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The Role of Oxidative Stress in Liver Fibrosis and Advances in Antioxidant Therapy Using Natural Products

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Abstract: ***The correlation between oxidative stress and liver fibrosis has garnered extensive attention from scholars worldwide. Research indicates that oxidative stress may be a key factor in the onset and progression of liver fibrosis. Given the complex array of oxidative stress-related genes and pathways, recent studies targeting specific pathways have demonstrated therapeutic potential for liver fibrosis using certain drugs. This review will summarize the mechanisms by which oxidative stress influences liver fibrosis. It will also compile recent research progress on various natural product antioxidants targeting oxidative stress for liver fibrosis treatment, aiming to provide more effective strategies for the prevention and management of liver fibrosis.***

Keywords: Oxidative stress, Liver fibrosis, Hepatic stellate cells, Natural products, Reactive oxygen species.

1. Introduction

Oxidative stress is defined as the phenomenon where excessive production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) [1] within the body exceeds the scavenging capacity of antioxidants, leading to an imbalance between oxidative and antioxidant processes that damages cells, tissues, and organs [2]. When various cell types within the liver are stimulated by external factors such as alcohol, viral infections, or high-calorie diets, the intracellular redox balance is disrupted. This leads to alterations in the structure and function of biomolecules including lipids, proteins, and DNA, ultimately impairing the liver's normal physiological functions. Research indicates that oxidative stress is closely associated with the development of non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), liver fibrosis (HF), and hepatocellular carcinoma (HCC). In strategies for preventing and treating liver fibrosis, antioxidant therapy shows significant potential. Inhibiting ROS accumulation and regulating antioxidant responses have become key anti-fibrotic strategies. Natural products, owing to their unique chemical structures and biological activities, have emerged as a focal point in antioxidant therapy research [3].

2. Oxidative Stress

Research on ROS indicates that these molecules are released during the incomplete reduction of oxygen molecules. They can be produced through enzymatic reactions in the cytoplasm or formed within organelles such as mitochondria. Hydroxyl radicals and superoxide anions within ROS are highly unstable free radicals [1]. Their outer electron orbitals contain unpaired electrons, granting them a strong ability to steal electrons from other molecules—that is, potent oxidizing power. In contrast, relatively stable non-radical oxidants like H_2O_2 possess single covalent bonds that readily break to form the more potent hydroxyl radical. Within the body, ROS are continuously neutralized by antioxidant enzymes and endogenous antioxidants, maintaining a dynamic equilibrium under physiological conditions. At low concentrations, ROS can function as second messengers to regulate various physiological activities, such as immune responses and gene expression. However, if intracellular ROS concentrations become excessively high and uncontrolled, disrupting the balance between oxidants and antioxidants, it leads to various cellular and tissue damages—this is the formation of "oxidative stress."

2.1 Oxidative Stress-Related Metabolic Substances

During the body's oxidative stress response, numerous related metabolic substances are produced and cleared. These include two major categories of oxidants crucial for regulating oxidative stress balance: ROS and RNS; as well as DNA, proteins, lipids, and other biomolecules oxidatively damaged by free radicals. Among these, 8-hydroxy-2'-deoxyguanosine (8-OHdG) is widely recognized as a biomarker for DNA oxidative damage, being one of the abundant base modification products resulting from DNA oxidation. 8-OHdG is also incorporated into diagnostic criteria as a significant risk factor in oxidative stress-related diseases such as cancer, diabetes, and cardiovascular disorders [4]. Protein oxidation and nitrosylation modifications are extremely common. Lysine and arginine are attacked by ROS to form protein carbonyl derivatives, making carbonyl groups one of the measurable indicators of protein oxidative damage. 3-Nitrotyrosine (3-NT), on the other hand, is formed through the nitrosylation of tyrosine at the ortho position of its aromatic ring by the attack of the nitric oxide radical. Lipid-related oxidative metabolites such as ethane, pentane, 4-hydroxy-2-nonenal, and malondialdehyde also reflect the oxidative state of lipids in the body. Concurrently, antioxidants within the organism promptly eliminate excess ROS to maintain equilibrium, with antioxidant enzymes and non-enzymatic antioxidants cooperating to accomplish this process. Antioxidant enzymes include superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX); non-enzymatic antioxidants comprise glutathione, Vitamin C, Vitamin A, and thioredoxin.

2.2 Oxidative Stress-Related Signaling Pathways

Under physiological conditions, cells typically counteract various oxidative stress-related signaling pathways by producing antioxidants such as superoxide dismutase and glutathione S-transferase, thereby maintaining the body's oxidative/antioxidative equilibrium. Key oxidative stress-related signaling pathways include the Keap1/Nrf2/ARE pathway, the MAPK pathway, and the NOX pathway.

2.2.1 Keap1/Nrf2/ARE Signaling Pathway

The Keap1/Nrf2/ARE signaling pathway plays a crucial role in repairing oxidative stress conditions. Under normal circumstances, NF-E2-related factor 2 (Nrf2) binds to Keap1 in the cytoplasm, undergoes ubiquitination, and is degraded by the proteasome. Following oxidative stress exposure, Nrf2 phosphorylation promotes dissociation from Keap1 [5]. Upon release, Nrf2 translocates to the nucleus and binds to the antioxidant response element (ARE), thereby enhancing expression of various downstream antioxidant enzymes such as heme oxygenase-1 (HO-1) to exert its antioxidant effects [6]. Research by Longtai You revealed that retinal pigment epithelial (RPE) cells can be protected from oxidative stress by activating the Keap1/Nrf2/ARE pathway and inactivating the oxidative stress-mediated apoptosis pathway [7].

2.2.2 MAPK Signaling Pathway

The MAPK family belongs to the serine/threonine kinase family, primarily comprising c-Jun N-terminal kinase (JNK), p38, and extracellular signal-regulated kinase (ERK). When excessive ROS accumulate, oxidative stress activates the MAPK signaling pathway, causing ERK, JNK, and p38 to translocate from the cytoplasm to the nucleus. This promotes transcription and expression of related target genes, leading to DNA damage and ultimately apoptosis. ROS can act as second messengers to activate the MAPK signaling pathway while simultaneously being affected by its activation [8]. Oleuropein (OP), as an effective antioxidant, inhibits the TLR4/MAPK signaling pathway activated by tert-butylhydroperoxide (tBHP) in H9C2 cells, thereby suppressing ROS production and subsequent oxidative stress and autophagy [9].

2.2.3 NOX Signaling Pathway

In cellular redox homeostasis, the NADPH oxidase (NOX) signaling pathway plays a central role. Enzymes within the NOX family catalyze the oxidation of NADPH to produce superoxide anion (O_2^-), which in turn generates a cascade of ROS, including hydrogen peroxide (H_2O_2) and other downstream reactive molecules. These ROS serve as key signaling molecules, participating in the regulation of multiple biological processes within cells, including proliferation, differentiation, migration, and apoptosis. The activity of the NOX signaling pathway is finely regulated to maintain a balance between ROS production and cellular demand alongside antioxidant capacity. When NOX enzyme activity becomes imbalanced, such as in chronic inflammation or certain genetic disorders, excessive ROS accumulation leads to oxidative stress.

The NOX1, NOX2, and NOX4 subtypes within the NOX family serve as primary ROS sources in hepatic stellate cells (HSCs) and Kupffer cells (KCs), playing pivotal roles in HSC activation and the progression of liver fibrosis [10]. Specifically, NOX1 and NOX2 primarily catalyze superoxide production, while NOX4 predominantly generates H_2O_2. The O_2^- produced by NOX4 in mitochondria, combined with O_2^- released from the mitochondrial electron transport chain (ETC), constitutes the primary source of mitochondrial ROS. Mitochondrial SOD (SOD2) participates in its conversion to H_2O_2, while H_2O_2 clearance is also regulated by CAT and GPX [11]. Research indicates that during liver fibrosis, ursodeoxycholic acid (UA) inhibits collagen deposition by suppressing NOX4 and exerts anti-fibrotic effects by regulating intestinal bacteria through the NOX4/NLRP3 inflammasome signaling pathway [12]. Exogenous 8-hydroxy-2'-deoxyguanosine also improves liver fibrosis progression by inhibiting Rac1 activation and reducing NOX-derived ROS [13].

3. The Role of Oxidative Stress in the Development of Liver Fibrosis

Oxidative stress can trigger abnormalities in multiple intracellular genes and signaling pathways, leading to apoptosis, necrosis, and other processes. It is present throughout the progression of various liver diseases. As a major site for ROS production and metabolism, the liver possesses antioxidant activity. Its antioxidant mechanisms comprise both enzymatic and non-enzymatic components. These diverse antioxidant mechanisms regulate the oxidative state of the internal environment to achieve a dynamic equilibrium between oxidation and antioxidation.

3.1 Oxidative Stress and Various Hepatocytes

3.1.1 Oxidative Stress and Hepatocytes

Due to the presence of numerous ROS-producing organelles and associated enzymes within hepatocytes, oxidative stress may induce apoptosis or necrosis in hepatic parenchymal cells. Following necrosis, hepatocytes release various mediators such as tumor necrosis factor-α (TNF-α) and transforming growth factor-β (TGF-β). These substances activate surrounding KCs and HSCs, triggering inflammatory responses and promoting a tendency toward fibrosis. One study found that cisplatin (DDP) may enhance voltage-dependent anion channel protein 1 (VDAC1) oligomerization, promoting the release of ROS and mtDNA from mitochondria into the cytoplasm via the VDAC1 channel. This leads to increased mitochondrial oxidative stress and DNA damage in hepatocytes. 4,4'-Dithiobis (2,2'-disulfonic acid) (DIDS), a VDAC1 oligomerization inhibitor, antagonizes DDP-induced hepatocyte apoptosis by reducing oxidative stress and DNA damage while protecting mitochondrial complex proteins. This experiment demonstrated that inhibiting disease progression while controlling hepatocyte apoptosis suggests that blocking the hepatocyte apoptosis process may also possess clinical efficacy [14].

3.1.2 Oxidative Stress and Liver Sinusoidal Endothelial Cells

Liver sinusoidal endothelial cells (LSECs) constitute

approximately 15–20% of total liver cells, representing the most abundant non-parenchymal cells in the liver [15]. Due to their unique position within the sinusoidal lumen, LSECs form the liver's primary defense barrier. When external injury occurs, LSECs are the first to detect it, making them the initial hepatic cell type affected by any type of liver injury. ROS can selectively damage LSECs and impair their physiological activity. Due to compromised antioxidant mechanisms, vascular endothelial dysfunction affects the synthesis of the vasodilator NO. LSECs become unable to neutralize oxidative stress, leading to morphological changes and the development of sinusoidal endothelial dysfunction [16]. In the early stages of liver injury, autophagy helps maintain cellular phenotype and protects LSECs from oxidative stress, but studies suggest its efficacy may diminish in later phases. Dysregulated endothelial autophagy activates HSCs and exacerbates fibrosis during mild acute liver injury. Clinically, downregulating oxidative damage in LSECs by enhancing autophagy during early liver injury can slow progression to chronic liver disease [17].

3.1.3 Oxidative Stress and Hepatic Stellate Cells

HSCs constitute 5–10% of hepatic cells and play a critical role in both normal liver function and injury responses to external insults. Located in the perisinusoidal space—the Disse space—between endothelial cells and hepatocytes, HSCs undergo activation during liver injury. During liver injury, HSCs become activated. In liver fibrosis, they undergo oxidative stress-induced differentiation into myofibroblasts. Concurrently, through paracrine effects, they secrete large amounts of collagen fibers, forming and depositing extracellular matrix (ECM). This process is crucial for liver regeneration and repair [18]. Furthermore, studies indicate that once activated, HSCs can sustain fibrosis independently of persistent inflammatory factors. Downstream transcription factors regulating ECM synthesis, such as NF-κB, can be targeted to reduce cellular oxidative stress levels, thereby clinically mitigating liver fibrosis progression. One study found that glucose oxidase (GO) stimulation significantly reduced SOD and glutathione (GSH) activity in HSCs while increasing ROS levels. This led to massive HSC activation, disruption of the antioxidant defense system, and a rapid decline in cellular antioxidant capacity. Conversely, cannabidiol (CBD) significantly increased SOD activity and GSH levels while decreasing ROS levels, indicating CBD possesses potent systemic antioxidant potential [19].

3.1.4 Oxidative Stress and Hepatic Macrophages

KCs primarily reside within hepatic sinusoids, constituting 80–90% of the body's resident macrophages. Following liver injury, KCs become activated and release large amounts of inflammatory cytokines and chemokines induced by pro-inflammatory mediators, including ROS. In fact, KCs are the primary source of ROS in the liver, typically generated by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Jae Sung Lim's research revealed the protective role of the Keap1-Nrf2 pathway in KC oxidative stress responses. This protection manifests through activation of the antioxidant Nrf2/HO-1 pathway and suppression of pro-inflammatory factors NF-κB and MAPK activity. This discovery holds significant implications for further understanding the regulatory mechanisms of oxidative stress in KCs [20].

3.2 Oxidative Stress and Liver Fibrosis

Liver fibrosis is a dynamic wound-healing process characterized by the progressive accumulation of ECM components, altered ECM degradation, and deformation of the hepatic parenchyma. However, if this response persists long-term, it may impair liver function and regenerative capacity, potentially leading to cirrhosis or even HCC. When the liver sustains external injury, it releases multiple cellular injury factors, including proinflammatory cytokines, growth factors, and ROS. These factors promote disease progression by activating proinflammatory and pro-fibrotic pathways and interacting with HSCs, LSECs, and various immune cells. Notably, elevated ROS levels serve as a key marker for HSC activation. ROS stimulates HSC activity, promoting their transformation into myofibroblasts. This process leads to excessive extracellular matrix production, ultimately forming scar tissue. The role of antioxidant mechanisms, such as Nrf2 activation, in treating liver fibrosis has been extensively studied and demonstrated significant efficacy. SIRT3 participates in regulating Nrf2 by enhancing ROS clearance, thereby protecting hepatocytes from oxidative stress [21]. Research by Ouyang et al. revealed that inhibiting HSC activation effectively mitigates CCl4-induced liver fibrosis and reduces inflammation levels. Concurrently, activating Nrf2 alleviates oxidative stress damage in the liver and promotes hepatic mitochondrial biogenesis [22]. Furthermore, mitochondrial autophagy plays a crucial role in the liver fibrosis process. ROS-induced mitochondrial dysfunction further exacerbates oxidative imbalance and drives the progression of liver fibrosis. Recent studies confirm correlations between mitochondrial oxidative stress, mitochondrial DNA (mtDNA) damage, and alterations in mitochondrial function and dynamics in advanced fibrosis of chronic hepatitis B and NASH [23]. ROS generated from mitochondrial damage are extensively released into the cytoplasm, regulating autophagy-related pathways to maintain and improve mitochondrial membrane potential, thereby repairing damaged cells and reducing hepatic injury. These findings reveal a close connection between oxidative stress during mitochondrial autophagy and the activation and proliferation of HSCs. As a primary pathway for mitochondrial autophagy, the PINK1/Parkin pathway regulates HSCs by influencing mitochondrial autophagy, thereby affecting the progression of liver fibrosis. Clearing damaged cells for clinical therapeutic purposes, this pathway may thus represent a potential target for treating oxidative stress-mediated liver fibrosis [24].

4. Natural Product Antioxidants in the Prevention and Treatment of Liver Fibrosis

With the advancement of fundamental research, our understanding of the pathogenesis of liver fibrosis and its potential reversal processes has deepened. Nevertheless, no drug has yet been approved to completely halt or reverse the progression of liver fibrosis. Antiviral or anti-inflammatory therapies cannot truly prevent ECM deposition or promote its degradation. Natural products, many of which contain multiple antioxidant active components, demonstrate

significant therapeutic potential for liver fibrosis. Compounds such as various flavonoids, terpenoids, alkaloids, and polyphenolic compounds. These antioxidants primarily exert their anti-oxidative stress effects by enhancing SOD and GST activity in liver tissue, reducing ROS activity and malondialdehyde levels, and modulating signaling pathways such as Keap1/Nrf2/ARE to improve liver fibrosis [25]. The following sections introduce novel natural products studied in various oxidative stress-related signaling pathways and elucidate their potential mechanisms.

4.1 Natural Products Modulating the Nrf2 Signaling Pathway

Resveratrol (Res) significantly mitigates mercury-induced increases in hepatic malondialdehyde (MDA) levels while restoring GSH levels and SOD activity. Under Res influence, exposure to mercury environment restores oxidative stress-related proteins Nrf2, HO-1, and and NQO1. Research indicates the Nrf2 pathway is regulated by Sirt1/PGC-1α activation, mitigating mercury-induced liver fibrosis by inhibiting hepatocyte cycle disruption and HSC activation [26].

Kaempferol improves the imbalanced redox state in CCl_4-induced SD rats by enhancing Nrf2 and HO-1 protein activation while inhibiting the MAPK/NF-κB signaling pathway. In experiments, kaempferol administration markedly reduced ROS and lipid peroxidation levels, suppressed MDA, and restored GSH levels, demonstrating potent antioxidant, anti-inflammatory, and hepatoprotective effects [27].

Astaxanthin (AST) treatment effectively reduced doxorubicin (DOX)-induced liver injury markers (ALT, GOT, ALP, TBil) and oxidative stress indicators (MDA, ROS), while enhancing SOD, CAT, and GPX activity. Furthermore, AST repaired damaged hepatocytes and reduced apoptosis. At the molecular level, AST activated Nrf2 by downregulating Keap1 and enhancing ERK levels, thereby modulating the expression of Keap1/Nrf2 signaling pathway-related genes and upregulating catalase to exert its protective effects [28].

Hesperetin improves hepatic oxidative stress by activating the PI3K/AKT-Nrf2 pathway. This antioxidant effect concurrently suppresses NF-κB-mediated inflammation during NAFLD progression and reduces fibrosis levels [29].

Studies on genistein indicate its protective effect against APAP-induced liver injury, primarily mediated by enhanced Nrf2-dependent antioxidant capacity alongside increased SIRT1 expression and activity [30].

Alpinetin exerts protective effects against CCl4-induced liver fibrosis in mice by controlling oxidative stress through Nrf2 signaling pathway activation [31].

In HF rats treated with Breviscapine, Keap1 protein and mRNA expression significantly decreased, while Nrf2 and HO-1 protein and mRNA expression levels increased. This indicates that breviscapine alleviates oxidative stress in rats by modulating the Keap1/Nrf2/HO-1 signaling pathway [32]. Obacunone (Oba) exerts antioxidant effects by upregulating Nrf2 and GPx4 while downregulating Nox2, concurrently inhibiting the TGF-β/Smad pathway to exert antifibrotic actions [33].

Esculin inhibits hepatic ferroptosis by activating the Nrf2/GPX4 signaling pathway, exerting antioxidant and anti-inflammatory effects, and holds potential for treating HF [34]. Sulforaphane suppresses LPS-induced pro-fibrotic activity by reducing NOX-derived ROS production in activated HSCs while activating Nrf2 to counteract oxidative stress [35]. Mulberrin significantly enhances nuclear expression of Nrf2 and other antioxidant genes (e.g., HO-1, NQO1) in liver tissue, improving the hepatic oxidative stress environment and thereby inhibiting HSC activation [36]. Piperine (PIP) reduces ROS accumulation by enhancing the Nrf2 antioxidant cascade, suppressing LX-2 cell activation and exerting hepatoprotective effects [37].

4.2 Natural Products Regulating the MAPK Signaling Pathway

Research indicates that nano-titanium dioxide induces hepatotoxicity via oxidative stress, while lycopene possesses potent antioxidant capacity. In experiments, lycopene significantly reversed the upregulation of p-p38 (phosphorylated p38) induced by nano-titanium dioxide. This suggests lycopene may mitigate nano-TiO_2–induced oxidative stress and hepatocyte apoptosis by inhibiting p38 MAPK pathway activation, thereby protecting mouse livers from injury [38].

Neferine exhibits therapeutic potential for HF by reducing oxidative stress through downregulating MAPK signaling pathways involving p38 MAPK, ERK 1/2, and JNK [39].

4.3 Natural Products Regulating NOX Signaling Pathways

Curcumin has been shown to block the expression of NOX1, NOX2, and NOX4, as well as ROS expression in human HSCs, by inhibiting the activation of TGFβ/phosphorylated Smad3C signaling. It holds potential as a natural antioxidant agent for treating liver fibrosis [40].

Aucubin (AU) may attenuate fibrosis progression and HSC activation by inhibiting NOX4, thereby negatively regulating the IRE1α/TXNIP/NLRP3 pathway through oxidative stress suppression [41].

Baicalin targets inflammation through its antioxidant capacity, manifested by enhanced hepatic SOD and GSH activity and levels, along with reduced hepatic MDA and nitric oxide (NOx) content. Studies reveal it significantly reduces TAA-induced hepatic NOX4 elevation while decreasing ROS, targeting the TGF-β1/NOX4/NF-κB/NLRP3 signaling pathway to exert anti-inflammatory and antioxidant effects [42].

4.4 Natural Products Modulating Other Signaling Pathways

YAP1 serves as a primary downstream target mediating oxidative stress. Emodin inhibits YAP1 phosphorylation by

reducing YES1 and AMPK expression, successfully mitigating acetaminophen (APAP)-induced hepatic oxidative damage [43].

Apigenin (API) modulates oxidative stress by inhibiting HIF-1α expression through suppression of PKM2 nuclear translocation, thereby inhibiting HSC activation and alleviating CCl_4-induced liver fibrosis [44].

Table 1: Natural Antioxidant Compounds and Their Mechanisms of Action

Therapeutic Agent	Compound Type	Mechanism of Action	Model Type	Reference
Resveratrol	Polyphenol	Nrf2/HO-1 , NQO1↑Cyp2e1↓	Hg	[26]
Kaempferol	Polyphenol	Nrf2/HO-1 ↑MAPK/NF-κB↓	CCl_4	[27]
Astaxanthin	Carotenoid	Keap1/Nrf2/HO-1 , ERK↑	DOX	[28]
Hesperidin	Flavonoid	PI3 K/AKT-Nrf2 ↑	HepG2	[29]
Genistein	Isoflavone	Nrf2↑	APAP	[30]
Alpinetin	Flavonoid	Nrf2, HO-1, NQO1↑	CCl_4	[31]
Breviscapine	Flavonoid	Keap1↓Nrf2, HO-1↑	CCl_4	[32]
Obacunone	Triterpenoids	Nrf2/Keap1, GPx4↑NOX2 ↓	LX-2	[33]
Esculin	Coumarin	Nrf2/GPX4↑	CCl_4	[34]
Sulforaphane	Isothiocyanate	Nrf2↑NOX1, NOX4↓	LX-2 , CCl_4	[35]
Mulberrin	Flavonoid	Nrf2, HO-1, NQO1↑Cyp2e1↓	CCl_4	[36]
Piperine	Alkaloids	Nrf2↑	LX-2	[37]
Lycopene	Carotenoids	p38 MAPK ↓	nano-TiO2	[38]
Neferine	Isoquinoline alkaloids	p38 MAPK, ERK 1/2, p-JNK↓	CCl_4	[39]
Curcumin	Polyphenol	NOX1, NOX2, NOX4, P-Smad3C↓	HSC	[40]
Aucubin	Cycloaromatic terpenoids	NOX4↓	LX-2	[41]
Baicalin	Flavonoid	NOX4, NLRP3, caspase-1↓	Thioacetamide (TAA)	[42]
Emodin	Anthraquinones	YES1, AMPK↓	APAP	[43]
Apigenin	Flavonoid	PKM2 , HIF-1α ↓	CCl_4	[44]

5. Conclusions

HF, as a pathological precursor to clinically challenging conditions such as liver cirrhosis and HCC, has become pivotal in the prevention and treatment of liver diseases. Numerous studies have demonstrated that many natural product antioxidants exhibit high safety, efficacy, and stability in preventing or treating liver fibrosis in animal models. A series of oxidative stress signaling pathways, represented by the Nrf2 pathway, play a crucial bridging role in the therapeutic process of liver fibrosis by various natural product antioxidants. These natural products not only enhance the activity of SOD and GSH-Px but also reduce MDA levels, thereby exerting significant effects in combating oxidative stress. The signaling mechanisms regulated by natural product antioxidants are complex, and balancing redox states through crosstalk among multiple signaling pathways may represent a key direction for future research. In summary, oxidative stress plays a pivotal role in liver fibrosis, and natural product antioxidant therapy offers novel therapeutic strategies. Future research should further explore the mechanisms of action of these natural products and evaluate their potential and efficacy in the clinical treatment of liver fibrosis.

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