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REVIEW

Deciphering the Role of Oroxylin A in Liver Fibrosis

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Abstract: Liver fibrosis is a dynamic and complex process characterized by the excessive accumulation of extracellular matrix (ECM) components, driven by a heterogeneous population of hepatic myofibroblasts (MFs). Current treatments for liver fibrosis primarily include pharmacological interventions such as antiviral and anti-fibrotic therapies, alongside lifestyle modifications, including dietary changes and alcohol abstinence. However, the therapeutic outcomes remain suboptimal. Existing anti-fibrotic medications are unable to fully reverse liver fibrosis, particularly in its advanced stages, and some drugs may even induce adverse effects. Recently, the challenge of combating liver fibrosis has attracted increasing attention from both the academic community and the general public, leading to extensive research efforts and several significant discoveries. Hepatocyte senescence, an irreversible and inevitable process, plays a crucial role in the onset and progression of various liver diseases. It serves as a key regulatory factor in the development of liver fibrosis, exerting a considerable impact on its progression. Senescent hepatocytes secrete the senescence-associated secretory phenotype (SASP), which interacts with hepatic stellate cells (HSCs), promoting their transformation into MFs. Additionally, SASP fosters a cellular microenvironment conducive to the advancement of hepatic fibrosis, thereby accelerating its progression. This review comprehensively examines the natural flavonoid compound Oroxylin A (OA), which regulates hepatocyte senescence in the context of liver fibrosis. The paper also discusses the current research landscape, trends, and critical challenges related to hepatocyte senescence in liver fibrosis, along with the mechanisms through which OA influences hepatocyte senescence, either promoting or delaying its onset.

Keywords: oroxylin A, liver fibrosis, cell senescence

Introduction

Liver fibrosis refers to the formation of fibrous scars.[1] Its pathogenesis is complex, often accompanying progressive liver injury that evolves from mild to severe stages. This process reflects the liver's general response to both acute and chronic injury.[2] The mechanisms underlying liver fibrosis involve various cells, signaling pathways, and intricate cellular interactions. Characterized by excessive deposition of extracellular matrix (ECM) components, liver fibrosis results from chronic liver injury, which progressively impairs normal liver function. This injury can be caused by factors such as viral infections,[3] non-alcoholic steatohepatitis (NASH),[4] alcohol-related liver disease (ALD),[5] and autoimmune disorders.[6] Over time, liver fibrosis can either resolve or advance to cirrhosis and end-stage liver disease.[7] Treatment strategies for hepatic disorders are primarily determined by the underlying etiology, focusing on eradicating or mitigating the pathogenic factors contributing to chronic liver disease (CLD).[8] In this context, modulation of hepatic stellate cell (HSC) activity plays a pivotal role.[9,10]

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Myofibroblasts (MFs) are central to fibrogenesis, with HSCs serving as the primary precursors to these cells.[11] Since HSCs were first identified as collagen-producing cells in the liver, key signaling pathways contributing to fibrosis have been delineated.[12] HSCs are located in the perisinusoidal space and typically remain quiescent.[10] However, upon liver injury, quiescent HSCs are activated and differentiate into highly proliferative, fibrotic, and contractile MFs under the influence of profibrotic cytokines, such as transforming growth factor-β1 (TGF-β1), epidermal growth factor (EGF), and platelet-derived growth factor (PDGF).[13,14] Thus, HSC activation is recognized as a central driver of liver fibrosis.[15] A substantial body of clinical and experimental evidence demonstrates that the removal or inactivation of HSCs via apoptosis can lead to the absorption of fibrous scars and the resolution of liver fibrosis.[15–17] Therefore, inducing HSC senescence may serve as a protective mechanism to mitigate the progression of liver fibrosis.[18]

The complex pathogenesis of liver fibrosis, coupled with the limited clinical efficacy of current anti-fibrotic therapies and the occurrence of adverse reactions, particularly in patients with advanced alcoholic steatosis and those with hereditary or autoimmune liver diseases (especially non-alcoholic steatosis), remains a significant challenge.[19] For instance, statins, which are commonly used as lipid-lowering agents, have recently been shown to have independent, multi-faceted effects in patients with CLD.[20] Animal studies on hepatic fibrosis have indicated that statins may slow the progression of fibrosis.[21] However, recent evidence suggests that statins can induce rhabdomyolysis, particularly in patients with liver cirrhosis.[22] Bafilomycin, a galectin-3 inhibitor, has shown potent antifibrotic efficacy in animal models of liver fibrosis,[23] but clinical trials have reported that it is associated with an increased risk of infections, gastrointestinal disorders, and connective tissue diseases in patients with hepatic fibrosis.[24] The potential of probiotics and prebiotics as antifibrotic agents has been explored in numerous studies. For example, probiotics have been found to alleviate hepatic fibrosis in diet-induced mouse models of NASH, though there is still insufficient clinical evidence to support their use.[25] Bioactive components from traditional Chinese medicines have also demonstrated antifibrotic properties. Curcumin, for instance, has been shown to slow the progression of hepatic fibrosis in experimental models of steatohepatitis,[26] but its low oral bioavailability and limited clinical trials hinder its widespread use.[27] There is a pressing need within the medical field to develop more effective and safer anti-fibrotic agents. Scutellaria baicalensis, a traditional Chinese herbal medicine, is widely recognized for its anti-fibrotic effects. Oroxylin A (OA), one of its active components, has been shown in network pharmacology studies to inhibit hepatic fibrosis through multiple targets and pathways.[28] These mechanisms include inducing apoptosis in senescent HSCs, suppressing HSC proliferation, reducing pro-inflammatory factor production, and blocking inflammatory signaling pathways for anti-inflammatory effects.[29] Compared to other drugs, OA's multi-target and multi-pathway synergistic effects contribute to more pronounced clinical efficacy.

Cellular Senescence

Aging is a highly intricate process driven by multiple cellular and molecular mechanisms, intricately linked to the passage of time. It is a dynamic event, marked by a combination of aging indicators that result in a decline at the molecular, cellular, and systemic levels of the organism.[30] This process is meticulously regulated and influenced by a range of internal and external factors, including irradiation, nutrient deprivation, genotoxicity, oxidative stress, telomere attrition, telomere structure modifications, mitotic signaling, oncogene activation, epigenetic modifications, chromatin rearrangements, mitochondrial dysfunction, immune regulation, infections, inflammation, and exposure to various environmental stressors.[31] These factors culminate in irreversible growth arrest, a condition known as cellular senescence.[32]

Cells, the fundamental units of both structure and function in organisms, are at the core of aging. Cellular senescence and aging are intrinsically linked concepts. Initially referred to as the Hayflick limit, cellular senescence was first described by Leonard Hayflick and Paul Moorhead in 1961, who demonstrated that fibroblasts in culture eventually lose their ability to divide, challenging the prevailing notion that mammalian cells in culture are immortal.[33] Cellular senescence is a homeostatic biological process critical to the aging process and includes both replicative senescence (RS) and stress-induced premature senescence (SIPS). It can occur at any stage of life, from the embryonic phase to adulthood.[34] Cellular senescence serves as a stress response, akin to differentiation, proliferation, or apoptosis, leading to permanent cell cycle arrest and profound phenotypic changes, such as the generation of a bioactive secretome known as the senescence-associated secretory phenotype (SASP).[35] By inducing cell growth arrest, cellular senescence restricts the

replication of aged or damaged cells. In addition to halting the cell cycle, senescent cells undergo significant phenotypic alterations, including metabolic reprogramming, chromatin rearrangements, and autophagy regulation.[36] Cellular senescence is regarded as a fundamental mechanism of aging in both animals and humans. The accumulation of DNA damage or other cellular stressors can induce senescence in proliferating cells as well as in terminally differentiated, non-dividing cells. Senescent cells are characterized by substantial chromatin changes, alterations in the secretory proteome, increased expression of senescence markers (such as Cdkn2a/p16Ink4a and Cdkn1a/p21Cip1), immune evasion, and resistance to apoptosis.[37]

Hepatocytes are composed of various cell types, including parenchymal cells and non-parenchymal cells, such as HSCs.[38] Similar to other cell types, hepatocyte senescence is a stress response characterized by permanent cell cycle arrest and the secretion of the SASP. As with other cellular types, the primary mechanisms driving senescence in hepatocytes include telomere shortening and mitochondrial dysfunction, both of which are particularly prominent in liver cells. In normal human cells lacking telomerase, telomeres progressively shorten with each cell division. This triggers DNA damage responses through the induction of tumor suppressors, such as p53 and p16, forcing hepatocytes into senescence and apoptosis.[39] Previous research has further established a direct relationship between telomere shortening in hepatocytes and the progression of hepatic fibrosis, as observed in human liver cirrhosis samples.[40] Mitochondrial dysfunction also plays a critical role in hepatocyte senescence. Senescent hepatocytes exhibit severe changes in mitochondrial structure, dynamics, and function.[41] One key mechanism through which mitochondria contribute to senescence is the production of reactive oxygen species (ROS). Excessive ROS, which are toxic metabolic byproducts, damage intracellular macromolecules, including those in the telomere regions. This damage accelerates telomere shortening and contributes to premature senescence.[42] Additionally, crosstalk between mitochondria and SASP factors further exacerbates hepatocyte senescence.[43]

Hepatocyte senescence represents a dualistic phenomenon within the context of liver fibrosis, regulating its progression through a complex network of interconnected mechanisms. On one hand, senescent cells can secrete SASP factors, which include interleukin-6 (IL-6), IL-8, and TGF-β.[35] IL-6 can bind to its receptors on the surface of HSCs, activating the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway. This activation upregulates the expression of α-smooth muscle actin (α-SMA), promoting the transformation of HSCs into MF-like cells, thereby accelerating the progression of fibrosis.[44] TGF-β, a key pro-fibrotic mediator in liver fibrosis, directly targets HSCs. Through the Smad signaling pathway, TGF-β enhances the synthesis of ECM components, such as collagen. Additionally, TGF-β interacts with other SASP factors to create a cellular microenvironment that fosters the development of fibrosis, thus worsening liver fibrosis.[45–47] On the other hand, cellular senescence may act as an endogenous protective mechanism in the liver in response to injury. When the liver is subjected to various injurious agents, such as viral infections, drug toxicity, and alcohol-induced damage, senescence-related signaling pathways (eg, p53/p21, p16/RB) are activated, initiating the cell senescence program. This results in cells becoming arrested at a specific stage of the cell cycle, halting further division and proliferation.[48] This process effectively prevents abnormal cell proliferation that could otherwise arise from the continued division of damaged cells, thereby reducing the risk of liver tumorigenesis.[49] Additionally, MF senescence reduces ECM secretion, increases the expression of ECM-degrading enzymes, and enhances immune surveillance, all of which help mitigate scar formation and fibrosis[50] Furthermore, evidence suggests that cell senescence, particularly hepatocyte senescence, may play a role in regulating lipid accumulation and inflammatory responses in patients with non-alcoholic fatty liver disease (NAFLD) at various stages.[11]

Introduction to OA

OA is a flavonoid found in the plants Oroxylum indicum and Scutellaria baicalensis Georgi.[28] Scutellaria baicalensis, commonly used in traditional Chinese medicine, is derived from the dried root of the Scutellaria baicalensis plant. It has a long history of use in both traditional formulations and modern herbal medicine, and possesses a wide range of therapeutic effects.[51] The plant has been employed as a promising candidate for analgesia, antipyretic, anti-inflammatory, anticancer, antiviral, and antibacterial treatments,[52] and is widely used in China, Japan, and South Korea for managing inflammation, fever, hepatitis, allergic diseases, and hypertension.[53] Scutellaria baicalensis contains various bioactive compounds, with OA being one of its principal flavonoids. Flavonoids, as polyphenolic compounds found in plant

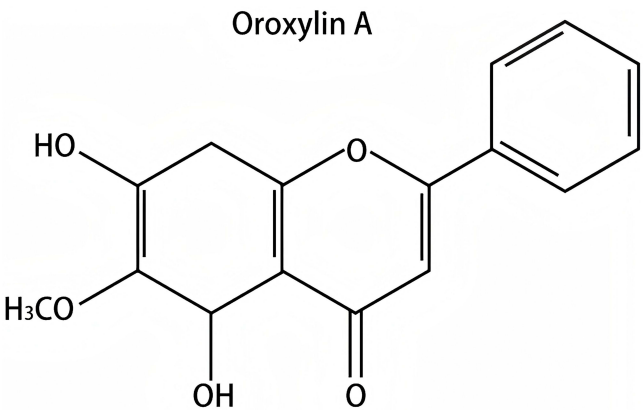

Figure 1 Molecular structure of Oroxylin A ($C_{16}H_{12}O_5$).

sources, exhibit diverse biological activities, including antibacterial, antioxidant, anti-inflammatory, antitumor, and anticancer properties. Due to their numerous biological activities and low toxicity, flavonoids have been extensively investigated as potential anticancer treatments in recent years.[54] The OA content in Scutellaria baicalensis varies based on factors such as plant origin, growth environment, harvest season, and extraction and detection methods. Currently, standardized data on its exact content are unavailable.

Chemical Structure and Physical Properties of OA

The molecular formula of OA is $C_{16}H_{12}O_5$, with a molecular weight of 284.263. Its chemical structure is 5,7-dihydroxy-6-methoxy-2-phenyl-4H-1-benzopyran-4-one, classifying it as an O-methylated flavonoid[55] (Figure 1). The structure exhibits typical flavonoid characteristics, including the benzopyranone core. The hydroxyl and methoxy functional groups within the molecule may significantly influence its biological activity and pharmacological properties. The two metabolites of OA are OA 7-O-β-D-glucuronide (or oroxyloside, OAG) and sodium OA sulfonate (OS). OA is a yellow, needle-like crystal that is soluble in organic solvents such as methanol, ethanol, and DMSO.[56]

Extraction and Synthesis of OA

Extraction

The crude extract of OA was first isolated from Oroxylum indicum using alcohol percolation and distillation, followed by extraction and crystallization, though the yield was low, at only 0.86%. In 2005, Cheng et al utilized the coexistence of enzymes and flavonoid glycosides in Scutellaria to extract total flavonoid aglycones (including baicalein, wogonin, and OA), achieving a content of up to 85%. The elution mixture was separated, collected, and the OA component was isolated. In 2011, Liu et al developed an effective method for extracting OA from Oroxylum indicum, achieving a purity of up to 99.2%.[57]

Synthesis

Due to the low concentration of OA in plants, its synthesis is necessary for practical use. In 2009, Li et al discovered a chemical synthesis method for OA that is simpler and more efficient than direct extraction, yielding greater amounts of OA.[58–60]

Mechanism of OA in Regulating Hepatocyte Senescence Against Liver Fibrosis

Flavonoids and their secondary metabolites from medicinal plants are widely recognized as natural sources for treating various diseases, owing to their low toxicity and significant therapeutic efficacy.[61] As natural pigments, flavonoids are abundant in fruits, vegetables, and other food crops. By modulating cytokines, inflammatory mediators, and enzymes, they can alleviate liver injuries caused by factors such as chemically induced damage, ALD, non-alcoholic liver disease,

immune-mediated liver injury, and hepatic ischemia-reperfusion injury.[62] Flavonoids exert broad inhibitory effects on hepatic fibrosis. For instance, quercetin combats hepatic fibrosis through multiple mechanisms. However, its poor water solubility and in vivo instability present significant barriers to its development as a pharmaceutical agent.[63] Additionally, quercetin has low oral bioavailability, with human pharmacokinetic studies confirming that its oral bioavailability is only 2% after a single dose.[64] Similar to OA, baicalein and baicalin, which are also derived from the roots of Scutellaria baicalensis, have shown therapeutic potential in treating hepatic fibrosis. However, the effective dose of baicalin required for treating hepatic fibrosis is significantly higher, reaching 70 mg/kg—3.5 times the dose of OA. While most studies on baicalin focus on its effects in renal fibrosis, research on its role in hepatic fibrosis remains relatively limited.[65] Compared to these other flavonoids, OA demonstrates more pronounced, multi-target therapeutic effects, making it a more promising candidate for treating hepatic fibrosis.

OA Prevents the Methylation of cGAS by Blocking the Production of Methionine Metabolites

DNA methylation plays a critical role in the development of liver fibrosis. Abnormal expression of the DNA sensing pathway is linked to the DNA damage response in senescent cells.[66,67] The cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) signaling pathway is a key component of the innate immune response. It triggers the SASP through the accumulation of cytoplasmic DNA, including chromatin fragments, mitochondrial DNA, and cDNA, in senescent cells.[68,69] A substantial body of evidence indicates that the cGAS-STING pathway activates the SASP and autologous DNA fragments in senescent cells.[70] cGAS catalyzes the synthesis of cyclic GMP-AMP (cGAMP) from ATP and GTP by recognizing double-stranded DNA. The STING receptor detects cGAMP and promotes the production of type I interferons and other cytokines through its involvement in downstream signaling pathways.[15] The expression of the cGAS-STING pathway is influenced by its methylation status,[71,72] with DNA methyltransferase (DNMT) and DNA demethylase enzymes maintaining its normal methylation levels. Alterations in methylation lead to changes in the expression of these pathways.

The methionine cycle serves as the primary catabolic pathway for methionine in the body, providing methyl groups through transmethylation.[73] S-adenosylmethionine (SAM), the main biological methyl donor, plays a crucial role in the methylation of DNA, RNA, and proteins.[74] Methionine adenosyltransferase II (MATII), composed of the catalytic subunit MAT2A and the regulatory subunit MAT2B, is a key enzyme in methionine cycle metabolism. These enzymes catalyze the conversion of methionine and ATP to SAM.[75] Liver fibrosis is associated with elevated levels of MATII.[76,77] Increased MATII levels affect the activity of DNMT and lead to abnormal methylation levels. OA can reverse the stimulatory effect of methionine cycle supplementation on DNMT activity, inhibit methionine cycle metabolism in HSCs, and downregulate the expression of MAT2A.[78] OA regulates protein expression to inhibit MAT2A, significantly reversing the upregulation of ATP, methionine, SAM, and S-adenosylhomocysteine (SAH) induced by MAT2A plasmid expression. Moreover, when human HSCs (LX2) were stably transfected with the DNMT3A plasmid, OA reversed the high DNA methylation levels of cGAS and promoted the expression of SASP. Hepatic fibrosis markers in human serum indicated that the DNMT3A plasmid diminished the therapeutic effect of OA[79] (Figure 2). Overall, OA may induce demethylation of the cGAS gene, resulting in the downregulation of DNMT, thereby inhibiting cGAS DNA methylation and activating the cGAS-STING pathway,[80,81] which promotes HSC senescence.[18,82]

OA Activates Ferritin Autophagy by Regulating the cGAS-STING Pathway, Which Leads to HSC Senescence and Alleviates Liver Fibrosis

Substantial iron ion accumulation occurs in cells during senescence, leading to changes in the levels of iron homeostasis proteins.[83] Excessive intracellular iron accumulation results in iron overload (Wu et al 2021), which is closely linked to the activation of ferritin autophagy.[84] Ferritin autophagy, mediated by nuclear receptor coactivator 4 (NCOA4), involves binding to ferritin heavy chain 1 (FTH1) in the autophagosome under conditions of low intracellular iron. This process transfers the autophagic vesicle to the lysosome, where ferritin is degraded, releasing free iron and inducing ferroptosis.[85] The Fenton reaction, catalyzed by iron ions, generates excessive lipid oxidation, causing cell damage and triggering

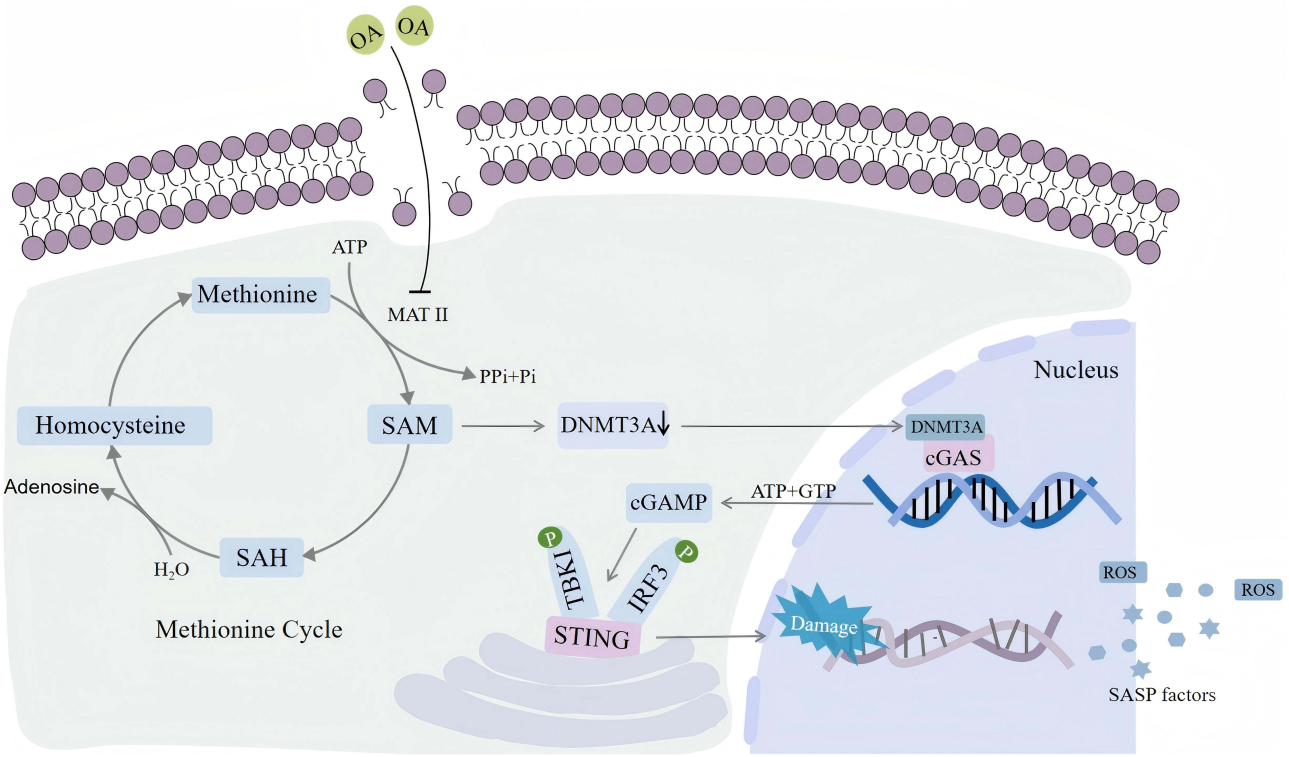

Figure 2 Mechanism diagram of Oroxylin A-induced senescence in hepatic stellate cells.

senescence by producing ROS.[86] Consequently, ferritin autophagy may contribute to cell senescence through this novel mechanism.

In the aforementioned cGAS-STING pathway, ATP and GTP serve as substrates in DNA-activated cGAS, producing the second messenger cGAMP. This promotes the phosphorylation of TANK-binding kinase 1 (TBK1) and interferon regulatory factor 3 (IRF3) by binding and activating STING, leading to the production of type I interferon (IFN-β) and other immune mediators.[87] OA can upregulate the expression of cytokines IL-1β, IL-6, and IFN-β, while silencing cGAS reduces their expression.[88] Additionally, increased IFN-β levels promote the expression of senescence markers p16 and p21 in LX2 cells. When the cGAS-STING pathway is inhibited, NCOA4 expression decreases in a dose-dependent manner, while FTH1 expression increases. Conversely, administering IFN-β increases NCOA4 expression and decreases FTH1 expression. Autophagy-related markers (LC3 and Beclin 1) significantly decreased, and p62 expression showed an inverse trend. Immunological analyses of LC3 and NCOA4 corroborated these results. Furthermore, intracellular ROS and iron ion levels in HSCs were reduced, indicating that OA-induced ferritin autophagy in HSCs is inhibited by this pathway[79] (Figure 3). In summary, OA regulates ferritin autophagy via the cGAS-STING pathway and induces HSC senescence, contributing to the alleviation of liver fibrosis.

OA Inhibits Ethanol-Induced Hepatocyte Senescence Through the YAP Pathway and May Alleviate Liver Fibrosis

Alcohol-related liver disease (ALD), which has replaced the term “alcoholic liver disease”, is a leading cause of CLD worldwide.[89] It primarily results from long-term alcohol consumption and is a significant contributor to morbidity and mortality in liver-related diseases.[90] In the hepatic cytosol, alcohol is metabolized into acetaldehyde by alcohol dehydrogenase, a key oxidative pathway in alcohol metabolism.[91] Acetaldehyde triggers a TGF-β1-dependent late response in HSCs, maintaining a profibrotic and pro-inflammatory state.[92] It also directly activates HSCs, promoting collagen I expression.[93] Furthermore, excessive alcohol consumption can increase intestinal permeability, allowing

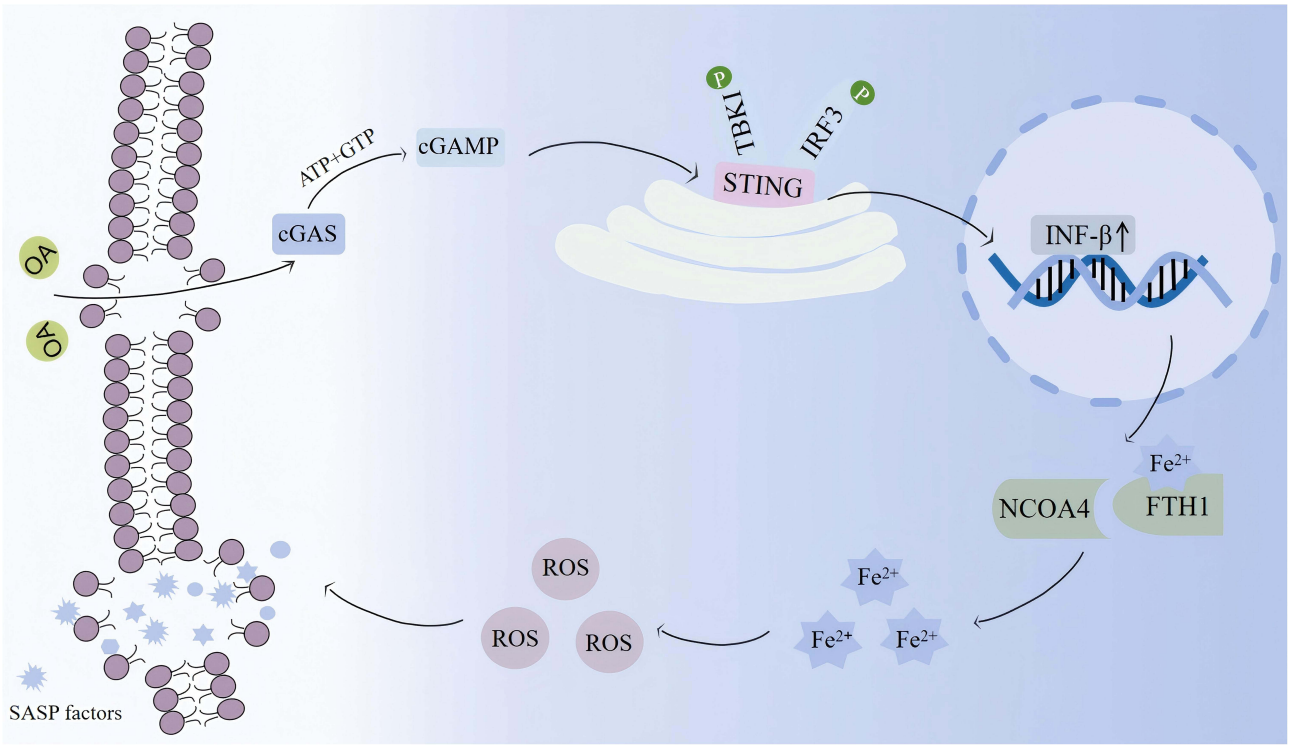

Figure 3 Mechanism diagram of Oroxylin A activating ferritinophagy and inducing hepatic stellate cell senescence by regulating the cGAS-STING pathway.

bacterial-derived lipopolysaccharide (LPS) to enter the liver. LPS binds to TLR4, stimulating Kupffer cells,[94] which secrete cytokines that activate HSCs and drive fibrosis, marking the early stages of ALD.[95]

The Hippo/YAP signaling pathway is known for its growth-inhibitory effects. Hippo pathway kinases inhibit the downstream effector Yes-associated protein (YAP) by promoting its cytoplasmic retention via S127 phosphorylation. YAP activation primarily influences gene expression through the TEAD family of transcription factors, thereby affecting cell fate.[95] YAP not only regulates cell proliferation and apoptosis[96] but also plays a critical role in cell senescence regulation.[97] As the main target of the Hippo pathway, YAP controls the fibrotic activity of HSCs[98] and is pivotal in liver regeneration, fibrosis, and cancer. Core factors in both the Hippo and Hedgehog (Hh) signaling pathways promote the transdifferentiation of HSCs, regulating the liver injury repair process.[99] Experimental evidence has shown that siRNA-mediated knockdown of YAP significantly inhibits the MF-HSC phenotype and reduces susceptibility to ferroptosis. The Hippo/YAP pathway influences ferroptotic sensitivity in HSCs by regulating the P21-GPX4 axis. Overall, YAP knockdown suppresses the myofibroblastic activity of HSCs and accelerates cellular senescence.[98] Furthermore, inducing HSC senescence has been found to reduce YAP activity.[45] Furthermore, the downregulation of YAP reduces the expression of LOXL2 in the lysyl oxidase (LOX) family (LOX, LOXL1-4), inhibiting collagen cross-linking and the progression of fibrosis in vivo.[100] Senescent cells typically exhibit characteristic alterations, such as enlarged and flattened morphology, swollen nuclei, and positive staining for senescence-associated β-galactosidase (SA-β-gal).[101] At the molecular level, cell senescence is marked by cell cycle arrest, evidenced by increased expression of p16 (a cyclin-dependent kinase family gene) and p21 (cyclin-dependent kinase inhibitor 1), along with reduced telomerase activity.[102] Ethanol induces hepatocyte senescence, as indicated by the accumulation of SA-β-gal-positive cells and elevated expression of p16, p21, and Hmga1—core events in ALD that directly damage hepatocytes.[103,104] Overexpression of YAP inhibits the expression of ethanol-induced senescence markers (p16, p21, and Hmga1) and the DNA damage marker γ-H2AX, thereby alleviating alcohol-induced hepatocyte damage.[97]

OA inhibits the protein expression of senescence markers, including p16,[105] p21,[106] and γ-H2AX[107] in ethanol-stimulated hepatocytes. OA attenuates the effects of ethanol on cell cycle arrest and ameliorates alcohol-induced hepatocyte damage by inhibiting hepatocyte senescence. Experiments have shown that in ethanol-treated hepatocytes,

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OA restores cell viability in a dose-dependent manner, with effective doses ranging between 20 and 40 μmol/L. Moreover, the use of verteporfin or YAP siRNA weakens the anti-aging effects of OA and diminishes its inhibitory effect on the expression of senescence markers, p16 and p21. These results indicate that OA reduces the number of ethanol-induced SA-β-gal-positive human hepatocytes in a dose-dependent manner.[108] Therefore, the molecular mechanism by which OA inhibits ethanol-induced hepatocyte senescence likely involves the regulation of YAP expression. This mechanism may offer a novel approach to mitigating alcoholic hepatocyte damage and combating liver fibrosis.

OA suppresses hepatocyte senescence through the YAP pathway to combat hepatic fibrosis in ALD, but its mechanism in NAFLD-associated fibrosis differs significantly. NAFLD, a prevalent condition among overweight and obese individuals and those with metabolic syndrome,[109] involves oxidative stress and ferroptosis, which exacerbate hepatic inflammation and fibrosis, driving disease progression.[110] Inflammation, a hallmark of NAFLD, plays a pivotal role in disease progression,[111] with hepatic fibrosis intensifying as NAFLD advances.[112] Experiments on high-fat diet (HFD)-induced NAFLD mice showed significant upregulation of inflammatory cytokines, which OA markedly inhibited.[113] These findings highlight OA's protective effects against inflammation and fibrosis in NAFLD. NASH, a severe subtype of NAFLD, relies on hepatocyte apoptosis for disease progression. Hepatocyte apoptosis activates the inflammasome and promotes the release of pro-inflammatory cytokines from immune cells and HSCs, contributing to liver fibrosis and NASH development. Studies indicate that OA treatment reduces palmitate-induced hepatocyte apoptosis, supporting its potential to prevent NASH.[114] Beyond its anti-apoptotic effects against high-dose palmitate, OA also suppresses hepatic steatosis.[115]

Limitations and Prospects

Despite strong evidence supporting the role of OA in treating liver fibrosis by regulating hepatocyte senescence, several limitations remain:

(1) Most studies to date have been limited to cell and animal models, with a lack of large-scale clinical trials;
(2) While OA holds promise as a potential therapeutic agent for liver fibrosis, its molecular mechanisms involve only a few molecules and pathways, leaving many aspects of its action yet to be fully explored and understood;
(3) The presence of any harmful substances in OA that might impact its use as a therapeutic drug remains unclear, and its safety profile needs further investigation.

Future directions for OA in combating liver fibrosis include:

(1) Investigating the synergistic use of OA with other drugs that modulate hepatocyte senescence, either promoting or inhibiting it;
(2) Expanding research on the molecular mechanisms by which OA combats liver fibrosis, including dynamic studies to deepen understanding;
(3) Conducting long-term, large-scale clinical trials to assess OA's efficacy and safety for human clinical application.

Author Contributions

All authors made substantial contributions to the work, including the conception, study design, execution, data acquisition, analysis, and interpretation. They participated in drafting, revising, or critically reviewing the manuscript, provided final approval for the version to be published, agreed on the journal to which the article has been submitted, and are accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest.

References

1. Hernandez-Gea V, Friedman SL. Pathogenesis of liver fibrosis. *Annu Rev Pathol*. 2011;6:425–456. doi:10.1146/annurev-pathol-011110-130246
2. Khanam A, Saleeb PG, Kottilil S. Pathophysiology and treatment options for hepatic fibrosis: can it be completely cured? *Cells*. 2021;10 (5):1097. doi:10.3390/cells10051097
3. Udompap P, Kim WR. Development of hepatocellular carcinoma in patients with suppressed viral replication: changes in risk over time. *Clin Liver Dis*. 2020;15(2):85–90. doi:10.1002/cld.904
4. Osna NA, Donohue TM, Kharbanda KK. Alcoholic liver disease: pathogenesis and current management. *Alcohol Res*. 2017;38(2):147–161.
5. Alkhouri N, McCullough AJ. Noninvasive diagnosis of NASH and liver fibrosis within the spectrum of NAFLD. *Gastroenterol Hepatol*. 2012;8 (10):661–668.
6. Yuan X, Duan SZ, Cao J, Gao N, Xu J, Zhang L. Noninvasive inflammatory markers for assessing liver fibrosis stage in autoimmune hepatitis patients. *Eur J Gastroenterol Hepatol*. 2019;31(11):1467–1474. doi:10.1097/meg.0000000000001437
7. Gan C, Cai Q, Tang C, Gao J. Inflammasomes and pyroptosis of liver cells in liver fibrosis. *Front Immunol*. 2022;13:896473. doi:10.3389/fimmu.2022.896473
8. Trautwein C, Friedman SL, Schuppan D, Pinzani M. Hepatic fibrosis: concept to treatment. *J Hepatol*. 2015;62(1 Suppl):S15–24. doi:10.1016/j.jhep.2015.02.039
9. Friedman SL. Mechanisms of hepatic fibrogenesis. *Gastroenterology*. 2008;134(6):1655–1669. doi:10.1053/j.gastro.2008.03.003
10. Friedman SL. Hepatic stellate cells: protean, multifunctional, and enigmatic cells of the liver. *Physiol Rev*. 2008;88(1):125–172. doi:10.1152/physrev.00013.2007
11. Engelmann C, Tacke F. The potential role of cellular senescence in non-alcoholic fatty liver disease. *Int J Mol Sci*. 2022;23(2):652. doi:10.3390/ijms23020652
12. Friedman SL, Roll FJ, Boyles J, Bissell DM. Hepatic lipocytes: the principal collagen-producing cells of normal rat liver. *Proc Natl Acad Sci U S A*. 1985;82(24):8681–8685. doi:10.1073/pnas.82.24.8681
13. Iwaisako K, Jiang C, Zhang M, et al. Origin of myofibroblasts in the fibrotic liver in mice. *Proc Natl Acad Sci U S A*. 2014;111(32):E3297–305. doi:10.1073/pnas.1400062111
14. Koyama Y, Wang P, Liang S, et al. Mesothelin/mucin 16 signaling in activated portal fibroblasts regulates cholestatic liver fibrosis. *J Clin Invest*. 2017;127(4):1254–1270. doi:10.1172/jci88845
15. Tsuchida T, Friedman SL. Mechanisms of hepatic stellate cell activation. *Nat Rev Gastroenterol Hepatol*. 2017;14(7):397–411. doi:10.1038/nrgastro.2017.38
16. Kisseleva T, Brenner D. Molecular and cellular mechanisms of liver fibrosis and its regression. *Nat Rev Gastroenterol Hepatol*. 2021;18 (3):151–166. doi:10.1038/s41575-020-00372-7
17. Higashi T, Friedman SL, Hoshida Y. Hepatic stellate cells as key target in liver fibrosis. *Adv Drug Deliv Rev*. 2017;121:27–42. doi:10.1016/j.addr.2017.05.007
18. Zhang M, Serna-Salas S, Damba T, Borghesan M, Demaria M, Moshage H. Hepatic stellate cell senescence in liver fibrosis: characteristics, mechanisms and perspectives. *Mech Ageing Dev*. 2021;199:111572. doi:10.1016/j.mad.2021.111572
19. Zhang D, Zhang Y, Sun B. The molecular mechanisms of liver fibrosis and its potential therapy in application. *Int J Mol Sci*. 2022;23 (20):12572. doi:10.3390/ijms232012572
20. Pose E, Trebicka J, Mookerjee RP, Angeli P, Ginès P. Statins: old drugs as new therapy for liver diseases? *J Hepatol*. 2019;70(1):194–202. doi:10.1016/j.jhep.2018.07.019
21. Moreno M, Ramalho LN, Sancho-Bru P, et al. Atorvastatin attenuates angiotensin II-induced inflammatory actions in the liver. *Am J Physiol Gastrointest Liver Physiol*. 2009;296(2):G147–56. doi:10.1152/ajpgi.00462.2007
22. Abraldes JG, Albillos A, Bañares R, et al. Simvastatin lowers portal pressure in patients with cirrhosis and portal hypertension: a randomized controlled trial. *Gastroenterology*. 2009;136(5):1651–1658. doi:10.1053/j.gastro.2009.01.043
23. Traber PG, Zomer E. Therapy of experimental NASH and fibrosis with galectin inhibitors. *PLoS One*. 2013;8(12):e83481. doi:10.1371/journal.pone.0083481
24. Chalasani N, Abdelmalek MF, Garcia-Tsao G, et al. Effects of belapectin, an inhibitor of galectin-3, in patients with nonalcoholic steatohepatitis with cirrhosis and portal hypertension. *Gastroenterology*. 2020;158(5):1334–1345.e5. doi:10.1053/j.gastro.2019.11.296
25. Velayudham A, Dolganiuc A, Ellis M, et al. VSL#3 probiotic treatment attenuates fibrosis without changes in steatohepatitis in a diet-induced nonalcoholic steatohepatitis model in mice. *Hepatology*. 2009;49(3):989–997. doi:10.1002/hep.22711
26. Li B, Wang L, Lu Q, Da W. Liver injury attenuation by curcumin in a rat NASH model: an Nrf2 activation-mediated effect? *Ir J Med Sci*. 2016;185(1):93–100. doi:10.1007/s11845-014-1226-9
27. Ireson C, Orr S, Jones DJ, et al. Characterization of metabolites of the chemopreventive agent curcumin in human and rat hepatocytes and in the rat in vivo, and evaluation of their ability to inhibit phorbol ester-induced prostaglandin E2 production. *Cancer Res*. 2001;61(3):1058–1064.
28. Wang PX, Mu XN, Huang SH, Hu K, Sun ZG. Cellular and molecular mechanisms of oroxylin A in cancer therapy: recent advances. *Eur J Pharmacol*. 2024;969:176452. doi:10.1016/j.ejphar.2024.176452
29. Wang J, Wu Z, Chen X, et al. Network pharmacology, molecular docking analysis and molecular dynamics simulation of Scutellaria baicalensis in the treatment of liver fibrosis. *Curr Pharm Des*. 2024;30(17):1326–1340. doi:10.2174/0113816128297074240327090020
30. Evangelou K, Vasileiou PVS, Papaspyropoulos A, et al. Cellular senescence and cardiovascular diseases: moving to the "heart" of the problem. *Physiol Rev*. 2023;103(1):609–647. doi:10.1152/physrev.00007.2022
31. Kammeyer A, Luiten RM. Oxidation events and skin aging. *Ageing Res Rev*. 2015;21:16–29. doi:10.1016/j.arr.2015.01.001
32. Colavitti R, Finkel T. Reactive oxygen species as mediators of cellular senescence. *IUBMB Life*. 2005;57(4–5):277–281. doi:10.1080/15216540500091890

33. Rattan S. International recognition for ageing research: John Scott Award-2014 to Leonard Hayflick and Paul Moorhead. *Biogerontology*. 2014;15(5):415. doi:10.1007/s10522-014-9524-1
34. Liu RM. Aging, cellular senescence, and Alzheimer's disease. *Int J Mol Sci*. 2022;23(4):1989. doi:10.3390/ijms23041989
35. Birch J, Gil J. Senescence and the SASP: many therapeutic avenues. *Genes Dev*. 2020;34(23–24):1565–1576. doi:10.1101/gad.343129.120
36. Herranz N, Gil J. Mechanisms and functions of cellular senescence. *J Clin Invest*. 2018;128(4):1238–1246. doi:10.1172/jci95148
37. Saul D, Kosinsky RL, Atkinson EJ, et al. A new gene set identifies senescent cells and predicts senescence-associated pathways across tissues. *Nat Commun*. 2022;13(1):4827. doi:10.1038/s41467-022-32552-1
38. Morio B, Panthu B, Bassot A, Rieusset J. Role of mitochondria in liver metabolic health and diseases. *Cell Calcium*. 2021;94:102336. doi:10.1016/j.ceca.2020.102336
39. McEachern MJ, Krauskopf A, Blackburn EH. Telomeres and their control. *Annu Rev Genet*. 2000;34:331–358. doi:10.1146/annurev.genet.34.1.331
40. Wiemann SU, Satyanarayana A, Tsahuridu M, et al. Hepatocyte telomere shortening and senescence are general markers of human liver cirrhosis. *FASEB J*. 2002;16(9):935–942. doi:10.1096/fj.01-0977com
41. Correia-Melo C, Marques FD, Anderson R, et al. Mitochondria are required for pro-ageing features of the senescent phenotype. *EMBO J*. 2016;35(7):724–742. doi:10.15252/embj.201592862
42. Jones DP. Redox theory of aging. *Redox Biol*. 2015;5:71–79. doi:10.1016/j.redox.2015.03.004
43. Birch J, Passos JF. Targeting the SASP to combat ageing: mitochondria as possible intracellular allies? *Bioessays*. 2017;39(5):1600235. doi:10.1002/bies.201600235
44. Lakner AM, Moore CC, Gulledge AA, Schrum LW. Daily genetic profiling indicates JAK/STAT signaling promotes early hepatic stellate cell transdifferentiation. *World J Gastroenterol*. 2010;16(40):5047–5056. doi:10.3748/wjg.v16.i40.5047
45. Xiang D, Zou J, Zhu X, et al. Physalin D attenuates hepatic stellate cell activation and liver fibrosis by blocking TGF-β/Smad and YAP signaling. *Phytomedicine*. 2020;78:153294. doi:10.1016/j.phymed.2020.153294
46. Mu M, Zuo S, Wu RM, et al. Ferulic acid attenuates liver fibrosis and hepatic stellate cell activation via inhibition of TGF-β/Smad signaling pathway. *Drug Des Devel Ther*. 2018;12:4107–4115. doi:10.2147/dddt.S186726
47. Dewidar B, Meyer C, Dooley S, Meindl-Beinker AN. TGF-β in hepatic stellate cell activation and liver fibrogenesis-updated 2019. *Cells*. 2019;8(11):1419. doi:10.3390/cells8111419
48. Ge T, Shao Y, Bao X, Xu W, Lu C. Cellular senescence in liver diseases: from mechanisms to therapies. *Int Immunopharmacol*. 2023;121:110522. doi:10.1016/j.intimp.2023.110522
49. Lei Q, Xia J, Feng X, Guo J, Li G, Zhou W. Nek2通过抵抗肝癌细胞衰老促进肝癌进展 [NEK2 promotes the progression of liver cancer by resisting the cellular senescence]. *Zhong Nan Da Xue Xue Bao Yi Xue Ban*. 2022;47(2):153–164. doi:10.11817/j.issn.1672-7347.2022.210058
50. Amengual J, Alay A, Vaquero J, et al. Iron chelation as a new therapeutic approach to prevent senescence and liver fibrosis progression. *Cell Death Dis*. 2024;15(9):680. doi:10.1038/s41419-024-07063-0
51. Wang YL, Gao JM, Xing LZ. Therapeutic potential of Oroxylin A in rheumatoid arthritis. *Int Immunopharmacol*. 2016;40:294–299. doi:10.1016/j.intimp.2016.09.006
52. Zhu R, Zeng G, Chen Y, et al. Oroxylin A accelerates liver regeneration in CCl_4-induced acute liver injury mice. *PLoS One*. 2013;8(8):e71612. doi:10.1371/journal.pone.0071612
53. Trinh HT, Joh EH, Kwak HY, Baek NI, Kim DH. Anti-pruritic effect of baicalin and its metabolites, baicalein and oroxylin A, in mice. *Acta Pharmacol Sin*. 2010;31(6):718–724. doi:10.1038/aps.2010.42
54. Tuli HS, Garg VK, Kumar A, et al. Anticancer potential of oroxylin A: from mechanistic insight to synergistic perspectives. *Naunyn Schmiedebergs Arch Pharmacol*. 2023;396(2):191–212. doi:10.1007/s00210-022-02298-0
55. Sajeev A, Hegde M, Girisa S, et al. Oroxylin A: a promising flavonoid for prevention and treatment of chronic diseases. *Biomolecules*. 2022;12(9):1185. doi:10.3390/biom12091185
56. Lu L, Guo Q, Zhao L. Overview of oroxylin A: a promising flavonoid compound. *Phytother Res*. 2016;30(11):1765–1774. doi:10.1002/ptr.5694
57. Li HB, Chen F. Isolation and purification of baicalein, wogonin and oroxylin A from the medicinal plant Scutellaria baicalensis by high-speed counter-current chromatography. *J Chromatogr A*. 2005;1074(1–2):107–110. doi:10.1016/j.chroma.2005.03.088
58. Pal-Bhadra M, Ramaiah MJ, Reddy TL, et al. Plant HDAC inhibitor chrysin arrest cell growth and induce p21WAF1 by altering chromatin of STAT response element in A375 cells. *BMC Cancer*. 2012;12:180. doi:10.1186/1471-2407-12-180
59. Ding Y, Zhou Y, Li Z, et al. Oroxylin A reversed Fibronectin-induced glioma insensitivity to Temozolomide by suppressing IP(3)R1/AKT/β-catenin pathway. *Life Sci*. 2020;260:118411. doi:10.1016/j.lfs.2020.118411
60. Liu CH, Chen MF, Tseng TL, Chen LG, Kuo JS, Lee TJ. Oroxylin a, but not vasopressin, ameliorates cardiac dysfunction of endotoxemic rats. *Evid Based Complement Alternat Med*. 2012;2012:408187. doi:10.1155/2012/408187
61. Li C, Wang J, Ma R, et al. Natural-derived alkaloids exhibit great potential in the treatment of ulcerative colitis. *Pharmacol Res*. 2022;175:105972. doi:10.1016/j.phrs.2021.105972
62. Tan P, Jin L, Qin X, He B. Natural flavonoids: potential therapeutic strategies for non-alcoholic fatty liver disease. *Front Pharmacol*. 2022;13:1005312. doi:10.3389/fphar.2022.1005312
63. Zhao B, Liu K, Liu X, et al. Plant-derived flavonoids are a potential source of drugs for the treatment of liver fibrosis. *Phytother Res*. 2024;38(6):3122–3145. doi:10.1002/ptr.8193
64. Xiong F, Zhang Y, Li T, et al. A detailed overview of quercetin: implications for cell death and liver fibrosis mechanisms. *Front Pharmacol*. 2024;15:1389179. doi:10.3389/fphar.2024.1389179
65. Wenbo Z, Jianwei H, Hua L, Lei T, Guijuan C, Mengfei T. The potential of flavonoids in hepatic fibrosis: a comprehensive review. *Phytomedicine*. 2024;133:155932. doi:10.1016/j.phymed.2024.155932
66. Bian EB, Huang C, Wang H, et al. DNA methylation: new therapeutic implications for hepatic fibrosis. *Cell Signal*. 2013;25(1):355–358. doi:10.1016/j.cellsig.2012.10.007
67. Page A, Paoli P, Moran Salvador E, White S, French J, Mann J. Hepatic stellate cell transdifferentiation involves genome-wide remodeling of the DNA methylation landscape. *J Hepatol*. 2016;64(3):661–673. doi:10.1016/j.jhep.2015.11.024

68. Lan YY, Londoño D, Bouley R, Rooney MS, Hacohen N. Dnase2a deficiency uncovers lysosomal clearance of damaged nuclear DNA via autophagy. *Cell Rep*. 2014;9(1):180–192. doi:10.1016/j.celrep.2014.08.074
69. Härtlova A, Erttmann SF, Raffi FA, et al. DNA damage primes the type I interferon system via the cytosolic DNA sensor STING to promote anti-microbial innate immunity. *Immunity*. 2015;42(2):332–343. doi:10.1016/j.immuni.2015.01.012
70. Rodier F, Coppé JP, Patil CK, et al. Persistent DNA damage signalling triggers senescence-associated inflammatory cytokine secretion. *Nat Cell Biol*. 2009;11(8):973–979. doi:10.1038/ncb1909
71. Hao F. Entanglement of methylation changes and cGAS-STING signaling in non-small-cell lung cancer. *Comb Chem High Throughput Screen*. 2023;26(1):224–235. doi:10.2174/1386207325666220517095503
72. Tumburu L, Ghosh-Choudhary S, Seifuddin FT, et al. Circulating mitochondrial DNA is a proinflammatory DAMP in sickle cell disease. *Blood*. 2021;137(22):3116–3126. doi:10.1182/blood.2020009063
73. Li Z, Wang F, Liang B, et al. Methionine metabolism in chronic liver diseases: an update on molecular mechanism and therapeutic implication. *Signal Transduct Target Ther*. 2020;5(1):280. doi:10.1038/s41392-020-00349-7
74. Pascale RM, Simile MM, Calvisi DF, Feo CF, Feo F. S-Adenosylmethionine: from the discovery of its inhibition of tumorigenesis to its use as a therapeutic agent. *Cells*. 2022;11(3):409. doi:10.3390/cells11030409
75. Ramani K, Lu SC. Methionine adenosyltransferases in liver health and diseases. *Liver Res*. 2017;1(2):103–111. doi:10.1016/j.livres.2017.07.002
76. Hu X, Zhou Y. Curcumin reduces methionine adenosyltransferase 2B expression by interrupting phosphorylation of p38 MAPK in hepatic stellate cells. *Eur J Pharmacol*. 2020;886:173424. doi:10.1016/j.ejphar.2020.173424
77. Zhu X, Jia X, Cheng F, Tian H, Zhou Y. c-Jun acts downstream of PI3K/AKT signaling to mediate the effect of leptin on methionine adenosyltransferase 2B in hepatic stellate cells in vitro and in vivo. *J Pathol*. 2020;252(4):423–432. doi:10.1002/path.5536
78. Zhao D, Gao Y, Su Y, et al. Oroxylin A regulates cGAS DNA hypermethylation induced by methionine metabolism to promote HSC senescence. *Pharmacol Res*. 2023;187:106590. doi:10.1016/j.phrs.2022.106590
79. Sun Y, Weng J, Chen X, et al. Oroxylin A activates ferritinophagy to induce hepatic stellate cell senescence against hepatic fibrosis by regulating cGAS-STING pathway. *Biomed Pharmacother*. 2023;162:114653. doi:10.1016/j.biopha.2023.114653
80. Kim H, Kim H, Feng Y, et al. PRMT5 control of cGAS/STING and NLRC5 pathways defines melanoma response to antitumor immunity. *Sci Transl Med*. 2020;12(551):eaaz5683. doi:10.1126/scitranslmed.aaz5683
81. Lai J, Fu Y, Tian S, et al. Zebularine elevates STING expression and enhances cGAMP cancer immunotherapy in mice. *Mol Ther*. 2021;29(5):1758–1771. doi:10.1016/j.ymthe.2021.02.005
82. Martínez-Zamudio RI, Dewald HK, Vasilopoulos T, Gittens-Williams L, Fitzgerald-Bocarsly P, Herbig U. Senescence-associated β-galactosidase reveals the abundance of senescent CD8+ T cells in aging humans. *Aging Cell*. 2021;20(5):e13344. doi:10.1111/acel.13344
83. Jin C, Li Y, Su Y, et al. Novel copper complex CTB regulates methionine cycle induced TERT hypomethylation to promote HCC cells senescence via mitochondrial SLC25A26. *Cell Death Dis*. 2020;11(10):844. doi:10.1038/s41419-020-03048-x
84. Santana-Codina N, Mancias JD. The role of NCOA4-mediated ferritinophagy in health and disease. *Pharmaceuticals*. 2018;11(4):114. doi:10.3390/ph11040114
85. Mancias JD, Wang X, Gygi SP, Harper JW, Kimmelman AC. Quantitative proteomics identifies NCOA4 as the cargo receptor mediating ferritinophagy. *Nature*. 2014;509(7498):105–109. doi:10.1038/nature13148
86. Kim CH, Leitch HA. Iron overload-induced oxidative stress in myelodysplastic syndromes and its cellular sequelae. *Crit Rev Oncol Hematol*. 2021;163:103367. doi:10.1016/j.critrevonc.2021.103367
87. Murthy AMV, Robinson N, Kumar S. Crosstalk between cGAS-STING signaling and cell death. *Cell Death Differ*. 2020;27(11):2989–3003. doi:10.1038/s41418-020-00624-8
88. Rao HY, Wang JH, Liu F, Fei R, Liu ZD, Wei L. Effect of glia maturation factor beta on the activation of hepatic stellate cells and on liver fibrosis. *Zhonghua Gan Zang Bing Za Zhi*. 2007;15(12):897–901.
89. Mackowiak B, Fu Y, Maccioni L, Gao B. Alcohol-associated liver disease. *J Clin Invest*. 2024;134(3):e176345. doi:10.1172/jci176345
90. Tuangratananon T, Wangmo S, Widanapathirana N, et al. Implementation of national action plans on noncommunicable diseases, Bhutan, Cambodia, Indonesia, Philippines, Sri Lanka, Thailand and Viet Nam. *Bull World Health Organ*. 2019;97(2):129–141. doi:10.2471/blt.18.220483
91. Edenberg HJ, McClintick JN. Alcohol dehydrogenases, aldehyde dehydrogenases, and alcohol use disorders: a critical review. *Alcohol Clin Exp Res*. 2018;42(12):2281–2297. doi:10.1111/acer.13904
92. Liu Y, Brymora J, Zhang H, et al. Leptin and acetaldehyde synergistically promotes αSMA expression in hepatic stellate cells by an interleukin 6-dependent mechanism. *Alcohol Clin Exp Res*. 2011;35(5):921–928. doi:10.1111/j.1530-0277.2010.01422.x
93. Seth D, Haber PS, Syn WK, Diehl AM, Day CP. Pathogenesis of alcohol-induced liver disease: classical concepts and recent advances. *J Gastroenterol Hepatol*. 2011;26(7):1089–1105. doi:10.1111/j.1440-1746.2011.06756.x
94. Suh YG, Jeong WI. Hepatic stellate cells and innate immunity in alcoholic liver disease. *World J Gastroenterol*. 2011;17(20):2543–2551. doi:10.3748/wjg.v17.i20.2543
95. Wu X, Fan X, Miyata T, et al. Recent advances in understanding of pathogenesis of alcohol-associated liver disease. *Annu Rev Pathol*. 2023;18:411–438. doi:10.1146/annurev-pathmechdis-031521-030435
96. Mannaerts I, Leite SB, Verhulst S, et al. The Hippo pathway effector YAP controls mouse hepatic stellate cell activation. *J Hepatol*. 2015;63(3):679–688. doi:10.1016/j.jhep.2015.04.011
97. Xie Q, Chen J, Feng H, et al. YAP/TEAD-mediated transcription controls cellular senescence. *Cancer Res*. 2013;73(12):3615–3624. doi:10.1158/0008-5472.Can-12-3793
98. Du K, Maeso-Díaz R, Oh SH, et al. Targeting YAP-mediated HSC death susceptibility and senescence for treatment of liver fibrosis. *Hepatology*. 2023;77(6):1998–2015. doi:10.1097/hep.0000000000000326
99. Zhao Y, Wang H, He T, Ma B, Chen G, Tzeng C. Knockdown of Yap attenuates TAA-induced hepatic fibrosis by interaction with hedgehog signals. *J Cell Commun Signal*. 2023;17(4):1335–1354. doi:10.1007/s12079-023-00775-6
100. Cheng F, Yang F, Wang Y, Zhou J, Qian H, Yan Y. Mesenchymal stem cell-derived exosomal miR-27b-3p alleviates liver fibrosis via downregulating YAP/LOXL2 pathway. *J Nanobiotechnology*. 2023;21(1):195. doi:10.1186/s12951-023-01942-y
101. He S, Sharpless NE. Senescence in health and disease. *Cell*. 2017;169(6):1000–1011. doi:10.1016/j.cell.2017.05.015

102. Kumari R, Jat P. Mechanisms of cellular senescence: cell cycle arrest and senescence associated secretory phenotype. *Front Cell Dev Biol*. 2021;9:645593. doi:10.3389/fcell.2021.645593
103. Deaciuc IV, Fortunato F, D'Souza NB, Hill DB, McClain CJ. Chronic alcohol exposure of rats exacerbates apoptosis in hepatocytes and sinusoidal endothelial cells. *Hepatol Res*. 2001;19(3):306–324. doi:10.1016/s1386-6346(00)00112-1
104. Cardin R, D'Errico A, Fiorentino M, Cecchetto A, Naccarato R, Farinati F. Hepatocyte proliferation and apoptosis in relation to oxidative damage in alcohol-related liver disease. *Alcohol Alcohol*. 2002;37(1):43–48. doi:10.1093/alcalc/37.1.43
105. Krizhanovsky V, Yon M, Dickins RA, et al. Senescence of activated stellate cells limits liver fibrosis. *Cell*. 2008;134(4):657–667. doi:10.1016/j.cell.2008.06.049
106. Burd CE, Sorrentino JA, Clark KS, et al. Monitoring tumorigenesis and senescence in vivo with a p16(INK4a)-luciferase model. *Cell*. 2013;152(1–2):340–351. doi:10.1016/j.cell.2012.12.010
107. Serrano M. Cancer: a lower bar for senescence. *Nature*. 2010;464(7287):363–364. doi:10.1038/464363a
108. Jin H, Lian N, Bian M, et al. Oroxylin A inhibits ethanol-induced hepatocyte senescence via YAP pathway. *Cell Prolif*. 2018;51(3):e12431. doi:10.1111/cpr.12431
109. Godoy-Matos AF, Silva Júnior WS, Valerio CM. NAFLD as a continuum: from obesity to metabolic syndrome and diabetes. *Diabetol Metab Syndr*. 2020;12:60. doi:10.1186/s13098-020-00570-y
110. Mridha AR, Wree A, Robertson AAB, et al. NLRP3 inflammasome blockade reduces liver inflammation and fibrosis in experimental NASH in mice. *J Hepatol*. 2017;66(5):1037–1046. doi:10.1016/j.jhep.2017.01.022
111. Arrese M, Cabrera D, Kalergis AM, Feldstein AE. Innate Immunity and Inflammation in NAFLD/NASH. *Dig Dis Sci*. 2016;61(5):1294–1303. doi:10.1007/s10620-016-4049-x
112. Parola M, Pinzani M. Liver fibrosis in NAFLD/NASH: from pathophysiology towards diagnostic and therapeutic strategies. *Mol Aspects Med*. 2024;95:101231. doi:10.1016/j.mam.2023.101231
113. Jiang Y, Jiang K, Sun P, Liu Y, Nie H. Oroxylin A ameliorates non-alcoholic fatty liver disease by modulating oxidative stress and ferroptosis through the Nrf2 pathway. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2025;1870(5):159628. doi:10.1016/j.bbalip.2025.159628
114. Kanda T, Matsuoka S, Yamazaki M, et al. Apoptosis and non-alcoholic fatty liver diseases. *World J Gastroenterol*. 2018;24(25):2661–2672. doi:10.3748/wjg.v24.i25.2661
115. Cho W, Choi SW, Oh H, et al. Oroxylin-A alleviates hepatic lipid accumulation and apoptosis under hyperlipidemic conditions via AMPK/FGF21 signaling. *Biochem Biophys Res Commun*. 2023;648:59–65. doi:10.1016/j.bbrc.2023.01.090