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REVIEW

Dihydroartemisinin: A Promising Therapeutic Agent Against the Hepatitis-to-Hepatocellular Carcinoma Cascade

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Abstract: Liver cancer progression is a multifactorial, multistage, and complex malignancy. Dihydroartemisinin (DHA) is widely recognized for its antimalarial, antifibrotic, and anticancer activities. This review highlights that DHA in the hepatitis-to-hepatocellular carcinoma (HCC) cascade and explores its underlying mechanisms. DHA has remarkable effectiveness in suppressing inflammatory cytokines and promoting tissue recovery, primarily targeting the phosphoinositide 3-Kinase (PI3K)/protein kinase B (Akt) and interleukin signaling pathways. During hepatic fibrosis, DHA inhibits hepatic stellate cell activation through mechanisms including α-smooth muscle actin (α-SMA) and nuclear factor kappa B (NF-kB) pathways. It further modulates inflammatory responses, suppresses hematopoietic stem cell proliferation, induces ferroptosis, and regulates lipid droplet metabolism. Moreover, DHA inhibits the PI3K/Akt/mammalian target of rapamycin (mTOR) pathway and yes-associated protein 1 (YAP1) signaling, thereby suppressing the proliferation, invasion, and metastatic potential of HCC cells, while simultaneously activating apoptotic and autophagic pathways. Additionally, it counteracts drug resistance and improves responsiveness to chemotherapy. Notably, lipid metabolism is identified as a promising therapeutic target in this cascade, and some nanoparticle drug delivery systems have been demonstrated to optimize DHA's therapeutic efficacy. DHA demonstrates broad therapeutic efficacy by targeting multiple molecular pathways, supporting its potential clinical application in hepatocellular carcinoma prevention and treatment.

Keywords: dihydroartemisinin, hepatitis, hepatic fibrosis, hepatocellular carcinoma, lipid metabolism

Introduction

Liver cancer, especially hepatocellular carcinoma(HCC), is the fifth most common cancer worldwide and the third leading cause of cancer mortality.[1] Asia is a major region for liver cancer, and Asia reported 72.5% of the world's cases in 2020.[2] Risk factors include Hepatitis B virus (HBV), Hepatitis C virus (HCV), hepatic steatosis, and others.[3,4] HCC is frequently characterized by delayed diagnosis and unfavorable prognosis, primarily attributable to its asymptomatic nature or nonspecific clinical manifestations during early stages.

HCC develops secondary to chronic hepatic disorders through complex pathogenetic mechanisms.[5] The development of liver inflammation is frequently associated with chronic liver injury, subsequently leading to the damage of the epithelial or endothelial barrier, the release of inflammatory cytokines, the production of transforming growth factor-β (TGF-β) by macrophages, the overproduction of extracellular matrix, and the formation of a fibrous scar, which

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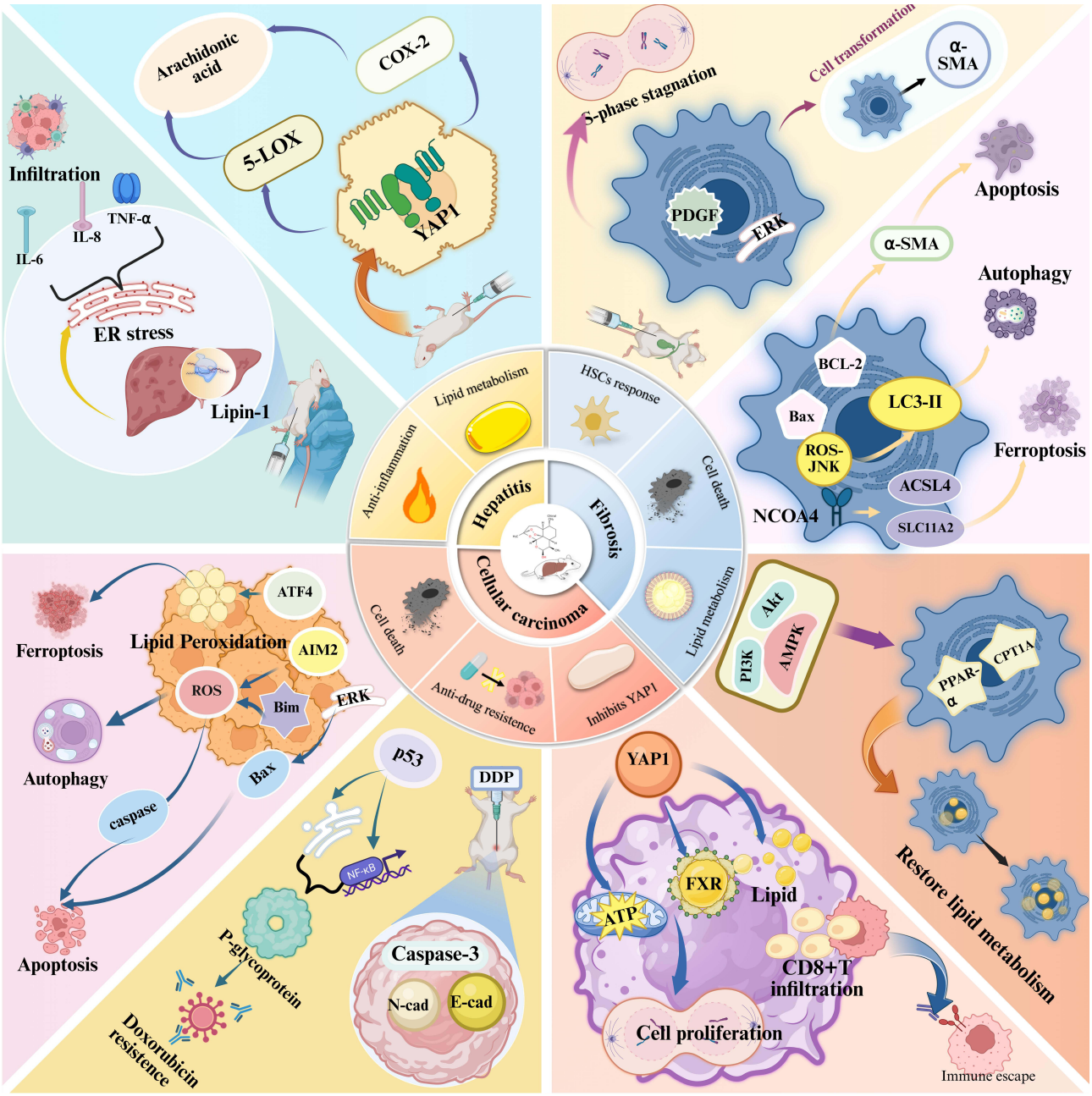
Graphical Abstract



progresses to hepatic fibrosis (HF).[6] Persistent HF injury is pathologically characterized mostly by three interconnected processes: hepatocyte apoptosis, sustained activation of inflammatory cascades, and aberrant mobilization of hematopoietic stem cells. These pathological alterations collectively drive a cascade of molecular events, synergistically promoting hepatocarcinogenesis and malignant transformation, ultimately leading to HCC.[7,8]

Viral infections are the primary pathogenic drivers in this process and represent the predominant factor leading to HCC. Anti-inflammatory and antiviral agents play a crucial role in disease management by simultaneously modulating inflammatory responses and suppressing viral replication, effectively attenuating the progression of HF and potentially preventing the malignant transformation to HCC.[9] However, orthotopic liver transplantation remains the sole curative

intervention for individuals with advanced-stage cirrhosis.[10] Consequently, the ongoing pursuit of novel therapeutic strategies remains an imperative focus in contemporary clinical research.

DHA, a sesquiterpene-lactone derivative, is a bioactive phytochemical compound isolated from the medicinal plant Artemisia annua. Extensive clinical studies have demonstrated its efficacy as a potent and rapid-acting antimalarial agent.[11] In addition to its antimalarial effects, DHA has a wide range of pharmacological activities. DHA demonstrates broad-spectrum antitumor activity against diverse malignancies, including but not limited to pancreatic, prostate, cervical, hepatic, and neuroblastoma cancers. The compound mediates its anticancer effects through multiple mechanisms, including cell cycle modulation, tumor angiogenesis suppression, and cancer cell apoptosis.[12–15]

Although extensive research has explored the therapeutic potential of DHA across various liver diseases, its therapeutic role across the disease continuum-from hepatitis and HF to HCC-remains unexplored. This review systematically addresses this critical knowledge gap by elucidating the mechanistic role of DHA in the prevention and treatment of hepatocarcinogenesis.

The Trilogy of "Hepatitis-HF-HCC"

Viral hepatitis primarily represents a major etiological factor contributing to the development and progression of HF and, ultimately, HCC.[16] Notably, HBV infection has stood as a dominant oncogenic driver, significantly contributing to the initiation and progression of HCC through both direct and indirect mechanisms.[17] These stress conditions activate critical signaling pathways, particularly signal transducer and activator of transcription 3 (STAT3) and NF-κB, which trigger the formation of inflammasomes and initiate inflammatory cascades. Furthermore, in chronic viral hepatitis, persistent reactive oxygen species (ROS) accumulation exacerbates hepatic injury through STAT3/NF-κB-mediated dysregulation, leading to enhanced lipid peroxidation and subsequent development of hepatic steatosis.[18,19] Hepatic Stellate Cells (HSCs) are the core effector cells of HF. In a normal liver, HSCs are quiescent and store vitamin A lipid droplets (LDs). The persistent inflammatory microenvironment facilitates the activation of HSCs by modulating the TGF-β, platelet-derived growth factor-β receptor (PDGF) signaling pathways, oxidative stress, dysregulated miRNA expression, and inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β). These inflammatory cytokines activate HSCs, transforming them into myofibroblasts that secrete large amounts of ECM components. The upregulation of tissue inhibitors of metalloproteinases inhibits extracellular matrix (ECM) degradation, resulting in fibrotic deposition.[20–24] Furthermore, activated HSCs can also promote neovascularization through the secretion of angiopoietin, thereby creating a microenvironment conducive to HCC metastasis, invasion, and metastatic progression[25] (Figure 1).

Phase I: DHA Prevention of Hepatitis

DHA Inhibits Inflammatory Cytokines in Alcoholic Hepatitis

The advancement of inflammatory processes in alcoholic liver disease can lead to hepatitis, HF, and ultimately HCC.[26,27] In a mouse model of alcoholic fatty liver induced by Red Star wine, intraperitoneal injection of 7 mg/kg DHA significantly attenuates alcohol-induced elevations in serum levels of TNF-α, interleukin-8 (IL-8), and IL-6 while also mitigating hepatic damage. In another model of ethanol-induced alcoholic fatty liver disease, DHA restored ethanol-impaired lipin-1β function, leading to reduced expression of SREBP-1c and FAS, along with upregulation of PPARα and CPT1α in the liver. The findings suggest that DHA curbs lipin-1β nuclear import, lowers the Lpin1β/α ratio, and disrupts lipin-1-dependent lipogenesis, all while stimulating lipid breakdown. Concomitantly, DHA also inhibited the activation of endoplasmic reticulum (ER) stress.[28] In vivo experiments further demonstrated that DHA attenuated the infiltration of inflammatory cells, notably those positive for CD45 and F4/80, in a model of alcoholic steatohepatitis.[29] Farnesoid X Receptor (FXR) has been demonstrated to attenuate diet-induced steatohepatitis in mice via modulation of enterocyte fat absorption.[30] By activating FXR, DHA reduces intracellular lipid accumulation and helps recover liver injury, thereby attenuating the alcohol-induced liver inflammatory response in mice. In a mouse model of alcohol-induced liver injury, DHA attenuated the alcohol-induced upregulation of hepatic lipogenic factors sterol regulatory element-binding protein-1c (SREBP-1c)[31] and fatty acid synthase (FAS) via activation of FXR, and concurrently enhanced the expression of

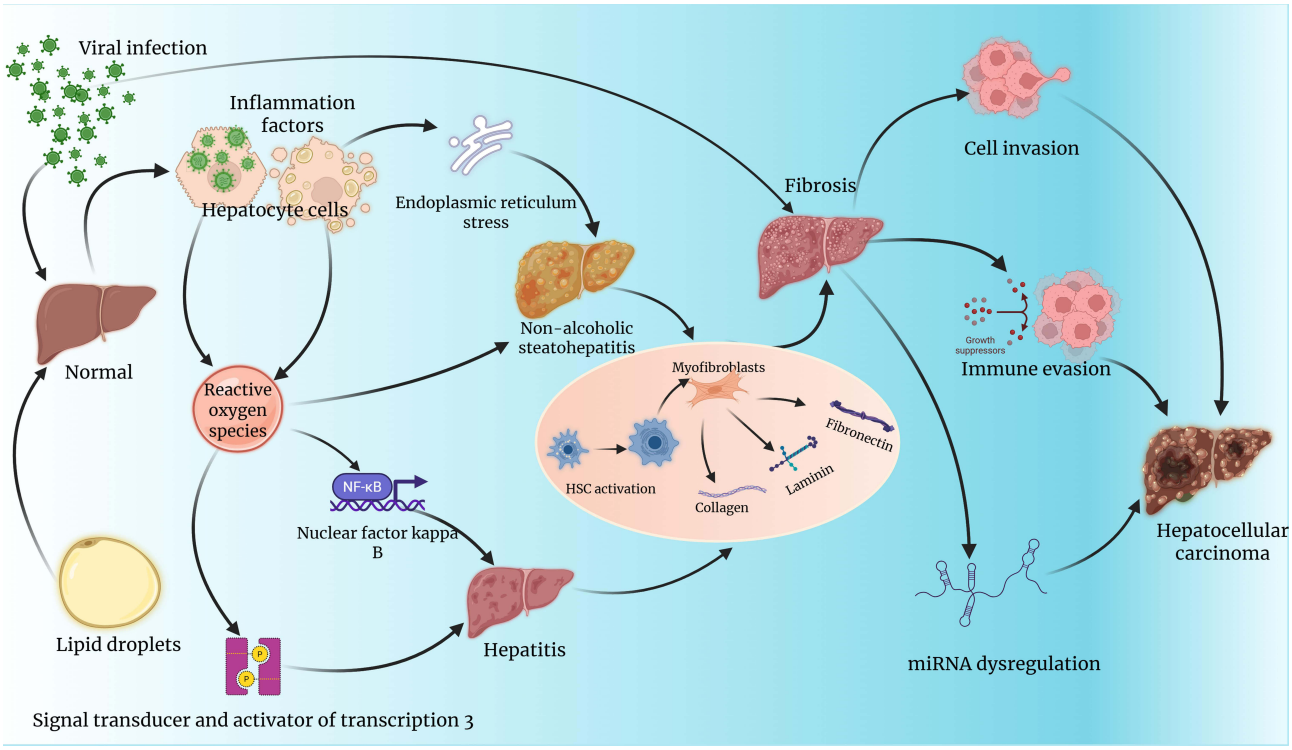


Figure 1 During the hepatitis stage, viral infection or metabolic damage triggers hepatocyte necrosis and inflammatory responses, activating Kupffer cells to release pro-inflammatory cytokines like TNF-α and IL-6. This process also generates ROS, leading to mitochondrial dysfunction and hepatocyte injury. In the liver fibrosis stage, inflammatory cytokines activate HSCs, transforming them into myofibroblasts that secrete large amounts of ECM components. The upregulation of tissue inhibitors of metalloproteinases inhibits ECM degradation, resulting in fibrotic deposition. During the HCC stage, the persistent inflammatory and fibrotic microenvironment promotes genetic mutations and epigenetic alterations, activating oncogenic signaling pathways such as PI3K/Akt/mTOR and Wnt/β-catenin. Additionally, HSCs can secrete factors like VEGF to promote tumor angiogenesis, driving the initiation and progression of HCC.

peroxisome proliferator-activated receptor alpha (PPAR-α) and carnitine palmitoyltransferase I (CPT1). These regulatory effects were abolished upon treatment with the FXR inhibitor Z-guggulsterone.[32]

DHA Regulates Lipid Metabolism

Yes-associated protein 1 (YAP1) is the key target in liver inflammation and lipid metabolism.[33] An animal study showed that in a hepatocyte-specific Yap1 knockout mouse model, an arachidonic acid metabolic pathway was abnormally activated and accompanied by the infiltration of inflammatory cells. After intraperitoneal injection of 25 mg/kg DHA, it was found that DHA majorly targets 5-lipoxygenase and cyclooxygenase-2 expression to reduce the metabolism of arachidonic acid. DHA attenuated the increase in metabolites, including prostaglandin E1 and leukotrienes caused by activation of the arachidonic acid metabolic pathway, suppressed lipid vacuole accumulation, and reduced levels of triglyceride and perilipin-2. These results indicate that DHA mitigates hepatic inflammation through regulation of the YAP1-related metabolic pathway.[34]

HCV also constitutes a major causative factor of liver cancer globally. Existing studies have demonstrated a profound interdependency between lipoproteins and HCV replication: the virus not only exploits lipoproteins such as apolipoprotein E (apoE) for cellular attachment and entry but also coats itself in lipid-rich particles to form HCV-lipoviroparticles, while actively manipulating host lipid metabolism to facilitate its own replication. Although DHA can indeed modulate lipid metabolism, direct evidence regarding its ability to suppress HCV replication via regulation of apoE or LDLR expression remains limited. Nevertheless, this close relationship between lipid metabolism and HCV replication offers considerable scope for developing novel anti-HCV therapeutic strategies based on DHA.[35,36]

Phase II: Halting the Advancement of Cirrhosis by DHA

DHA Inhibits HSC Action and Cell Proliferation

HSC activation represents an essential pathological event in HF. Through HSC activation, the transformation of α-SMA-positive myofibroblasts has been increased, which increased the ECM accumulation, especially collagen I, and finally led to HSC proliferation.[37] Some research showed that the platelet-derived growth factor-β receptor (PDGF-βR) is a potent proliferative cytokine, linked to cell proliferation in the pathogenesis of HF.[38] In a rat model of bile duct ligation, administration of 14 mg/kg DHA markedly attenuated liver injury and HSCs activation by targeting the PDGF-βR/ERK signaling pathway. This intervention resulted in diminished hepatocyte degeneration, suppressed collagen deposition, reduced pseudolobule formation in liver tissue, and decreased activation of α-SMA-positive cells. Meanwhile, in vitro experiments, the PDGF-βR signal and the fibrosis marker protein in HSCs are observed to be changed. Furthermore, DHA also induced S-phase blockade in HSCs division to inhibit their proliferation and exert antifibrotic effects.[39]

DHA Inhibits HSC Cell Contraction and Fibrotic Portal Hypertension

Portal hypertension is the hallmark complication of decompensated HF.[40,41] Hepatic injury triggers the activation of quiescent HSCs and HSCs contracted, contributing to portal hypertension.[42] FXR is an effective regulatory factor of liver fibrosis and portal hypertension. Activation of the FXR receptor can effectively inhibit liver fibrosis-related portal hypertension.[43] In vitro experiments indicated that by activating the FXR/S1PR2 signal, DHA at 20 μmol/L effectively inhibits the contraction of HSCs.[44] These results were also demonstrated in the CCL4-induced rat model of liver cirrhosis and accompanied by TNF-α, IL-6, and NF-kB expression reduction.[45]

DHA Induces Ferroptosis in HSC Cells

Ferroptosis is defined as a non-apoptotic, iron-dependent form of regulated cell death, initiated by the accumulation of lipid peroxides. This process results in irreversible plasma membrane damage and elevated intracellular lipid ROS, distinguishing it mechanistically from other cell death modalities.[46] A PDGF-BB-induced HSCs activation model study indicated that DHA exhibited antifibrotic effects by inducing ferroptosis. Specifically, 20μM DHA significantly upregulated Nuclear receptor coactivator 4 (NCOA4) expression and promoted the upregulation of iron death markers SLC11A2 and ACSL4, accompanied by several columns of iron death alterations (like lipid ROS generation or iron overload) to induce HSC cell death.[47] Moreover, N6-methyladenosine (m6A) emerges as a potential therapeutic target in liver fibrosis. Interestingly, m6A exerts an antagonistic effect on DHA-induced ferroptosis in HSC and may provide a new basis for the mechanism of DHA-induced ferroptosis.[48]

DHA Triggers Both Autophagy and Apoptosis in HSCs

Apoptosis, a type of controlled cell suicide, inhibits HSCs' activation and contributes to the amelioration of HF.[49] In a bile duct-ligated rat model, intraperitoneal DHA (14 mg/kg) up-regulated cysteinyl aspartate specific proteinase (caspase)-3, the pro-apoptotic protein BCL2-Associated X (Bax), and down-regulated the anti-apoptotic protein B-cell lymphoma-2 (Bcl-2), exerting anti-fibrotic effects via PI3K/Akt pathway regulation.[50]

Autophagy is a self-degradation of damaged organelles and macromolecules within a cell, characterized by the formation of autophagosomes and lysosomes.[51] 20 μM DHA activates autophagy by activating the ROS-c-Jun N-terminal kinase (JNK)1/2 signal. Studies have shown that in PDGF-BB-induced HSCs, DHA increased the formation of autophagosomes and microtubule-associated protein 1A/1B-light chain 3 (LC3)-II. The detection of inflammatory cytokines in cell supernatants by ELISA revealed that phosphorylation of Autophagy Related 5 (pAtg5), like DHA, inhibited the release of interferon γ (IFN-γ), IL-4, and IL-6 and promoted the anti-inflammatory cytokines in activated HSCs to inhibit the inflammatory response.[52]

DHA Modulates Lipid Droplet Metabolism in HSCs

Loss of LDs is observed during activation of HSCs.[53] Resting HSCs are enriched with vitamin A LDs, and retinol (vitamin A) stored in the LDs inhibits HSC activation-associated gene expression by binding to retinoic acid receptors.[54]

During the activation of HSCs, HSCs upregulate PPAR-α and generate adenosine triphosphate (ATP) to support their proliferation and ECM synthesis.[55] IncRNA-H19 (RNA-H19) is a potential diagnostic biomarker and therapeutic target in liver fibrosis treatment.[56]

Reduction of LDs was found in activated HSC-LX2 cells. DHA at a concentration of 20 μM significantly inhibited the PI3K/Akt pathway activation, which inhibited the H19 expression, and ultimately inhibited the activation of the adenosine monophosphate-activated protein kinase (AMPK) signal, reducing the expression of carnitine palmitoyltransferase I A (CPT1A) and PPAR-α in activated HSC cells, reducing lipid oxidation levels in hematopoietic stem cells, restoring the content of cholesteryl esters, triglycerides, and retinyl esters in activated HSCs, thereby suppressing their activation. The same was demonstrated in the CCL4-rat model.[57] Moreover, following DHA inhibits RNA-H19 expression, alcohol dehydrogenase III activity is elevated, promoting the conversion of retinol to retinaldehyde and thereby facilitating the storage of retinyl esters within lipid droplets, activating the retinoic acid signal, and restoring lipid droplet metabolism in activated HSCs.[58] Recent studies have demonstrated that DHA reduces lipid droplet accumulation during HSC activation and restores HSC quiescence by targeting nuclear receptor subfamily 1 group D member.[59]

The regulatory effects of DHA on lipid metabolism in both hepatitis and HF involve multifaceted and interconnected mechanisms. The AMPK signaling pathway appears to serve as a central node through which DHA modulates lipid homeostasis in both pathological contexts. During hepatitis, DHA attenuates endoplasmic reticulum (ER) stress by targeting the lipin-1 signaling pathway. Considering the established crosstalk between ER stress and AMPK, it is plausible that DHA fine-tunes AMPK activity indirectly via the lipin-1–ER stress axis, thereby contributing to its lipid-modulating effects. During the HF stage, DHA activates nuclear receptor subfamily 1 group D member 1, which helps restore lipid droplet content in HSCs and inhibits their activation. In the HF stage, although not directly linked to lipid droplet metabolism in existing reports, DHA regulates key fatty acid synthases, including FAS, thereby modulating intracellular lipid droplet synthesis and metabolism and subsequently affecting HSC activation. Furthermore, in both stages, DHA regulated the expression of key proteins involved in lipid synthesis and oxidation—such as PPARα and CPT1A—thereby promoting lipid metabolic homeostasis.

Alternative Approaches Utilizing DHA for the Treatment of HF

DHA targets the VEGFA proteins via miR-29b-3 and inhibits the rate of CCL4-induced liver damage, such as hepatocellular disorders, inflammatory responses, and collagen accumulation. This was accompanied by a decrease in the expression of α-SMA and collagen type 1 alpha chain. This experiment also demonstrated that vascular endothelial growth factor receptor (VEGFR)2 regulates autophagy and degradation in HSC cells through the PI3K/Akt/mTOR/UNC-51-like Kinase 1 (ULK1) signaling pathway. The anti-fibrotic effects of DHA may also be associated with this mechanism.[60]

Cellular senescence represents a stress-induced, irreversible state primarily regulated by the tumor suppressor proteins p53 and p16INK4a. DHA targeted GATA-binding factor 6 (GATA6) to promote the senescence markers p53, p16, p21, and Hmga1 expression in SA-β-Gal-positive HSC cells, and DHA-induced senescent HSC cell aggregation in rat fibrotic livers, and the senescence markers were found in an in vivo CCL4-induced animal model. In addition, this study also found that DHA at a concentration of 20 μM was effective in inhibiting p62 accumulation, inducing autophagosome formation, and disrupting the p62-GATA6 interaction, thereby promoting cellular senescence in HSC cells and inhibiting HF.[61]

YAP1: A Potential Therapeutic Target of DHA in HF

YAP1, a key effector of the Hippo signaling pathway, becomes rapidly activated upon hepatic stellate cell (HSC) stimulation—whether induced by CCl4 in mice or by other means in vitro. This activation is characterized by nuclear translocation and upregulated expression of YAP1 target genes, including Ankrd1 (cardiac ankyrin repeat protein) and Ctgf (connective tissue growth factor). Consistent with these findings, nuclear localization of YAP1 has also been observed in HSCs from human fibrotic livers. Moreover, both knockdown of YAP1 expression and pharmacological inhibition of YAP1 suppressed HSC activation in vitro, with pharmacological intervention also attenuating fibrotic progression in vivo.[62] In a separate experiment, it was also demonstrated that modulation of YAP activity influences the

phenotype of myofibroblast-like hepatic stellate cells (MF-HSCs). Specifically, YAP silencing suppressed the MF-HSC phenotype, reduced susceptibility to ferroptosis, and inhibited HSC activation.[63]

Phase III: DHA-Mediated Molecular Pathways in HCC Pathogenesis and Treatment

DHA Promotes Ferroptosis in HCC Cells

Activating transcription factor 4 (ATF4) was found to effectively activate the expression of solute carrier family 7a member 11, which is the small subunit of the cystine-glutamate antiporter (xCT) that has been demonstrated to increase the HCC vulnerability to ferroptosis, thereby suppressing the progression of HCC. In a mouse xenograft model of HCC, DHA at 100 mg/kg suppressed the expression of xCT, subsequently inhibiting ATF4 and promoting lipid peroxidation in HCC cells, ultimately leading to ferroptosis.[64] Furthermore, the chemosensitivity of HCC to sorafenib (SRF) was enhanced through the ATF4-xCT signaling pathway.[65] The synergistic use of DHA and SRF holds significant promise as a new therapeutic strategy for HCC treatment. Recently, a novel nanosheet loading DHA demonstrated multiple roles in inducing iron death, apoptosis, and immune activation driven by HCC, thereby proposing an innovative paradigm for its treatment.[66] In HCC cell lines, consistent findings were observed. 15-Lipoxygenase (15-LO), a key enzyme catalyzing the peroxidation of polyunsaturated fatty acids, drives the accumulation of lipid peroxidation products in cell membranes when its activity is enhanced. DHA upregulates PEBP1 protein expression, which in turn indirectly activates 15-LO, elevating lipid peroxidation and ultimately inducing ferroptosis.[67]

The nuclear factor erythroid 2-related factor 2 (NRF2) signaling pathway may serve as an upstream regulator in DHA-induced ferroptosis in HSCs and HCC. NRF2 deficiency downregulates HECT and RLD domain containing E3 ubiquitin protein ligase 2 (HERC2) expression, enhances NCOA4 stability, and promotes ferritin degradation, leading to increased release of free iron. Specifically, NCOA4 recruits ferritin to autophagosomes for degradation, thereby facilitating ferritinophagy.[68] Furthermore, NRF2 and ATF4 bind to the antioxidant response element (ARE) and amino acid response element (AARE) in the xCT promoter, synergistically upregulating xCT expression. This enhanced expression diminishes cellular sensitivity to ferroptosis.[69] Accordingly, NRF2 likely functions as an upstream regulatory factor for both the NCOA4-dependent and ATF4-xCT signaling axes.

The JNK signaling pathway may represent an additional upstream regulatory mechanism involved in this process. In IL-1β-stimulated mouse chondrocytes, administration of the JNK inhibitor SP600125 downregulated NCOA4 expression, impeded autolysosome formation, and ultimately suppressed ferroptosis.[70] β-Lapachone activates the JNK signaling pathway, resulting in upregulation of NCOA4 expression and promotion of ferritinophagy. Concurrently, it suppresses xCT transcription, leading to diminished cystine uptake and subsequent glutathione (GSH) depletion.[71]

DHA Triggers Both Apoptosis and Autophagy in HCC Cells

In HepG2 cell lines, DHA treatment results in elevated intracellular levels of ROS and Ca^{2+}. Meanwhile, it upregulates DNA damage-inducible gene 153 protein expression, induces ER stress, modulates Bax and Bcl-2 expression, triggers apoptosis, and suppresses the proliferation of HepG2 cells.[72] The transcription factor specificity protein 1, a ubiquitously expressed transcription factor, orchestrates fundamental biological processes ranging from cell cycle progression to survival signaling and apoptosis control.[73] In SK-Hep-1 and AML12 cells, by inhibiting the transcription factor specificity protein 1 signaling pathway, DHA inhibited the X-linked inhibitor of apoptosis and increased the caspase-3, caspase-8, and caspase-9 expression to induce apoptosis and promote HCC cell destruction.[74] Activator BH3-only molecules Bim trigger the activation of the BAX/BAK, leading to the induction of apoptosis.[75] In Hep3B cell lines, Bim is involved in DHA-induced apoptosis in HCC cells, accompanied by activation of ROS and caspase, and found that Bcl-2 family member Bak is a dominant marker in the apoptosis process.[76] In MHCC97-L cells, DHA inhibits proliferation and promotes apoptosis. Mediated by the JNK/NF-κB pathway, this effect consequently enhances the expression of TNF and executioner caspase.[77] Another comprehensive in vitro and in vivo study further confirmed that DHA induces caspase and PARP activation, triggers G2/M cell cycle arrest, exerts potent cytotoxic effects, and significantly inhibits tumor growth in HCC cell lines.[78]

In HepG2215 cells, DHA activated the Absent in melanoma 2 inflammasome and promoted ROS generation, leading to enhanced autophagosome formation and increased conversion of LC3-II, ultimately inhibiting HCC cell proliferation.[79] Meanwhile, DHA inhibited the PI3K/Akt signaling pathway, markedly upregulated LC3 expression, promoted AMPK phosphorylation, and elevated p62 expression to inhibit HCC cell migration.[80]

DHA Reduces Drug Resistance and Boosts Immunological Responsiveness in HCC Cells

Chemoresistance poses a significant clinical challenge in the management of HCC. P-glycoprotein represents a critical molecular target implicated in chemotherapeutic drug resistance.[81] In mutant p53 (R248Q)-harbored HCC cells, DHA exerts its antitumor effects by targeting the ERK1/2-NF-κB pathway through direct binding to the p53 mutant protein, leading to suppression of P-glycoprotein expression, reduction of doxorubicin efflux, induction of apoptosis in Hep3B cell lines, and ultimately enhancing chemosensitivity to doxorubicin in HCC.[82] In the N-nitroso diethylamine/1,4-Bis [2-(3,5-Dichloropyridyloxy)] benzene-induced anti-cisplatin (DDP) liver tumor mice model, intraperitoneal administration of DHA (25 mg/kg) demonstrated superior tumor growth inhibition compared to DDP treatment, with statistically significant differences observed, and the combination of DHA and DDP reduced TGF-β and enhanced the immune function of tumor-bearing mice.[83] Similarly, co-treatment of HepG2 cells with 100 μM DHA and DDP upregulated the expression of cleaved caspase-3 and cleaved caspase-8 while modulating the protein levels of E-cadherin and N-cadherin. This combined treatment suppressed the proliferation and migration of HCC cells.[84]

SRF, a widely used therapeutic agent for liver cancer, faces persistent therapeutic obstacles, primarily attributable to prevalent drug resistance mechanisms. A TMT-based proteomic analysis demonstrated that the combination of DHA and SRF inhibits HCC cell proliferation.[85] In HepG2 cells, the combined administration of DHA and SRF induced more substantial disruption of the tumor microenvironment in HepG2 hepatocellular carcinoma cells than either agent alone. DHA potentiated the suppressive effects of SRF on key energy metabolism processes—mitochondrial oxidative phosphorylation and glycolysis—and concurrently promoted ferroptosis.[86] The combination of SRF with chemotherapeutic agents represents one of the earliest explored combination strategies. A Phase II clinical trial demonstrated that SRF plus capecitabine is a safe and effective conservative treatment for patients with Child–Pugh class A or B-7 cirrhosis. However, due to the small sample size, no meaningful conclusions could be drawn regarding its efficacy compared to sorafenib monotherapy. Treatment-related adverse events included neutropenia, thrombocytopenia, and abnormal liver function.[87] Combining the novel immunotherapeutic agent R848 (a Toll-like receptor 7/8 agonist) with SRF elevated the infiltration of CD45+ immune cells and neutrophils, decreased the abundance of immunosuppressive cells, including Tregs and M2 macrophages, and inhibited the remodeling of the tumor immune microenvironment.[88] Compared to the DHA–SRF combination, the primary advantage of combining SRF with immunotherapy lies in its ability to activate antitumor immune responses. However, this approach carries an increased risk of immune-related adverse events. In contrast, the DHA–SRF regimen primarily acts by directly inducing tumor cell death.

Immunotherapy has emerged as a promising therapeutic strategy and research focus in HCC treatment, improving the tumor microenvironment and helping to alleviate HCC drug resistance.[89] An animal study indicated that DHA intraperitoneal injection of 50 mg/kg inhibited Cyclin-dependent kinases, increased intracellular ROS to induce immunogenic cell death, and remodeled the tumor microenvironment to inhibit tumor growth in hepatocellular carcinoma in HCC xenograft mice's model.[90]

DHA Achieves Its Therapeutic Effects on HCC by Modulating the YAP1 Signaling Pathway

YAP1 regulates Plasminogen activator inhibitor-1 (PAI-1) transcription to promote HCC,[91] and targets YAP1 has been shown to suppress tumor progression.[92] Increased aerobic glycolysis is a critical driver of HCC progression and pathogenesis.[93] DHA suppressed aerobic glycolysis in HepG2 and HEPG2215 cells by disrupting the YAP-Hypoxia-inducible factor (HIF)-1α complex formation, leading to reduced lactate production, decreased glycolytic flux, and diminished glycolytic capacity. This novel mechanism of aerobic glycolysis inhibition represents a promising therapeutic

strategy for controlling HCC tumor proliferation.[94] Treatment with 21.5 μM DHA in HepG2 and HepG2215 cells was shown to inhibit YAP1 activity, which subsequently suppressed the glycolytic response mediated by solute carrier family 2 member 1. This effect was achieved by down-regulating YAP1 promoter-binding proteins, GA-binding protein transcription factor subunit beta 1, and cAMP-responsive element binding protein 1.[95]

YAP1 knockdown in HepG2215 cells resulted in downregulation of Interleukin-18 (IL-18). Consistent with this finding, DHA treatment effectively suppressed YAP1 expression and subsequently reduced IL-18 levels in HepG2215 cells, a result that was later confirmed in in vivo models.[96] The results above suggest that IL-18 represents a promising therapeutic target for DHA in HCC management. The FXR serves as a characteristic molecular marker during HCC development and tumorigenesis. DHA enhances FXR protein expression and reduces YAP1 protein expression to inhibit bile acid metabolism.[97]

In clinical practice, anti-programmed death 1 blockade has emerged as a cornerstone therapeutic strategy in HCC management.[98] In both HepG2215 cells and their corresponding mouse xenograft models, DHA treatment significantly attenuated lipid droplet accumulation through inhibiting YAP1 expression. This was accompanied by an upregulation in the expression of perilipin-2, an adipocyte differentiation-related protein, consequently potentiating the therapeutic efficacy of anti-programmed death 1 immunotherapy.[99] Moreover, DHA disrupts the YAP1-PD-L1 interaction in hepatic tumor cells while promoting CD8+ T cell infiltration, overcoming tumor immune evasion, and potentiating anti-PD-1 therapeutic efficacy in HCC.[100]

In summary, DHA suppresses the initiation and progression of HCC by modulating multiple pathways, including lipid metabolism, ferroptosis, and autophagy (Figure 2).

Targeting Lipid Metabolism in the Hepatitis-to-HCC Progression: A Promising Therapeutic Strategy

During the hepatitis stage, DHA suppresses arachidonic acid metabolism, thereby reducing lipid accumulation. In the HF stage, it modulates lipid droplet metabolism in HSCs, influencing their activation and thus regulating HF progression. At the HCC stage, DHA acts through the YAP1 pathway to inhibit intracellular lipid droplet formation and disrupt the tumor microenvironment. Collectively, our findings highlight the modulation of lipid metabolism by DHA as a critical and consistent mechanism throughout the hepatitis-HF-HCC sequence, positioning it as a highly promising research avenue for curbing HCC progression.

During hepatitis infection, hepatitis viruses interact with LDs within the ER compartment. They enter the ER through lipoprotein assembly procession and secretion and produce apoE to facilitate the assembly and secretion of very low-density lipoproteins. This mechanism ultimately enhances the replication of HCV virions.[101,102] It was also demonstrated that lipoprotein lipase treatment significantly reduced the apoE content within HCV particles. This treatment enhanced the binding of cell culture-derived HCV to the low-density lipoprotein receptor (LDLR). Subsequently, soluble LDLR inhibited the infectivity of such HCV, thereby suppressing its replication.[103]

Free cholesterol in HSCs is regulated through the sterol-regulatory element-binding protein negative feedback pathway. This results in elevated toll-like receptor 4 expression, sensitizing HSCs to TGF-β-induced activation. Consequently, cholesterol accumulation occurs, which further contributes to the activation of HSCs and accelerates liver fibrosis.[104] Fatty acid binding protein 1 facilitates the upregulation of VEGFR in HCC and promotes HCC cell migration through the VEGFR2/steroid receptor coactivator signaling pathway.[105] Moreover, oleate treatment activates the fatty acid-binding protein 5/HIF-1α signaling axis, driving lipid accumulation and enhancing cell proliferation in HCC cells.[106] Lipid metabolism may emerge as a potential therapeutic strategy for DHA in HCC treatment. However, further research is required to elucidate the mechanisms by which DHA modulates lipid metabolism (Figure 3).

Ferroptosis represents one of the key mechanisms through which DHA exerts its preventive and therapeutic effects against HCC. Previous studies have demonstrated that polyunsaturated fatty acids are critical drivers of ferroptosis. Upon peroxidation, polyunsaturated fatty acids suppress the expression of glutathione peroxidase 4 (GPX4), leading to lipid peroxide accumulation and ferroptosis induction.[107–109] Emerging research findings indicate that during the process of ferroptosis, an increase in cell volume accompanied by the accumulation of lipid peroxides on the membrane has been

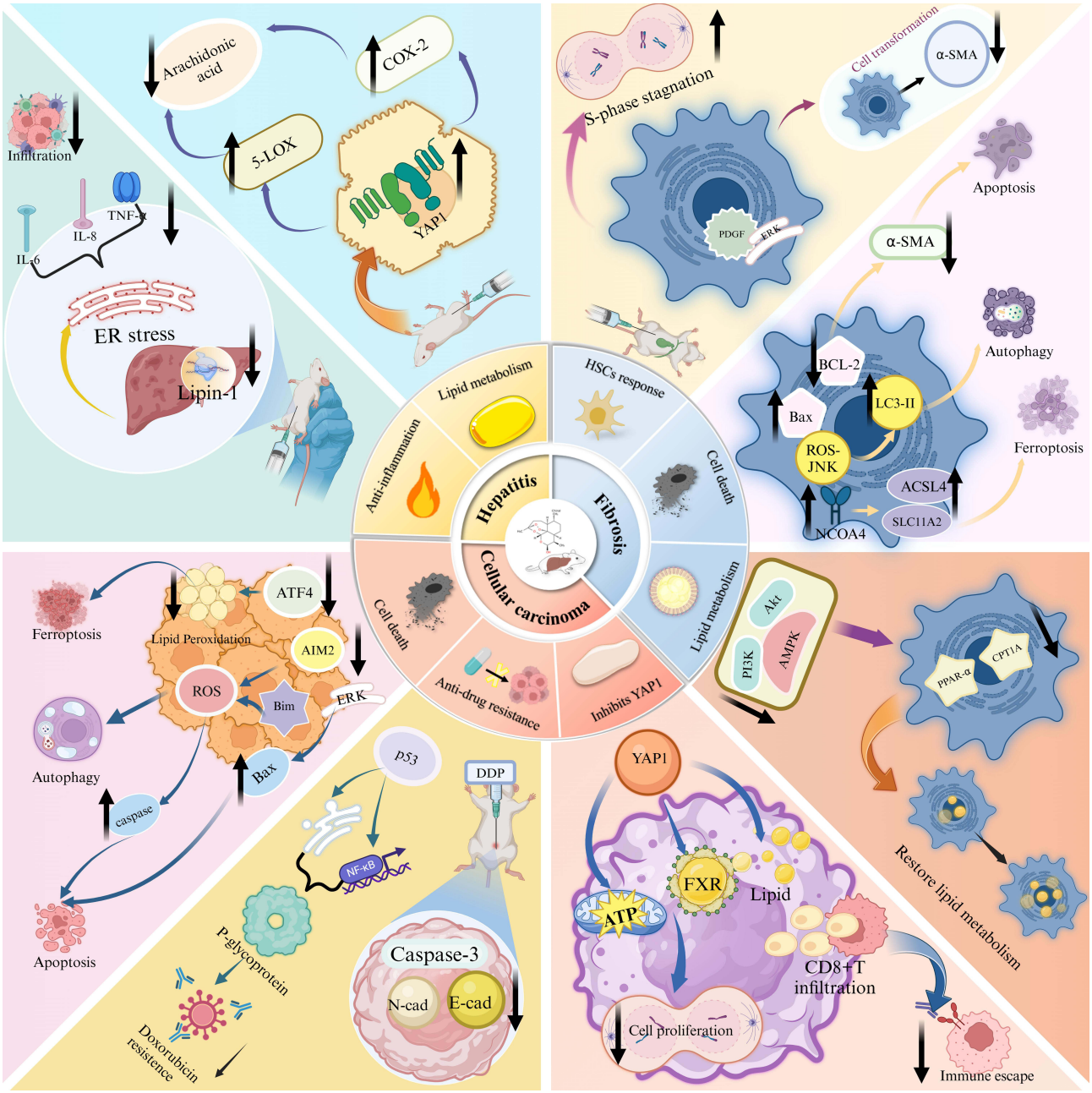


Figure 2 Mechanism of DHA in Hepatitis: DHA exerts its effects by inhibiting pro-inflammatory cytokines such as TNF-α, IL-6, and IL-8, as well as reducing the infiltration of inflammatory cells marked by CD45 positivity. Primarily, DHA targets the 5-lipoxygenase and cyclooxygenase-2, thereby reducing the metabolism of arachidonic acid and mitigating inflammatory responses. Mechanism of DHA in HF: DHA significantly alleviates liver injury and inhibits the activation of HSCs through the PDGF-βR/ERK signaling pathway. It reduces hepatocyte degeneration, suppresses collagen accumulation and pseudo-lobule formation in liver tissue, and decreases the transformation of α-SMA-positive cells. Additionally, DHA modulates the FXR to inhibit HSC contraction and downregulate the expression of TNF-α, IL-6, and NF-kB. Furthermore, DHA reverses hepatic fibrosis by inducing apoptosis, autophagy, and ferroptosis. Therapeutic Effects of DHA in HCC: DHA demonstrates anti-cancer effects by inhibiting cell proliferation, invasion, and migration. It induces apoptosis, autophagy, and ferroptosis, overcomes drug resistance in cancer cells, and enhances sensitivity to chemotherapeutic agents. (Arrows are primarily used to denote the directionality of biological processes, signal transduction and activation, transitions in cellular states, as well as drug-target interactions and their corresponding effects.).

observed, ultimately leading to cell lysis.[110] DHA has been demonstrated to modulate lipid metabolism. In lung cancer cells, DHA enhances the production and intracellular accumulation of lipid peroxides, thereby inducing ferroptosis in cancer cells.[111] It also promotes the accumulation of lipid ROS in glioblastoma and inhibits the expression of GPX4, accompanied by alterations in mitochondrial cristae structure, indicative of ferroptosis induction.[112] A novel DHA-iron

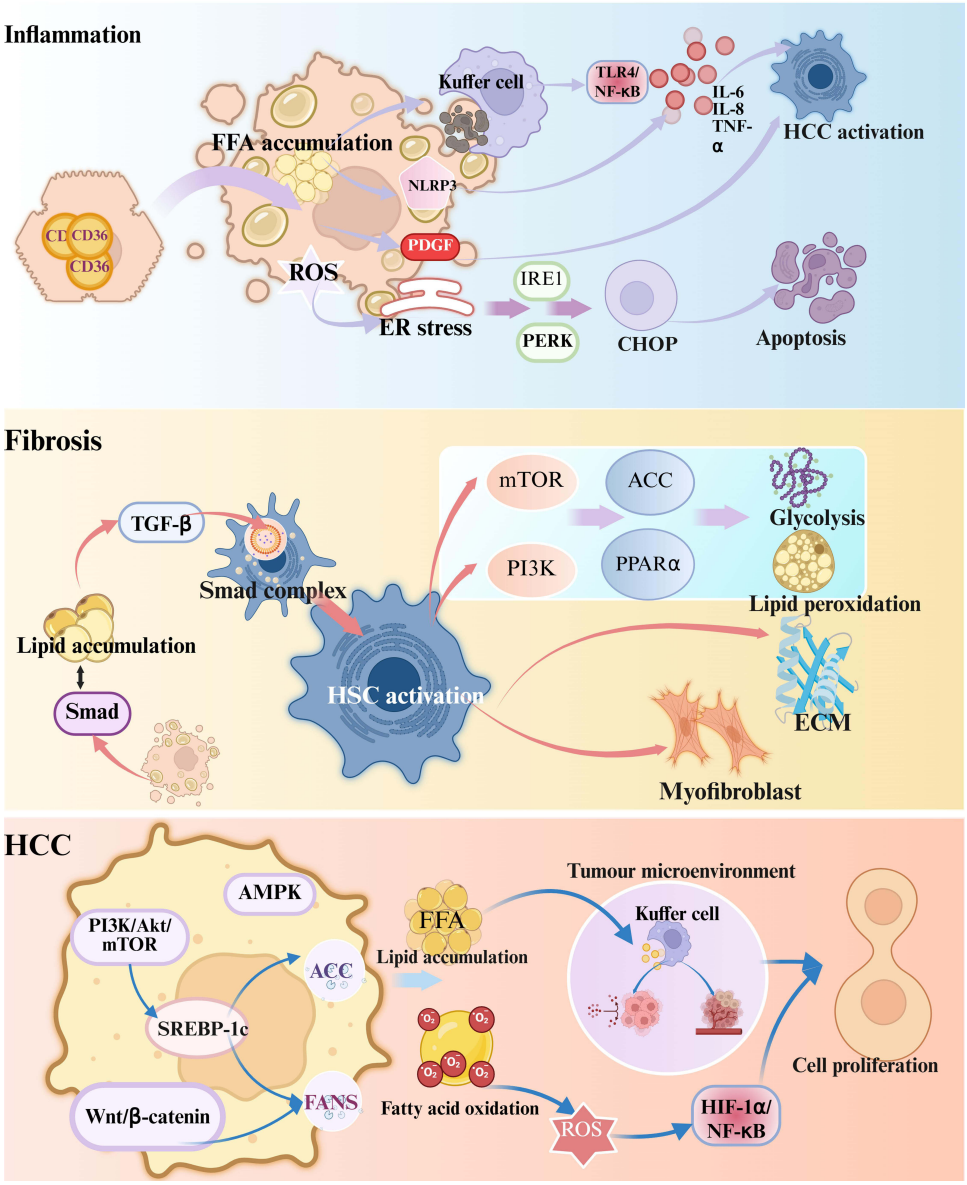


Figure 3 During the hepatitis stage, lipid metabolism dysregulation leads to excessive lipid accumulation within hepatocytes, triggering oxidative stress and inflammatory responses. This activates Kupffer cells and HSCs, promoting the release of inflammatory cytokines, which further damage hepatocytes and drive disease progression. In the liver fibrosis stage, the persistent accumulation of lipotoxic products activates HSCs, transforming them into myofibroblasts that secrete large amounts of ECM, leading to fibrosis. Concurrently, metabolic reprogramming reduces fatty acid oxidation and increases glycolysis, accelerating the fibrotic process. In the HCC stage, tumor cells meet their energy and biosynthetic demands for rapid proliferation by upregulating key enzymes involved in lipid synthesis and undergoing metabolic reprogramming. Additionally, activating lipid metabolism-related signaling pathways (like PI3K/Akt/mTOR) further promotes tumor growth and metastasis. Moreover, abnormal lipid metabolism supports HCC development by modulating the tumor microenvironment, such as promoting the polarization of tumor-associated macrophages.

protein nanosensitizer has been developed, which significantly downregulates GPX4 expression, thereby enhancing lipid peroxidation and ultimately promoting ferroptosis.[113]

Novel Approaches to Enhance the Therapeutic Efficacy of DHA

DHA demonstrates superior pharmacological properties to artemisinin, including enhanced water solubility, better therapeutic efficacy, improved absorption, broader tissue distribution, faster metabolic clearance, higher efficiency, and reduced toxicity. Following intravenous administration, DHA concentrations reached peak levels within 25 minutes and were eliminated with a half-life of 30 to 60 minutes. After oral administration, the half-life of DHA averaged 0.5 to 1.5 hours, which is 2 to 3 times longer than that of artesunate.[114,115]

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Currently, surgical resection, liver transplantation, and targeted therapy remain the primary treatment modalities for HCC. However, these approaches are inevitably associated with significant limitations, including high costs, drug resistance, limited efficacy, and substantial side effects. DHA can modulate multiple phenotypic responses, including cell proliferation and migration inhibition, reduced lipid metabolism, induced cellular autophagy, and apoptosis.

Despite its advantages over other artemisinin products in terms of pharmacological properties unique structural characteristics of DHA impose major constraints on its clinical translation for cancer treatment.[116] Emerging studies have demonstrated that novel drug carriers, advanced delivery systems, or combination therapies can significantly enhance DHA sensitivity and utilization while reducing toxicity. Nanotechnology has emerged as a promising strategy for drug efficacy. SRF/DHA-loaded LDL-based lipid nanoparticles exhibit significantly enhanced affinity for LDLR overexpressed in HepG2 cells compared to DHA or SRF alone, enabling effective activation of programmed cell death in malignant cells.[117] Fluorescent nanoparticles (CDs-DHA), engineered through the supramolecular assembly of carbon dots (CDs) and DHA, markedly enhanced the solubility and stability of DHA. These nanoparticles demonstrated the ability to inhibit glycolysis in HCC cells, effectively suppressing tumor growth.[118] Moreover, a lipid nanoparticle featuring a lipid bilayer structure has been developed to enhance the synergistic therapeutic effects of DHA and chloroquine in the treatment of colon cancer. Nanomaterial-encapsulated DHA represents a novel and promising approach to HCC management[119] (Figure 4).

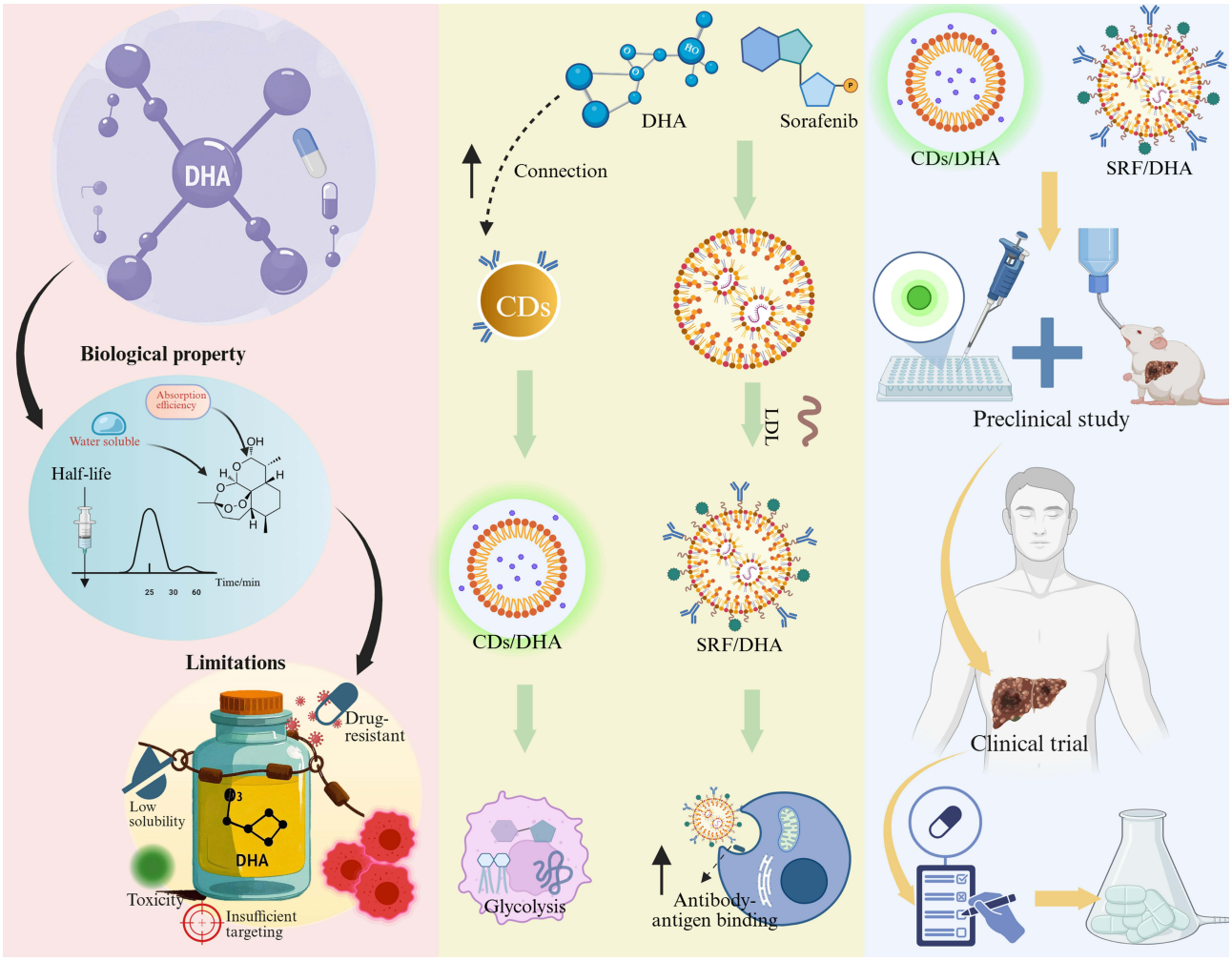

Figure 4 Clinical Translation of DHA: DHA exhibits enhanced biological activities, such as superior water solubility and improved therapeutic efficacy. However, its unique structural properties result in poor water solubility and limited bioavailability. These challenges can be effectively addressed through nanotechnology, which enhances the therapeutic potential of DHA and provides a robust foundation for its future clinical translation.

Time-Dose Analysis of DHA

In the studies analyzed, demonstrating statistical significance ($P < 0.05$) at the experimental dosage and duration of DHA treatment were integrated into a comprehensive time-dose framework. In hepatitis treatment, intraperitoneal injections were delivered at doses spanning from 7 mg/kg to 25 mg/kg for 1 to 8 weeks. In the context of HF treatment, the dose range was similar, starting at 7 mg/kg and reaching up to 20 mg/kg for 4–8 weeks. In HCC treatment, intraperitoneal injections were administered at doses ranging from 20 to 50 mg/kg for 18 days to 4 weeks, with 25 mg/kg identified as the optimal dosage. Preclinical studies have demonstrated that DHA could attenuate the disease progression from hepatitis through fibrotic transformation to hepatocellular carcinoma. In the HF intervention phase, an intraperitoneal injection dose of 25 mg/kg over 4 weeks has been identified as optimal. For HCC treatment, doses ranging from 20 to 50 mg/kg administered over 4 to 8 weeks have shown therapeutic effectiveness. Collectively, these data demonstrate that DHA is a promising clinical candidate for HCC prevention and treatment. However, the potential of DHA in HCC prevention and treatment necessitates further validation through comprehensive clinical trials (Figure 5).

Conclusion

HCC is a multifactorial disease characterized by complex and diverse pathogenic mechanisms. Persistent inflammatory infiltrates during this progression foster a tumor-permissive microenvironment, facilitating HCC development. Throughout the progression of liver disease, DHA modulates key signaling pathways, including PI3K/Akt and interleukin cascades, which underlie its versatile role in reducing inflammation, alleviating fibrosis, and inhibiting tumor development.

During the inflammatory phase of hepatitis, DHA demonstrates anti-inflammatory properties through dual inhibition of the PI3K/Akt signaling cascade and interleukin-mediated pathways. As the disease progresses to HF, DHA exhibits multifaceted antifibrotic activity via: suppression of hepatic stellate cell activation, reduction of leukocyte infiltration, inhibition of aberrant hematopoietic stem cell expansion, induction of ferroptosis, and regulation of intestinal microbial ecology. During hepatocellular carcinoma development, DHA exerts oncostatin effects through: impairment of neoplastic cell proliferation and motility, activation of programmed cell death pathways, and reversal of chemoresistance to

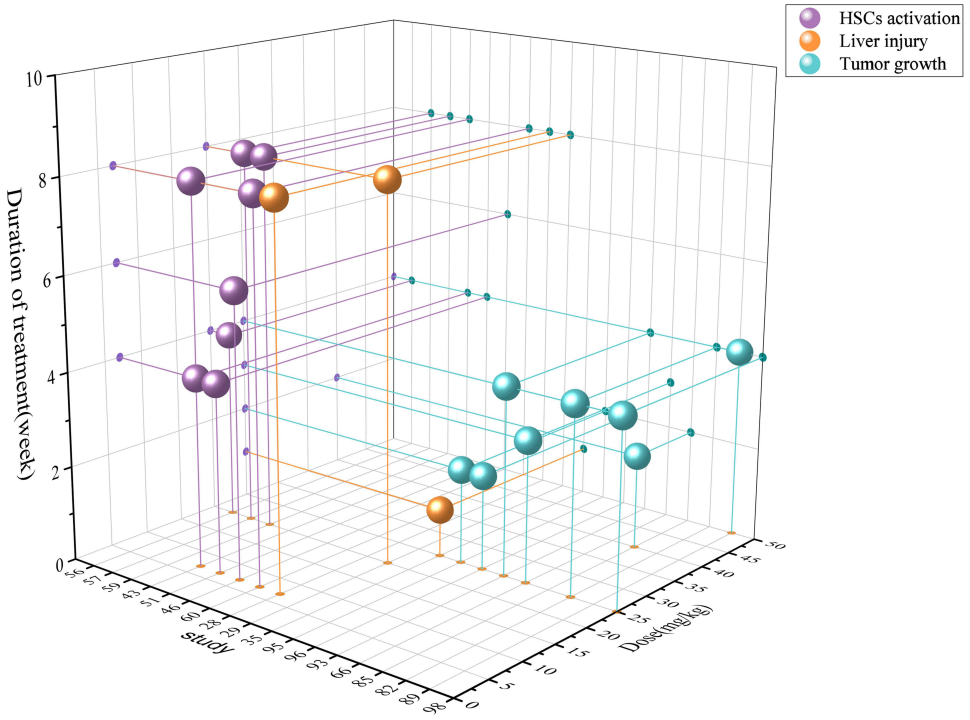

Figure 5 Scatter plot of time-dose interval analysis.

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conventional agents, including cisplatin and chloroquine. Central to this disease continuum, lipid metabolism emerges as a critical pathological nexus, positioning DHA's metabolic modulation as a strategic intervention point for HCC chemoprevention.

Although DHA demonstrates significant therapeutic potential in the context of HCC, current research lacks comprehensive in vitro and in vivo investigations into DHA's dual effects on hepatitis viral suppression and lipid homeostasis modulation, which is critical for understanding its potential to halt HCC progression. In this review, we identify DHA as a therapeutic agent capable of exerting beneficial effects across the three-stage progression of hepatitis–HF–HCC. We also elaborate on the multi-target and multi-pathway mechanisms of DHA, highlighting the central role of lipid metabolism throughout its action in all three stages. By modulating lipid metabolism, DHA effectively attenuates inflammatory responses, suppresses HSC activation, promotes HCC cell death, and ultimately inhibits carcinogenesis. While existing studies have demonstrated DHA's efficacy in suppressing HCC progression, current research remains predominantly confined to the preclinical stage. Clinical evidence regarding its therapeutic effects on HBV- and NASH-related HCC, as well as advanced HCC, remains scarce, underscoring the need for further validation. In summary, DHA represents a promising therapeutic agent for the hepatitis-to-hepatocellular carcinoma cascade, offering new avenues for treatment and hope for HCC patients.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Disclosure

Tingyao Wang and Wei Jiang contributed equally to this work and shared first authorship. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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