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The Mechanism of Action and Clinical Application Progress of Apigenin in the Treatment of Liver Diseases

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ABSTRACT

Apigenin, as a natural flavonoid compound, is widely present in various fruits, vegetables, and herbal medicines. In recent years, numerous studies have shown that apigenin exhibits significant potential in multiple liver diseases through various pathways such as anti-inflammation, antioxidation, anti-fibrosis, regulation of lipid metabolism, induction of autophagy and apoptosis. This article elaborates on the pharmacological mechanisms and clinical application progress of apigenin in major liver diseases including non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), liver fibrosis, liver cancer, and drug-induced liver injury, and also looks forward to future research directions, aiming to provide a basis for the in-depth exploration of apigenin as a therapeutic drug for liver diseases.

KEYWORDS

apigenin, non-alcoholic liver disease, alcoholic liver disease, liver fibrosis, liver cancer, oxidative stress, inflammation

INTRODUCTION

The liver, as the metabolic center of the human body, performs critical functions such as detoxification, synthesis, storage, and secretion. Liver diseases, including non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease, hepatic fibrosis, hepatitis, and hepatocellular carcinoma, have become one of the leading causes of mortality worldwide [1]. Currently, most liver diseases, particularly NAFLD and hepatic fibrosis, lack effective therapeutic agents and primarily rely on etiological control and lifestyle interventions [2]. Therefore, the identification of safe and effective drugs for liver disease prevention and treatment remains a focal point in contemporary pharmaceutical research.

Against this backdrop, natural products have garnered significant attention due to their multi-targeted, multi-pathway mechanisms of action and relatively high safety profiles. Apigenin, a representative member of flavonoids, is abundantly present in common dietary sources such as celery and parsley. Early studies have revealed its broad biological activities, including anticancer, anti-inflammatory, antioxidant, and neuroprotective effects [3]. In recent years, with the advanced application of molecular biology and systems pharmacology technologies, research on apigenin in hepatology has experienced explosive growth, leading to more systematic and profound understanding of its mechanisms of action [4]. This article aims to synthesize and integrate recent research findings through a comparative analysis of experimental outcomes across various models, providing a semi-quantitative overview of effective dose ranges (typically 20-100 mg/kg in rodents) to comprehensively elucidate the protective effects and mechanisms of apigenin in liver diseases, while outlining future research directions.

PHARMACOKINETICS AND BIOAVAILABILITY OF APIGENIN

Apigenin is a flavonoid compound widely found in various fruits, vegetables (such as celery and parsley), and herbs, with the chemical name 4′,5,7-trihydroxyflavone and molecular formula C15H10O5, having a molecular weight of 270.4 [5]. Studies have demonstrated its broad biological activities, but its bioavailability poses a challenge for clinical applications, requiring further investigation. After oral administration, apigenin is primarily absorbed in the intestines, yet its absolute bioavailability remains low (typically below 20%), mainly due to poor water solubility, significant first-pass effect, and rapid microbial degradation in the gut [6]. Its primary metabolic pathways include glucuronidation, sulfation, and methylation [7-8]. Crucially, while doses in animal models often range from 25 to 100 mg/kg to overcome this low bioavailability, these levels significantly exceed standard human dietary intake. Therefore, the subsequent sections evaluate therapeutic effects while acknowledging that clinical translation requires human equivalent doses (HED) achievable only through the advanced delivery systems discussed below. In recent years, research has focused on developing novel delivery systems to enhance bioavailability: Nanoparticles such as liposomes, polymer nanoparticles, and solid lipid nanoparticles can significantly improve the stability and targeting of apigenin. Liu et al. [9] reported that nanocapsules derived from chitosan derivatives showed markedly improved oral bioavailability and anti-fibrotic effects. Phospholipid complexes: Studies indicate that apigenin-phospholipid complexes exhibit enhanced liver distribution and anti-NAFLD activity in mouse models [10].

MECHANISM OF ACTION AND RESEARCH PROGRESS OF APIGENIN IN LIVER DISEASES

Non-Alcoholic Fatty Liver Disease (NAFLD)

NAFLD is characterized by excessive accumulation of lipids in the liver, which may progress to non-alcoholic steatohepatitis, liver fibrosis, and cirrhosis. Apigenin can intervene in the pathological process of NAFLD through multiple mechanisms.

However, it is noteworthy that the efficacy of apigenin is highly context-dependent; some studies utilizing low-fat control diets or specific genetic models have reported negligible improvements in lipid accumulation, suggesting that its metabolic benefits may be primarily restorative rather than preventative in non-stress conditions. Traditional views suggest that while apigenin often intervenes in NAFLD progression, its effects on lipid metabolism can vary significantly based on the dosage and the specific stage of the disease model employed. Lipid metabolism regulation: Apigenin activates the adenosine monophosphate-activated protein kinase pathway, thereby inhibiting the expression of sterol regulatory element-binding protein-1c (SREBP-1c) and its downstream fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC), reducing hepatic neofatty acid synthesis [11]. Singh L et al. [12] found that flavonoids (to which apigenin belongs) can be metabolized by gut microbiota, improving hepatic metabolism by enhancing intestinal barrier function and modulating gut microbiota. Anti-inflammatory and antioxidant effects: Apigenin effectively inhibits the activation of nuclear factor κB (NF-κB) and reduces the production of pro-inflammatory factors such as tumor necrosis factor-α (TNF-α), interleukin IL-β, and IL-6 [13]. Additionally, its potent free radical scavenging capacity and activation of the nuclear factor E2-related factor 2 (Nrf2) signaling pathway can stimulate the expression of antioxidant enzymes such as heme oxygenase-1 (HO-1) and quinone oxidoreductase 1 (NQO1), mitigating oxidative stress damage [14].

Recent studies have demonstrated that anti-fibrotic effects can delay disease progression. Research has found that apigenin effectively ameliorates hepatic fibrosis in diet-induced NASH mouse models. The mechanism involves inhibiting the Notch signaling pathway in hepatocytes, downregulating the expression of its downstream product bone bridging protein, indirectly suppressing the activation of hepatic stellate cells, reducing extracellular matrix deposition, and thereby slowing the progression of hepatic fibrosis [15].

Alcoholic Liver Disease (ALD)

The pathological mechanisms of ALD involve oxidative stress, inflammation, and intestinal sepsis induced by ethanol metabolites. The protective effects of apigenin on ALD exhibit multidimensional characteristics.

Traditional studies primarily focused on the role of apigenin in ethanol metabolism, suggesting its ability to enhance the activity of alcohol dehydrogenase (ADH) and alcohol dehydrogenase-like enzymes (ALDH), while downregulating CYP2E1 protein expression. This mechanism promotes safe ethanol metabolism and reduces the accumulation of toxic ethanol and free radicals [16].

Recent studies have revealed the critical role of apigenin in iron homeostasis regulation. Patients with alcoholic liver disease often exhibit hepatic iron overload, while apigenin can modulate the advanced glycation end product receptor signaling pathway, ameliorating alcohol-induced hepatic iron metabolism disorders [17]. This finding establishes a link between iron overload, lipid peroxidation, and inflammatory responses, adding a new dimension to the mechanistic studies on apigenin's role in alcoholic liver disease.

Liver Fibrosis

Hepatic fibrosis is a reparative response characterized by excessive deposition of extracellular matrix (ECM) following chronic liver injury, with the activation of hepatic stellate cells (HSCs) serving as the central mechanism [18]. Apigenin exhibits potent anti-fibrotic potential.

Basic studies have demonstrated that apigenin can revert activated collagen-producing myofibroblasts (HSCs) to a resting state or induce their apoptosis, promote degradation, and regulate autophagy and cellular senescence. The mechanisms involved include: ① Inhibition of the transforming growth factor-β1 (TGF-β1)/Smad classical pathway to block fibrotic signaling; suppression of platelet-derived growth factor (PDGF)-mediated MAPK/ERK and PI3K/Akt pathways to inhibit HSC proliferation and migration; and suppression of HSC activation through activation of the PPARγ pathway [19]. ② Downregulation of tissue inhibitor of metalloproteinases-1 (TIMP-1) expression to facilitate degradation of deposited collagen [20]. ③ Reduction of autophagy-related protein expression to inhibit hepatic stellate cell activation and autophagy, thereby alleviating hepatic fibrosis [21].

A recent study systematically elucidated the dose-dependent protective effects of apigenin on carbon tetrachloride-induced liver fibrosis by integrating proteomics and transcriptomics technologies. The study identified 48 key proteins, among which 6 cross-species conserved targets exhibited both biomarker potential and therapeutic prospects, providing novel insights for anti-fibrotic strategies [22].

Hepatocellular Carcinoma (HCC)

Apigenin exhibits inhibitory effects on various cancer cells and plays a significant role in the chemoprevention and treatment of hepatocellular carcinoma.

Its classic mechanisms of action include inducing cell cycle arrest, triggering apoptosis, inhibiting invasion and metastasis, and regulating epigenetics and signaling pathways. These mechanisms are achieved through the following aspects: Inducing cell cycle arrest: By activating the p38 MAPK signaling pathway, it upregulates cyclin-dependent kinase inhibitors (CDKIs) such as p21/WAF1 and p27, while downregulating cyclin D1 and CDK4, thereby blocking HCC cells in the G2/M phase or G0/G1 phase [23]. Inducing apoptosis: Both the mitochondrial pathway (endogenous pathway) and the death receptor pathway (exogenous pathway) are activated by apigenin. It reduces mitochondrial membrane potential, promotes cytochrome C release, and activates the caspase cascade reaction; simultaneously, it upregulates the expression of receptors such as Fas and TRAIL [24]. Inhibiting invasion and metastasis: Apigenin downregulates the expression of matrix metalloproteinases (MMP-2, MMP-9) and vascular endothelial growth factor (VEGF), while upregulating epithelial cadherin (E-cadherin), thereby inhibiting epithelial-mesenchymal transition (EMT) and suppressing the invasion, metastasis, and angiogenesis of HCC cells [25-26]. Epigenetics and signaling pathways: Studies have found that apigenin exerts its anticancer effects by regulating microRNAs (e.g., upregulating mir-520b) [27]. It also effectively inhibits aberrantly activated oncogenic signaling pathways in HCC, including PI3K/AKT/MTOR, JAK/STAT3, and Wnt/β-catenin pathways [28].

Recent studies have identified a novel anticancer target for apigenin. Apigenin can delay the progression of hepatocellular carcinoma by inhibiting SLC1A5-mediated glutamine dependence. Glutamine is one of the primary nutrients for tumor cells, and apigenin can suppress SLC1A5 expression, thereby reducing glutamine metabolism and disrupting the energy supply for hepatocellular carcinoma proliferation, ultimately slowing liver cancer progression [29].

Drug-Induced Liver Injury (DILI)

Acetaminophen (APAP) overdose is a common cause of acute liver failure. Apigenin exhibits protective effects against acute liver injury induced by APAP, carbon tetrachloride (CCl_4), cisplatin, and other agents. The mechanism of action is as follows:

APAP-induced injury: Excessive APAP is metabolized by cytochrome P450 in hepatocytes to generate N-acetylphenanthroquinone imine (NAPQI). NAPQI activates the JNK pathway, inducing mitochondrial permeability transition and inhibiting mitochondrial biological functions, leading to mitochondrial dysfunction and oxidative stress damage, which ultimately causes hepatocyte necrosis [30]. Celery extract can effectively inhibit the overactivation of the JNK pathway and activate the Nrf2 signaling pathway, restoring the expression

of downstream glutathione synthase and antioxidant proteins, thereby enhancing hepatocyte detoxification and antioxidant capacity, and mitigating mitochondrial loss and hepatocyte necrosis [31].

CCl_4 loss: CCl_4 is metabolized by P450 to produce trichloromethyl radicals ($\cdot CCl_3$), which induce intense lipid peroxidation and oxidative stress. Apigenin can enhance the activity of endogenous antioxidant enzymes such as superoxide dismutase (SOD) and glutathione (GSH) in liver tissue, significantly reducing serum transaminase levels [32].

Loss of chemotherapeutic agents such as cisplatin: While killing tumor cells, cisplatin and other chemotherapeutic agents also cause damage to normal tissues by inducing oxidative stress and inflammatory responses. Apigenin can promptly eliminate free radicals, inhibit the production of inflammatory factors (e.g., TNF-α, IL-6), and regulate related signaling pathways, thereby protecting hepatocytes from toxic damage caused by chemotherapeutic agents [33-34].

CONVERGENT SIGNALING NETWORKS AND MULTI-TARGET PHARMACOLOGY

The hepatoprotective effects of apigenin transcend single-target interactions, operating instead through a sophisticated “multi-component-multi-target-multi-pathway” network that synchronizes various metabolic and immune responses: energy and metabolic sensor AMPK, oxidative stress master regulator Nrf2, inflammatory central switch NF-κB and NLRP3, fibrosis core pathway TGF-β/Smad, and critical cell proliferation pathways such as PI3K/AKT and MAPK [35]. Apigenin can skillfully synergistically regulate these interconnected signaling networks to restore hepatic metabolic and immune homeostasis [36]. This multi-target property enables it to simultaneously intervene in multiple stages of liver disease progression, including steatosis, inflammation, oxidative stress, fibrosis, and carcinogenesis.

Multi-omics studies further support the multi-targeted properties of apigenin. The findings revealed generally low mRNA-protein abundance correlations with significant variability, highlighting the importance of post-transcriptional regulation in hepatic fibrosis and explaining why single omics analyses may miss critical mechanisms [37].

PRECLINICAL AND CLINICAL RESEARCH

Currently, the vast majority of studies remain at the cellular and animal model stages, yet the conclusions consistently support its hepatoprotective effects. In animal models, apigenin significantly improves liver

function parameters (e.g., ALT, AST), reduces hepatic pathological damage, and decreases inflammation and fibrosis.

Clinical research has lagged behind, but initial findings are emerging. A few small-scale human trials or epidemiological studies suggest that a diet rich in apigenin is associated with lower liver enzyme levels and reduced risk of non-alcoholic fatty liver disease (NAFLD) [38]. For instance, a study based on NHANES data revealed a negative correlation between apigenin intake and the risk of metabolic-associated fatty liver disease (MASLD). After adjusting for multiple confounding factors, the highest intake group showed a 29% lower risk compared to the lowest intake group [39]. However, current studies still have significant limitations: (1) Lack of high-quality, large-sample randomized controlled trials (RCTs) to evaluate the exact efficacy and safety of apigenin preparations in patients with liver disease. (2) Significant translational hurdles remain, including the absence of standardized pharmacological extracts and the high variability of bioavailability across different oral formulations, which complicates the establishment of a therapeutic window. (3) Clinical application is further hindered by a lack of Phase I/II safety data and the potential for significant herb-drug interactions, as apigenin may modulate cytochrome P450 enzymes (e.g., CYP2E1), potentially altering the metabolism of co-administered medications in liver patients . (4) Most mechanistic studies rely on animal models, which cannot fully replicate the complex processes of human liver disease. (5) Variations in dosage and administration methods across studies make direct comparison and integration of results challenging.

SAFETY, CHALLENGES, AND FUTURE PERSPECTIVES

Apigenin is generally regarded as safe, and no significant adverse effects have been reported following dietary intake. Animal studies at high doses also indicate low acute toxicity [40]. However, caution is still required for its potential pharmaceutical application, focusing on drug-drug interactions, long-term safety at high doses, and the bottleneck of low bioavailability. Therefore, future research directions of apigenin should center on the following key areas:

(1) Develop efficient delivery systems and continuously advance nanotechnology to achieve more effective delivery.

(2) Conduct well-designed multicenter randomized controlled trials to investigate the efficacy and safety of apigenin in patients with liver diseases.

(3) Explore combination therapy strategies and evaluate the synergistic effects of apigenin with existing drugs.

(4) Deepen mechanistic research by systematically dissecting the action network of apigenin using multi-omics and artificial intelligence.

(5) Promote personalized therapy by precisely tailoring therapeutic regimens according to individual characteristics of different liver disease patients.

In summary, recent studies have convincingly demonstrated that apigenin exerts potent protective effects against liver diseases via synergistic multi-target and multi-pathway actions, covering core pathological processes including hepatic steatosis, inflammation, oxidative stress, fibrosis, and carcinogenesis. Although challenges remain in bioavailability and clinical translation, apigenin represents a highly promising candidate for the prevention and treatment of liver diseases owing to its natural origin and favorable safety profile. With breakthroughs in delivery technologies and further clinical investigations, apigenin is expected to serve as an effective dietary supplement or adjuvant therapeutic agent in the comprehensive management of liver diseases in the future.

CONCLUSION

In conclusion, this comprehensive review underscores apigenin as a highly promising natural flavonoid with potent multi-target hepatoprotective properties across a spectrum of liver pathologies, including non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), hepatic fibrosis, drug-induced liver injury, and hepatocellular carcinoma (HCC). By orchestrating a complex regulatory network involving critical signaling nodes such as Nrf2 for antioxidant defense, NF-κB and NLRP3 for inflammatory control, AMPK for metabolic homeostasis, and TGF-β/Smad for anti-fibrotic intervention, apigenin effectively restores hepatic equilibrium and mitigates pathological progression. Despite the compelling preclinical evidence demonstrating its efficacy in various rodent models—typically at dose ranges of 20 to 100 mg/kg—significant challenges remain for successful clinical translation. The inherent limitations of apigenin, notably its low absolute oral bioavailability (often below 20%) and rapid first-pass metabolism, necessitate the continued development of innovative delivery systems such as nano-liposomes, polymer nanoparticles, and phospholipid complexes to enhance systemic exposure and targeting. Furthermore, while initial epidemiological data suggest a negative correlation between apigenin intake and the risk of metabolic-associated fatty liver disease, there is an urgent need for high-quality, large-sample multicenter randomized controlled trials to establish standardized dosing regimens and evaluate long-term safety profiles. Future research should leverage integrated multi-omics technologies and artificial intelligence to precisely map its “multi-component-multi-target” action network

and address potential herb-drug interactions. Ultimately, apigenin represents a versatile candidate that, with advancements in formulation science and robust clinical validation, is poised to serve as an effective therapeutic agent or adjuvant dietary supplement in the comprehensive management of the global liver disease burden.

Author Contributions

Conceptualization –WEI Zhiming and WU Yakun; methodology – WEI Zhiming and WU Yakun; investigation – WEI Zhiming and WU Yakun; writing-original draft preparation – WEI Zhiming and WU Yakun. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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