

## Nuclear factor erythroid 2-related factor 2-mediated signaling and metabolic associated fatty liver disease

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### Abstract

Oxidative stress is a key driver in the development and progression of several diseases, including metabolic associated fatty liver disease (MAFLD). This condition includes a wide spectrum of pathological injuries, extending from simple steatosis to inflammation, fibrosis, cirrhosis, and hepatocellular carcinoma. Excessive buildup of lipids in the liver is strictly related to oxidative stress in MAFLD, progressing to liver fibrosis and cirrhosis. The nuclear factor erythroid 2-related factor 2 (NRF2) is a master regulator of redox homeostasis. NRF2 plays an important role for cellular protection by inducing the expression of genes related to antioxidant, anti-inflammatory, and cytoprotective response. Consistent evidence demonstrates that NRF2 is involved in every step of MAFLD development, from simple steatosis to inflammation, advanced fibrosis, and initiation/progression of hepatocellular carcinoma. NRF2 activators regulate lipid metabolism and oxidative stress alleviating the fatty liver disease by inducing the expression of cytoprotective genes. Thus, modulating NRF2 activation is crucial not only in understanding specific mechanisms underlying MAFLD progression but also to characterize effective therapeutic strategies. This review outlined the current knowledge on the effects of NRF2 pathway, modulators, and mechanisms involved in the therapeutic implications of liver steatosis, inflammation, and fibrosis in MAFLD.

**Key Words:** Nonalcoholic fatty liver disease; Metabolic-associated fatty liver disease; Nuclear factor erythroid 2-related factor 2; Oxidative stress; Antioxidants; Liver injury

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**Core Tip:** This updated literature review contributes to the role of nuclear factor erythroid 2-related factor 2 in combating inflammation, oxidative stress, steatosis, and fibrosis in metabolic associated fatty liver disease. There are several reviews that elucidated the advantages of nuclear factor erythroid 2-related factor 2 in human diseases, but this is the first review reporting the broad range of nuclear factor erythroid 2-related factor 2 modulators and their therapeutic implications in metabolic associated fatty liver disease.

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## INTRODUCTION

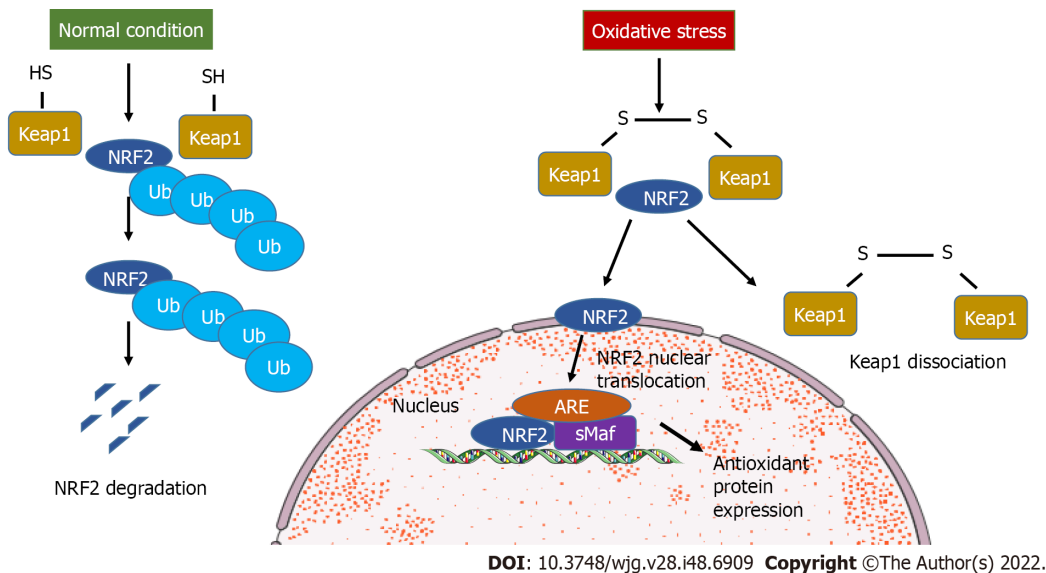
Nonalcoholic fatty liver disease is the most frequent chronic liver disease, affecting about 25% of the global population. Due to the reappraisal in its nomenclature, a group of experts changed the terminology from nonalcoholic fatty liver disease to metabolic-associated fatty liver disease (MAFLD), strengthening the link of this disease to metabolic alterations[1]. MAFLD is defined as a condition where hepatic fat accumulation exceeds 5% of the liver weight without alcohol consumption (< 30 g per day). It covers a wide spectrum of pathological conditions, extending from simple steatosis (deposit of fat in hepatocytes) to nonalcoholic steatohepatitis (characterized by the presence of 5% hepatic steatosis and inflammation with hepatocellular damage, with or without fibrosis), cirrhosis, and ultimately leading to hepatocellular carcinoma[2]. MAFLD is emerging with the prevalence of type 2 diabetes mellitus, obesity, and metabolic syndrome[3]. Of note, patients with MAFLD, and particularly with nonalcoholic steatohepatitis, exhibit an increased liver-related mortality rate and higher incidence of cardiovascular-related morbidity and mortality[2].

MAFLD is the hepatic expression of metabolic syndrome, but its pathogenesis is still not clearly known. Insulin resistance (IR) seems to play a key role in the initiation and progression of the disease from simple fatty liver to advanced forms[4]. MAFLD pathogenesis is complex and multifactorial. The first theory was based on a two-hit hypothesis, where the first hit is liver steatosis, which is due to increased hepatic lipogenesis and reduced free fatty acid degradation caused by IR. This alteration is followed by the second hit of oxidative stress, which induces hepatocyte inflammation and cell death[5, 6]. However, this simplistic theory has been recently replaced by the multiple hit hypothesis, where many factors including systemic and hepatic IR, intestinal microbiota, genetic predisposition, and oxidative stress act simultaneously resulting in a cascade of detrimental effects such as hepatic inflammation, free radical production from gut and adipose tissue, mitochondrial dysfunction, endoplasmic reticulum (ER) stress, and hepatocyte apoptosis[7]. Among all the contributing factors of MAFLD, oxidative stress plays a major role. Oxidative stress promotes inflammation by activating Kupffer cells and stimulating the release of proinflammatory cytokines, directly leading to lipid, protein, and DNA/RNA damage. Nuclear factor erythroid 2-related factor 2 (NRF2) is the most important transcription factor in preserving redox homeostasis in the cell and counteracting oxidative or electrophilic stress by producing antioxidant and cytoprotective enzymes such as heme oxygenase 1 (HO-1), NAD(P)H quinone oxidoreductase 1 (NQO1), and those involved in glutathione (GSH) metabolism[8].

Thus, due to its antioxidative and detoxicant properties, it is currently accepted that NRF2 plays a pivotal role and has been recognized as a potential target to prevent the pathological spectrum of MAFLD. Even though the beneficial role of NRF2 in human diseases has been the topic of several recent reviews, the broad range of NRF2 modulators and their therapeutic implications in MAFLD were not completely summarized in recent literature. In this review, we described the current knowledge on the effects of NRF2-dependent mechanisms involved in the therapeutic implications of liver steatosis, inflammation, and fibrosis in MAFLD.

## NRF2 PATHWAY

NRF2 belongs to the basic leucine zipper transcription factors in the Cap “n” Collar subfamily including seven functional domains, Nrf2-ECH homology (Neh) 1 to Neh7[9]. Neh2 is important for interaction between NRF2 and Kelch-like ECH-associated protein 1 (Keap1), a negative modulator of NRF2[10]. Keap1 is a substrate for Cullin based E3 ubiquitin ligase. During homeostatic conditions, Keap1 targets NRF2 that is localized in cytoplasm, causing its polyubiquitination and degradation. The binding and regulation of NRF2 by Keap1 has been defined as the “hinge and latch model”[11]. During oxidative stress, hyperactive cysteine residues of Keap1 undergo thiol modification and NRF2 is dissociated from Keap1, preventing ubiquitination and proteasomal degradation (Figure 1). The newly generated NRF2



**Figure 1 Kelch-like ECH-associated protein 1-dependent nuclear factor-erythroid 2-related factor 2 signaling.** During oxidative stress, nuclear factor-erythroid 2-related factor 2 (NRF2) detaches from kelch-like ECH-associated protein 1 (Keap1) and translocates to the nucleus to bind the target genes. In normal conditions, NRF2 is ubiquitinated and undergoes degradation. ARE: Antioxidant responsive element; sMaf: Small musculoaponeurotic fibrosarcoma oncogene homologue; Ub: Ubiquitin.

escaped from Keap1 control translocates to the nucleus and heterodimerizes with the Maf proteins, promoting the expression of antioxidant response element genes like *HO-1*, superoxide dismutase (*SOD*), catalase, glutathione-S-transferase, glutathione reductase, glutathione peroxidase (*GSH-Px*), *NQO1*, etc[12].

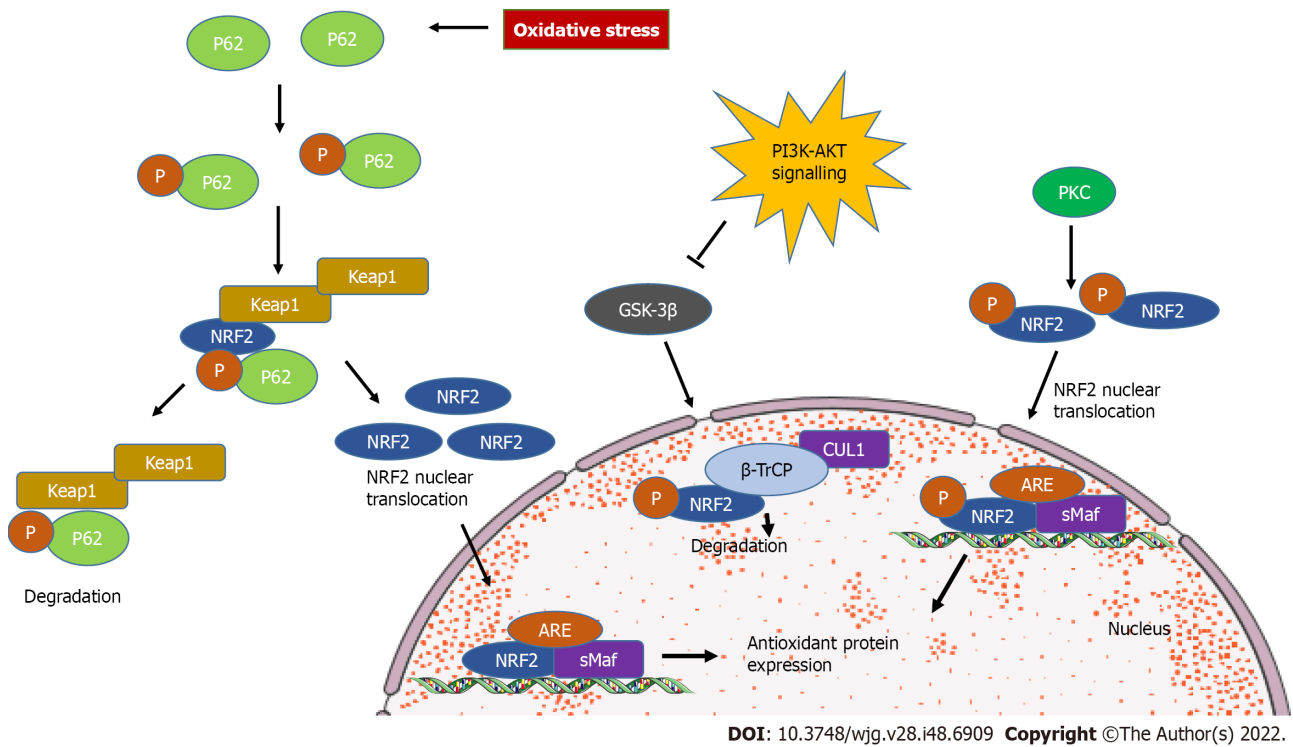
Of note, emerging evidence revealed Keap1-independent novel mechanisms of NRF2 regulation. The phosphatidylinositol 3'-kinase/protein kinase B pathway is protective against oxidative stress and is able to activate NRF2 signaling[13]. Phosphatidylinositol 3'-kinase-protein kinase B-NRF2 signaling pathway involves the glycogen synthase kinase-3 $\beta$  as a key mediator. Glycogen synthase kinase 3 $\beta$  can phosphorylate the NRF2 domain Neh6, containing serine residues that can be recognized by the  $\beta$ -transducin repeats-containing protein.  $\beta$ -transducin repeats-containing protein is a substrate receptor for ubiquitin ligase complex, which targets NRF2 for ubiquitination and proteasomal degradation[14, 15]. During autophagy, NRF2 is stabilized by the binding of p62 (autophagy substrate) to Keap1 at the NRF2 binding site, resulting in the transcriptional activation of NRF2-target genes[16,17]. In addition, oxidative stress-induced protein kinase C phosphorylates Neh2 at serine and threonine residue on Ser40, dissociating the Keap1 homodimer and transferring NRF2 to the nucleus, thus binding to the antioxidant response element-mediated cytoprotective genes[18] (Figure 2).

## NRF2 IN THE PATHOGENESIS OF MAFLD

MAFLD is the most widespread chronic liver condition worldwide, potentially leading to end stage disease, which requires liver transplantation[19,20]. MAFLD is a lipotoxic disease characterized by both structural and functional mitochondria abnormalities and oxidative stress. Impairment in mitochondrial electron transport chain causes excessive production of reactive oxygen and nitrogen species (ROS and RNS)[21]. ROS and RNS play a crucial role in cellular signaling, proliferation and differentiation, metabolism, and immune defense mechanisms. Besides mitochondria, ROS and RNS are continuously produced by the ER and peroxisomes as byproducts during their normal physiological processes. Oxidative stress is described as the imbalance between production of ROS/RNS and antioxidant systems[22]. Oxidative stress is intrinsically linked to the pathogenesis of MAFLD, and NRF2 has been found to be a key regulator to protect against the hepatocellular injury. Since MAFLD development and progression are characterized by alterations of redox balance, NRF2 is involved in every stage of disease, from simple steatosis to inflammation, advanced fibrosis, and initiation/progression of hepatocellular carcinoma[8].

### NRF2 and liver steatosis

Accumulation of lipids in hepatocytes is the first step characterizing MAFLD development. This process is the result of increased fatty acid uptake/synthesis and decreased fatty acid oxidation/removal[23]. Fatty acid oxidation in peroxisomes produces  $H_2O_2$ , which in turn decreases the expression of enzymes



**Figure 2 Kelch-like ECH-associated protein 1-independent nuclear factor-erythroid 2 signaling.** During oxidative stress, selective autophagy substrate p62 competes with nuclear factor-erythroid 2 (NRF2) to bind with kelch-like ECH-associated protein 1 (Keap1). As a consequence, NRF2 dissociates from Keap1 and translocates to the nucleus to induce target genes. Glycogen synthase kinase 3β (GSK-3β) phosphorylates the NRF2 subunit Nrf-ECH homology (Neh) 6, leading to degradation by β-transducin repeats containing protein (β-TrCP). Phosphatidylinositol 3'-kinase-protein kinase B (AKT) signaling could inhibit GSK-3β. Protein kinase C phosphorylates Ser40 in Neh2, inducing NRF2 translocation to the nucleus. ARE: Antioxidant responsive element; sMaf: Small musculoaponeurotic fibrosarcoma oncogene homologue.

involved in fatty acid oxidation as carnitine palmitoyltransferase 1A and acyl-CoA oxidase through their regulatory factor peroxisome proliferator activated receptor alpha. Besides, H<sub>2</sub>O<sub>2</sub> promotes lipid accumulation by upregulating the expression of sterol regulatory element-binding protein-1c (SREBP-1c), which further activates fatty acid synthase, and stearyl coenzyme-A desaturase 1, contributing to MAFLD pathogenesis[24]. In addition, ER-stress activates SREBP-1c and increases the expression of hepatic very-low density lipoprotein receptor, leading to deposition of triglycerides (TG)[12,24].

NRF2 is a key player in maintaining cellular homeostasis, suppressing MAFLD promotion and progression. A microarray analysis of mouse hepatic gene expression revealed that pharmacologic and genetic activation of *NRF2* suppresses key enzymes involved in lipid synthesis and reduces hepatic lipid storage. *NRF2*<sup>-/-</sup> mice fed a high-fat diet (HFD) are more prone to develop steatosis and oxidative stress than wild-type mice[25]. Consistent to this, *NRF2*-knockout mice fed a methionine- and choline-deficient (MCD) diet developed a severe form of micro- and macrovesicular steatosis and neutrophil recruitment compared to wild-type mice[26-28]. Studies on hepatic protein expression in *NRF2*-null and wild-type mice found two major groups of *NRF2*-modulated proteins. One group of proteins in *NRF2* wild-type animals was implicated in phase II drug metabolism and antioxidant defense, while the other group of proteins in *NRF2*-null animals was involved in lipid and fatty acid synthesis and metabolism [29]. Another study in *NRF2*-null 8-wk old mice revealed a higher expression of SREBP-1c and fatty acid synthase than wild-type mice[30]. Nonetheless, *NRF2* has little effect on hepatic fatty acid metabolism in 12-25 wk old mice[31,32].

In addition, flavonoid glycoside scutellarin ameliorates MAFLD pathogenesis by reducing blood lipid levels and enhances antioxidant capacity by activating peroxisome proliferator-activated receptor gamma (PPAR-γ) and its cofactor-1α as well as *NRF2*-dependent enzymes HO-1 and glutathione-S-transferase. Moreover, scutellarin suppresses nuclear factor κ B (NF-κB) and Keap1 mitigating MAFLD [33]. Another study revealed that scutellarin contains breviscapine as its active component, possibly exerting its antioxidant effects through phosphatidylinositol 3'-kinase/protein kinase B activation and subsequent enhancement of *NRF2* nuclear translocation, increasing the expression of HO-1 and NQO1. Thus, breviscapine could be used in MAFLD and hyperlipidemia due to its potential therapeutic effects [34].

In addition, the food-derived compound apigenin is a modulator of PPAR-γ, which attenuates the *NRF2*-associated antioxidative response and hepatocyte lipid metabolism in MAFLD[35]. The specific deletion of *NRF2* in mice diminished the signs of MAFLD induced by HFD, decreasing the accumulation of TGs. Hepatic *NRF2* deficiency dampens the expression of PPAR-γ, suggesting that the *NRF2*-

dependent expression of PPAR- $\gamma$  is critical in initiation and progression of MAFLD[36].

Liver X receptors are a family of nuclear receptors implicated in the modulation of lipid homeostasis. Directly or *via* SREBP-1c, liver X receptor  $\alpha$  triggers the expression of lipogenic genes involved in the uptake and synthesis of fatty acids, TGs, cholesterol, and phospholipids. Treatment with the NRF2 activator sulforaphane suppresses T0901317-induced lipogenesis, promoting deacetylation of farnesoid X receptor (FXR) by competitive binding of p300, a protein necessary for the acetylation of FXR. The FXRE chromatin immunoprecipitation assay confirmed that NRF2 may complex with p300 and, as a result, dissociate from the FXR complex[37-39]. Moreover, NRF2 activator inhibits SREBP-1c and lipogenic genes by promoting deacetylation of FXR and inducing small heterodimer partner, which accounts for the repression of liver X receptor  $\alpha$ -dependent gene transcription, protecting the liver from excessive fat accumulation[40].

### **NRF2 and liver inflammation**

NRF2 is further involved in the regulation of pro- and anti-inflammatory mediators. NRF2 is known for its anti-inflammatory effects as it inhibits the expression of proinflammatory cytokines like interleukin-6 (IL-6), tumor necrosis factor, and inducible nitric oxide synthase. Moreover, NRF2-dependent antioxidant genes, such as *HO-1*, *NQO1*, and glutamate cysteine ligase catalytic and modifier subunits, inhibit the transcription of proinflammatory mediators by blocking NF- $\kappa$ B activation[41-43]. Of note, NRF2 also triggers the NLR family pyrin domain containing 3 inflammasome, which cleaves caspase-1 and initiates the processing of pro-IL-1 $\beta$  to mature IL-1 $\beta$ [44]. NLR family pyrin domain containing 3-dependent production of proinflammatory response can be inhibited by activation of NRF2 through dimethyl fumarate in alcoholic liver disease[45], and 4-acetyltroquinonol B in mice fed with a methionine- and choline-deficient diet[46] inducing the expression of *NQO1*, which inhibits the ROS/RNS-dependent priming.

NRF2-KO mice fed the methionine- and choline-deficient diet lose the antioxidant and detoxification enzymes and show an increase in steatosis, inflammation, oxidative stress, lipid peroxidation, and fibrinogenesis[26,28]. In line with these results, feeding the NRF2-KO mice with the HFD yielded significantly greater amounts of lipids and inflammation compared to wild-type mice. NRF2-KO mice fed a diet containing 4% soyabean oil and 16% lard for 12 wk exhibited massive lipid accumulation, inflammation, oxidative stress, and iron accumulation when compared to their wild-type counterparts [47]. NRF2-KO mice fed a diet containing 45 kcal% fat (0.02% cholesterol) for 24 wk displayed a higher MAFLD activity score compared to wild-type animals. In HFD-fed NRF2-KO mice, livers scored higher for steatosis, ballooning, inflammation, and fibrosis when compared to *Nrf2*<sup>+/+</sup> mice. The biochemical characterization studies of such mice revealed higher expression of sterol regulatory element binding transcription factor 1 and 2 and carbohydrate response element binding protein also known as MLX-interacting protein-like in HFD-fed NRF2-KO mice, suggesting exaggerated lipogenic transcription[48]. In another study, NRF2-KO mice fed a high-fat plus 30% fructose in drinking water exhibited a higher MAFLD score than wildtype. Moreover, these NRF2-KO mice overexpress lipogenic transcription factor sterol regulatory element binding transcription factor 1, fatty acid synthase, stearoyl coenzyme-A desaturase 1, and CD36 and exhibited higher proinflammatory factors as NF- $\kappa$ B p65 and p50 subunits [49].

In another investigation, NRF2-KO mice fed a chow diet were subjected to scanty inflammation with minimal increases in *IL-1 $\beta$* , *Cox2*, and *Nos2* mRNA[26,28]. This is due to the compromised expression of zonula occludens-1 and claudin-1, which are responsible for the translocation of lipopolysaccharides from the gut microbiota to the liver through the portal vein. In addition, the phagocytic ability of Kupffer cells is diminished in NRF2-KO due to lower expression of the macrophage receptor with collagenous structure that restricts TLR4 signaling and boosts the inflammatory response on exposure to lipopolysaccharide[50].

### **NRF2 and liver fibrosis**

Liver fibrosis is a reversible wound healing response and degenerative condition caused by extensive deposition of extracellular matrix proteins like collagen fibrils[51]. Mechanisms underlying liver fibrosis include the activation of both hepatic stellate cells and Kupffer cells, resulting in functional and biological alterations[52]. Oxidative stress is a serious process involved in liver damage, and the activation of the Keap1/NRF2 pathway plays a protective role in liver fibrosis[12]. NRF2 activation triggers the reverse IR and attenuates liver fibrosis by inhibiting hepatic steatosis. These noticeable effects during NRF2 activation are due to the disruption of JAK2/STAT3 signaling and higher expression of suppressor of cytokine signaling 3[53]. Moreover, administration of fibroblast growth factor 1 variants carrying substitutions of heparin-binding sites in 9-mo-old mice inhibited activity and expression of lipogenic genes, improving both steatohepatitis and fibrosis[54].

CCl<sub>4</sub>-induced hepatic fibrosis is accompanied by elevated serum transaminases, alkaline phosphatase, and bilirubin, decreased albumin, and increased proinflammatory cytokines. In addition, CCl<sub>4</sub>-intoxicated rats display an increase in NF- $\kappa$ B, p65, malondialdehyde and a decrease in antioxidants. Bone marrow-derived mesenchymal stem cells show favorable effects in ameliorating the hepatic effects of CCl<sub>4</sub> through NRF2/HO-1 signaling, suppressing liver fibrosis, inflammation, and oxidative stress [55].

A major bioactive extract from the plant *Schisandra chinensis*, known as Schisandrin B, exerts anti-inflammatory, anti-tumor, antioxidative, and hepatoprotective properties. Schisandrin B effectively improves liver function and decreases collagen deposition in the CCl<sub>4</sub>-induced liver fibrosis in rats through the modulation of NRF2-antioxidant response element and transforming growth factor- $\beta$ /Smad signaling pathways[56]. Tanshinol, a water-soluble compound isolated from *Salvia miltiorrhiza Bunge*, is known to exert a variety of biological effects, including anti-fibrotic effects. Rats with CCl<sub>4</sub>-induced liver fibrosis treated intraperitoneally with tanshinol show lower serum levels of aspartate aminotransferase, alanine aminotransferase, and total bilirubin, as well as circulating hyaluronic acid, laminin, type IV collagen, and procollagen III peptide as compared to controls. Tanshinol is also able to suppress the expression of inflammatory cytokines such as transforming growth factor- $\beta$ , tumor necrosis factor, Cox2, IL-1 $\beta$ , and IL-6 through regulation of the NF- $\kappa$ B pathway. In addition, tanshinol treatment is able to regulate the NRF2/HO-1 signaling pathway increasing SOD and GSH-Px and decreasing malondialdehyde levels. In this regard, tanshinol exerts protective effects on CCl<sub>4</sub>-induced liver fibrosis by activating the NRF2 pathway[57].

Asiatic acid (AA), a bioactive compound extracted from *Centella asiatica*, is known to have anti-inflammatory, antioxidative, and hepatoprotective properties[19-22]. Fan *et al*[34] showed that treatment with AA in the CCl<sub>4</sub>-induced liver fibrosis dramatically ameliorates oxidative stress, inflammation, and fibrosis in rats. The nuclear NRF2 levels were increased after AA treatment, and the NRF2-dependent proteins like HO-1, NQO-1, and Glutamate cysteine ligase catalytic subunit were significantly increased to counteract oxidative stress. Furthermore, AA inhibited the NF- $\kappa$ B/I $\kappa$ B $\alpha$  and JAK1/STAT3 signaling pathway to suppress the activation of hepatic stellate cells and the production of inflammatory markers, suggesting that AA could be used for the treatment of liver fibrosis[58]. Another water soluble compound, salvianolic acid A, extracted from a traditional Chinese herb *Radix Salvia miltiorrhiza*, was found to have anti-fibrotic effects. salvianolic acid A is able to modulate the NRF2/HO-1, NF- $\kappa$ B/I $\kappa$ B $\alpha$ , p38 MAPK, and JAK1/STAT3 signaling pathways, and to ameliorate the CCl<sub>4</sub>-induced liver fibrosis, improve morphology and attenuate collagen deposition in the fibrotic liver. Besides, salvianolic acid A is able to increase the levels of SOD and GSH-Px and decrease the malondialdehyde levels, indicating the effectiveness in preventing liver fibrosis by inhibiting inflammation and oxidative stress[59].

Pharmacological stimulation of NRF2 by acetylenic tricyclic bis (cyano enone) TBE-31 reverses IR in wild-type mice, decreases liver steatosis by increasing hepatic fatty acid oxidation and reducing ER stress, and lessens markers of oxidative stress, apoptosis, and fibrosis. Of note, histology studies showed that TBE-31 decreases the fibrosis score and MAFLD activity score[59]. In another study, NRF2 activator NK-252 (1-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)-3-(pyridin-2-ylmethyl)urea) significantly reduced markers of fibrosis like COL1A1, TIMP-1, and transforming growth factor- $\beta$  in rats, suggesting that this compound could be used as a therapeutic agent to reverse liver fibrosis. In addition, NK-252 attenuated the serum aspartate aminotransferase and alanine aminotransferase levels in male Fischer rats and upregulates *NQO1* gene expression[60].

## THERAPEUTIC IMPLICATIONS OF NRF2 IN MAFLD

Currently, there is no medicine that can treat MAFLD, but some therapeutic agents are useful in managing the problems associated with the disease (Table 1). Thus, it is necessary to develop and test drugs for the prevention and treatment of MAFLD, and it is conceivable that NRF2-activating compounds can attenuate MAFLD progression. Plant-derived compounds including resveratrol, curcumin, quercetin, and synthetic molecules like oltipraz and pirfenidone could be used to prevent oxidative stress by modulating the NRF2 pathway[12,21].

Flavonoids represent a class of bioactive antioxidants extracted from vegetables, plants, and fruits known to exhibit therapeutic properties in MAFLD. The flavonoid 7-mono-O-( $\beta$ -hydroxyethyl)-rutoside activates NRF2 and improves the ratio of GSH/ glutathione disulfide and increases the expression of HO-1 and GSH-Px[61,62]. The flavonoid scutellarin (4',5,6-trihydroxy flavonoid-7-glucuronide) increases NRF2 protein in C57BL/6J mice, increases the expression of HO-1, glutathione-S-transferase, and NQO1, and inhibits both NF- $\kappa$ B and Keap1[33]. Furthermore, 7,8-dihydroxyflavone upregulates NRF2 activity to counteract alcohol-induced and HFD-induced liver toxicity[63]. Apigenin (4',5,7-trihydroxyflavone), a flavonoid derived from fruits, inhibits lipid peroxidation and exerts protective effects against hepatic steatosis. Moreover, apigenin increases the activities of SOD, CAT, and GSH-Px [35,64].

Gastrodin is a water-soluble extract of *Gastrodia elata* BI that exerts antioxidative activity and improves lipid metabolism in MAFLD mice by promoting NRF2 nuclear translocation[65]. Clusterin, a glycoprotein extracted from ram rete testis fluid, improves steatosis and hepatitis induced by methionine and choline-deficient diet by triggering NRF2 and HO-1 expression[66]. Osteocalcin treatment improves hepatic TG accumulation, promotes NRF2 nuclear translocation, and inhibits phosphorylation of c-Jun N-terminal kinase pathway[67].

In addition, compounds like scutellarin containing breviscapine, hesperitin, apigenin, scoparone, Schisandrin B, tanshinol, and AA and other tabulated compounds are known to exert antioxidative and

Table 1 Modulators of nuclear factor erythroid 2-related factor 2 pathway in metabolic associated fatty liver disease

Compound name	Species	Diet/duration	Treatment	Key findings	Reference
MonoHER	Female C57BL/6J mice (Ldlr <sup>-/-</sup> )	High fat and high cholesterol/13 wk	Administered daily subcutaneously at a dosage of 500 mg/kg of body weight (25 $\mu$ L/g of body weight)	NRF2 activation, $\uparrow$ GSH/GSSG ratio, $\uparrow$ HO-1, GSH-Px	[62]
Scutellarin	Male C57BL/6 mice, hepaG2 cells	High fat/10 wk	Administration of 12.5, 25.0, and 50.0 mg/kg per day	$\uparrow$ PPAR $\gamma$ , PGC-1 $\alpha$ , NRF2, HO-1, NQO1, Keap1, NF- $\kappa$ B	[33]
	Sprague-Dawley rats	High fat/12 wk	Administered orally 50, 100, and 300 mg/kg/d	NRF2, HO-1, NQO1; PI3K/AKT activation	[34]
Apigenin	Male C57BL/6J mice	High fat/16 wk	Injected intraperitoneally 30 mg/kg daily for 3 wk	NRF2 activation; PPAR $\gamma$ inhibition; SOD, CAT, GSH-Px	[35]
7,8-dihydroxyflavone	Male wistar rats	High fat, ethanol/12 wk	Administered intraperitoneally at 5 mg/kg/d for 4 wk	Amelioration of liver architecture, vesicular changes, infiltration; restored serum biomarkers like AST, ALT, and TC; $\uparrow$ NRF2; $\downarrow$ NF- $\kappa$ B	[63]
Resveratrol	Male C57BL/6 mice	High fat/16 wk	Supplemented with 0.4% resveratrol in HFD for 16 wk	Attenuated liver steatosis; $\uparrow$ NRF2 activation; attenuated HFD induced methylation of NRF2 promoter; $\downarrow$ oxidative stress	[68]
Quercetin	HepG2 cells	-	Treated with quercetin at 5-50 $\mu$ M concentrations for 0, 10, 30, 60, 120, 240, and 1080 min	$\uparrow$ GSH, GSH-Px, GCS; p38-MAPK is involved in NRF2 modulation; $\downarrow$ oxidative stress	[69]
Curcumin (1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione)	Male C57BL/6 mice	High fat and high fructose/8 wk	Administered orally 50 and 100 mg/kg/d for 4 wk	$\uparrow$ CYP3A, CYP7A; regulation of NRF2/FXR/LXR $\alpha$ pathway; $\downarrow$ SREBP-1C, FAS	[70]
	Male Sprague-Dawley rats	High fat/6 wk	Administered orally 50 mg/kg daily for 6 wk	$\downarrow$ Steatosis and inflammation; $\downarrow$ Serum aminotransferases, lipids, and insulin resistance; $\downarrow$ TNF, IL-6, MDA; $\uparrow$ NRF2, GSH, HO-1, SOD	[71]
Oltipraz	Male Fischer 344 rats	Choline-deficient L-amino acid-defined/10 wk	Administered orally at 60 mg/kg/d for 9 wk	$\uparrow$ NRF2 activation; antifibrotic and anti-inflammatory; $\downarrow$ AST and ALT; $\uparrow$ NQO1 gene expression	[61]
GSTD	HL-7702 cells, male C57BL/6J, male Sprague-Dawley rats	Oleic acid (OA)/24 h, high fat/10 wk; high fat and high cholesterol/10 wk	Cells were treated with GSTD for 24 h, administered orally at 10, 20, 50 mg/kg per day for 10 wk, administered orally at 20, 50 mg/kg per day for 10 wk	$\uparrow$ NRF2, HO-1, SOD; activate AMPK/NRF2; $\downarrow$ proinflammatory response, and hepatic steatosis; $\downarrow$ MDA, ROS	[65]
NK-252 1-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)-3-(pyridin-2-ylmethyl)urea)	Male Fischer 344 rats	Choline-deficient L-amino acid-defined/10 wk	Administered orally at 20, 60 mg/kg/d for 9 wk	Attenuated histological abnormalities; $\uparrow$ antifibrotic effects; $\downarrow$ TGF- $\beta$ 1, collagen $\alpha$ 1; NRF2 activation; $\uparrow$ NQO1 expression	[61]
Clusterin	Male hCLU-tg mice	MCD/3 wk	Generated hepatocyte-specific clusterin overexpression transgenic mice and fed with MCD diet	$\downarrow$ Hepatic TGs; less infiltration of macrophages; $\downarrow$ TNF; $\uparrow$ NRF2 activation and mRNA of HO-1	[66]
Osteocalcin	Male C57/BL6J mice	High fat/12 wk	Injected intraperitoneally at concentration 3 ng/ $\mu$ L/d for 12 wk	$\downarrow$ Hepatic TG accumulation; $\uparrow$ NRF2 activation; $\uparrow$ CAT, SOD, GSH-Px; $\downarrow$ JNK activation	[67]
Orlistat	Male Sprague-Dawley rats	High fat/12 wk	Administered at 10 mg/kg/d for 12 wk	$\uparrow$ NRF2 activation; protection against insulin resistance, hyperlipidemia, oxidative stress, and liver injury	[72]
Garcinia Cambogia	Male C57BL/6N mice	High fat/8 wk	Administered 200, 400 mg/kg/d for 8 wk	$\uparrow$ NRF2 activation; $\downarrow$ ROS production; suppressed lipogenic factors C/EBP $\alpha$ and	[73]

				PPAR $\gamma$ ; suppressed apoptosis by normalizing Bcl-2/BAX ratio and PARP cleavage	
HTT	Male Sprague-Dawley rats, 3T3-L1 murine embryo fibroblast cells	High fat/4 wk, 3T3-L1 cells treated with FBS/DMEM for 8 d	Administered orally HTT at 350, 700, and 1400 mg/kg/d, 3T3-L1 cells treated with HTT at 500 $\mu$ g/mL for 24 h or 48 h	$\uparrow$ NRF2-HO-1 activation, antioxidant activities; HTT inhibited liver weight gain; reduced lipid profile; improved liver function; HTT promoted lipolysis and increased antioxidant activities in 3T3-L1 cells	[74]
Hesperitin	HepG2 cells, male wistar rats	OA/24 h, high fat/16 wk	Treated cells at 0.25, 0.50, 1.00, 2.50, 5.00, and 10.00 $\mu$ M; administered 100 mg/kg in 0.5% CMC-Na	Alleviated hepatotoxicity and oxidative stress by increasing SOD, GSH-Px, GCLC, and HO-1; $\uparrow$ NRF2 activation; suppressed OA induced inflammation; reduced TC, TGs, and LDLC in a dose-dependent manner	[75]
Glucoraphanin	Male C57BL/6JSlc mice	High fat/14 wk	Administered 0.3% glucoraphanin orally for 14 wk	Decrease in weight gain; improved insulin resistance; reduced hepatic steatosis and oxidative stress; decrease in circulating LPS; $\uparrow$ NRF2 activation; $\uparrow$ energy expenditure and; UCP1 protein expression	[76]
<i>Scutellaria baicalensis</i> extract	Male KK-A $^y$ mice	1% Orotic acid and 33% sugar/7 d	Supplemented with diet for 7 d	Diminished increase in liver weight; attenuated hepatic steatosis; $\uparrow$ NRF2 expression; suppress <i>SREBP-1c</i> gene and protein expression	[77]
Ginkgolide B	Male C57/BL6 ApoE $^{-/-}$ mice, HepG2 cells	High fat/5 wk, 100 $\mu$ M palmitic acid (PA) and 200 $\mu$ M OA/24 h	Administered orally at 20, 30, and 1.3 mg/kg/d; treated cells at dosages 0, 1, 2, 4, 8, 16, and 32 $\mu$ g/mL	NRF2 activation; inhibition of oxidative stress and lipid peroxidation through NRF2 pathway; increase in HO-1 and GSH-Px4	[78]
Scoparone	Male C57BL/6 J mice, AML2 and RAW264.7 cells	MCD/4 wk; AML12/300 $\mu$ M PA and RAW264.7/10 $\mu$ M/Chloroquine	Administered daily intraperitoneally for 4 wk at 20, 40, and 80 mg/kg; AML12 and RAW264.7 cells were pretreated with scoparone for 2 h	Ameliorated hepatic inflammation; improved hepatic autophagy; suppressed inflammation by inhibiting ROS/P38/NRF2 axis and PI3K/AKT/mTOR pathway	[79]
DA	Male C57BL/6J mice, HL7702 cells	High fat/12 wk, 0.6 mM OA/24 h	Administered by gavage at 10 and 20 mg/kg/d for 9 wk; treated with 2.5, 5.0, and 10.0 $\mu$ M DA	Ameliorated liver ferroptosis in mice and cells; improved oxidative stress and lipid peroxidation <i>in vivo</i> ; $\uparrow$ NRF2-HO-1 expression; $\uparrow$ GSH, GSH-Px4	[80]
Silibinin	Male C57BL/6 mice, NCTC-1469 cells	MCD/6 wk, OA plus PA/24 h	Administered by gavage at 10 and 20 mg/kg/d for 6 wk, 0.25 mM/L PA and 0.5 mM/L OA/24 h	Prevented CFLAR-JNK pathway; $\uparrow$ $\beta$ -oxidation and efflux of fatty acids; $\uparrow$ expression of CAT, GSH, GSH-Px, and HO-1; $\downarrow$ expression of CYP2E1 and CYP4A; $\uparrow$ NRF2 activation	[81]
Chicoric acid	Male C57BL/6 mice	High fat/9 wk	Administered by gavage at 15 and 30 mg/kg/d for 9 wk	Attenuated hyperglycemia, dyslipidemia, and systemic inflammation; alleviated hepatic lipid accumulation and oxidative stress; suppressed hepatic inflammation and NF- $\kappa$ B pathway; $\uparrow$ NRF2/Keap1 activation; improved gut microbiota	[82]
Carbon monoxide releasing molecule-A1	Male C57BL/6J mice	High fat/16 wk	Administered intraperitoneally 2 mg/kg/d for 7 wk	$\uparrow$ NRF2/ARE activation; improved lipid homeostasis; $\uparrow$ AIP production; improved mitochondrial biogenesis; ameliorated oxidative stress	[83]



NRF2: Nuclear factor erythroid 2-related factor 2; GSH: Reduced glutathione; GSSG: Oxidized glutathione; HO-1: Heme oxygenase-1; GSH-Px: Glutathione peroxidase; PPAR- $\gamma$ : Peroxisome proliferator-activated receptor- $\gamma$ ; PGC-1 $\alpha$ : Proliferator-activated receptor gamma coactivator-1 $\alpha$ ; NQO1: NAD(P)H quinone oxidoreductase 1; DA: Dehydroabiatic acid; PA: Palmitic acid; NF- $\kappa$ B: Nuclear factor  $\kappa$  B; PI3K: Phosphatidylinositol 3'-kinase; SOD: Superoxide dismutase; CAT: Catalase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; TC: Total cholesterol; HFD: High-fat diet; GCS: Glutamylcysteine-synthetase; MAPK: Mitogen-activated protein kinase; CYP3A: Cytochrome P450, family 3, subfamily A, CYP7A Cytochrome P450, family 7, subfamily A; FXR: Farnesoid-X-receptor; LXRA: Liver X receptor  $\alpha$ ; SREBP-1C: Sterol regulatory element-binding protein-1c; FAS: Fatty acid synthase; TNF: Tumor necrosis factor; IL-6: Interleukin-6; MDA: Malondialdehyde; AMPK: AMP kinase; ROS: Reactive oxygen species; TGF- $\beta$ 1: Transforming growth factor- $\beta$ 1; TG: Triglycerides; JNK: c-Jun N-terminal kinase; C/EBP $\alpha$ : CCAAT/enhancer binding protein  $\alpha$ ; Bcl-2: B-Cell Leukemia/Lymphoma 2; BAX: BCL2 associated X protein; PARP: Poly-ADP ribose polymerase; HTT: Hedansanqi Tiaozhi Tang; GCLC: Glutamate cysteine ligase catalytic; LDLC: Low density lipoprotein cholesterol; LPS: Lipopolysaccharide; UCP1: Uncoupling protein 1; GSH-Px4: Glutathione peroxidase 4; mTOR: Mammalian target of rapamycin; CFLAR: CASP8 And FADD like apoptosis regulator; CYP2E1: Cytochrome P450 family 2 subfamily E member 1; CYP4A: Cytochrome P450 family 4 subfamily A; ARE: Antioxidant response element; AKT: Protein kinase B; MCD: Methionine- and choline-deficient; GSTD: Gastrodin; Keap1: Kelch-like ECH-associated protein 1.

hepatoprotective activity by modulating the NRF2 pathway.

## CONCLUSION

Oxidative stress can be a potent inducer of inflammation and fibrosis in the spectrum of chronic liver diseases. Among them, MAFLD is the most widespread chronic liver condition worldwide. The transcription factor NRF2 has gained importance in recent years as a possible therapeutic target for the treatment of liver diseases. The expression of antioxidant protective genes through the NRF2 pathway counteracts oxidative stress and prevents progression of liver damage in MAFLD. The different antioxidant molecules modulating the NRF2 pathway have exerted beneficial effects in ameliorating liver damage. Currently, there is no efficient treatment to counteract the complex pathophysiology of liver diseases. Thus, compounds having antioxidative properties could be useful candidates for the treatment of liver diseases by modulating the NRF2 signaling pathway. NRF2 activators could improve and prevent the advanced stages of MAFLD such as liver fibrosis and liver cirrhosis. Natural plant-derived and synthetic NRF2 activators require further experimental validation to be promoted as efficient therapeutic agents. Some drugs have entered clinical trials, and further attempts are ongoing to find NRF2 inducers with high bioavailability, safety, and specificity.

## FOOTNOTES

**Author contributions:** Bukke VN and Moola A collected information for the review and provided a significant contribution in writing the manuscript; The senior authors Serviddio G, Vendemiale G, and Bellanti F drafted and supervised the paper.

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