygenase-1 by hepatitis C virus infection in vivo and by the in vitro expression of hepatitis C core protein. *J Infect Dis*, 190(6):1109-1118. https://doi.org/10.1086/423488

Abdelaziz AI, Mantawy EM, Gad AM, et al., 2019. Activation of pCREB/Nrf-2 signaling mediates re-positioning of liraglutide as hepato-protective for methotrexate-induced liver injury (MILI). *Food Chem Toxicol*, 132:110719. https://doi.org/10.1016/j.fct.2019.110719

Abdelhamid AM, Elsheakh AR, Suddek GM, et al., 2021. Telmisartan alleviates alcohol-induced liver injury by activation of PPAR-γ/Nrf-2 crosstalk in mice. *Int Immunopharmacol*, 99:107963. https://doi.org/10.1016/j.intimp.2021.107963

Abulikemu A, Zhao XY, Xu HL, et al., 2023. Silica nanoparticles aggravated the metabolic associated fatty liver disease through disturbed amino acid and lipid metabolisms-mediated oxidative stress. *Redox Biol*, 59:102569. https://doi.org/10.1016/j.redox.2022.102569

Ahn SB, Wu WH, Lee JH, et al., 2018. Fermented soymilk alleviates lipid accumulation by inhibition of SREBP-1 and activation of NRF-2 in the hepatocellular steatosis model. *J Microbiol Biotechnol*, 28(2):236-245. https://doi.org/10.4014/jmb.1707.07061

Aita VM, Liang XH, Murty VVVS, et al., 1999. Cloning and genomic organization of *Beclin 1*, a candidate tumor suppressor gene on chromosome 17q21. *Genomics*, 59(1): 59-65. https://doi.org/10.1006/geno.1999.5851

Ajiboye TO, Ajala-Lawal RA, Adeyiga AB, 2019. Caffeic acid abrogates 1,3-dichloro-2-propanol-induced hepatotoxicity by upregulating nuclear erythroid-related factor 2 and downregulating nuclear factor-kappa B. *Hum Exp Toxicol*, 38(9):1092-1101. https://doi.org/10.1177/0960327119851257

Ali FEM, Saad Eldien HM, Mostafa NAM, et al., 2021. The impact of royal jelly against hepatic ischemia/reperfusion-induced hepatocyte damage in rats: the role of cytoglobin, Nrf-2/HO-1/COX-4, and $P_{38}$-MAPK/NF-κB-p65/TNF-α signaling pathways. *Curr Mol Pharmacol*, 14(1):88-100. https://doi.org/10.2174/1874467213666200514223829

Aliyu NO, Ajala-Lawal RA, Ajiboye TO, 2018. Lophirones B and C halt acetaminophen hepatotoxicity by upregulating redox transcription factor Nrf-2 through Akt, PI3K, and PKC pathways. *J Biochem Mol Toxicol*, 32(6):e22055. https://doi.org/10.1002/jbt.22055

Ampawong S, Isarangkul D, Aramwit P, 2017. Sericin improves heart and liver mitochondrial architecture in hypercholesterolaemic rats and maintains pancreatic and adrenal cell biosynthesis. *Exp Cell Res*, 358(2):301-314. https://doi.org/10.1016/j.yexcr.2017.07.001

Ariffianto A, Deng L, Abe T, et al., 2023. Oxidative stress sensor Keap1 recognizes HBx protein to activate the Nrf2/ARE signaling pathway, thereby inhibiting hepatitis B virus replication. *J Virol*, 97(10):e0128723. https://doi.org/10.1128/jvi.01287-23

Aslaminabad R, Rahimianshahreza N, Hosseini SA, et al., 2022. Regulation of Nrf2 and Nrf2-related proteins by ganoderma lucidum ın hepatocellular carcinoma. *Mol Biol Rep*, 49(10):9605-9612. https://doi.org/10.1007/s11033-022-07862-8

Aslan A, Gok O, Erman O, et al., 2018. Ellagic acid impedes carbontetrachloride-induced liver damage in rats through suppression of NF-κB, Bcl-2 and regulating Nrf-2 and caspase pathway. *Biomed Pharmacother*, 105:662-669. https://doi.org/10.1016/j.biopha.2018.06.020

Axley PD, Richardson CT, Singal AK, 2019. Epidemiology of alcohol consumption and societal burden of alcoholism and alcoholic liver disease. *Clin Liver Dis*, 23(1):39-50. https://doi.org/10.1016/j.cld.2018.09.011

Bae SH, Sung SH, Oh SY, et al., 2013. Sestrins activate Nrf2 by promoting p62-dependent autophagic degradation of Keap1 and prevent oxidative liver damage. *Cell Metab*, 17(1):73-84. https://doi.org/10.1016/j.cmet.2012.12.002

Baird L, Yamamoto M, 2023. Immunoediting of *KEAP1-NRF2* mutant tumours is required to circumvent NRF2-mediated immune surveillance. *Redox Biol*, 67:102904. https://doi.org/10.1016/j.redox.2023.102904

Baird L, Taguchi K, Zhang AQ, et al., 2023. A NRF2-induced secretory phenotype activates immune surveillance to remove irreparably damaged cells. *Redox Biol*, 66:102845. https://doi.org/10.1016/j.redox.2023.102845

Baulies A, Ribas V, Núñez S, et al., 2015. Lysosomal cholesterol accumulation sensitizes to acetaminophen hepatotoxicity by impairing mitophagy. *Sci Rep*, 5:18017. https://doi.org/10.1038/srep18017

Bhogal RH, Weston CJ, Velduis S, et al., 2018. The reactive oxygen species-mitophagy signaling pathway regulates liver endothelial cell survival during ischemia/reperfusion injury. *Liver Transpl*, 24(10):1437-1452. https://doi.org/10.1002/lt.25313

Bi YG, Liu SL, Qin X, et al., 2024. FUNDC1 interacts with GPx4 to govern hepatic ferroptosis and fibrotic injury through a mitophagy-dependent manner. *J Adv Res*, 55: 45-60. https://doi.org/10.1016/j.jare.2023.02.012

Cai CZ, Ma HL, Peng J, et al., 2023. USP25 regulates KEAP1-NRF2 anti-oxidation axis and its inactivation protects acetaminophen-induced liver injury in male mice. *Nat Commun*, 14:3648. https://doi.org/10.1038/s41467-023-39412-6

Cai XP, Hua SY, Deng JW, et al., 2022. Astaxanthin activated the Nrf2/HO-1 pathway to enhance autophagy and inhibit ferroptosis, ameliorating acetaminophen-induced liver injury. *ACS Appl Mater Interfaces*, 14(38):42887-42903. https://doi.org/10.1021/acsami.2c10506

Chao TN, Shih HT, Hsu SC, et al., 2021. Autophagy restricts

mitochondrial DNA damage-induced release of ENDOG (endonuclease G) to regulate genome stability. *Autophagy*, 17(11):3444-3460.
https://doi.org/10.1080/15548627.2021.1874209

Chao XJ, Wang H, Jaeschke H, et al., 2018. Role and mechanisms of autophagy in acetaminophen-induced liver injury. *Liver Int*, 38(8):1363-1374.
https://doi.org/10.1111/liv.13866

Chao XJ, Wang SG, Fulte S, et al., 2022. Hepatocytic p62 suppresses ductular reaction and tumorigenesis in mouse livers with mTORC1 activation and defective autophagy. *J Hepatol*, 76(3):639-651.
https://doi.org/10.1016/j.jhep.2021.10.014

Che JY, Yang S, Qiao ZJ, et al., 2019. *Schisandra chinensis* acidic polysaccharide partialy reverses acetaminophen-induced liver injury in mice. *J Pharmacol Sci*, 140(3):248-254.
https://doi.org/10.1016/j.jphs.2019.07.008

Chen L, Zhang WL, Xie DQ, et al., 2021. Sulforaphane alleviates hepatic ischemia-reperfusion injury through promoting the activation of Nrf-2/HO-1 signaling. *Transpl Immunol*, 68:101439.
https://doi.org/10.1016/j.trim.2021.101439

Chen LY, Yang BS, Zhou L, et al., 2015. Promotion of mitochondrial energy metabolism during hepatocyte apoptosis in a rat model of acute liver failure. *Mol Med Rep*, 12(4):5035-5041.
https://doi.org/10.3892/mmr.2015.4029

Chen SY, Huang YS, Su HM, et al., 2022. The integrated analysis of transcriptomics and metabolomics unveils the therapeutical effect of asiatic acid on alcoholic hepatitis in rats. *Inflammation*, 45(4):1780-1799.
https://doi.org/10.1007/s10753-022-01660-x

Chen WC, Wang SY, Chiu CC, et al., 2013. Lucidone suppresses hepatitis C virus replication by Nrf2-mediated heme oxygenase-1 induction. *Antimicrob Agents Chemother*, 57(3):1180-1191.
https://doi.org/10.1128/AAC.02053-12

Chen WC, Wei CK, Lee JC, 2019. MicroRNA-let-7c suppresses hepatitis C virus replication by targeting Bach1 for induction of haem oxygenase-1 expression. *J Viral Hepat*, 26(6):655-665.
https://doi.org/10.1111/jvh.13072

Chen Y, Chen HN, Wang K, et al., 2019. Ketoconazole exacerbates mitophagy to induce apoptosis by downregulating cyclooxygenase-2 in hepatocellular carcinoma. *J Hepatol*, 70(1):66-77.
https://doi.org/10.1016/j.jhep.2018.09.022

Chen YQ, Park HJ, Park J, et al., 2019. Carbon monoxide ameliorates acetaminophen-induced liver injury by increasing hepatic HO-1 and Parkin expression. *FASEB J*, 33(12):13905-13919.
https://doi.org/10.1096/fj.201901258RR

Chen YT, Lin YC, Lin JS, et al., 2018. Sugary kefir strain *Lactobacillus mali* APS1 ameliorated hepatic steatosis by regulation of SIRT-1/Nrf-2 and gut microbiota in rats. *Mol Nutr Food Res*, 62(8):1700903.
https://doi.org/10.1002/mnfr.201700903

Chen YY, Wang WH, Che L, et al., 2020. BNIP3L-dependent mitophagy promotes HBx-induced cancer stemness of hepatocellular carcinoma cells via glycolysis metabolism reprogramming. *Cancers (Basel)*, 12(3):655.
https://doi.org/10.3390/cancers12030655

Chi HC, Chen SL, Lin SL, et al., 2017. Thyroid hormone protects hepatocytes from HBx-induced carcinogenesis by enhancing mitochondrial turnover. *Oncogene*, 36(37):5274-5284.
https://doi.org/10.1038/onc.2017.136

Chida T, Watanabe S, Ohta K, et al., 2024. Impact of amino acid substitutions in hepatitis C virus core region on the severe oxidative stress. *Free Radic Biol Med*, 212:199-206.
https://doi.org/10.1016/j.freeradbiomed.2023.12.014

Choi BK, Kim TW, Lee DR, et al., 2015. A polymethoxy flavonoids-rich *Citrus aurantium* extract ameliorates ethanol-induced liver injury through modulation of AMPK and Nrf2-related signals in a binge drinking mouse model. *Phytother Res*, 29(10):1577-1584.
https://doi.org/10.1002/ptr.5415

Chowdhry S, Nazmy MH, Meakin PJ, et al., 2010. Loss of Nrf2 markedly exacerbates nonalcoholic steatohepatitis. *Free Radic Biol Med*, 48(2):357-371.
https://doi.org/10.1016/j.freeradbiomed.2009.11.007

Chu JYK, Ou JHJ, 2021. Autophagy in HCV replication and protein trafficking. *Int J Mol Sci*, 22(3):1089.
https://doi.org/10.3390/ijms22031089

Ding WX, Li M, Yin XM, 2011. Selective taste of ethanol-induced autophagy for mitochondria and lipid droplets. *Autophagy*, 7(2):248-249.
https://doi.org/10.4161/auto.7.2.14347

di Paola R, Modafferi S, Siracusa R, et al., 2022. *S*-Acetyl-glutathione attenuates carbon tetrachloride-induced liver injury by modulating oxidative imbalance and inflammation. *Int J Mol Sci*, 23(8):4429.
https://doi.org/10.3390/ijms23084429

Dodson M, Castro-Portuguez R, Zhang DD, 2019. NRF2 plays a critical role in mitigating lipid peroxidation and ferroptosis. *Redox Biol*, 23:101107.
https://doi.org/10.1016/j.redox.2019.101107

Du P, Zhang XJ, Luo KF, et al., 2022. Curculigoside mitigates hepatic ischemia/reperfusion-induced oxidative stress, inflammation, and apoptosis via activation of the Nrf-2/HO-1 pathway. *Hum Exp Toxicol*, 41:9603271221087146.
https://doi.org/10.1177/09603271221087146

Ezhilarasan D, Lakshmi T, 2022. A molecular insight into the role of antioxidants in nonalcoholic fatty liver diseases. *Oxid Med Cell Longev*, 2022:9233650.
https://doi.org/10.1155/2022/9233650

Faghihzadeh F, Adibi P, Rafiei R, et al., 2014. Resveratrol supplementation improves inflammatory biomarkers in patients with nonalcoholic fatty liver disease. *Nutr Res*, 34(10):837-843.
https://doi.org/10.1016/j.nutres.2014.09.005

Gao Y, Chu SF, Zhang Z, et al., 2017. Early stage functions of mitochondrial autophagy and oxidative stress in acetaminophen-induced liver injury. *J Cell Biochem*, 118(10):3130-3141.

https://doi.org/10.1002/jcb.25788

Gao ZM, Yi W, Tang JY, et al., 2022. Urolithin A protects against acetaminophen-induced liver injury in mice via sustained activation of Nrf2. *Int J Biol Sci*, 18(5):2146-2162. https://doi.org/10.7150/ijbs.69116

Ge CX, Xu MX, Qin YT, et al., 2019. Loss of RIP3 initiates annihilation of high-fat diet initialized nonalcoholic hepatosteatosis: a mechanism involving Toll-like receptor 4 and oxidative stress. *Free Radic Biol Med*, 134:23-41. https://doi.org/10.1016/j.freeradbiomed.2018.12.034

Ge J, Li GM, Chen ZW, et al., 2024. Kaempferol and nicotiflorin ameliorated alcohol-induced liver injury in mice by miR-138-5p/SIRT1/FXR and gut microbiota. *Heliyon*, 10(1):e23336. https://doi.org/10.1016/j.heliyon.2023.e23336

Guo J, Li C, Yang CX, et al., 2018. Liraglutide reduces hepatic glucolipotoxicity-induced liver cell apoptosis through NRF2 signaling in Zucker diabetic fatty rats. *Mol Med Rep*, 17(6):8316-8324. https://doi.org/10.3892/mmr.2018.8919

Guo JY, Chen HY, Mathew R, et al., 2011. Activated Ras requires autophagy to maintain oxidative metabolism and tumorigenesis. *Genes Dev*, 25(5):460-470. https://doi.org/10.1101/gad.2016311

Guo M, Gu LW, Hui HP, et al., 2022. Extracts of *Dracocephalum tanguticum* maxim ameliorate acute alcoholic liver disease *via* regulating transcription factors in mice. *Front Pharmacol*, 13:830532. https://doi.org/10.3389/fphar.2022.830532

Haga S, Ozawa T, Yamada Y, et al., 2014. p62/SQSTM1 plays a protective role in oxidative injury of steatotic liver in a mouse hepatectomy model. *Antioxid Redox Signal*, 21(18):2515-2530. https://doi.org/10.1089/ars.2013.5391

Hallis SP, Kim JM, Kwak MK, 2023. Emerging role of NRF2 signaling in cancer stem cell phenotype. *Mol Cells*, 46(3): 153-164. https://doi.org/10.14348/molcells.2023.2196

Hammoutene A, Laouirem S, Albuquerque M, et al., 2023. A new NRF2 activator for the treatment of human metabolic dysfunction-associated fatty liver disease. *JHEP Rep*, 5(10):100845. https://doi.org/10.1016/j.jhepr.2023.100845

Han X, Li WF, Huang D, et al., 2016. Polyphenols from hawthorn peels and fleshes differently mitigate dyslipidemia, inflammation and oxidative stress in association with modulation of liver injury in high fructose diet-fed mice. *Chem Biol Interact*, 257:132-140. https://doi.org/10.1016/j.cbi.2016.08.002

Hassanein EHM, Khader HF, Elmansy RA, et al., 2021. Umbelliferone alleviates hepatic ischemia/reperfusion-induced oxidative stress injury via targeting Keap-1/Nrf-2/ARE and TLR4/NF-κB-p65 signaling pathway. *Environ Sci Pollut Res Int*, 28(47):67863-67879. https://doi.org/10.1007/s11356-021-15184-8

He F, Huang YR, Song Z, et al., 2021. Mitophagy-mediated adipose inflammation contributes to type 2 diabetes with hepatic insulin resistance. *J Exp Med*, 218(3):e20201416. https://doi.org/10.1084/jem.20201416

He F, Zhang P, Liu JL, et al., 2023. ATF4 suppresses hepatocarcinogenesis by inducing SLC7A11 (xCT) to block stress-related ferroptosis. *J Hepatol*, 79(2):362-377. https://doi.org/10.1016/j.jhep.2023.03.016

Holmström KM, Baird L, Zhang Y, et al., 2013. Nrf2 impacts cellular bioenergetics by controlling substrate availability for mitochondrial respiration. *Biol Open*, 2(8):761-770. https://doi.org/10.1242/bio.20134853

Hong JM, Kim SJ, Lee SM, 2016. Role of necroptosis in autophagy signaling during hepatic ischemia and reperfusion. *Toxicol Appl Pharmacol*, 308:1-10. https://doi.org/10.1016/j.taap.2016.08.010

Huang QH, Xu LQ, Liu YH, et al., 2017. Polydatin protects rat liver against ethanol-induced injury: involvement of CYP2E1/ROS/Nrf2 and TLR4/NF-κB p65 pathway. *Evid Based Complement Alternat Med*, 2017:7953850. https://doi.org/10.1155/2017/7953850

Hui B, Shu YT, Yang DD, et al., 2022. Sinomenine pretreatment alleviates hepatic ischemia/reperfusion injury through activating Nrf-2/HO-1 pathway. *Immun Inflamm Dis*, 10(10):e700. https://doi.org/10.1002/iid3.700

Hwang KA, Hwang Y, Hwang HJ, et al., 2022. Hepatoprotective effects of radish (*Raphanus sativus* L.) on acetaminophen-induced liver damage via inhibiting oxidative stress and apoptosis. *Nutrients*, 14(23):5082. https://doi.org/10.3390/nu14235082

Ibitoye OB, Ajiboye TO, 2020. Protocatechuic acid protects against menadione-induced liver damage by up-regulating nuclear erythroid-related factor 2. *Drug Chem Toxicol*, 43(6):567-573. https://doi.org/10.1080/01480545.2018.1523187

Inami Y, Waguri S, Sakamoto A, et al., 2011. Persistent activation of Nrf2 through p62 in hepatocellular carcinoma cells. *J Cell Biol*, 193(2):275-284. https://doi.org/10.1083/jcb.201102031

Innokentev A, Kanki T, 2021. Mitophagy in yeast: molecular mechanism and regulation. *Cells*, 10(12):3569. https://doi.org/10.3390/cells10123569

Jiang T, Harder B, Rojo de la Vega M, et al., 2015. p62 links autophagy and Nrf2 signaling. *Free Radic Biol Med*, 88: 199-204. https://doi.org/10.1016/j.freeradbiomed.2015.06.014

Jiang ZT, Yang X, Han Y, et al., 2022. Sarmentosin promotes USP17 and regulates Nrf2-mediated mitophagy and cellular oxidative stress to alleviate APAP-induced acute liver failure. *Phytomedicine*, 104:154337. https://doi.org/10.1016/j.phymed.2022.154337

Joe Y, Zheng M, Kim HJ, et al., 2015. Cilostazol attenuates murine hepatic ischemia and reperfusion injury via heme oxygenase-dependent activation of mitochondrial biogenesis. *Am J Physiol Gastrointest Liver Physiol*, 309(1):G21-G29. https://doi.org/10.1152/ajpgi.00307.2014

Kalantari L, Ghotbabadi ZR, Gholipour A, et al., 2023. A state-of-the-art review on the NRF2 in hepatitis virus-associated liver cancer. *Cell Commun Signal*, 21:318. https://doi.org/10.1186/s12964-023-01351-6

Kathiswar Raj R, Ezhilarasan D, Rajeshkumar S, 2020. β-Sitosterol-assisted silver nanoparticles activates Nrf2 and triggers mitochondrial apoptosis via oxidative stress in human hepatocellular cancer cell line. *J Biomed Mater Res A*, 108(9):1899-1908.
https://doi.org/10.1002/jbm.a.36953

Khambu B, Huda N, Chen XY, et al., 2018. HMGB1 promotes ductular reaction and tumorigenesis in autophagy-deficient livers. *J Clin Invest*, 128(6):2419-2435.
https://doi.org/10.1172/JCI91814

Khan MI, Karima G, Khan MZ, et al., 2022. Therapeutic effects of saponins for the prevention and treatment of cancer by ameliorating inflammation and angiogenesis and inducing antioxidant and apoptotic effects in human cells. *Int J Mol Sci*, 23(18):10665.
https://doi.org/10.3390/ijms231810665

Kim JY, Ou JHJ, 2018. Regulation of apolipoprotein E trafficking by hepatitis C virus-induced autophagy. *J Virol*, 92(14): e00211-18.
https://doi.org/10.1128/JVI.00211-18

Kojima H, Kadono K, Hirao H, et al., 2023. $CD4^+$ T cell NRF2 signaling improves liver transplantation outcomes by modulating T cell activation and differentiation. *Antioxid Redox Signal*, 38(7-9):670-683.
https://doi.org/10.1089/ars.2022.0094

Komatsu M, Kurokawa H, Waguri S, et al., 2010. The selective autophagy substrate p62 activates the stress responsive transcription factor Nrf2 through inactivation of Keap1. *Nat Cell Biol*, 12(3):213-223.
https://doi.org/10.1038/ncb2021

Kudoh K, Uchinami H, Yoshioka M, et al., 2014. Nrf2 activation protects the liver from ischemia/reperfusion injury in mice. *Ann Surg*, 260(1):118-127.
https://doi.org/10.1097/SLA.0000000000000287

Kumar D, Dwivedi DK, Lahkar M, et al., 2019. Hepatoprotective potential of 7,8-dihydroxyflavone against alcohol and high-fat diet induced liver toxicity *via* attenuation of oxido-nitrosative stress and NF-κB activation. *Pharmacol Rep*, 71(6):1235-1243.
https://doi.org/10.1016/j.pharep.2019.07.002

Lau A, Wang XJ, Zhao F, et al., 2010. A noncanonical mechanism of Nrf2 activation by autophagy deficiency: direct interaction between Keap1 and p62. *Mol Cell Biol*, 30(13):3275-3285.
https://doi.org/10.1128/MCB.00248-10

Leboeuf SE, Wu WL, Karakousi TR, et al., 2020. Activation of oxidative stress response in cancer generates a druggable dependency on exogenous non-essential amino acids. *Cell Metab*, 31(2):339-350.e4.
https://doi.org/10.1016/j.cmet.2019.11.012

Lee JC, Lin CK, Tseng CK, et al., 2018. Discovery of 3-amino-2-hydroxypropoxyisoflavone derivatives as potential anti-HCV agents. *Molecules*, 23(11):2863.
https://doi.org/10.3390/molecules23112863

Lee LY, Harberg C, Matkowskyj KA, et al., 2016. Overactivation of the nuclear factor (erythroid-derived 2)-like 2-antioxidant response element pathway in hepatocytes decreases hepatic ischemia/reperfusion injury in mice. *Liver Transpl*, 22(1):91-102.
https://doi.org/10.1002/lt.24303

Lee YA, Noon LA, Akat KM, et al., 2018. Autophagy is a gatekeeper of hepatic differentiation and carcinogenesis by controlling the degradation of Yap. *Nat Commun*, 9:4962.
https://doi.org/10.1038/s41467-018-07338-z

Lei YM, Xu X, Liu HL, et al., 2021. HBx induces hepatocellular carcinogenesis through ARRB1-mediated autophagy to drive the $G_1$/S cycle. *Autophagy*, 17(12):4423-4441.
https://doi.org/10.1080/15548627.2021.1917948

Li D, Sun FF, Wang D, et al., 2020. Programmed death ligand-1 (PD-L1) regulated by NRF-2/microRNA-1 regulatory axis enhances drug resistance and promotes tumorigenic properties in sorafenib-resistant hepatoma cells. *Oncol Res*, 28(5):467-481.
https://doi.org/10.3727/096504020X15925659763817

Li H, Chen YB, Ding MJ, et al., 2023. Pectolinarigenin attenuates hepatic ischemia/reperfusion injury via activation of the PI3K/AKT/Nrf2 signaling pathway. *Chem Biol Interact*, 386:110763.
https://doi.org/10.1016/j.cbi.2023.110763

Li L, Guo CC, Yu Y, et al., 2023. Differential effects of PGAM5 knockout on high fat high fructose diet and methionine choline-deficient diet induced non-alcoholic steatohepatitis (NASH) in mice. *Cell Biosci*, 13:154.
https://doi.org/10.1186/s13578-023-01095-3

Li Q, Zhang W, Cheng N, et al., 2023. Pectolinarigenin ameliorates acetaminophen-induced acute liver injury via attenuating oxidative stress and inflammatory response in Nrf2 and PPARa dependent manners. *Phytomedicine*, 113: 154726.
https://doi.org/10.1016/j.phymed.2023.154726

Li RB, Xin T, Li DD, et al., 2018. Therapeutic effect of Sirtuin 3 on ameliorating nonalcoholic fatty liver disease: the role of the ERK-CREB pathway and Bnip3-mediated mitophagy. *Redox Biol*, 18:229-243.
https://doi.org/10.1016/j.redox.2018.07.011

Li XW, Shi Z, Zhu YW, et al., 2020. Cyanidin-3-*O*-glucoside improves non-alcoholic fatty liver disease by promoting PINK1-mediated mitophagy in mice. *Br J Pharmacol*, 177(15):3591-3607.
https://doi.org/10.1111/bph.15083

Lin Y, Wu CC, Wang XY, et al., 2020. Glucosamine promotes hepatitis B virus replication through its dual effects in suppressing autophagic degradation and inhibiting MTORC1 signaling. *Autophagy*, 16(3):548-561.
https://doi.org/10.1080/15548627.2019.1632104

Lin ZF, Wu F, Lin SQ, et al., 2014. Adiponectin protects against acetaminophen-induced mitochondrial dysfunction and acute liver injury by promoting autophagy in mice. *J Hepatol*, 61(4):825-831.
https://doi.org/10.1016/j.jhep.2014.05.033

Liu C, Wu Z, Wang LP, et al., 2022. A mitophagy-related gene signature for subtype identification and prognosis prediction of hepatocellular carcinoma. *Int J Mol Sci*, 23(20): 12123.

https://doi.org/10.3390/ijms232012123

Liu K, Lee J, Kim JY, et al., 2017. Mitophagy controls the activities of tumor suppressor p53 to regulate hepatic cancer stem cells. *Mol Cell*, 68(2):281-292.e5. https://doi.org/10.1016/j.molcel.2017.09.022

Liu PF, Anandhan A, Chen JJ, et al., 2023. Decreased autophagosome biogenesis, reduced NRF2, and enhanced ferroptotic cell death are underlying molecular mechanisms of non-alcoholic fatty liver disease. *Redox Biol*, 59:102570. https://doi.org/10.1016/j.redox.2022.102570

Liu WJ, Chen WW, Chen JY, et al., 2025. Baicalin attenuated metabolic dysfunction-associated fatty liver disease by suppressing oxidative stress and inflammation via the p62-Keap1-Nrf2 signalling pathway in *db*/*db* mice. *Phytother Res*, 39(4):1663-1678. https://doi.org/10.1002/ptr.8010

Liu YQ, Wu QL, Zhang FY, et al., 2023. Antioxidants-related nuclear factor erythroid 2-related factor 2 gene variants associated with HBV-related liver disease. *Cancer Cell Int*, 23:72. https://doi.org/10.1186/s12935-023-02918-6

Liu ZG, Ren B, Wang YH, et al., 2017. Sesamol induces human hepatocellular carcinoma cells apoptosis by impairing mitochondrial function and suppressing autophagy. *Sci Rep*, 7:45728. https://doi.org/10.1038/srep45728

Lu CF, Xu WX, Zhang F, et al., 2016. Nrf2 knockdown disrupts the protective effect of curcumin on alcohol-induced hepatocyte necroptosis. *Mol Pharm*, 13(12):4043-4053. https://doi.org/10.1021/acs.molpharmaceut.6b00562

Lu XY, Xuan WT, Li JJ, et al., 2021. AMPK protects against alcohol-induced liver injury through UQCRC2 to up-regulate mitophagy. *Autophagy*, 17(11):3622-3643. https://doi.org/10.1080/15548627.2021.1886829

Ma XW, McKeen T, Zhang JH, et al., 2020. Role and mechanisms of mitophagy in liver diseases. *Cells*, 9(4):837. https://doi.org/10.3390/cells9040837

Mahmoud AR, Ali FEM, Abd-Elhamid TH, et al., 2019. Coenzyme $Q_{10}$ protects hepatocytes from ischemia reperfusion-induced apoptosis and oxidative stress via regulation of Bax/Bcl-2/PUMA and Nrf-2/FOXO-3/Sirt-1 signaling pathways. *Tissue Cell*, 60:1-13. https://doi.org/10.1016/j.tice.2019.07.007

Mao H, Chen W, Chen LX, et al., 2022. Potential role of mitochondria-associated endoplasmic reticulum membrane proteins in diseases. *Biochem Pharmacol*, 199:115011. https://doi.org/10.1016/j.bcp.2022.115011

Medvedev R, Ploen D, Spengler C, et al., 2017. HCV-induced oxidative stress by inhibition of Nrf2 triggers autophagy and favors release of viral particles. *Free Radic Biol Med*, 110:300-315. https://doi.org/10.1016/j.freeradbiomed.2017.06.021

Meng B, Zhang YZ, Wang ZQ, et al., 2019. Hepatoprotective effects of *Morchella esculenta* against alcohol-induced acute liver injury in the C57BL/6 mouse related to Nrf-2 and NF-κB signaling. *Oxid Med Cell Longev*, 2019: 6029876. https://doi.org/10.1155/2019/6029876

Miyakawa K, Jeremiah SS, Ogawa M, et al., 2022a. Crosstalk between the innate immune system and selective autophagy in hepatitis B virus infection. *Autophagy*, 18(8):2006-2007. https://doi.org/10.1080/15548627.2022.2059747

Miyakawa K, Nishi M, Ogawa M, et al., 2022b. Galectin-9 restricts hepatitis B virus replication via p62/SQSTM1-mediated selective autophagy of viral core proteins. *Nat Commun*, 13:531. https://doi.org/10.1038/s41467-022-28171-5

Mizushima N, Komatsu M, 2011. Autophagy: renovation of cells and tissues. *Cell*, 147(4):728-741. https://doi.org/10.1016/j.cell.2011.10.026

Mohs A, Otto T, Schneider KM, et al., 2021. Hepatocyte-specific NRF2 activation controls fibrogenesis and carcinogenesis in steatohepatitis. *J Hepatol*, 74(3):638-648. https://doi.org/10.1016/j.jhep.2020.09.037

Morsy MA, Ibrahim YF, Abdel Hafez SMN, et al., 2022. Paeonol attenuates hepatic ischemia/reperfusion injury by modulating the Nrf2/HO-1 and TLR4/MYD88/NF-κB signaling pathways. *Antioxidants (Basel)*, 11(9):1687. https://doi.org/10.3390/antiox11091687

Munakarmi S, Gurau Y, Shrestha J, et al., 2023. Synergistic effects of *Vitis vinifera* L. and *Centella asiatica* against $CCl_4$-induced liver injury in mice. *Int J Mol Sci*, 24(14): 11255. https://doi.org/10.3390/ijms241411255

Namachivayam A, Valsala Gopalakrishnan A, 2021. A review on molecular mechanism of alcoholic liver disease. *Life Sci*, 274:119328. https://doi.org/10.1016/j.lfs.2021.119328

Ni HM, Boggess N, McGill MR, et al., 2012. Liver-specific loss of Atg5 causes persistent activation of Nrf2 and protects against acetaminophen-induced liver injury. *Toxicol Sci*, 127(2):438-450. https://doi.org/10.1093/toxsci/kfs133

Ni HM, Du K, You M, et al., 2013. Critical role of FoxO3a in alcohol-induced autophagy and hepatotoxicity. *Am J Pathol*, 183(6):1815-1825. https://doi.org/10.1016/j.ajpath.2013.08.011

Ni HM, Woolbright BL, Williams J, et al., 2014. Nrf2 promotes the development of fibrosis and tumorigenesis in mice with defective hepatic autophagy. *J Hepatol*, 61(3): 617-625. https://doi.org/10.1016/j.jhep.2014.04.043

Ni HM, McGill MR, Chao XJ, et al., 2016. Removal of acetaminophen protein adducts by autophagy protects against acetaminophen-induced liver injury in mice. *J Hepatol*, 65(2):354-362. https://doi.org/10.1016/j.jhep.2016.04.025

Ning XJ, Yan X, Wang YF, et al., 2018. Parkin deficiency elevates hepatic ischemia/reperfusion injury accompanying decreased mitochondrial autophagy, increased apoptosis, impaired DNA damage repair and altered cell cycle distribution. *Mol Med Rep*, 18(6):5663-5668. https://doi.org/10.3892/mmr.2018.9606

Nio Y, Sasai M, Akahori Y, et al., 2019. Bardoxolone methyl as

a novel potent antiviral agent against hepatitis B and C viruses in human hepatocyte cell culture systems. *Antiviral Res*, 169:104537.
https://doi.org/10.1016/j.antiviral.2019.104537

Ou Q, Weng YY, Wang SW, et al., 2018. Silybin alleviates hepatic steatosis and fibrosis in NASH mice by inhibiting oxidative stress and involvement with the NF-κB pathway. *Dig Dis Sci*, 63(12):3398-3408.
https://doi.org/10.1007/s10620-018-5268-0

Pan ZS, Guo JY, Tang KJ, et al., 2022. Ginsenoside Rc modulates SIRT6-NRF2 interaction to alleviate alcoholic liver disease. *J Agric Food Chem*, 70(44):14220-14234.
https://doi.org/10.1021/acs.jafc.2c06146

Patel F, Parwani K, Patel D, et al., 2021. Metformin and probiotics interplay in amelioration of ethanol-induced oxidative stress and inflammatory response in an *in vitro* and *in vivo* model of hepatic injury. *Mediators Inflamm*, 2021: 6636152.
https://doi.org/10.1155/2021/6636152

Petersen DR, Saba LM, Sayin VI, et al., 2018. Elevated Nrf-2 responses are insufficient to mitigate protein carbonylation in hepatospecific PTEN deletion mice. *PLoS ONE*, 13(5):e0198139.
https://doi.org/10.1371/journal.pone.0198139

Protzer U, Seyfried S, Quasdorff M, et al., 2007. Antiviral activity and hepatoprotection by heme oxygenase-1 in hepatitis B virus infection. *Gastroenterology*, 133(4):1156-1165.
https://doi.org/10.1053/j.gastro.2007.07.021

Qi DB, Chen P, Bao HL, et al., 2023. Dimethyl fumarate protects against hepatic ischemia-reperfusion injury by alleviating ferroptosis via the NRF2/SLC7A11/HO-1 axis. *Cell Cycle*, 22(7):818-828.
https://doi.org/10.1080/15384101.2022.2155016

Qian QW, Zhang ZY, Orwig A, et al., 2018. *S*-Nitrosoglutathione reductase dysfunction contributes to obesity-associated hepatic insulin resistance via regulating autophagy. *Diabetes*, 67(2):193-207.
https://doi.org/10.2337/db17-0223

Qu XP, Yu J, Bhagat G, et al., 2003. Promotion of tumorigenesis by heterozygous disruption of the *beclin 1* autophagy gene. *J Clin Invest*, 112(12):1809-1820.
https://doi.org/10.1172/JCI20039

Rabie MA, Zaki HF, Sayed HM, 2019. Telluric acid ameliorates hepatic ischemia reperfusion-induced injury in rats: involvement of TLR4, Nrf2, and PI3K/Akt signaling pathways. *Biochem Pharmacol*, 168:404-411.
https://doi.org/10.1016/j.bcp.2019.08.001

Rinella ME, Lazarus JV, Ratziu V, et al., 2023. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *J Hepatol*, 79(6):1542-1556.
https://doi.org/10.1016/j.jhep.2023.06.003

Rockwell CE, Zhang MC, Fields PE, et al., 2012. Th2 skewing by activation of Nrf2 in CD4$^+$ T cells. *J Immunol*, 188(4): 1630-1637.
https://doi.org/10.4049/jimmunol.1101712

Russomanno G, Sison-Young R, Livoti LA, et al., 2023. A systems approach reveals species differences in hepatic stress response capacity. *Toxicol Sci*, 196(1):112-125.
https://doi.org/10.1093/toxsci/kfad085

Schneider JL, Cuervo AM, 2014. Liver autophagy: much more than just taking out the trash. *Nat Rev Gastroenterol Hepatol*, 11(3):187-200.
https://doi.org/10.1038/nrgastro.2013.211

Settembre C, de Cegli R, Mansueto G, et al., 2013. TFEB controls cellular lipid metabolism through a starvation-induced autoregulatory loop. *Nat Cell Biol*, 15(6):647-658.
https://doi.org/10.1038/ncb2718

Shan SL, Shen ZY, Zhang CQ, et al., 2019. Mitophagy protects against acetaminophen-induced acute liver injury in mice through inhibiting NLRP3 inflammasome activation. *Biochem Pharmacol*, 169:113643.
https://doi.org/10.1016/j.bcp.2019.113643

Shao N, Yu XY, Ma XF, et al., 2018. Exenatide delays the progression of nonalcoholic fatty liver disease in C57BL/6 mice, which may involve inhibition of the NLRP3 inflammasome through the mitophagy pathway. *Gastroenterol Res Pract*, 2018:1864307.
https://doi.org/10.1155/2018/1864307

Shen J, Wang GF, Zuo JP, 2018. Caffeic acid inhibits HCV replication via induction of IFNα antiviral response through p62-mediated Keap1/Nrf2 signaling pathway. *Antiviral Res*, 154:166-173.
https://doi.org/10.1016/j.antiviral.2018.04.008

Shen YM, Zhang HL, Wu YH, et al., 2015. Dynamic correlation between induction of the expression of heme oxygenase-1 and hepatitis B viral replication. *Mol Med Rep*, 11(6): 4706-4712.
https://doi.org/10.3892/mmr.2015.3278

Sir D, Chen WL, Choi J, et al., 2008a. Induction of incomplete autophagic response by hepatitis C virus via the unfolded protein response. *Hepatology*, 48(4):1054-1061.
https://doi.org/10.1002/hep.22464

Sir D, Liang CY, Chen WL, et al., 2008b. Perturbation of autophagic pathway by hepatitis C virus. *Autophagy*, 4(6): 830-831.
https://doi.org/10.4161/auto.6566

Sir D, Tian YJ, Chen WL, et al., 2010. The early autophagic pathway is activated by hepatitis B virus and required for viral DNA replication. *Proc Natl Acad Sci USA*, 107(9): 4383-4388.
https://doi.org/10.1073/pnas.0911373107

Sir D, Kuo CF, Tian YJ, et al., 2012. Replication of hepatitis C virus RNA on autophagosomal membranes. *J Biol Chem*, 287(22):18036-18043.
https://doi.org/10.1074/jbc.M111.320085

Smirnova OA, Ivanova ON, Mukhtarov F, et al., 2023. Hepatitis delta virus antigens trigger oxidative stress, activate antioxidant Nrf2/ARE pathway, and induce unfolded protein response. *Antioxidants (Basel)*, 12(4):974.
https://doi.org/10.3390/antiox12040974

Solano-Urrusquieta A, Morales-González JA, Castro-Narro GE, et al., 2020. NRF-2 and nonalcoholic fatty liver disease. *Ann Hepatol*, 19(5):458-465.
https://doi.org/10.1016/j.aohep.2019.11.010

Song JZ, Zhao X, Bo JQ, et al., 2024. A polysaccharide from Alhagi honey protects the intestinal barrier and regulates the Nrf2/HO-1-TLR4/MAPK signaling pathway to treat alcoholic liver disease in mice. *J Ethnopharmacol*, 321: 117552.
https://doi.org/10.1016/j.jep.2023.117552

Soto G, Rodríguez MJ, Fuentealba R, et al., 2020. Maresin 1, a proresolving lipid mediator, ameliorates liver ischemia-reperfusion injury and stimulates hepatocyte proliferation in Sprague-Dawley rats. *Int J Mol Sci*, 21(2):540.
https://doi.org/10.3390/ijms21020540

Sun C, Wang ZH, Liu XX, et al., 2015. Disturbance of redox status enhances radiosensitivity of hepatocellular carcinoma. *Am J Cancer Res*, 5(4):1368-1381.

Suzuki T, Murakami S, Biswal SS, et al., 2017. Systemic activation of NRF2 alleviates lethal autoimmune inflammation in scurfy mice. *Mol Cell Biol*, 37(15):e00063-17.
https://doi.org/10.1128/MCB.00063-17

Taguchi K, Fujikawa N, Komatsu M, et al., 2012. Keap1 degradation by autophagy for the maintenance of redox homeostasis. *Proc Natl Acad Sci USA*, 109(34):13561-13566.
https://doi.org/10.1073/pnas.1121572109

Takamura A, Komatsu M, Hara T, et al., 2011. Autophagy-deficient mice develop multiple liver tumors. *Genes Dev*, 25(8):795-800.
https://doi.org/10.1101/gad.2016211

Tamilmani P, Sathibabu Uddandrao VV, Chandrasekaran P, et al., 2023. Linalool attenuates lipid accumulation and oxidative stress in metabolic dysfunction-associated steatotic liver disease via Sirt1/Akt/PPRA-α/AMPK and Nrf-2/HO-1 signaling pathways. *Clin Res Hepatol Gastroenterol*, 47(10):102231.
https://doi.org/10.1016/j.clinre.2023.102231

Tang KZ, Chen Q, Liu YM, et al., 2022. Combination of metformin and sorafenib induces ferroptosis of hepatocellular carcinoma through p62-Keap1-Nrf2 pathway. *J Cancer*, 13(11):3234-3243.
https://doi.org/10.7150/jca.76618

Targher G, Byrne CD, Tilg H, 2024. MASLD: a systemic metabolic disorder with cardiovascular and malignant complications. *Gut*, 73(4):691-702.
https://doi.org/10.1136/gutjnl-2023-330595

Thimmulappa RK, Lee H, Rangasamy T, et al., 2006. Nrf2 is a critical regulator of the innate immune response and survival during experimental sepsis. *J Clin Invest*, 116(4): 984-995.
https://doi.org/10.1172/JCI25790

Thomes PG, Trambly CS, Fox HS, et al., 2015. Acute and chronic ethanol administration differentially modulate hepatic autophagy and transcription factor EB. *Alcohol Clin Exp Res*, 39(12):2354-2363.
https://doi.org/10.1111/acer.12904

Tian C, Min XW, Zhao YX, et al., 2022. MRG15 aggravates non-alcoholic steatohepatitis progression by regulating the mitochondrial proteolytic degradation of TUFM. *J Hepatol*, 77(6):1491-1503.
https://doi.org/10.1016/j.jhep.2022.07.017

Tomulic Brusich K, Škrtić A, Sobočan N, et al., 2023. Role of NRF2 and reactive aldehydes in acute cellular rejection in liver transplant recipients. *Pathol Res Pract*, 250:154826.
https://doi.org/10.1016/j.prp.2023.154826

Tong GZ, Chen YM, Chen XX, et al., 2023. FGF18 alleviates hepatic ischemia-reperfusion injury via the USP16-mediated KEAP1/Nrf2 signaling pathway in male mice. *Nat Commun*, 14:6107.
https://doi.org/10.1038/s41467-023-41800-x

Twu WI, Lee JY, Kim H, et al., 2021. Contribution of autophagy machinery factors to HCV and SARS-CoV-2 replication organelle formation. *Cell Rep*, 37(8):110049.
https://doi.org/10.1016/j.celrep.2021.110049

Urrunaga NH, Jadeja RN, Rachakonda V, et al., 2015. M1 muscarinic receptors modify oxidative stress response to acetaminophen-induced acute liver injury. *Free Radic Biol Med*, 78:66-81.
https://doi.org/10.1016/j.freeradbiomed.2014.09.032

Wang CL, Wang YJ, 2023. The role and mechanism of action of mitophagy in various liver diseases. *Antioxid Redox Signal*, 38(7-9):529-549.
https://doi.org/10.1089/ars.2022.0114

Wang CR, Gong JH, Zhao ZB, et al., 2024. $m^6A$ demethylation of *FOSL1* mRNA protects hepatoma cells against necrosis under glucose deprivation. *Cell Death Differ*, 31:1029-1043.
https://doi.org/10.1038/s41418-024-01308-3

Wang H, Ni HM, Chao XJ, et al., 2019. Double deletion of PINK1 and Parkin impairs hepatic mitophagy and exacerbates acetaminophen-induced liver injury in mice. *Redox Biol*, 22:101148.
https://doi.org/10.1016/j.redox.2019.101148

Wang L, Liu XL, Nie J, et al., 2015. ALCAT1 controls mitochondrial etiology of fatty liver diseases, linking defective mitophagy to steatosis. *Hepatology*, 61(2):486-496.
https://doi.org/10.1002/hep.27420

Wang SY, Tao J, Chen HG, et al., 2021. Ablation of Akt2 and AMPKα2 rescues high fat diet-induced obesity and hepatic steatosis through Parkin-mediated mitophagy. *Acta Pharm Sin B*, 11(11):3508-3526.
https://doi.org/10.1016/j.apsb.2021.07.006

Wang X, Liu JR, Zhang XH, et al., 2018. Seabuckthorn berry polysaccharide extracts protect against acetaminophen induced hepatotoxicity in mice via activating the Nrf-2/HO-1-SOD-2 signaling pathway. *Phytomedicine*, 38:90-97.
https://doi.org/10.1016/j.phymed.2017.11.007

Wang XY, Wei ZQ, Lan TY, et al., 2022a. CCDC88A/GIV promotes HBV replication and progeny secretion via enhancing endosomal trafficking and blocking autophagic degradation. *Autophagy*, 18(2):357-374.
https://doi.org/10.1080/15548627.2021.1934271

Wang XY, Wei ZQ, Cheng B, et al., 2022b. Endoplasmic reticulum stress promotes HBV production by enhancing use of the autophagosome/multivesicular body axis. *Hepatology*, 75(2):438-454.
https://doi.org/10.1002/hep.32178

Wang Y, Wang Z, Sun JJ, et al., 2021. Identification of HCC subtypes with different prognosis and metabolic patterns based on mitophagy. *Front Cell Dev Biol*, 9:799507. https://doi.org/10.3389/fcell.2021.799507

Wayal V, Hsieh CC, 2023. Bioactive dipeptides mitigate high-fat and high-fructose corn syrup diet-induced metabolic-associated fatty liver disease via upregulation of Nrf2/HO-1 expressions in C57BL/6J mice. *Biomed Pharmacother*, 168:115724. https://doi.org/10.1016/j.biopha.2023.115724

White E, Mehnert JM, Chan CS, 2015. Autophagy, metabolism, and cancer. *Clin Cancer Res*, 21(22):5037-5046. https://doi.org/10.1158/1078-0432.CCR-15-0490

Williams JA, Ni HM, Haynes A, et al., 2015a. Chronic deletion and acute knockdown of Parkin have differential responses to acetaminophen-induced mitophagy and liver injury in mice. *J Biol Chem*, 290(17):10934-10946. https://doi.org/10.1074/jbc.M114.602284

Williams JA, Ni HM, Ding YF, et al., 2015b. Parkin regulates mitophagy and mitochondrial function to protect against alcohol-induced liver injury and steatosis in mice. *Am J Physiol Gastrointest Liver Physiol*, 309(5):G324-G340. https://doi.org/10.1152/ajpgi.00108.2015

Wu H, Wang T, Liu YQ, et al., 2020a. Mitophagy promotes sorafenib resistance through hypoxia-inducible ATAD3A dependent Axis. *J Exp Clin Cancer Res*, 39:274. https://doi.org/10.1186/s13046-020-01768-8

Wu H, Chen GY, Wang JY, et al., 2020b. TIM-4 interference in Kupffer cells against $CCl_4$-induced liver fibrosis by mediating Akt1/Mitophagy signalling pathway. *Cell Prolif*, 53(1):e12731. https://doi.org/10.1111/cpr.12731

Wu KC, Liu J, Klaassen CD, 2012. Role of Nrf2 in preventing ethanol-induced oxidative stress and lipid accumulation. *Toxicol Appl Pharmacol*, 262(3):321-329. https://doi.org/10.1016/j.taap.2012.05.010

Xiang XH, Fu YN, Zhao K, et al., 2021. Cellular senescence in hepatocellular carcinoma induced by a long non-coding RNA-encoded peptide PINT87aa by blocking FOXM1-mediated *PHB2*. *Theranostics*, 11(10):4929-4944. https://doi.org/10.7150/thno.55672

Xie L, Huang WG, Li JL, et al., 2022. The protective effects and mechanisms of modified Lvdou Gancao decoction on acute alcohol intoxication in mice. *J Ethnopharmacol*, 282: 114593. https://doi.org/10.1016/j.jep.2021.114593

Xie WY, Jiang ZH, Wang J, et al., 2016. Protective effect of hyperoside against acetaminophen (APAP) induced liver injury through enhancement of APAP clearance. *Chem Biol Interact*, 246:11-19. https://doi.org/10.1016/j.cbi.2016.01.004

Xie ZY, Xiao ZH, Wang FF, 2018. Inhibition of autophagy reverses alcohol-induced hepatic stellate cells activation through activation of Nrf2-Keap1-ARE signaling pathway. *Biochimie*, 147:55-62. https://doi.org/10.1016/j.biochi.2017.12.013

Xu M, Hang HL, Huang M, et al., 2021. DJ-1 deficiency in hepatocytes improves liver ischemia-reperfusion injury by enhancing mitophagy. *Cell Mol Gastroenterol Hepatol*, 12(2):567-584. https://doi.org/10.1016/j.jcmgh.2021.03.007

Xu PF, Xi Y, Wang PC, et al., 2022. Inhibition of p53 sulfoconjugation prevents oxidative hepatotoxicity and acute liver failure. *Gastroenterology*, 162(4):1226-1241. https://doi.org/10.1053/j.gastro.2021.12.260

Yamada T, Murata D, Adachi Y, et al., 2018. Mitochondrial stasis reveals p62-mediated ubiquitination in Parkin-independent mitophagy and mitigates nonalcoholic fatty liver disease. *Cell Metab*, 28(4):588-604.e5. https://doi.org/10.1016/j.cmet.2018.06.014

Yang L, Li P, Fu SN, et al., 2010. Defective hepatic autophagy in obesity promotes ER stress and causes insulin resistance. *Cell Metab*, 11(6):467-478. https://doi.org/10.1016/j.cmet.2010.04.005

Yang MM, Xia LQ, Song J, et al., 2023. Puerarin ameliorates metabolic dysfunction-associated fatty liver disease by inhibiting ferroptosis and inflammation. *Lipids Health Dis*, 22:202. https://doi.org/10.1186/s12944-023-01969-y

Yang Q, Zhao ZZ, Xie J, et al., 2021. Senkyunolide I attenuates hepatic ischemia/reperfusion injury in mice via anti-oxidative, anti-inflammatory and anti-apoptotic pathways. *Int Immunopharmacol*, 97:107717. https://doi.org/10.1016/j.intimp.2021.107717

Yang RQ, Zhang M, Gustafson AR, et al., 2015. Loss of protein targeting to glycogen sensitizes human hepatocellular carcinoma cells towards glucose deprivation mediated oxidative stress and cell death. *Biosci Rep*, 35(3):e00207. https://doi.org/10.1042/BSR20150090

Yang T, Qu XY, Zhao JY, et al., 2023. Macrophage PTEN controls STING-induced inflammation and necroptosis through NICD/NRF2 signaling in APAP-induced liver injury. *Cell Commun Signal*, 21:160. https://doi.org/10.1186/s12964-023-01175-4

Yao JY, Wang JB, Xu Y, et al., 2022. CDK9 inhibition blocks the initiation of PINK1-PRKN-mediated mitophagy by regulating the SIRT1-FOXO3-BNIP3 axis and enhances the therapeutic effects involving mitochondrial dysfunction in hepatocellular carcinoma. *Autophagy*, 18(8):1879-1897. https://doi.org/10.1080/15548627.2021.2007027

Yao PY, Liu YJ, 2022. Terpenoids: natural compounds for non-alcoholic fatty liver disease (NAFLD) therapy. *Molecules*, 28(1):272. https://doi.org/10.3390/molecules28010272

Yates MS, Tran QT, Dolan PM, et al., 2009. Genetic versus chemoprotective activation of Nrf2 signaling: overlapping yet distinct gene expression profiles between Keap1 knockout and triterpenoid-treated mice. *Carcinogenesis*, 30(6):1024-1031. https://doi.org/10.1093/carcin/bgp100

Yeligar SM, Machida K, Kalra VK, 2010. Ethanol-induced HO-1 and NQO1 are differentially regulated by HIF-1α and Nrf2 to attenuate inflammatory cytokine expression. *J Biol Chem*, 285(46):35359-35373.

https://doi.org/10.1074/jbc.M110.138636

Yi ZW, Xia YJ, Liu XF, et al., 2020. Antrodin A from mycelium of *Antrodia camphorata* alleviates acute alcoholic liver injury and modulates intestinal flora dysbiosis in mice. *J Ethnopharmacol*, 254:112681.
https://doi.org/10.1016/j.jep.2020.112681

Yu LC, Liu YY, Jin YC, et al., 2021. Zinc supplementation prevented type 2 diabetes-induced liver injury mediated by the Nrf2-MT antioxidative pathway. *J Diabetes Res*, 2021: 6662418.
https://doi.org/10.1155/2021/6662418

Yu Z, Guo JF, Hu MY, et al., 2020. Icaritin exacerbates mitophagy and synergizes with doxorubicin to induce immunogenic cell death in hepatocellular carcinoma. *ACS Nano*, 14(4):4816-4828.
https://doi.org/10.1021/acsnano.0c00708

Yun NR, Cho HI, Lee SM, 2014. Impaired autophagy contributes to hepatocellular damage during ischemia/reperfusion: heme oxygenase-1 as a possible regulator. *Free Radic Biol Med*, 68:168-177.
https://doi.org/10.1016/j.freeradbiomed.2013.12.014

Zeng YN, Wu R, Wang FZ, et al., 2023. Liberation of daidzein by gut microbial β-galactosidase suppresses acetaminophen-induced hepatotoxicity in mice. *Cell Host Microbe*, 31(5): 766-780.e7.
https://doi.org/10.1016/j.chom.2023.04.002

Zhan YQ, Xu DW, Tian YZ, et al., 2022. Novel role of macrophage TXNIP-mediated CYLD-NRF2-OASL1 axis in stress-induced liver inflammation and cell death. *JHEP Rep*, 4(9):100532.
https://doi.org/10.1016/j.jhepr.2022.100532

Zhang H, Zhang YQ, Zhu XY, et al., 2019. DEAD box protein 5 inhibits liver tumorigenesis by stimulating autophagy via interaction with p62/SQSTM1. *Hepatology*, 69(3): 1046-1063.
https://doi.org/10.1002/hep.30300

Zhang WP, Chen LH, Feng H, et al., 2017. Rifampicin-induced injury in HepG2 cells is alleviated by TUDCA via increasing bile acid transporters expression and enhancing the Nrf2-mediated adaptive response. *Free Radic Biol Med*, 112:24-35.
https://doi.org/10.1016/j.freeradbiomed.2017.07.003

Zhang XR, Wang MY, Teng SS, et al., 2018. Indolyl-chalcone derivatives induce hepatocellular carcinoma cells apoptosis through oxidative stress related mitochondrial pathway *in vitro* and *in vivo*. *Chem Biol Interact*, 293:61-69.
https://doi.org/10.1016/j.cbi.2018.07.025

Zhang YJ, Wei H, Wang MM, et al., 2023. Dexmedetomidine alleviates ferroptosis following hepatic ischemia-reperfusion injury by upregulating Nrf2/GPx4-dependent antioxidant responses. *Biomed Pharmacother*, 169:115915.
https://doi.org/10.1016/j.biopha.2023.115915

Zhang YKJ, Yeager RL, Tanaka Y, et al., 2010. Enhanced expression of Nrf2 in mice attenuates the fatty liver produced by a methionine- and choline-deficient diet. *Toxicol Appl Pharmacol*, 245(3):326-334.
https://doi.org/10.1016/j.taap.2010.03.016

Zhao N, Guo FF, Xie KQ, et al., 2018. Targeting Nrf-2 is a promising intervention approach for the prevention of ethanol-induced liver disease. *Cell Mol Life Sci*, 75(17):3143-3157.
https://doi.org/10.1007/s00018-018-2852-6

Zhao Z, Wei QY, Hua WW, et al., 2018. Hepatoprotective effects of berberine on acetaminophen-induced hepatotoxicity in mice. *Biomed Pharmacother*, 103:1319-1326.
https://doi.org/10.1016/j.biopha.2018.04.175

Zheng J, Chen L, Lu TY, et al., 2020. MSCs ameliorate hepatocellular apoptosis mediated by PINK1-dependent mitophagy in liver ischemia/reperfusion injury through AMPKα activation. *Cell Death Dis*, 11(4):256.
https://doi.org/10.1038/s41419-020-2424-1

Zheng YH, Huang C, Lu L, et al., 2021. STOML2 potentiates metastasis of hepatocellular carcinoma by promoting PINK1-mediated mitophagy and regulates sensitivity to lenvatinib. *J Hematol Oncol*, 14:16.
https://doi.org/10.1186/s13045-020-01029-3

Zhong WZ, Rao ZQ, Xu J, et al., 2022. Defective mitophagy in aged macrophages promotes mitochondrial DNA cytosolic leakage to activate STING signaling during liver sterile inflammation. *Aging Cell*, 21(6):e13622.
https://doi.org/10.1111/acel.13622

Zhou H, Zhu PJ, Wang J, et al., 2019. DNA-PKcs promotes alcohol-related liver disease by activating Drp1-related mitochondrial fission and repressing FUNDC1-required mitophagy. *Signal Transduct Target Ther*, 4:56.
https://doi.org/10.1038/s41392-019-0094-1

Zhou QH, Shi Y, Chen C, et al., 2021. A narrative review of the roles of indoleamine 2,3-dioxygenase and tryptophan-2,3-dioxygenase in liver diseases. *Ann Transl Med*, 9(2): 174.
https://doi.org/10.21037/atm-20-3594

Zhu H, Jia ZQ, Misra H, et al., 2012. Oxidative stress and redox signaling mechanisms of alcoholic liver disease: updated experimental and clinical evidence. *J Dig Dis*, 13(3):133-142.
https://doi.org/10.1111/j.1751-2980.2011.00569.x

Zhu QL, Zhuo HL, Yang LM, et al., 2022. A peptide HEPFYGNEGALR from *Apostichopus japonicus* alleviates acute alcoholic liver injury by enhancing antioxidant response in male C57BL/6J mice. *Molecules*, 27(18):5839.
https://doi.org/10.3390/molecules27185839

Zhu ZW, Wilson AT, Mathahs MM, et al., 2008. Heme oxygenase-1 suppresses hepatitis C virus replication and increases resistance of hepatocytes to oxidant injury. *Hepatology*, 48(5):1430-1439.
https://doi.org/10.1002/hep.22491

Zhu ZW, Wilson AT, Luxon BA, et al., 2010. Biliverdin inhibits hepatitis C virus nonstructural 3/4A protease activity: mechanism for the antiviral effects of heme oxygenase? *Hepatology*, 52(6):1897-1905.
https://doi.org/10.1002/hep.23921