Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology) in press
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, The Affiliated Hangzhou First People's Hospital, School of Medicine, Westlake University, Hangzhou, 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, College of Medicine, Zhejiang University, Hangzhou, China*

Abstract: Nuclear factor (erythroid-derived 2)-like 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 functioning 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 diseases

Unedited

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 exogeneous inflammation and oxidative stress, mitochondrial respiratory chain failure and other mechanisms(Solano-Urrusquieta et al., 2020).

Several cellular pathways participate in maintaining internal homeostasis. 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 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 nucleus to regulate the transcription of antioxidant response elements (AREs), including HO-1, glutathione (GSH) and thioredoxin-dependent enzymes involved in DNA repair, anti-oxidation, 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 mitochondrion biogenesis by promoting peroxisome proliferator-activated receptor-γ (PPAR-γ) coactiva-

✉ 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 xxx. xx, 20xx; Published online xxx. xx, 20xx

© Zhejiang University Press 2024

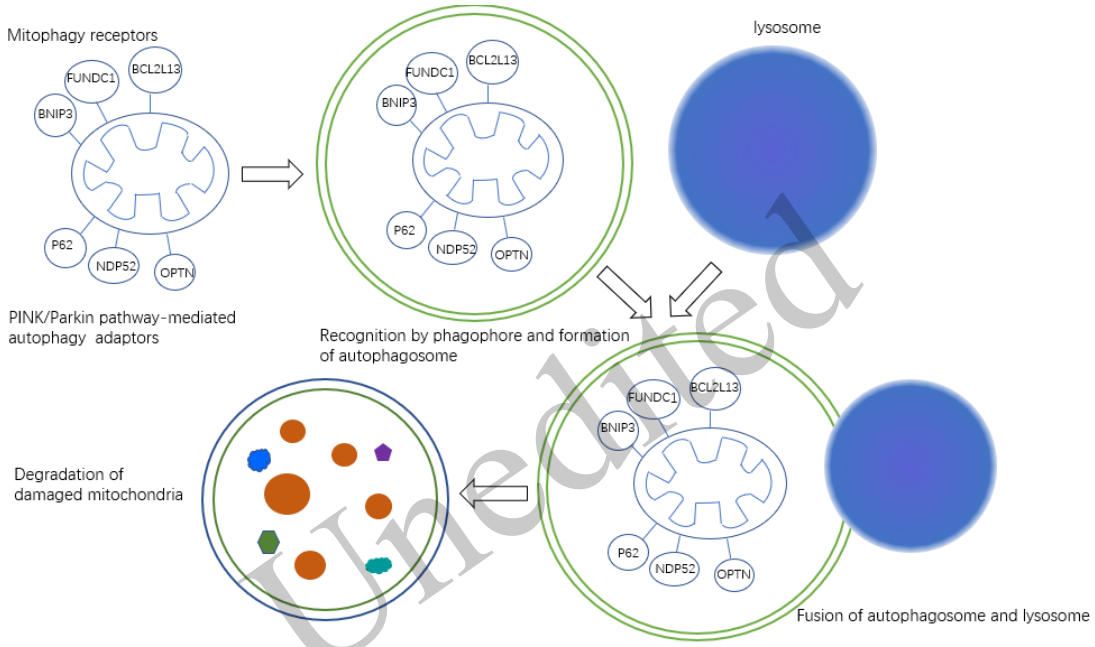
tor-1alpha (PGC-1α) levels. Pharmacologically targeting Nrf2 mediates several diseases through ferroptosis in some manner(Dodson et al., 2019). Nrf2 increases the level of NADPH by upregulating the genes responsible for it. In cancers with activated Nrf2, glutamates are recruited into GSH biosynthesis or exported through the system x_c^- antiporter. This results in the depletion of intracellular glutamate and restriction of its use in the synthesis of non-essential amino acids (NEAAs), limiting tumor growth(Leboeuf et al., 2020). The expression of Nrf2 is inversely correlated with that of inflammatory cytokines, including Interlukin-1β (IL-1β) and IL-6(Solano-Urrusquieta, et al., 2020). Thimmulappa et al.(Thimmulappa et al., 2006) revealed that Nrf2 improved survival rate by downregulating the proinflammatory 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 activities(Suzuki et al., 2017). In addition, Nrf2 promotes the differentiation of CD4+T cells into Th2 cells by producing the cytokines IL-4 and IL-5 and inhibiting interferon gamma (IFN-γ)(Rockwell et al., 2012). However, in Pten::Keap1 and Keap1::Atg7 double knockout mice models of hepatic disease, Baird et al.(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 (CCR2+) classical monocytes to suppress early stage tumors. They also found that not only monocytes but also activated NK cells and γδ T cells were enriched in tumors with the activating mutated gene NRF2 (specifically the $NNFE2L2^{E82D}$ mutation)(Baird and Yamamoto, 2023). In addition, more pro-inflammatory immune cells and cytokines, such as macrophages, neutrophils，CCL2 and IL-1β, were enriched in the livers of $NEMO^{\triangle hepa}$/$KEAP1^{\triangle hepa}$ mice with consecutive Nrf2 activation(Mohs et al., 2021). The potential mechanisms might involve the inactivation of 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 is metabolized through selective and nonselective degradation. Selective degredation occurs commonly.

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 its 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 ubiquitin-independent or ubiquitin-dependent pathways, involving the mammalian Atg8 family members including microtubule-associated protein light chain 3 (LC3) and GABARAP, especially the LC3 interacting region (LIR)-domain receptor pathway or phosphatase and tensin homolog induced kinase 1 (PINK1)/Parkin pathway, respectively(Wang and Wang, 2023). The LIR-domain receptor pathway involves outer mitochondrial membrane (OMM) receptors such as BCL2 and adenovirus E1B 19-kDa-interacting protein 3(BNIP3), BNIP3L (also known as NIX), FUN14 domain-containing protein 1(FUNDC1), and B-cell lymphoma 2-like

Unedited

13(BCL2L13). These receptors interact with LC3, which promotes mitophagy. It is reported that BNIP3 and NIX also play a part in PINK1/Parkin pathway. For example, BNIP3 interacts with PINK1, which leads to the accumulation of PINK1 and Parkin at the OMM. NIX can be ubiquitylated by Parkin to promote mitophagy. FUNDC1 is integrated into the OMM and acts with LC3 under hypoxial conditions. The overexpression of BCL2L13 promotes mitochondrial fragmentation and its interaction with 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 NDP52, which interact with the Atg8 family to promote mitophagy. Accumulation of p62 and polyubiquitinated proteins always infers a deficiency of autophagy (Fig. 1).



Unedited

Fig. 1 The main process of mitophagy. Under stress conditions (presence of ROS, nutrient deficiency, cell aging, and other external stimuli), damaged mitochondria depolarize and lose 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, there are many receptors including NIX/BNIP3L, BNIP3, and FUNDC1 binding directly with LC3 without ubiquitination.

Nrf2 interacts with PGC-1α in mitochondrial biogenesis. Activation of Nrf2 upregulates the mitochondrial membrane potential and the level of ATP, directly impacting energy metabolism(Holmstrom et al., 2013). There is positive feedback between Nrf2 and mitophagy. Under oxidative conditions, Nrf2 elevates the expression of p62 and PINK, 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 relationship between them (Table 1).

Table 1 The Roles of Nrf2 Signaling Pathway and Mitophagy in Diverse Liver Diseases

Liver Diseases	Roles of Nrf2 signaling pathway	Roles of mitophagy
Metabolic dysfunction-associated steatotic liver disease	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 suppresses HBV replication. Mitophagy supports HCV replication, maturation and release.
Alcoholic liver disease	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 disease	Nrf2 is upregulated to fight against DILI.	Mitophagy protects liver from APAP injury through suppression of NF-κB, the NLRP3 inflammasome and IL-1β；Parkin-knockout mitophagy protects APAP injury.
Hepatic ischemia–reperfusion injury	Nrf2 is suppressed to aggravate hepatic IRI; however, Nrf2 is also elevated to improve hepatic IRI.	Mitophagy attenuates hepatic ischemia–reperfusion injury.
Liver Carcinoma	Nrf2 prevents against carcinogenesis in normal cells and promotes tumor cells in cancer tissues.	Mitophagy suppresses liver cancer in the initial stage；while supports the development of liver cancer in the formed tumors.

Unedited

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 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 (SIRT-1)/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 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 nuclear factor-κB (NF-κB) signaling pathway were all observed by downregulating Keap1 and activating Nrf2 expression in RIP3$^{-/-}$ mice(Chenxu 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, dithiolethiones, isothiocyanates, triterpenoids, pioglitazone, vitamin E, type 2 sodium-glucose cotransporter inhibitors (iSGLT2) 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 cell 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 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 2 diabetes-induced liver injuries. Nrf2 bridges zinc supplementation and metallothionein expression to exert antioxidative effects in diabetes-induced liver injury(Yu et al., 2021). Han et al.(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. PGAM5-knockout mice fed with a high fat high fructose diet showed reduced hepatic steatosis and inflammation by upregulating antioxidant genes including HO-1 and glutathione peroxidase-6(Li et al., 2023b). Bioactive dipeptides tyrosine (Tyr) and phenylalanine (Phe) dose-dependently exert antioxidant effects and protect against high-fat diet 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 (TGF- β 1)- signaling(Hammoutene et al., 2023). Linalool, a kind of monoterpene in a variety of aromatic plants, also protects against HFD-induced MASLD through activating Nrf2 signaling and Sirt1/Akt/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., 2023b). Puerarin, another advantageous Chinese medicine, improves MAFLD by inhibiting ferroptosis and inflammation, mainly by activating the SIRT1/Nrf2 signaling pathway(Yang et al., 2023a). However, Kumar et al(Kumar et al., 2019) showed that the expression of Nrf2 and HO-1 was significantly decreased in HFD- and ethanol-fed rats. Liu et al.(Liu et al., 2023a) 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-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 PERK, dysregulated association between the endoplasmic reticulum and mitochondria, and mitochondrial

Unedited

dysfunction and 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 NLRP3 inflammasome activation(Tian et al., 2022). Restoration of hepatic autophagy alleviates endoplasmic reticulum stress and enhances insulin action(Yang, et al., 2010). Double knockout of Akt and AMP-activated protein kinase (AMPK) amplifies Parkin-mediated mitophagy and protects against hepatic steatosis in NAFLD(Wang et al., 2021a). The mitophagy inducer cyanidin-3-O-glucoside enhances PINK-mediated mitophagy, which is blunted in NAFLD, and alleviates hepatic oxidative stress(Li et al., 2020b). Exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist, is used to regulate glycemia and serum lipids, improve β cell function and control weight, enhance mitophagy and inhibit NLRP3 inflammasome activation to suppress hepatic inflammation in NAFLD(Shao et al., 2018). Sirtuin 3, which protects mitochondria under several kinds of stress, promotes BNIP3-mediated mitophagy and protects the liver in NAFLD via activation of the ERK-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.(Ampawong et al., 2017) demonstrated that liver Nrf2 expression is negatively correlated with the percentage of dysmorphic mitochondria, especially the fission marker 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 thioredoxin (Trx)2 increases hepatic insulin resistance and steatosis through excessive mitophagy and inflammation(He et al., 2021). Petersen et al.(Petersen et al., 2018) showed that Nrf2 and autophagic markers, including P62 and LC3-II, are simultaneously increased in liver-specific phosphatase and tensin homolog (PTEN)-deletion mice, which mimicks NASH-like conditions, indicating activation of both the antioxidant response and mitophagy. Bae et al.(Bae et al., 2013) demonstrated that Nrf2 activation induced by 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 mimicking hepatic steatosis, suppressed levels of p62 and antioxidant molecules through inhibition of Nrf2, overexpression of Fas/FasL and the hyporesponsiveness of Akt jointly accelerated liver injury and retarded liver regeneration(Haga et al., 2014).

Unedited

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 (ccc)DNA(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 promotor ability and HBV replication(Ariffianto et al., 2023). The anti-HCV activity of 3-amino-2hydroxy-propoxy isoflavone derivatives, natural isoflavonoids with anticancer, antiviral, and anti-inflammatory effects, relies on Keap1/Nrf2/HO-1 pathway induction(Lee et al., 2018a). 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 Bach1 and induction of HO-1(Chen et al., 2019a). A study conducted on the anti-HCV effect of caffeic acid demonstrated that 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.(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 were 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 hepatitis C virus core region affect hepatocellular carcinoma progression via impaired nuclear Nrf2 translocation and enhanced oxidative stress(Chida et al., 2024). In Huh7 cells, Smirnova et al.(Smirnova et al., 2023) showed that expression of hepatitis delta virus (HDV) antigen provoked the antioxidant Nrf2/ARE pathway, endoplasmic reticulum (ER) stress, and an unfolded protein response (UPR).

HBx is involved in the chronic process of hepatocellular carcinoma (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 beta 1 (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 serum total T_3 levels in HBV-related liver cirrhosis were observed in a previous study. Chi et al.(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 endoplasmic reticulum 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., 2022a). Miyakawa et al.(Miyakawa et al., 2022a; Miyakawa et al., 2022b) demonstrated that galectin 9 worked together with RSAD2/viperin, RNF13 and p62 to form autophagosomes to selectively degrade HBc in HBV-infected hepatocytes, thereby contributing to intracellular antiviral immunity. CCDC88A/GIV promotes HBV replication by reducing autophagic degradation of HBV antigens(Wang et al., 2022b). 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 its replication through multiple mechanisms, including activation of ER stress and the UPR, as well as 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; Sir et al., 2008b). Mechanistically, HCV-induced autophagy is not dependent on the Class III phosphatidylinositol 3-kinase (PI3K) pathway, and HCV replicate on autophagosomal membranes(Sir et al., 2012). However, Twu et al.(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. Inhibition of autophagy leads to colocalization of ApoE and the HCV E2 envelope protein and elevated progeny viral titers (Kim and Ou, 2018).

Unedited

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 hepatocellular carcinoma. 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 THP-1 cells treated with ethanol show increased mRNA levels of HO-1, *quinone oxidoreductase 1 (*NQO1), and hypoxia-inducible factor-1 (HIF-1)(Yeligar et al., 2010). Wu et al.(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 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 LPS/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 the activation of Nrf2 signaling and inhibition of the P65/NF-κB signaling pathways(Guo et al., 2022). A supplement of a peptide from sea cucumber attenuates hepatitis, lipid accumulation and hepatocyte apoptosis, and enhances antioxidant enzyme activities in ALD by activating the Nrf2 pathway and mitochondrial dynamics(Zhu et al., 2022). Alcohol induces a high expression of miR-138-5p, low expression of deacetylase SIRT1 and decreased FXR activity. Downregulation of miR-138-5p by a kaempferol and nicotiflorin treatment upregulates the level of SIRT1, thereby strengthening FXR activity and phosphorylated Nrf2 levels, 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 et al., 2018a). However, there were contradictory results indicating 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.(Abdelhamid, et al., 2021) showed that the binding capacities of PPAR-γ and Nrf2 were decreased in alcohol-fed mice. Patel et al.(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.(Xie et al., 2022) observed decreased levels of Nrf2 and HO-1 in mice fed only alcohol compared to those administered alcohol and a modified Lvdou Gancao decoction. Yi et al.(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 Sirtuin 6, 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 mitochondrial DNA by ethanol, manifesting as mtDNA strand breakage and integrity damage(Ding et al., 2011; Axley et al., 2019). Mitophagy works as a

Unedited

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 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., 2015a). 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.(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-SMA or CoL1A1 downregulation. This suggests an antifibrotic relationship between autophagy blockade and Nrf2 activation. However, Lu et al.(Lu et al., 2021) suggested that AMPK upregulated ubiquinol-cytochrome c reductase core protein 2 (UQCRC2) gene transcription by activating NFE2L2/NRF2 (nuclear factor, erythroid 2 like 2) to enhance mitophagy, thereby attenuating the liver injury induced by alcohol.

5 Drug-Induced Liver Injury (DILI)

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 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 kinases (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). Activation of the Nrf2/Mn-SOD pathway might account for the antioxidative roles of berberine in APAP-triggered hepatotoxicity(Zhao et al., 2018b). Aliyu et al.(Aliyu et al., 2018) suggested that the expression of Nrf2 and its upstream kinases, including Akt1, PI3K and 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 a 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 USP17-mediated Nrf2 pathway and PINK-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.(Cai et al., 2022) indicated that astaxanthin fights against liver injury induced by APAP mainly through activation of the Nrf2 pathway and autophagy, as well as inhibition of ferroptosis and the NF-κB pathway. Based on these observations, they were first to develop astaxanthin-loaded hollow mesoporous silica nanoparticles with biodegradability and biocompatibility to target liver diseases. Similarly, Daidzein released by *Lactobacilus vaginalis* β-galactosidase alleviates APAP toxicity to hepatocytes by inhibiting farnesyl diphosphate synthase-mediated ferroptosis mainly through activation of Akt-glycogen synthase kinase-3β (GSK3β)-Nrf2 signaling(Zeng et al., 2023). Pectolinarigenin ameliorates

Unedited

APAP-induced oxidative stress by upregulating Nrf2 and PPAR α signaling, as well as phase II detoxification enzymes(Li et al., 2023c). Blockout of macrophage phosphatase and a tensin homolog deletion on chromosome 10 attenuates 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 et al., 2023b). The ablation of PAPS synthase 2 protects APAP-mediated hepatotoxicity mainly through activation of 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 (RFP) 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 (MTX)-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 group, demonstrating the antioxidant property of ellagic acid(Aslan et al., 2018). *Vitis vinifera* L. (VE) and *Centella asiatica* (CE) 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 et al.(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.(Urrunaga et al., 2015) demonstrated that the expression of Nrf2 and its downstream cytoprotective gene 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 DILI through suppression of NF-κB, the NLRP3 inflammasome and IL-1β, while mice treated with the mitophagy inhibitor chloroquine suffered from DILI through 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 shRNA, which showed exacerbated liver injury(Williams et al., 2015b). Chao et al.(Chao, et al., 2018) also found that Parkin-KO 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 PINK/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.(Wang et al., 2019) observed a similar phenomenon in which PINK or Parkin single

Unedited

knockout mice showed mild defects in mitophagy and an improved survival rate. However, PINK 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. 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 et al., 2019c).

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.(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.(Ali, et al., 2021) hinted that there are marked declines in the expression of Nrf2/HO-1，cytochrome c oxidase (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.(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.(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, FOXO-3 and Sirt-1 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 than 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 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 had been shown to be helpful in DILI, is also protective to hepatic IRI through activation of PI3K/Akt/Nrf2 pathway(Li et al., 2023a). Zhang et al.(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.(Qi et al., 2023) also demonstrated that

Unedited

dimethyl fumarate-induced ferroptosis inhibition protects against hepatic IRI by upregulating the Nrf2/SLC7A11/HO-1 axis. The overexpression of fibroblast growth factor 18 exerts protection against hepatic IRI mainly through reduction of ubiquitin carboxyl-terminal hydrolase 16 (USP16), and 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 Bax/Bcl-2 signaling pathways(Morsy et al., 2022). To our knowledge, thioredoxin-interacting protein (TXNIP), p- STING and p-TBK1 are increased during hepatic IRI. Myeloid-specific deficiency of TXNIP enhances 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.(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 IR-stress. However, several studies have reported the opposite phenomenon. Nrf2 and HO-1 were elevated in a rat IRI group compared to normal or sham groups, indicating that there might be a defense mechanism against hepatic IRI(Hui et al., 2022). Not only Nrf2 but also its down target genes HO-1, NQO-1 and COX-2 were activated in IRI groups compared to a 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 mimick 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 injury through augmented mitophagy(Xu et al., 2021). Umbilical cord-derived mesenchymal stem cells (UC-MSCs) attenuate hepatic IRI through activation of AMPKα and consequent 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).

Unedited

7 Hepatocellular carcinoma

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, sometimes contributing to HCC(Aslaminabad et al., 2022). Nrf2 has long been considered a tumor suppressor. The synergistic induction of solute carrier family 7a member 11 (SLC7A11) by 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 in HepG2 cells also showed that Nrf2 expression was high after 24 h of BSS-SNP treatment due to an increase in ROS(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 N6-methyladenosine (m6A) and upregulating 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 clone capacity with the help of the higher expression of Nrf2，which may also lead to multidrug resistance(Kalantari, et al., 2023). Baird et al.(Baird and Yamamoto, 2023) put forward the theory that highly immunoedited Nrf2-activated cells in the later stage of human cancer are able to escape immune surveillance and are resistant to immune checkpoint inhibitors therapies through reducing antigen presentation by the 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 PD-L1, leading to migration, invasion, clone formation, and tumorigenicity of sorafenib-resistant hepatoma cells(Li et al., 2020a). Sun et al.(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 et al.(Liu et al., 2023c) found that Nrf2 gene rs6721961 variation was a potential marker for HBV-associated HCC. Autophagy is correlated with the pathogenesis of Nrf2 in the development of HCC. Inami et al.(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.(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 facilitates growth of HCC cells(Hallis et al., 2023). Chao et al.(Chao et al., 2022) revealed that the antitumorigenic effect of p62 in hepatocytes is achieved via activation of the 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 cyclooxygenase 2 and inducing mitophagy(Chen et al., 2019b). 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.(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, autophagy-dependent degradation of Yap and the control of HMGB1 release also play important roles in suppressing inflammation, fibrosis and hepatocarcinogenesis(Khambu et al., 2018; Lee et al., 2018b). However, a few studies have demonstrated that autophagy may support the development of tumor cells in formed tumors,

Unedited

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 blocked 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 (TIM)-4 mediates the production of H_2O_2 via the Akt1 pathway, thus upregulating mitophagy in Kupffer cells(Wu et al., 2020a). FUNDC1-glutathione peroxidase (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., 2023). Mitophagy downregulates PINK-mediated p53 and promotes the expression of NANOG, a critical transcription factor that promotes the self-renewal ability of hepatic cancer stem cells (LCSCs), to maintain the LCSC population(Liu et al., 2017a). Mitophagy helps cancer cells survive drug treatment through mitochondrial dysfunction. Wu et al. indicated that hypoxia-induced miR-210-5P suppressed the ATPase family AAA domain containing 3A (ATAD3A) and hyperactivated mitophagy in sorafenib-resistant HCC(Wu et al., 2020b). 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 et al., 2021b). Another study using data from The Cancer Genome Atlas 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 activities acted by inhibiting mitophagy through impeding the PI3K Class III/Belin-1 pathway(Liu et al., 2017b). Oroxylin, an inhibitor of cyclin-dependent kinase 9 (CDK9), blocked mitophagy through 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.

Unedited

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.

Data availability statement

Not applicable.

Acknowledgements

This study was supported by the Medical Science and Technology Project of Zhejiang Province (Grant No.2018KY566). All authors were thankful to the key laboratory of integrated oncology and intelligent medicine of Zhejiang Province for their contributions.

Authors' contributions

Q.Z., Conceptualization, writing the original draft; P.C., formal analysis, investigation; Z.C., supervision; J.J., supervision, project administration. All Authors read and approved the final manuscript.

Compliance with ethics guidelines

Conflict of Interest: Qihui Zhou, Panpan Cen, Zhi Chen and Jie Jin declare that they have no conflict of interest.
Ethics statement: This article does not contain any studies with human or animal subjects performed by any of the authors.
Consent for publication: Not applicable

Abbreviations

Nrf2/HO-1	Nuclear factor (erythroid-derived 2)-like 2/heme oxygenase-1
ROS	Reactive oxygen species
AREs	Antioxidant response elements
GSH	Glutathione
PPAR-γ	Peroxisome proliferator-activated receptor-γ
PGC-1α	Peroxisome proliferator-activated receptor-γ (PPAR-γ) coactivator-1alpha
NEAAs	Non-essential amino acids
IL-1β	Interlukin-1β
Tregs	Regulatory T cells
IFN-γ	Interferon-γ
CCR2+	Chemokine C-C-motif receptor 2
Atg	Autophagy-related genes
OXPHOS	Oxidative phosphorylation
LC3	Light chain 3
LIR	Light chain 3 (LC3) interacting region
PINK1	Phosphatase and tensin homolog induced kinase 1
OMM	Outer mitochondrial membrane
BNIP3	BCL2 and adenovirus E1B 19-kDa-interacting protein 3
FUNDC1	FUN14 domain-containing protein 1
BCL2L13	B-cell lymphoma 2-like 13
MAFLD	Metabolic dysfunction-associated fatty liver disease
NAFLD	Nonalcoholic fatty liver disease
MASLD	Metabolic dysfunction-associated steatotic liver disease
MASH	Metabolic dysfunction-associated steatohepatitis
NASH	Nonalcoholic steatosis hepatitis
HFD	High-fat diet
SREBP-1	Sterol regulatory element binding protein-1
RIP3	Receptor-interacting kinase-3
NF-κB	Nuclear factor-κB
KO	Knockout
iSGLT2	Sodium-glucose cotransporter inhibitors
ZDF	Zucker diabetic fatty
MCD	Methionine- and choline-deficient
Tyr	Tyrosine
Phe	Phenylalanine
SiNPs	Silica nanoparticles
TGF-β1	Transforming growth factor-β
ALCAT1	Acyl-CoA: lysocardiolipin acyltransferase-1
Mst1	Macrophage stimulating 1
BNIP3	BCL2/adenovirus E1B 19 kd-interacting protein
MORF4L1	Mortality Factor 4-like protein 1
TUFM	Tu translation elongation factor
AMPK	AMP-activated protein kinase
GLP-1	Glucagon-like peptide-1
TFEB	Transcription factor EB
Trx	Thioredoxin
PTEN	Phosphatase and tensin homolog
HBV	Hepatitis B virus
HCV	Hepatitis C virus

Unedited

pgRNA Pregenomic RNA
HBsAg Hepatitis B surface antigen
HBeAg Hepatitis B e antigen
ccc DNA Covalently closed circular DNA
HBx HBV X protein
HDV Hepatitis delta virus
ER Endoplasmic reticulum
UPR Unfolded protein response
HCC Hepatocellular carcinoma
CHB Chronic hepatitis B
ENDOG Endonuclease G
ER Endoplasmic reticulum
PI3K Phosphatidylinositol 3-kinase
DFCP1 Double FYVE-containing protein 1
ApoE Apolipoprotein E
ALD Alcoholic liver disease
SOD Superoxide dismutase
NQO1 Q*uinone oxidoreductase 1*
HIF-1 Hypoxia-inducible factor-1
NAC N-acetyl cysteine
mtDNA Mitochondrial DNA
NR4A1 Nuclear receptor subfamily 4 Group A member 1
DNA-PKcs DNA-dependent protein kinase catalytic subunit
UQCRC2 Ubiquinol-cytochrome c reductase core protein 2
NFE2L2/NRF2 Nnuclear factor, erythroid 2 like 2
DILI Drug-Induced Liver Injury
APAP Acetaminophen
JNK Jun N-terminal kinases
GSK3β Glycogen synthase kinase-3β
NICD Notch intracellular domain
STING Stimulator of interferon genes
TBK1 TANK-binding kinase 1
TUDCA Tauroursodeoxycholic acid
RFP Rifampicin
BSEP Bile salt export pump
MDR1 Multidrug resistance protein 1
MTX Methotrexate
pCREB Phosphorylated cAMP response element-binding protein
mTORC1 Mechanistic target of rapamycin complex 1
CCL_4 Carbon tetrachloride
ASMase Acid sphingomyelinase
CO Carbon monoxide
IRI Ischemia–reperfusion injury
COX-4 Cytochrome c oxidase 4
USP16 Ubiquitin carboxyl-terminal hydrolase 16
TXNIP Thioredoxin-interacting protein
UC-MSCs Umbilical cord-derived mesenchymal stem cells
HCC Hepatocellular carcinoma
SLC7A11 Solute carrier family 7a member 11
m6A N6-methyladenosine
DDX5 DEAD box protein 5
PTG Protein targeting to glycogen
TIM T-cell immunoglobulin domain and mucin domain
GPx4 Glutathione peroxidase
LCSCs Liver cancer stem cells
ATAD3A ATPase family AAA domain containing 3A

Unedited

PINT87aa	P53-induced transcript 87aa
CDK9	Cyclin-dependent kinase 9
STOML2	Stomatin-like protein 2

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-gamma/ nrf-2 crosstalk in mice. *Int Immunopharmacol*, 99:107963. https://doi.org/10.1016/j.intimp.2021.107963

Abulikemu A, Zhao X, Xu H, 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 VV, 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 p38-mapk/nf-kappab-p65/tnf-alpha 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 in 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-kb, 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, Taguchi K, Zhang A, 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

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

Baulies A, Ribas V, Nunez 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 Y, Liu S, Qin X, et al., 2023. Fundc1 interacts with gpx4 to govern hepatic ferroptosis and fibrotic injury through a mitophagy-dependent manner. *J Adv Res*, https://doi.org/10.1016/j.jare.2023.02.012

Cai C, Ma H, 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(1):3648. https://doi.org/10.1038/s41467-023-39412-6

Cai X, Hua S, Deng J, et al., 2022. Astaxanthin activated the nrf2/ho-1 pathway to enhance autophagy and inhibit ferroptosis,

Unedited

ameliorating acetaminophen-induced liver injury. *ACS Appl Mater Interfaces*, 14(38):42887-42903. https://doi.org/10.1021/acsami.2c10506

Chao T, 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 X, 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 X, Wang S, 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 J, Yang S, Qiao Z, 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 B, 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 S, Huang Y, Su H, 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, 2019a. 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., 2019b. 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 Y, Park HJ, Park J, et al., 2019c. 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):e1700903. 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) https://doi.org/10.3390/cancers12030655

Chenxu G, Minxuan X, Yuting Q, 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

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 JJ, 2021. Autophagy in hcv replication and protein trafficking. *Int J Mol Sci*, 22(3) https://doi.org/10.3390/ijms22031089

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) https://doi.org/10.3390/ijms23084429

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

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 X, Luo K, 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 S, Zhang Z, et al., 2017. Early stage functions of mitochondrial autophagy and oxidative stress in

Unedited

acetaminophen-induced liver injury. *J Cell Biochem*, 118(10):3130-3141. https://doi.org/10.1002/jcb.25788

Gao Z, Yi W, Tang J, 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 J, Li G, Chen Z, 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 C, 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 L, Hui H, 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 W, 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-kappab-p65 signaling pathway. *Environ Sci Pollut Res Int*, 28(47):67863-67879. https://doi.org/10.1007/s11356-021-15184-8

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

He F, Zhang P, Liu J, 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

Holmstrom 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-kappab p65 pathway. *Evid Based Complement Alternat Med*, 2017:7953850. https://doi.org/10.1155/2017/7953850

Hui B, Shu Y, Yang D, 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) 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) 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(Pt B):199-204. https://doi.org/10.1016/j.freeradbiomed.2015.06.014

Jiang Z, 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):G21-29. 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(1):318. https://doi.org/10.1186/s12964-023-01351-6

Khambu B, Huda N, Chen X, 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

Unedited

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) https://doi.org/10.3390/ijms231810665

Kim JY, Ou JJ, 2018. Regulation of apolipoprotein e trafficking by hepatitis c virus-induced autophagy. *J Virol*, 92(14) 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-kappab 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 e334. https://doi.org/10.1016/j.cmet.2019.11.012

Lee JC, Lin CK, Tseng CK, et al., 2018a. Discovery of 3-amino-2-hydroxypropoxyisoflavone derivatives as potential anti-hcv agents. *Molecules*, 23(11) 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., 2018b. Autophagy is a gatekeeper of hepatic differentiation and carcinogenesis by controlling the degradation of yap. *Nat Commun*, 9(1):4962. https://doi.org/10.1038/s41467-018-07338-z

Lei Y, Xu X, Liu H, 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., 2020a. 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 Y, Ding M, et al., 2023a. 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 C, Yu Y, et al., 2023b. 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(1):154. https://doi.org/10.1186/s13578-023-01095-3

Li Q, Zhang W, Cheng N, et al., 2023c. 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 R, Xin T, Li D, 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 X, Shi Z, Zhu Y, et al., 2020b. 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 C, Wang X, 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 Z, Wu F, Lin S, 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 L, et al., 2022. A mitophagy-related gene signature for subtype identification and prognosis prediction of hepatocellular carcinoma. *Int J Mol Sci*, 23(20) https://doi.org/10.3390/ijms232012123

Liu K, Lee J, Kim JY, et al., 2017a. Mitophagy controls the activities of tumor suppressor p53 to regulate hepatic cancer stem cells. *Mol Cell*, 68(2):281-292 e285. https://doi.org/10.1016/j.molcel.2017.09.022

Liu P, Anandhan A, Chen J, et al., 2023a. 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., 2023b. Baicalin attenuated metabolic dysfunction-associated fatty liver disease by suppressing

Unedited

oxidative stress and inflammation via the p62-keap1-nrf2 signalling pathway in db/db mice. *Phytother Res*, https://doi.org/10.1002/ptr.8010

Liu Y, Wu Q, Zhang F, et al., 2023c. Antioxidants-related nuclear factor erythroid 2-related factor 2 gene variants associated with hbv-related liver disease. *Cancer Cell Int*, 23(1):72. https://doi.org/10.1186/s12935-023-02918-6

Liu Z, Ren B, Wang Y, et al., 2017b. 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 C, Xu W, 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 X, Xuan W, Li J, 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 X, Mckeen T, Zhang J, et al., 2020. Role and mechanisms of mitophagy in liver diseases. *Cells*, 9(4) 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 L, 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 Y, Wang Z, 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-kappab 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(1):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-kappab signaling pathways. *Antioxidants (Basel)*, 11(9) 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) 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 X, 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 Y, Wang S, et al., 2018. Silybin alleviates hepatic steatosis and fibrosis in nash mice by inhibiting oxidative stress and involvement with the nf-kappab pathway. *Dig Dis Sci*, 63(12):3398-3408. https://doi.org/10.1007/s10620-018-5268-0

Pan Z, Guo J, Tang K, 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

Unedited

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 D, Chen P, Bao H, 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 Q, Zhang Z, 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 X, 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

Raj RK, D E, S R, 2020. Beta-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

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 M, 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 S, Shen Z, Zhang C, 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 G, Zuo J, 2018. Caffeic acid inhibits hcv replication via induction of ifnalpha 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 C, 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 Y, 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 U S A*, 107(9):4383-4388. https://doi.org/10.1073/pnas.0911373107

Sir D, Kuo CF, Tian Y, 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) https://doi.org/10.3390/antiox12040974

Solano-Urrusquieta A, Morales-Gonzalez 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 J, Zhao X, Bo J, 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, Rodriguez 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) 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) https://doi.org/10.1128/MCB.00063-17

Unedited

Taguchi K, Fujikawa N, Komatsu M, et al., 2012. Keap1 degradation by autophagy for the maintenance of redox homeostasis. *Proc Natl Acad Sci U S A*, 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-alpha/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 K, Chen Q, Liu Y, 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 X, Zhao Y, 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, Skrtic A, Sobocan 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 G, Chen Y, Chen X, et al., 2023. Fgf18 alleviates hepatic ischemia-reperfusion injury via the usp16-mediated keap1/nrf2 signaling pathway in male mice. *Nat Commun*, 14(1):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 C, Wang Y, 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(6)a demethylation of fosl1 mrna protects hepatoma cells against necrosis under glucose deprivation. *Cell Death Differ*, https://doi.org/10.1038/s41418-024-01308-3

Wang H, Ni HM, Chao X, 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 X, 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 S, Tao J, Chen H, et al., 2021a. Ablation of akt2 and ampkalpha2 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 J, Zhang X, 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 X, Wei Z, Cheng B, et al., 2022a. 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 X, Wei Z, Lan T, et al., 2022b. 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 Y, Wang Z, Sun J, et al., 2021b. 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, Ding Y, et al., 2015a. 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):G324-340. https://doi.org/10.1152/ajpgi.00108.2015

Williams JA, Ni HM, Haynes A, et al., 2015b. 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.

Unedited

https://doi.org/10.1074/jbc.M114.602284
Wu H, Chen G, Wang J, et al., 2020a. Tim-4 interference in kupffer cells against ccl4-induced liver fibrosis by mediating akt1/mitophagy signalling pathway. *Cell Prolif*, 53(1):e12731. https://doi.org/10.1111/cpr.12731
Wu H, Wang T, Liu Y, et al., 2020b. Mitophagy promotes sorafenib resistance through hypoxia-inducible atad3a dependent axis. *J Exp Clin Cancer Res*, 39(1):274. https://doi.org/10.1186/s13046-020-01768-8
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 X, Fu Y, 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 W, Li J, 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 W, Jiang Z, 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 H, 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 P, Xi Y, Wang P, 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 e585. https://doi.org/10.1016/j.cmet.2018.06.014
Yang L, Li P, Fu S, 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 M, Xia L, Song J, et al., 2023a. Puerarin ameliorates metabolic dysfunction-associated fatty liver disease by inhibiting ferroptosis and inflammation. *Lipids Health Dis*, 22(1):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 R, 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) https://doi.org/10.1042/BSR20150090
Yang T, Qu X, Zhao J, et al., 2023b. Macrophage pten controls sting-induced inflammation and necroptosis through nicd/nrf2 signaling in apap-induced liver injury. *Cell Commun Signal*, 21(1):160. https://doi.org/10.1186/s12964-023-01175-4
Yao J, Wang J, 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 P, Liu Y, 2022. Terpenoids: Natural compounds for non-alcoholic fatty liver disease (nafld) therapy. *Molecules*, 28(1) 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-1alpha 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 L, Liu Y, Jin Y, 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 J, Hu M, 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 N, 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 Y, Wu R, Wang F, et al., 2023. Liberation of daidzein by gut microbial beta-galactosidase suppresses acetaminophen-induced hepatotoxicity in mice. *Cell Host Microbe*, 31(5):766-780 e767. https://doi.org/10.1016/j.chom.2023.04.002
Zhan Y, Xu D, Tian Y, 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

Unedited

Zhang H, Zhang Y, Zhu X, 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 W, Chen L, 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 X, Wang M, Teng S, 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 Y, Wei H, Wang M, 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 YK, 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., 2018a. 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 Q, Hua W, et al., 2018b. 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 T, et al., 2020. Mscs ameliorate hepatocellular apoptosis mediated by pink1-dependent mitophagy in liver ischemia/reperfusion injury through ampkalpha activation. *Cell Death Dis*, 11(4):256. https://doi.org/10.1038/s41419-020-2424-1

Zheng Y, 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(1):16. https://doi.org/10.1186/s13045-020-01029-3

Zhong W, Rao Z, 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 P, 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 Q, 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 Z, 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 Q, Zhuo H, Yang L, 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) https://doi.org/10.3390/molecules27185839

Zhu Z, 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 Z, 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

Unedited