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The NRF-2/HO-1 Signaling Pathway: A Promising Therapeutic Target for Metabolic Dysfunction-Associated Steatotic Liver Disease

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Abstract: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a progressive liver disorder with a rising prevalence. It begins with lipid accumulation in hepatocytes and gradually progresses to Metabolic-associated steatohepatitis (MASH), fibrosis, cirrhosis, and potentially hepatocellular carcinoma (HCC). The pathophysiology of MASLD is complex and involves multiple factors, with oxidative stress playing a crucial role. Oxidative stress drives the progression of MASLD by causing cellular damage, inflammatory responses, and fibrosis, making it a key pathogenic mechanism. The Nuclear Factor Erythroid 2-Related Factor 2 / Heme Oxygenase-1 (Nrf2/HO-1) signaling axis provides robust multi-organ protection against a spectrum of endogenous and exogenous insults, particularly oxidative stress. It plays a pivotal role in mediating antioxidant, anti-inflammatory, and anti-apoptotic responses. Many studies indicate that activating the Nrf2/HO-1 signaling pathway can significantly mitigate the progression of MASLD. This article examines the role of the Nrf2/HO-1 signaling pathway in MASLD and highlights natural compounds that protect against MASLD by targeting Nrf2/HO-1 activation. The findings indicate that the Nrf2/HO-1 signaling pathway holds great promise as a therapeutic target for MASLD.

Keywords: the NRF-2/HO-1 signaling pathway, antioxidants, anti-inflammatory, natural compounds, non-alcoholic fatty liver disease

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a condition characterized by excessive fat accumulation in the liver, excluding alcohol and other specific causes of liver damage.[1] To more accurately reflect the metabolic basis of the disease, an international expert panel introduced a new term in 2020: Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD), which replaced the old term "Non-Alcoholic Fatty Liver Disease" (NAFLD).[2] In 2023, a multi-society Delphi consensus statement on the new nomenclature for fatty liver disease introduced the term Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and formally discontinued the use of NAFLD.[3] Based on disease progression, MASLD can be classified into four distinct stages: simple steatosis, Metabolic-Associated Steatohepatitis (MASH), fibrosis, and cirrhosis.[4] The clinical manifestations of MASLD are diverse, with the majority of patients being asymptomatic. However, some patients may report symptoms such as fatigue, discomfort in the right upper quadrant, hepatomegaly, acanthosis nigricans, and lipomas.[5] In more severe cases, symptoms like jaundice, loss of appetite, nausea, and vomiting may occur.[6] Furthermore, MASLD is closely associated with metabolic and systemic diseases such as cardiovascular disease, obesity, type 2 diabetes, and sarcopenia. These conditions are not only common complications of MASLD,[7–9] but may also exacerbate its progression, leading to further deterioration of the patient's condition.[10–12]

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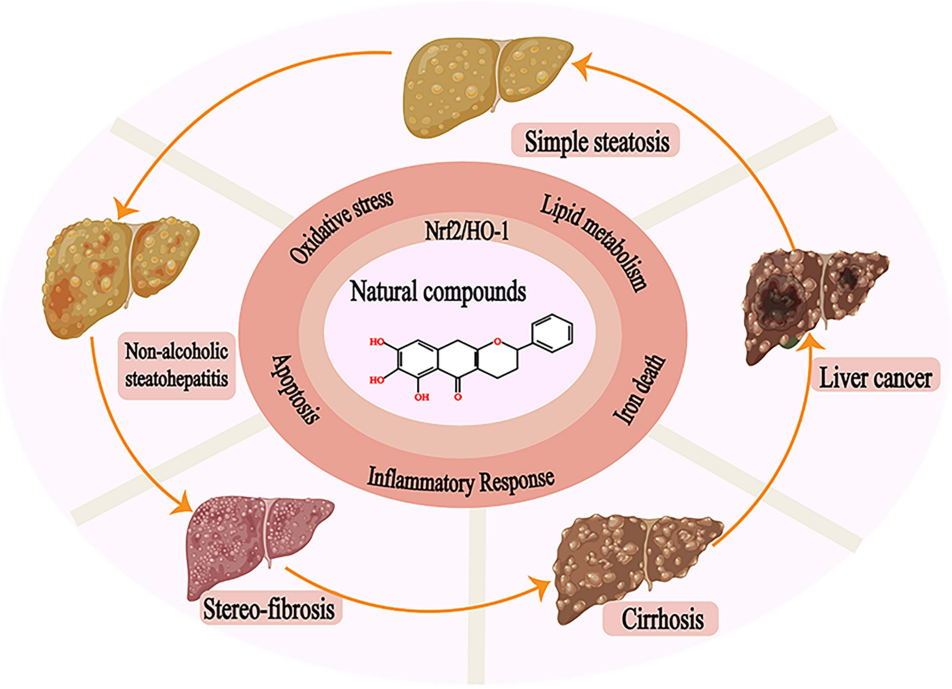
Graphical Abstract



MASLD has become the most common liver disease worldwide and is expected to be the leading cause of end-stage liver disease in the coming decades.[13,14] According to statistics, the global prevalence of MASLD ranges from 25% to 34%, with 30% in Europe, 35% in South and North America, and 29.29% in Asia. Notably, the prevalence in Southeast Asia is as high as 42%.[15–18] The mortality rate for individuals with MASLD is 1.6 times higher than that of the general population,[19–21] with an all-cause mortality rate of 12.60 per 1000 person-years, posing a significant public health crisis.[22] Among the management strategies for MASLD, weight loss is considered one of the most effective measures; however, patients often struggle to maintain long-term adherence in practice.[23,24] Pharmacological and surgical treatments have also been shown to improve patients' metabolic conditions and increase survival rates effectively. Commonly used medications include insulin sensitizers such as pioglitazone,[23] statins,[24] and vitamin E,[25] which can effectively alleviate fatty liver and inflammatory responses, particularly in patients with metabolic syndrome. Resmetirom, as an emerging drug, selectively activates the hepatic thyroid hormone receptor β, which can improve metabolic function, reduce hepatic fat accumulation, alleviate liver inflammation, enhance liver fibrosis, and potentially increase insulin sensitivity.[26] Weight loss surgery, such as gastric bypass, significantly reduces weight, improves liver function, and decreases the incidence of MASH and liver fibrosis.[27] Moreover, liver transplantation is the ultimate treatment option for end-stage MASH.[28,29] Although these treatments have demonstrated certain clinical efficacy, the overall management of MASLD patients remains suboptimal due to the lack of early effective diagnostic tools and targeted therapeutic agents.[30] Therefore, there is an urgent need to intensify efforts to develop new treatment strategies for MASLD.

The "second hit" theory is a classic pathogenic mechanism of MASLD, where the "first hit" typically refers to insulin resistance leading to excessive fat accumulation in the liver (hepatic steatosis), oxidative stress is considered the "second hit", significantly promoting the development of steatohepatitis.[31] In recent years, the "multiple-hit" hypothesis has increasingly replaced the "second hit" theory, gaining widespread acceptance.[32] This hypothesis posits that MASLD is influenced by multiple pathological factors that collectively lead to hepatic fat deposition, inflammatory response, and fibrosis.[33,34]

Nevertheless, oxidative stress remains one of the key factors in alleviating MASLD.[35–37] When the balance between oxidants and antioxidants is disrupted, oxidative stress can trigger lipotoxicity, lipid peroxidation, endoplasmic reticulum (ER) stress, and mitochondrial dysfunction, while also increasing the production of inflammatory cytokines. This cascade of events leads to inflammatory and fibrotic responses, ultimately progressing to MASH and end-stage liver disease.[37,38]

The nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) pathway is a critical signaling mechanism in the body's response to oxidative stress.[39] Nrf2, a basic leucine zipper transcription factor, is essential for regulating the cellular antioxidant response and is widely expressed in various tissues and cells.[40,41] Research indicates that Nrf2 exerts dual protective effects in MASLD: (1) it negatively regulates genes that promote hepatic lipid accumulation. (2) it eliminates Reactive Oxygen Species (ROS) and electrophiles produced by lipid peroxidation, thereby preventing oxidative stress and mitochondrial dysfunction in hepatocytes.[42] The downstream effector of Nrf2, HO-1, plays a crucial role in anti-inflammatory, antioxidant, and anti-apoptotic processes.[43] HO-1 significantly improves MASLD by enhancing mitochondrial function, inhibiting ferroptosis, reducing ROS production, and suppressing inflammatory responses.[44–47] Qiu et al[48] demonstrated that activating the Nrf2/HO-1 pathway can regulate antioxidant enzyme levels, eliminate lipid peroxides, maintain the balance between oxidation and antioxidation, reduce weight gain, and improve lipid metabolic dysfunction, effectively suppressing the progression of MASLD both in vitro and in vivo. Additionally, Qiao et al[49] indicated that iNOS upregulates HO-1 expression by promoting Nrf2 nuclear translocation, thereby protecting the liver from MASH damage. Once HO-1 expression is inhibited, the protective effects of iNOS on hepatocytes diminish. This underscores the potential of the Nrf2/HO-1 signaling pathway as a therapeutic target for the progression of MASLD.

Based on the aforementioned information, the Nrf2/HO-1 pathway presents significant potential as a therapeutic target for non-alcoholic fatty liver disease (NAFLD). Recent studies indicate that various natural compounds, such as Aucubin,[50] Gastrodin,[51] and Ganoderma lucidum polysaccharides,[52] can activate the Nrf2/HO-1 pathway, exerting antioxidant, anti-inflammatory, and lipid metabolism-improving effects that effectively inhibit the pathological progression of NAFLD. Therefore, we propose targeting the Nrf2/HO-1 pathway as an innovative approach to intervene in NAFLD, which may not only slow disease progression but also improve associated complications. In the future, as our understanding of this pathway deepens, Nrf2/HO-1 targeted therapies are expected to serve as a valuable complement to existing treatments, opening new avenues for NAFLD research.

Heading

Oxidative Stress and MASLD

In 1998, British scholar Day first proposed the "two-hit theory" of MASLD pathogenesis, which has been widely accepted within the scientific community. According to this hypothesis, the "first hit" is peripheral insulin resistance leading to the accumulation of free fatty acids in the liver, resulting in hepatic steatosis. This condition predisposes the liver to further damage, preparing it for the subsequent "second hit". The "second hit" involves oxidative stress and the production of pro-inflammatory cytokines, which contribute to the progression of steatohepatitis.[31] However, as research has advanced, scientists have increasingly recognized that the complexity of this disease far exceeds the "two-hit" theory. The "multiple-hit theory" has been proposed and gradually replaced the "two-hit" hypothesis as a widely accepted perspective.[32] This theory posits that the onset and progression of MASLD are not triggered by two singular events but rather involve a synergistic interplay of various pathological factors, including but not limited to genetic susceptibility, epigenetic regulation, metabolic dysregulation, gut microbiota imbalance, insulin resistance, lipid peroxidation, and immune responses,[33,34] these factors interact in complex ways, promoting the accumulation of fat in the liver, inflammatory responses, and the acceleration of fibrosis. The "two-hit" hypothesis emphasizes that steatosis occurs first, followed by hepatitis and fibrosis triggered by oxidative stress and other factors, while the "multiple-hit" hypothesis posits that multiple pathogenic factors can act simultaneously or sequentially to lead to the onset and progression of MASLD.

Despite the complex pathogenesis of NAFLD involving multiple factors, oxidative stress is consistently recognized as a crucial contributor to disease progression.[53] Oxidative stress arises from an imbalance between the production and elimination of ROS,[54] which serves as a primary cause of both hepatic and extrahepatic injury.[55] Clinical studies have shown that compared to the normal group, patients with NAFLD exhibit significantly higher body mass index,

cholesterol levels, and transaminases, while levels of glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), and glutathione peroxidase (GPX) are significantly lower.[56,57] The decreased activity of these antioxidant enzymes leads to exacerbated oxidative stress, further aggravating liver cell damage, inflammation, and fibrosis.[37,58,59] Additionally, oxidative stress initiates a series of pathophysiological changes in MASLD, including mitochondrial dysfunction, ER stress, disturbances in iron metabolism, disruption of the gut-liver axis, insulin resistance, and endothelial dysfunction.[55]

Nrf2/HO-1 Signaling Pathway

Nrf2 is pivotal in cellular antioxidant defense, ensuring redox homeostasis.[60] This key transcription factor dissociates from its inhibitory protein, Kelch-like ECH-related protein 1 (Keap1), during oxidative stress and relocates to the nucleus. In the nucleus, Nrf2 engages with the Antioxidant Response Element (ARE) to activate the transcription of multiple antioxidant genes, including HO-1. HO-1 plays a crucial role in shielding cells from damage caused by ROS and is essential for anti-inflammatory, antioxidant, and anti-apoptotic functions.[61,62] As the primary regulatory mechanism for cellular protection against oxidative stress, the Nrf2/HO-1 pathway is essential in managing MASLD.[63]

The Structure and Properties of Nrf2

Nrf2 also referred to as Nfe2l2, a transcription factor, is encoded by the NFE2L2 gene on chromosome 2q31.2.[64] This protein is part of the cap "n" collar (CNC) basic leucine zipper (bZIP) family of transcription factors.[65] Nrf2 is ubiquitously expressed in multiple tissues, including the liver, kidneys, spleen, and heart. It is critically involved in protecting these tissues from oxidative stress and chemical-induced cellular damage.[66] Nrf2 consists of 605 amino acids and features seven distinct structural domains, which are sequentially arranged from the N-terminus to the C-terminus as Neh2, Neh4, Neh5, Neh7, Neh6, Neh1, and Neh3.[67] Each domain fulfills a specific and irreplaceable function.[68] The Neh2 domain, located at the N-terminus of Nrf2, contains two highly conserved amino acid sequences: 29DLG (low affinity) and 79ETGE (high affinity)[69], which are the two sites that bind to the Kelch domain of the Nrf2 repressor protein (Keap1).[70,71] Nrf2 is subject to ubiquitination by the Keap1-Cullin3 E3 ubiquitin ligase, which results in its degradation via the proteasome system.[72] The Neh4 and Neh5 domains, together with the C-terminal Neh3, act as transactivation domains for Nrf2, binding to coactivators.[73,74] The Neh7 domain, serving a negative regulatory function, binds to retinoid X receptor alpha (RXR α) and inhibits the transcriptional activity of Nrf2.[75] The Neh6 domain is a key negative regulatory domain that mediates the ubiquitination and proteasomal degradation of Nrf2, containing the amino acid sequences DSGIS338 and DSAPGS378,[76] which are recognized by GSK-3/β-TrCP and targeted for degradation by the Cullin1/Rbx1 complex.[77] Lastly, the Neh1 domain, defined by its conserved CNC and bZIP structures, is crucial for Nrf2 to bind to small Maf proteins in the nucleus, facilitating the formation of dimers that recognize and attach to the DNA sequences of target genes,[78] particularly the Antioxidant Response Element (ARE)[79](Figure 1).

The Structure and Characteristics of HO-1

HO-1 is a 32 kDa stress-inducible protein that belongs to the heme oxygenase family.[80] It is a type II detoxifying enzyme regulated by Nrf2 and serves as the rate-limiting enzyme in the oxidative degradation of heme into free iron, carbon monoxide (CO), and biliverdin.[81] HO-1 is highly expressed in various digestive organs, including the gastrointestinal tract, pancreas, and liver.[82] HO-1 is an enzyme encoded by the HMOX-1 gene, located on human chromosome 22q12.3.[83] The gene spans approximately 13,148 bp and contains 5 exons and 4 introns, accompanied by 3 regulatory regions. A proximal regulatory region is positioned at about −0.3 Kb, while two distal enhancer regions, designated E1 and E2, are located at approximately −4 Kb and −10 Kb, respectively.[84–86] These regulatory regions contain numerous transcription factor binding sites, such as hypoxia-inducible factor 1 (HIF-1), nuclear factor kappa B (NF-κB), activator protein 1 (AP-1), stress response element (StRE), metal response element (MtRE), and heat shock element (HSE).[87,88] These regulatory elements facilitate the transcriptional response of the HMOX-1 gene to various oxidative and inflammatory stimuli.[87] StRE is the primary sequence motif, functioning analogously to the Maf response element (MARE) and the antioxidant response element (ARE).[89] Among the transcription factors, nuclear erythroid 2-related factor (Nrf2) and BTB and CNC homolog 1 (Bach1) (transcriptional repressors of HMOX1) play key roles in HMOX1 regulation, regulating gene expression by activating and repressing its

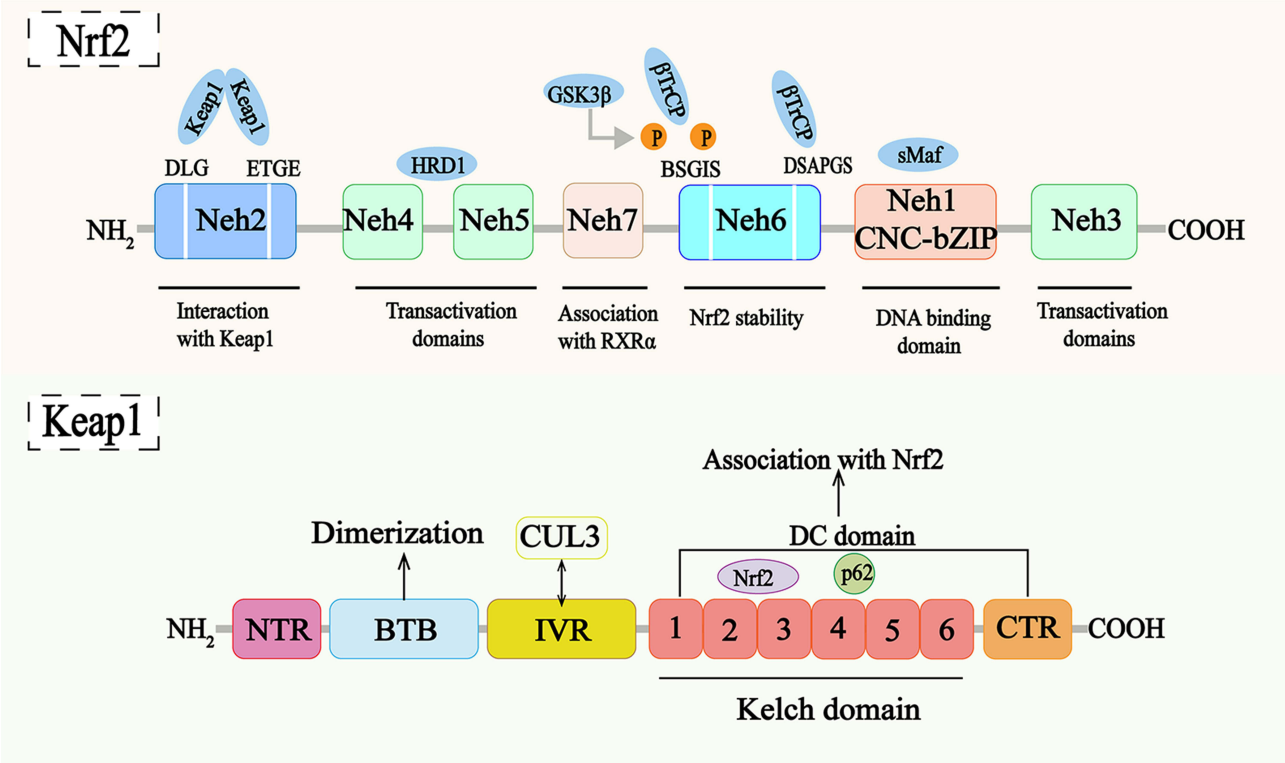


Figure 1 The schematic diagram of Nrf2 and Keap1 domain structure: Nrf2, is a transcription factor characterized by multiple functional domains, including Neh2, Neh4, Neh5, Neh6, Neh7, Neh1, and Neh3. Neh2 interacts with the Kelch domain of Keap1 through DLG and ETGE motifs, while Neh4, Neh5, and Neh3 engage with co-activators to enhance transcriptional activity. Neh7 serves as a negative regulatory domain, and Neh6 is critical for the recognition of Nrf2 by GSK-3/β-TrCP, facilitating its degradation via the ubiquitin-proteasome pathway. Neh1 is responsible for binding to DNA, thereby regulating gene expression. Keap1, contains several functional domains, including the N-terminal region (NTR), BTB, IVR, Kelch domain, and CTR. Keap1 interacts with Nrf2 through its Kelch domain and mediates Nrf2 ubiquitination via CUL3, leading to its degradation. The BTB domain binds to CUL3 and promotes the dimerization of Keap1, thereby forming an effective ubiquitin ligase complex.

transcription, respectively.[90] HO-1 is present at low levels in most mammalian tissues but plays a crucial protective role in cells, including anti-inflammatory, antioxidant, anti-apoptotic, and pro-angiogenic.[91] Upon activation, HO-1 degrades heme into biliverdin, carbon monoxide (CO), and ferrous iron. Biliverdin is subsequently converted to bilirubin by biliverdin reductase, which scavenges or neutralizes ROS, thus mitigating oxidative stress.[82,92] As a gaseous signaling molecule, CO exerts various effects in signal transduction, including vasodilation, anti-inflammatory responses, anti-apoptotic effects, and the promotion of angiogenesis.[93] Additionally, the activation of HO-1 upregulates the expression of ferritin, which binds ferrous iron, thereby reducing oxidative stress[94](Figure 2).

The Nrf2/HO-1 Signaling Pathway

The Nrf2/HO-1 signaling axis plays a pivotal role in maintaining homeostasis by regulating calcium ion influx, oxidative stress, ferroptosis, pyroptosis, autophagy, and programmed cell necrosis.[95] Nrf2, as an endogenous antioxidant transcription regulator, serves as a primary modulator of cellular defense and survival.[96,97] Under physiological conditions, Nrf2 binds to Keap1 to form a complex sequestered in the cytoplasm.[68,98] Keap1 interacts with Cullin3 and the Rbx1 subunit of the E3 ubiquitin ligase complex to form a protein complex. This complex binds to the Neh2 domain of Nrf2, leading to its ubiquitination and maintaining Nrf2 in a low activity state within the cell. Keap1 acts as a redox sensor, and upon oxidative thiol modification, it loses its ability to inhibit Nrf2. HO-1 is a crucial mediator of the antioxidant and anti-inflammatory effects of Nrf2.[99] Under normal conditions, the chromatin structure of HO-1 remains in a pre-activated state, with its transcription inhibited by Bach1.[100] Specifically, the HMOX1 promoter is suppressed by the Bach1/Maf dimer binding to the StRE element.[101]

Upon exposure to oxidative stress or other pathological stimuli, the regulatory cysteine thiols on Keap1 react with ROS, leading to the dissociation of Keap1 from Nrf2. This dissociation allows Nrf2 to translocate into the nucleus. Inside the nucleus, Nrf2 forms a heterodimer with small Maf proteins (sMaf) and Jun bZip transcription

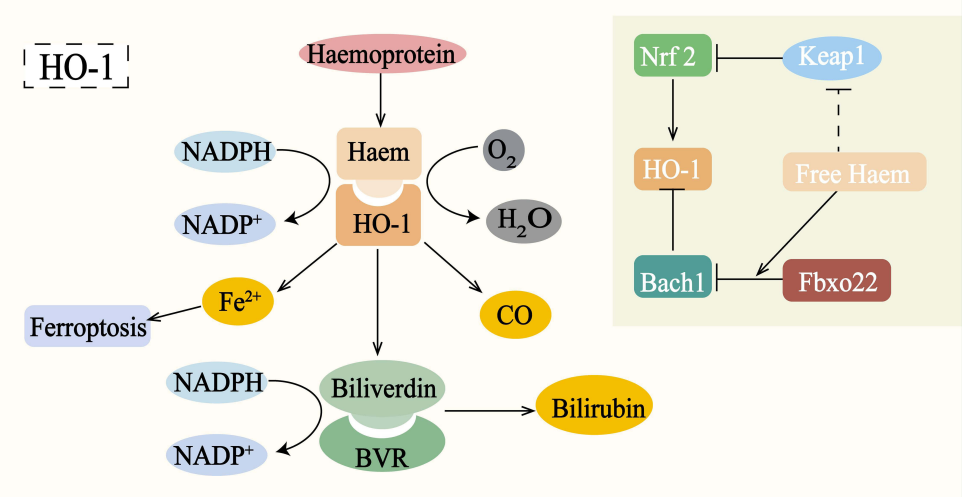


Figure 2 The Cytoprotective Mechanisms of HO-1: Heme oxygenase 1 is an enzyme responsible for the breakdown of heme into Fe^{2+}, CO, and bilirubin, which is subsequently converted to bilirubin by BVR. This process also involves the participation of NADPH and is associated with the regulation of ferroptosis. As shown in the upper right corner of the figure, when free heme accumulates, Nrf2 dissociates from Keap1 and translocates to the nucleus, promoting the expression of HO-1. Additionally, free heme recruits the E3 ubiquitin ligase component Fbxo22, facilitating the degradation of Bach1, an inhibitor of HO-1. Following ubiquitination, Bach1 is degraded via the proteasome pathway.

factors, collectively referred to as the Nrf2-Maf complex, this complex accurately recognizes sequences containing antioxidant response elements (ARE) and binds to the Neh4 and Neh5 domains of Nrf2.[102–104] Through interactions with cAMP response element-binding protein (CREB) and other transcriptional activators, the Nrf2-mediated transcription process is initiated, the regulation of downstream gene expression includes HO-1, NAD(P)H quinone oxidoreductase 1 (NQO1), glutamate cysteine ligase (GCL), peroxiredoxin (Prdx), SOD, CAT, GR, and glutathione peroxidase (GSH-Px).[63] These genes facilitate the clearance of ROS and other harmful substances, promoting mechanisms of antioxidant response, anti-inflammation, and anti-apoptosis.[63] Studies have shown that, in addition to Keap1, several protein kinase signaling pathways can induce Nrf2 phosphorylation and participate in its transcriptional regulation.[60] Among these, mitogen-activated protein kinases (MAPK), protein kinase C (PKC), and phosphoinositide 3-kinase (PI3K) positively regulate NRF2 activity, while glycogen synthase kinase 3 (GSK-3) negatively regulates NRF2 activity through phosphorylation at different sites.[105,106] Additionally, oxidative stress can cause heme to be released from hemoproteins. Free heme binds to Bach1, inducing conformational changes in its structure. This results in the dissociation of Bach1 from StRE, thereby increasing the transcription of HO-1 within cell[107](Figure 3).

The Role of the Nrf2/HO-1 Signaling Pathway in MASLD

MASLD is a prevalent chronic liver disorder primarily driven by oxidative stress and lipid peroxidation, which result in cellular damage, apoptosis, inflammation, and fibrosis. Improving lipid metabolism and reducing hepatic oxidative stress and inflammatory responses are considered effective strategies for preventing and treating MASLD.[108] Nrf2 is an intracellular transcription regulator, with HO-1 as one of its most significant downstream products. The cascade reaction between Nrf2 and HO-1 is crucial for the body's anti-inflammatory and antioxidant systems.[39] Studies have demonstrated that the Nrf2/HO-1 pathway is involved in regulating every stage of the MASLD spectrum.[47,109] Moreover, a range of natural compounds has demonstrated potential therapeutic effects across various stages of MASLD, including simple steatosis, MASH, fibrosis, cirrhosis, and even HCC. This is largely attributed to their ability to activate the Nrf2/HO-1 signaling pathway (Table 1).

Impact of the Nrf2/HO-1 Signaling Pathway on Simple Steatosis

Nrf2/HO-1 Signaling Pathway and Simple Steatosis

The early stages of MASLD are characterized by the accumulation of lipids within hepatocytes. This condition results

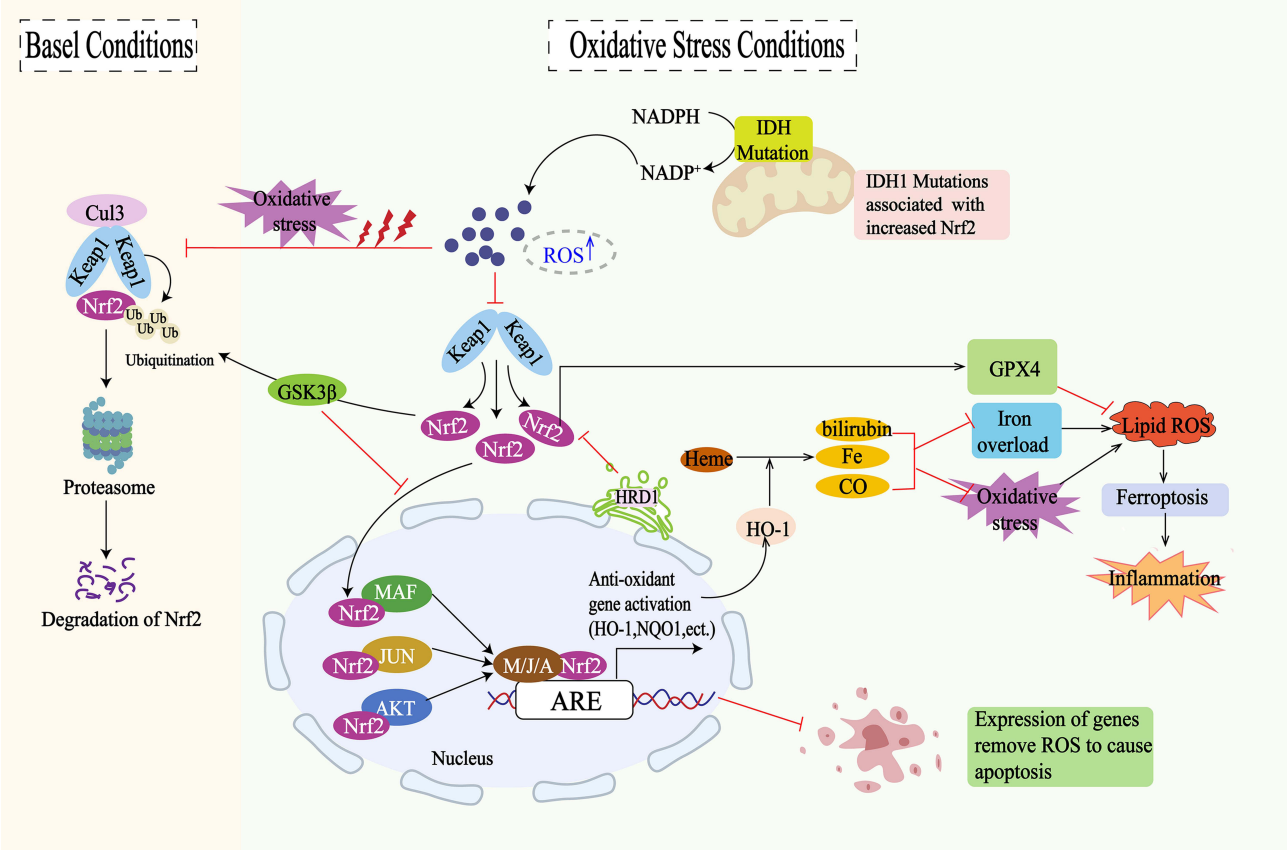


Figure 3 The regulatory mechanisms for Nrf2/HO-1 signaling pathway: Under normal conditions, Keap1 mediates the ubiquitination and proteasomal degradation of Nrf2 by binding to Nrf2 and interacting with the CUL3 ubiquitin ligase complex. Under oxidative stress conditions, the accumulation of ROS prompts Nrf2 to dissociate from Keap1 and translocate to the nucleus, activating the expression of antioxidant genes such as HO-1 and NQO1. HO-1 metabolizes free heme to produce bilirubin, iron, and carbon monoxide, thereby regulating the antioxidant response. However, excessive iron and oxidative stress can trigger lipid peroxidation and ferroptosis, leading to inflammatory responses. The expression of antioxidant genes can inhibit apoptosis by removing ROS. Additionally, GSK3β regulates the stability of Nrf2 through phosphorylation, while IDH mutations, associated with increased Nrf2 activity, can modulate the oxidative stress response via the NADPH/NADP+ pathway.

from increased fatty acid uptake and synthesis, coupled with decreased fatty acid oxidation and removal.[138] Reducing oxidative stress and inflammation is crucial for the effective prevention and treatment of high-fat diet (HFD)-induced steatosis.[139] The Nrf2/HO-1 pathway is a crucial mechanism for mitigating oxidative stress. Activation of this pathway effectively reduces ROS production in hepatocytes and inhibits RIP3 expression, thereby decreasing inflammation and lipid deposition.[140] As a negative regulator of genes associated with hepatic steatosis, Nrf2 suppresses key lipid-synthesizing enzymes, reduces hepatic fat storage, and participates in fatty acid metabolism.[42] Its activation enhances lipid breakdown and inhibits de novo lipogenesis,[141] thus reducing lipid accumulation and oxidative stress in HFD-fed mice.[142] Increased HO-1 activity also aids in the treatment of MASLD by significantly impacting hepatic steatosis and preventing its progression to MASH, cirrhosis, and related complications.[45,47]

Natural Compounds Modulating the Nrf2/HO-1 Pathway to Mitigate Simple Steatosis

Linalool inhibits lipid accumulation and oxidative stress by activating the Nrf2/HO-1 signaling pathway, thus preventing HFD-induced MASLD.[110] Aucubin (AU) significantly reduces lipid accumulation and oxidative stress by activating the Nrf2/HO-1 and AMPK signaling pathways.[50] Gastrodin (GSTD) promotes the phosphorylation of Nrf2 at serine 40, stimulating Nrf2 nuclear translocation and increasing hepatic expression of HO-1. Concurrently, it activates AMPK, thereby inhibiting oxidative stress and inflammatory responses, and improving hepatic steatosis.[51] Ganoderma lucidum polysaccharides (GDLP) activate Nrf2, inducing the expression of antioxidant enzymes such as HO-1, SOD, CAT, and GSH-Px, reducing MDA levels, and inhibiting hepatic steatosis, oxidative stress, and inflammation in db/db mice.[52] Limonene upregulates the hepatic Nrf2/HO-1 signaling pathway, reduces ROS accumulation, inhibits macrophage

Table 1 Natural Compounds Modulating the Nrf2/HO-1 Pathway to Mitigate MASLD

Natural Compound	Source	Pharmacological Effect	Cell	Dose	Animal Model	Medication Administration	Mechanism Of Action	Outcome	References
Monoterpenes Compounds									
Linalool	Tea, Vanilla	Anti-stress, Hepatoprotective, Anticancer, Antibacterial, Anxiolytic			Male Wistar rats, HFD	100 mg/kg, qd, Gavage, 45days	Activates Nrf-2/HO-1 pathway	Inhibits lipid accumulation and oxidative stress, prevents HFD-induced MASLD	[110,111]
Triterpenes Compounds									
Limonin	Citrus Fruits	Antioxidant, Hepatoprotective, Anticancer, Anti-inflammatory, Antiviral	Human fetal hepatocyte cell line (LO2), Lipid mixture 1 (L0288)	10, 20, 40 μM	Zebrafish larvae at 3 days post fertilization (dpf) Thioacetamide (TAA)	12.5, 25, 50 μM, 72 hours	Upregulates Nrf2/HO-1 signaling in the liver, reduces ROS accumulation, inhibits macrophage infiltration, decreases expression of pro-inflammatory cytokines (IL-6, IL-1β, TNF-α)	Anti-lipid accumulation, Antioxidant, Anti-inflammatory	[112]
Dehydroabietic acid (DA)	Coniferous Plants	Anti-inflammatory, Antisteatosis, Antitumor	Human liver cells HL7702, Oleic Acid (OA)	2.5, 5, 10 μM	Male C57BL/6J mice, HFD	10, 20 mg/kg, qd, Gavage, 9 weeks	Binds to Keap1, activates Nrf2-ARE, promotes expression of HO-1, GSH, GPX4; inhibits ferroptosis, increases expression of key genes like FSP1	Inhibits Oxidative Stress and Ferroptosis to Alleviate HFD-Induced MASLD.	[113]
Betulin (BE)	Betula Platyphylla	Antioxidant, Anti-inflammatory, Anticancer, Antiviral, Antibacterial			Male Sprague-Dawley rats, HFD	15, 30 mg/kg, qd, Gavage, 12 weeks	Upregulates Nrf2 and HO-1 expression inhibits NF-kB gene expression	Mitigates Oxidative Stress and Inflammatory Responses to Attenuate Serum Lipids and Transaminase Levels in HFD-Fed Rats, thereby Preventing Hepatic Lipid Accumulation, Steatosis, and Fibrosis.	[114]

Asiatic Acid (AA)	Centella Asiatica	Antioxidant, Anti-inflammatory, Anti-apoptotic			Male Sprague-Dawley rats, CCl_4	5, 15 mg/kg, qd, Oral, 6 weeks	Activates Nrf2/ARE pathway, increases nuclear Nrf2 expression, significantly upregulates HO-1, NQO-1, GCLC expression; inhibits NF-κB/IkBα and JAK1/STAT3 pathways	Effectively counteracts oxidative stress-induced liver injury; reduces the release of inflammatory factors and activation of HSCs	[115,116]
Astragaloside IV (AS-IV)	Astragalus	Antioxidant, Anti-inflammatory, Anti-apoptotic, Immunomodulatory, Anticancer	Immortalized rat HSC lines (HSC-T6) cells and HepG2 cells, TGF-β1	5, 10, 20 μM	Male C57BL/6J mice, DCC (DEN/CCl4/C2H5OH)	20, 40, 80 mg/kg, qd, 20 weeks	Activates Nrf2/HO-1 and pSmad3C/3L pathways	Inhibits Oxidative Stress and Collagen Deposition to Suppress the Onset of HCC	[117,118]
Iridoids Compounds									
Aucubin (AU)	Eucommia, Plantain, Japanese Ash	Antioxidant, Anti-inflammatory, Hepatoprotective, Antifibrotic, Neuroprotective, Osteoprotective, Anticancer	3T3-L1 cells, Apolipoprotein C-III (apoC-III)	35, 70, 140μg/mL	Male C57BL/6 mice, Tyloxapol	10, 20, 40 mg/kg, Intraperitoneal injection, 24 hours	Activates Nrf2/HO-1 and AMPK pathways	Significantly inhibits lipid accumulation and oxidative stress in vitro and in vivo	[50,119]
Geniposide (GEN)	Gardenia, Eucommia	Anti-inflammatory, Hepatoprotective	HepG2 cells, OA+PA	65, 130, 260, 390, 520 μmol/L	The male wild-type (WT) AND $Nrf2^{-/-}$ C57BL/6J mice, Tyloxapol	50, 75, 100 mg/kg, Injection, 18 hours	Activates Nrf2 expression, increases cytoplasmic HO-1 protein levels	Protects liver from oxidative damage, reduces lipid accumulation in HepG2 cells	[120]
Phenolic Compounds									
Gastrodin (GSTD)	Gastrodia elata Blume	Anti-inflammatory, Antioxidant, Anti-apoptotic, Antitumor activities	HL-7702 cells, Oleic acid (OA)	25, 50, 100, 200μg/mL	Male C57BL/6Jmice, HFD	10, 20, 50mg/kg, qd, Oral, 10 weeks	Promotes Nrf2 phosphorylation at serine (Ser) 40, stimulates Nrf2 nuclear translocation, increases hepatic HO-1 expression, and activates AMPK	Inhibits oxidative stress and inflammatory responses, improving hepatic steatosis	[51,121]

(*Continued*)

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Table 1 (Continued).

Natural Compound	Source	Pharmacological Effect	Cell	Dose	Animal Model	Medication Administration	Mechanism Of Action	Outcome	References
Polysaccharide Compounds									
Ganoderma lucidum Polysaccharides (GDLP)	Ganoderma lucidum	Anti-inflammatory, Antioxidant, Liver protection, Immunomodulation, Anti-tumor			C57BL/KsJ-db /db male mice, HFD	100, 400 mg/kg, qd, Gavage, 8 weeks	Activates Nrf2, induces increased expression of antioxidant enzymes such as HO-1, SOD, CAT, and GSH-Px, and reduces MDA levels	Inhibits the progression of hepatic steatosis, mitigates oxidative stress, and attenuates inflammatory responses.	[52]
Flavonoid compounds									
Naringin	Grape, Tomato, Citrus Fruits	Antioxidant, Lipid-lowering, Metabolic Syndrome Protection, Anticancer			Male Sprague Dawley rats, Fructose solution	100 mg/kg, qd, Oral, 4 weeks	Activates the Nrf2/HO-1 pathway, inhibits the NF-κB/TNF-α pathway, and reduces endogenous triglyceride synthesis	Inhibits Oxidative Stress and Inflammatory Responses to Attenuate the progression of MASLD	[108,122]
Hesperetin	Citrus Fruits (Oranges, Grapefruits, and Lemons)	Anti-cancer, Anti-Alzheimer's, Anti-diabetic	HepG2 cell, OA	2.5, 5, 10 μM	Male Wistar rats, HFD	100, 300 mg / kg, qd, Gavage, 16 weeks	Activate the PI3K/AKT-Nrf2 pathway to upregulate antioxidant levels (SOD/GPX/GR/GCLC/HO-1), inhibit NF-κB activation, and reduce the secretion of inflammatory factors (TNF-α and IL-6)	Alleviate hepatic steatosis, oxidative stress, inflammatory cell infiltration, and fibrosis.	[123]
Total Flavonoids from Hawthorn Leaves	Hawthorn Leaves	Antioxidant, Anti-inflammatory, Lipid-lowering, Hepatoprotective			Male SD rats, HFD	125, 250mg/kg, qd, Gavage, 12 weeks	Enhances Nrf2/HO-1 expression and inhibits COX-2 overexpression	Mitigates oxidative stress-induced cellular damage and inflammatory responses, prevents MASH progression	[124]

Baicalein	Scutellaria Baicalensis Georgi	Lipid-lowering, Antioxidant, Hepatoprotective			Male Sprague-Dawley (SD) rats, MCD (methionine and choline deficient diet)	10 mg/kg, qd, Intraperitoneal injection, 8 weeks	Enhances the Nrf2/HO-1 pathway and increases the activity of SOD and CAT; inhibits iNOS activation to reduce NO production in the liver; and suppresses NF-κB activation, leading to decreased levels of IL-6 and TNFα.	Inhibits oxidative stress and inflammatory responses, significantly alleviating MCD diet-induced NASH.	[125]
			HepG2, BSA and free fatty acids (FFAs, palmitate acid/ oleic acid = 1/2)	16 μM	Male C57BL/6J mice, HFD	50, 200 mg/kg, qd, Gavage, 12 weeks	Activates the Nrf2/HO-1 signaling pathway while inhibiting the NLRP3/Caspase-1/ GSDMD pathway.	Inhibits oxidative stress and pyroptosis, alleviating liver damage in NASH mice.	[126]
Scutellarin	Erigeron Breviscapus	Anti-inflammatory, Antioxidative, Antiapoptosis	HepG2 cells, OA	50, 100, 200μmmol/ L	Male C57BL/6J mice, HFD	12.5, 25, 50 mg/ kg, qd, 8 weeks	Activates PPARγ and upregulates the expression of PGC-1α and Nrf2 proteins; Nrf2 activation subsequently enhances the expression of HO-1, NQO1, and GST proteins.	Inhibits oxidative stress, significantly improving lipid metabolism in NAFLD and reducing fat accumulation in the liver.	[127]
					Sprague-Dawley rats, HFD	50, 100, 300 mg/ kg, qd, Oral, 4 weeks	Activates the PI3K/AKT pathway, facilitating Nrf2 nuclear translocation and enhancing the expression of key antioxidant (HO-1, NQO1)	Reduces oxidative stress, leading to improvements in NAFLD and hyperlipidemia.	[128]

(*Continued*)

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Table 1 (Continued).

Natural Compound	Source	Pharmacological Effect	Cell	Dose	Animal Model	Medication Administration	Mechanism Of Action	Outcome	References
Wogonoside	Scutellaria baicalensis Georgi	Antioxidant, Antimicrobial, Anti-inflammatory, Anticancer, Neuroprotective, Cardiovascular protective, Antidiabetic			Male C57BL/6 mice, HFD	5, 10, 20 mg/kg, qd, Gavage, 12 weeks	Activates Nrf2/HO-1 and NF-κB pathways	Reduces oxidative stress and inflammatory responses, provides hepatoprotection in MASLD models	[129]
Anthraquinone Compounds									
Aloin	Aloe Vera Leaves	Antioxidant, Anti-inflammatory, Anticancer, Antibacterial			Male wild-type or nuclear erythroid 2-related factor 2 (Nrf2) knock-out (KO) mice, Choline-deficient, L-amino acid-defined, high-fat (CDAAH) diet	10, 20, 40mg/kg, qd, Gavage, 12 weeks	Activates the Nrf2/HO-1 pathway	Antioxidant, Anti-Inflammatory, and Anti-Apoptotic Effects to Inhibit the Progression of MASH.	[130]
Polyacetylene Compounds									
Capillin	Artemisia capillaris Thunb	Anti-inflammatory, Anti-allergic, Anticancer, Antibacterial	FL83B hepatocytes, Palmitic acid (PA)	25, 50, 100, 200 μM	C57BL/6J mice, HFD	25, 50, 100 μmol/kg, fed, 5 weeks	Promotes Nrf2/HO-1 expression and inhibits the NLRP3-ASC-Caspase1 inflammasome	Inhibits palmitic acid (PA)-mediated oxidative stress and hepatocyte apoptosis, improves liver fat accumulation, oxidative stress, and liver injury in MASH models	[131]

Lignan Compounds									
Schisandrin B	Schisandra Chinensis	Antihyperlipidemic, Antioxidant, Anti-ER stress, Anti-inflammatory, Cardioprotective, Neuroprotective	HSC-T6 cells, TGF-β	5, 10, 30 μM	Male Wistar rats, CCl_4	25, 50 mg/kg, qd, Gavage, 4 weeks	Activates nuclear Nrf2 and HO-1, GCLC, NQO1 expression; inhibits TGF-β/Smad signaling pathway	Reduces oxidative stress and HSCs activation	[132,133]
Polyphenol Compounds									
Raspberry Extract (RBE)	Raspberry	Antioxidant, Anti-inflammatory, Anticancer, Endothelial function regulation	HSC-T6 cell, FBS	125, 250, 500 μg/mL	Wistar rats, DMN	25, 50 mg/kg, qod, Oral, 4 weeks	Upregulates Nrf2/HO-1 and PPAR-γ signaling pathways	Eliminates oxidative stress, induces HSC apoptosis, alleviates liver fibrosis	[134]
Saponin Compounds									
Ginsenoside Rg1	Ginseng	Antioxidant, Anti-inflammatory, Anti-apoptotic	HSCs, CCl_4	1 μmol/L	Male Wistar rats, CCl_4	10, 20, 40 mg/kg, qd, 14 days	Promotes Nrf2 nuclear translocation, increases expression of antioxidant enzymes (HO-1, SOD, GSH-Px, CAT)	Inhibits Oxidative Stress to Suppress Hepatic Fibrosis.	[135]
Phenolic Acid Compounds									
Tanshinol	Salvia Miltiorrhiza	Antioxidant, Anticancer, Anticoagulant, Cardiovascular protection, Neuroprotection			Sprague-Dawley rats, CCl_4	20, 40 mg/kg, qd, Intraperitoneal injection, 8 weeks	Activates Nrf2/HO-1 signaling pathway, increases SOD and GSH-Px expression, reduces MDA levels; suppresses NF-κB signaling pathway, reduces expression of inflammatory factors (TGF-β, TNF-α, COX-2, IL-1β, IL-6)	Reduces oxidative stress and inflammatory responses, decreases liver fibrosis in rat models	[136]
Salvianolic Acid A	Salvia Miltiorrhiza	Antioxidant, Anti-platelet, Antithrombotic			Male Balb/c mice, CCl_4	20, 40 mg/kg, qd, Gavage, 6 weeks	Regulates Nrf2/HO-1, NF-κB/IκBα, p38 MAPK, and JAK1/STAT3 signaling pathways, increases SOD and GSH-Px levels, reduces MDA levels	Reduces oxidative stress and inflammatory responses, improves liver fibrosis	[137]

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infiltration, and decreases the expression of pro-inflammatory cytokines, thereby exerting anti-lipid deposition, antioxidant, and anti-inflammatory effects.[112] Hesperetin can alleviate hepatic steatosis, oxidative stress, inflammatory cell infiltration, and fibrosis by activating the PI3k/AKT-Nrf2 pathway, up-regulating antioxidant levels (SOD/GPX/GR/GCLC/HO-1), decreasing ROS production, inhibiting NF-κB activation, and decreasing the secretion of inflammatory factors (TNF-α and IL-6).[123] Wogonoside activates the Nrf2/HO-1 pathway to inhibit oxidative stress and reduces inflammation by inhibiting the NF-κB pathway to protect MASLD mice from liver injury, and significantly reduces liver mass, liver index, and levels of LDL, TG, and TC in the wogonoside group as compared to the MASLD group.[129] Scutellarin can alleviate non-alcoholic fatty liver disease (NAFLD) by activating the Nrf2/HO-1 signaling pathway, thereby reducing oxidative stress.[127,128] Naringin activates the Nrf2/HO-1 pathway, inhibits the NF-κB/TNF-α pathway, and reduces endogenous triglyceride synthesis, thereby preventing the progression of MASLD.[108] Geniposide (GEN) activates Nrf2 expression, increasing cytoplasmic HO-1 protein levels and significantly reducing lipid accumulation in HepG2 cells. Knockdown of Nrf2 diminishes the liver's antioxidant capacity and nullifies GEN's beneficial effects on TC, TG, and LDL levels.[120] Dehydroabietic acid (DA) binds to Keap1, activates Nrf2-ARE, and promotes the expression of HO-1, GSH, and GPX4, thereby inhibiting ROS accumulation and reducing MDA levels, which alleviates HFD-induced MASLD. Additionally, DA inhibits ferroptosis by upregulating key genes, including ferroptosis suppressor protein 1 (FSP1).[113]

Impact of the Nrf2/HO-1 Signaling Pathway on MASH

Nrf2/HO-1 Signaling Pathway and MASH

Non-alcoholic steatohepatitis (NASH), also known as metabolic dysfunction-associated steatohepatitis (MASH), is a severe inflammatory form of MASLD.[143] MASH is characterized by fatty infiltration, oxidative stress, and necrotic inflammation of the liver, with or without fibrosis[144,145] significantly increasing the risk of progressing to severe liver disease.[146] Nrf2 regulates the recruitment of inflammatory cells and induces antioxidant responses to counteract the inflammatory process.[147] Studies have shown that Nrf2 activation can inhibit NF-κB activity, thereby reducing the expression of pro-inflammatory cytokines and inflammatory mediators such as IL-1, IL-6, IL-10, TNF-α, COX, NO, and iNOS, as well as adhesion molecules like ICAM-1 and VCAM-1.[148,149] During this process, the Nrf2/HO-1 pathway plays a crucial role by reducing ROS levels through the inhibition of hepatic oxidative stress. Since ROS and their oxidized lipid peroxides can activate NF-κB, leading to enhanced pro-inflammatory signaling, the Nrf2/HO-1 pathway mitigates this inflammation by decreasing the production of ROS and lipid peroxides.[150,151] Clearly, the activation of the Nrf2/HO-1 pathway not only enhances the activity of antioxidant enzymes (such as superoxide dismutase and CAT), reducing oxidative damage to hepatocytes but also effectively suppresses the excessive expression of NF-κB-dependent inflammatory factors, thereby alleviating the inflammatory response.[123] Okada et al[152] discovered that mice with Nrf2 gene deficiency displayed increased oxidative stress, steatosis, inflammation, fibrosis, and ferroptosis under a methionine- and choline-deficient (MCD) diet, resulting in the rapid progression of MASH.[153] In contrast, activating Nrf2 can inhibit MASH by reducing oxidative stress and ameliorating lipotoxicity, inflammation, ER stress, and iron overload.[154] Furthermore, upregulation of the HO-1 gene can alleviate hepatic steatosis and necroinflammatory responses, significantly lowering serum ALT and AST levels in MASH mice.[155] Li et al[156] further confirmed that upregulating the Nrf2/HO-1 signaling pathway effectively inhibits oxidative stress and inflammatory damage and significantly reduces lipid levels, as well as levels of ALT, AST, MDA, IL-1β, and TNF-α. Additionally, it enhances the activity of SOD and GSH-Px, thereby alleviating hepatic steatosis, ballooning degeneration, and inflammation. These findings indicate that activation of the Nrf2/HO-1 pathway is crucial for combating MASH.[49]

Natural Compounds Modulating the Nrf2/HO-1 Pathway to Mitigate MASH

Aloin exerts protective effects against MASH by mediating antioxidant, anti-inflammatory, and anti-apoptotic actions through activation of the Nrf2/HO-1 pathway.[130] Capillin can inhibit PA-mediated oxidative stress in hepatocytes by promoting the expression of Nrf2/HO-1 and reduce PA-mediated hepatocyte apoptosis by suppressing the NLRP3-ASC-Caspase1 inflammasome. Through these mechanisms, Capillin effectively ameliorates hepatic fat accumulation, oxidative stress, and liver injury in MASH mice.[131] Flavones of hawthorn leafonon mitigate oxidative stress-induced cellular

damage and liver inflammation by promoting Nrf2/HO-1 expression and inhibiting COX-2 overexpression, thus preventing the development of MASH.[124] Xin et al[125] found that baicalin alleviates oxidative stress by activating the Nrf2/HO-1 pathway in the liver and inhibits NF-κB activation, reducing the expression of IL-6 and TNF-α, thus suppressing inflammation. Additionally, baicalin regulates liver mitochondrial function. Further research by Shi et al[126] revealed that baicalin reduces NLRP3/Caspase1/GSDMD levels by activating Nrf2/HO-1 expression, thereby inhibiting pyroptosis and decreasing lipid accumulation and inflammation in the liver tissues of MASH mice.

Impact of the Nrf2/HO-1 Signaling Pathway on Hepatic Fibrosis

Nrf2/HO-1 Signaling Pathway and Hepatic Fibrosis

Hepatic fibrosis is a reversible wound-healing response and degenerative disease caused by the excessive deposition of extracellular matrix proteins such as collagen. This response represents the liver's mechanism to counteract prolonged injury or disease, aiming to contain the damaged area and promote healing. However, persistent fibrosis can progress to cirrhosis and liver failure, ultimately necessitating a liver transplant.[157] Oxidative stress is a major factor in hepatocyte injury and may exacerbate inflammation and fibrosis in MASH patients.[158] Activation of Nrf2 and HO-1 can effectively ameliorate hepatic fibrosis.[159–161] Khadrawy et al[162] demonstrated that activating the Nrf2/HO-1 signaling pathway improves oxidative stress, inflammation, and hepatic fibrosis in rats. This improvement is evidenced by decreased levels of serum transaminases, ALP, γGT, and bilirubin, inhibition of MDA, NF-κB p65, and inflammatory cytokine expression, and reduced histological changes and collagen accumulation in the liver, thereby ameliorating hepatic fibrosis.

Natural Compounds Modulating the Nrf2/HO-1 Pathway to Mitigate Hepatic Fibrosis

Schisandrin B activates nuclear Nrf2 and Nrf2-related antioxidant genes (HO-1, NQO1, GCLC), thereby inhibiting oxidative stress-mediated hepatocyte injury in fibrotic rats. Additionally, it suppresses hepatic stellate cell (HSC) activation by inhibiting the TGF-β/Smad signaling pathway.[132] Raspberry extract (RBE) upregulates the Nrf2/HO-1 and PPAR-γ signaling pathways, eliminates oxidative stress, induces HSC apoptosis, and alleviates hepatic fibrosis.[134] Tanshinol not only enhances SOD and GSH-Px levels and reduces MDA levels via the Nrf2/HO-1 signaling pathway, thereby inhibiting oxidative stress-induced damage, but also inhibits the NF-κB signaling pathway, reducing the expression of inflammatory factors such as TGF-β and TNF-α. Consequently, tanshinol lowers the levels of alanine transaminase, aspartate transaminase, total bilirubin, hyaluronic acid, type IV collagen, laminin (LN), and procollagen III peptide (PIIIP) in fibrotic rats, significantly inhibiting hepatic fibrosis.[136] Salvianolic acid A increases SOD and GSH-Px levels, decreases MDA levels, inhibits inflammation and oxidative stress, and ameliorates CCl4-induced hepatic fibrosis by modulating the Nrf2/HO-1, NF-κB/IκBα, p38 MAPK, and JAK1/STAT3 signaling pathways.[137] Ginsenoside Rg1 promotes the nuclear translocation of Nrf2 and enhances the expression of antioxidant enzymes such as HO-1, SOD, and GSH-Px, thereby inhibiting hepatic fibrosis.[135] Betulin (BE) upregulates Nrf2 and HO-1 expression in a dose-dependent manner and inhibits NF-κB gene expression, effectively reducing serum lipid and transaminase levels in HFD-fed rats, thereby preventing hepatic fat accumulation, steatosis, and fibrosis.[114] Fan et al[115] demonstrated that Asiatic acid (AA) effectively ameliorates CCl_4-induced hepatic fibrosis in rats. The underlying mechanisms include the activation of the Nrf2/ARE signaling pathway, resulting in increased nuclear Nrf2 expression and decreased cytoplasmic Nrf2 levels. This upregulates Nrf2 target proteins such as HO-1 and NQO-1, effectively countering oxidative stress-induced liver damage. Additionally, AA inhibits the NF-κB/IκBα and JAK1/STAT3 signaling pathways, reducing the release of inflammatory factors and the activation of HSCs, further preventing the progression of hepatic.

Impact of the Nrf2/HO-1 Signaling Pathway on Liver Cirrhosis and Liver Cancer

Nrf2/HO-1 Signaling Pathway in Liver Cirrhosis and Liver Cancer

Liver cirrhosis and liver cancer represent the advanced stages of MASLD. Cirrhosis significantly impairs liver structure and function, potentially resulting in liver failure, portal hypertension, and liver cancer. Oxidative stress is a key mechanism driving hepatic lipid metabolism disorders, cirrhosis, and fibrosis.[163] Studies have indicated that Nrf2-deficient mice are more prone to developing MASH accompanied by cirrhosis.[164] During liver cirrhosis, the activation of the ER stress response pathway, specifically XBP1-Hrd, upregulates Hrd1 transcription and inhibits Nrf2-mediated antioxidant responses, thereby promoting the progression of cirrhosis.[165] However, enhanced Nrf2 can prevent cirrhosis

by reducing ROS levels and subsequently decreasing HSCs activation.[166] Additionally, once induced, HO-1 can exert protective effects in cirrhosis.[167] Xue et al demonstrated that HO-1 protects hepatocytes in cirrhotic rats from liver I/R injury by reducing oxidative stress, apoptosis, and inflammation.[168]

Hepatocellular carcinoma (HCC) is the most prevalent form of primary liver cancer, constituting over 80% of all cases.[169] Research indicates that Astragaloside IV facilitates the phosphorylation of Nrf2, enhances the activation of HO-1 expression, mitigates oxidative stress, and inhibits the progression of HCC.[170] Furthermore, Purslane (Portulaca oleracea) has been shown to effectively suppress the phosphorylation of PI3K, Akt, mTOR, NF-κB, and IκBα, upregulate the expression of Nrf2 and HO-1, exhibit anti-inflammatory and antioxidant properties, reduce the levels of ALT, AST, IL-6, IL-1β, TNF-α, and MDA in HCC mice, restore SOD activity, and markedly ameliorate liver pathological alterations.[171] Additionally, HO-1 inhibits the proliferation and migration of HCC in vivo by downregulating the levels of miR-30d and miR-107 through its metabolites, thereby significantly suppressing HCC progression.[172] Hence, the activation of the Nrf2/HO-1 signaling pathway presents a potential therapeutic approach for HCC.

However, the application of the Nrf2/HO-1 signaling pathway in MASLD-related cirrhosis and liver cancer remains controversial. Some researchers suggest that Nrf2/HO-1 activation may, in certain cases, increase portal vein pressure and cause abnormal visceral hemodynamics in cirrhotic rats with portal hypertension.[173] Moreover, sustained activation of Nrf2 may exacerbate the progression of HCC,[174] and promote chemoresistance in cancer cells.[174] Additionally, short (GT)n variants in the HO-1 gene may increase susceptibility to cirrhosis and cancer.[175] Therefore, the molecular mechanisms and potential advantages and disadvantages of the Nrf2/HO-1 antioxidant pathway in cirrhosis and liver cancer require further investigation and discussion.

Natural Compounds Modulating the Nrf2/HO-1 Pathway to Liver Cirrhosis and Liver Cancer

Astragaloside IV (AS-IV), one of the primary active components of Astragalus, possesses pharmacological properties including anti-inflammatory and anticancer effects. Zhang et al[117] demonstrated that AS-IV activates the pSmad3C/3L and Nrf2/HO-1 pathways, thereby inhibiting collagen fiber deposition and the development of primary liver cancer. Furthermore, the Nrf2/HO-1 pathway is notably more effective in contributing to the anti-HCC effects of AS-IV compared to pSmad3C/3L.[118]

Conclusion

MASLD is a complex lipotoxic disease characterized by hepatic steatosis and oxidative stress, which plays a central role in its pathophysiology. The Nrf2/HO-1 pathway is a critical antioxidant mechanism in MASLD. Activation of Nrf2 regulates the gene expression of various endogenous antioxidant enzymes, including HO-1, NQO1, SOD, potentially alleviating hepatic steatosis, MASH,[153] liver fibrosis,[176] and the onset and progression of HCC.[177] HO-1, regulated by Nrf2, is essential for the removal of toxic heme. Upregulation of HO-1 can reverse the progression of hepatic steatosis, liver fibrosis, cirrhosis, and systemic complications.[47] Furthermore, targeting the Nrf2/HO-1 pathway can not only effectively inhibit the progression of MASLD but also serve as an effective treatment for related complications such as obesity, type 2 diabetes, and sarcopenia.[178,179]

Studies have shown that various natural compounds mitigate the progression of MASLD by activating the Nrf2/HO-1 pathway, which regulates lipid metabolism, oxidative stress, inflammatory responses, and apoptosis in hepatocytes (Table 1). Additionally, other drugs also modulate MASLD through the Nrf2/HO-1 pathway. For example, liraglutide[180] and lansoprazole[181] have been shown to improve hepatic lipid metabolism and oxidative stress via the activation of the Nrf2/HO-1 pathway. Moreover, traditional Chinese medicine formulations, such as Hedansanqi Tiaozhi Tang (HTT)[48] and Di'ao Xinxuekang (DXXK),[156] alleviate MASLD by activating Nrf2/HO-1, thus inhibiting oxidative stress and inflammation.

In summary, the Nrf2/HO-1 pathway regulates various pathological processes, including lipid metabolism, oxidative stress, inflammatory response, and apoptosis, effectively inhibiting the pathological progression of MASLD. Targeting this pathway holds promise for providing a more comprehensive treatment strategy for MASLD compared to existing drugs. However, the development of this pathway as a therapeutic target still faces numerous challenges. Firstly, precisely activating Nrf2 is a critical issue, as excessive activation may lead to adverse effects such as abnormal cell

proliferation and immune suppression, which need to be addressed in future studies. Secondly, while various natural compounds have shown potential therapeutic effects on MASLD in animal models, their clinical translation still faces significant challenges. Currently, there is a lack of large-scale, randomized controlled clinical trials to validate the efficacy and safety of these compounds. Additionally, optimizing their dosage and administration routes to ensure effectiveness and long-term safety across different individuals remains an urgent issue to be resolved.

Future research should focus on the precise regulatory mechanisms of the Nrf2/HO-1 pathway, exploring how to selectively activate Nrf2 without eliciting adverse effects. Additionally, the clinical applicability of natural compounds in MASLD needs to be validated through further large-scale clinical trials. By conducting in-depth studies on the Nrf2/HO-1 pathway, optimizing natural compounds, and investigating their synergistic effects with existing medications, we can develop more personalized and safe treatment strategies for MASLD. This endeavor will require the collaborative efforts of more researchers in the field.

Consent for Publication

All authors have agreed to the publication of this manuscript.

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