

Resveratrol's hepatic symphony: conducting a multi-stage intervention in liver cancer's progression

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Review

Resveratrol's hepatic symphony: conducting a multi-stage intervention in liver cancer's progression

Cui Guo^{a,b,Δ}, Fang Cao^{b,Δ}, Ling Zhou^{c,Δ}, Guijun Guo^d, Shaoyuan Zheng^d, Ruixue Xia^{e,*}, Qinghua Zou^{a,*}^a Department of Rheumatology and Immunology, First Affiliated Hospital of Army Military Medical University, Chongqing 400038, china^b Clinical Medical College, Chengdu University of Traditional Chinese Medicine, Chengdu 610075, China^c Department of Endocrinology, First Affiliated Hospital of Army Military Medical University, Chongqing 400038, China^d Respiratory and Critical Care Medicine Department, Chongqing university Fuling hospital, Chongqing 408000, China^e Department of Pediatrics, the Second Affiliated Hospital of Chongqing Medical University, Chongqing 408000, China

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ABSTRACT

The development of hepatocellular carcinoma (HCC) is a multistep process often associated with chronic hepatitis, liver fibrosis, and cirrhosis. Natural products, like resveratrol, have attracted considerable attention as anticancer drugs due to their diverse pharmacological activities. Resveratrol is a natural polyphenol present in plant foods, which has antioxidant, anti-inflammatory, anti-tumor, and anti-angiogenesis effects. The growing consensus shows that resveratrol plays a therapeutic role in liver diseases positively. The therapeutic effect observed in chronic hepatitis may be related to its ability to interfere with viral replication through PI3K/Akt, NF-κB, and MAPK signaling modulation, as well as to diminish hepatocellular injury by anti-inflammatory and antioxidant means. In liver fibrosis and cirrhosis, resveratrol decelerates the progression of fibrosis by suppressing the activation of hepatic stellate cells (HSC) and collagen production as well as by regulating signaling pathways, Hippo, Nrf2/Keap1, and SIRT1. Resveratrol also prevents tumor growth, induces apoptosis and inhibits migration, invasion and angiogenesis by various signaling pathways, which include PI3K/AKT, JNK, NF-κB, and p53 in advanced HCC. It is the first time that a multi-stage mechanism of resveratrol is presented in the development of HCC, which highlights its multi-target regulation and treatment capabilities.

1. Introduction

Hepatocellular carcinoma (HCC) is the most prevalent primary cancer of the liver and is generally associated with chronic liver diseases, especially viral hepatitis and cirrhosis¹. According to the Web of Science data, the incidence and mortality rates of HCC are increasing, making it the third-ranking cause of cancer-related deaths globally². The abnormal proliferation and invasion of hepatocytes are the characteristic features of HCC. Clinical manifestation differs according to the size of tumor, location and stage. The lack of apparent symptoms in early-stage HCC frequently contributes to diagnostic delay. Later in the course of the disease, the patient can experience general symptoms including abdominal pain, fatigue, and lack of appetite, weight loss, jaundice, ascites, and liver enlargement³. These characteristics emphasize the role of routine liver screening and surveillance in the high-risk groups such as people having chronic hepatitis or cirrhosis to enable early diagnosis and treatment of the HCC.

The existing treatment modalities for HCC include surgical resection, radiotherapy, chemotherapy, and targeted therapy.

The intention of surgical resection is complete tumor tissue removal, but this therapeutic approach may be limited for advanced or metastatic disease. Chemotherapy involves the use of drugs to suppress the growth of cancer cells, but it is mostly linked to side effects and drug resistance. Radiotherapy uses high-energy radiations to destroy cancer cells, but it can also destroy adjacent normal tissues⁴. Targeted therapies are aimed at particular proteins or signaling pathways, yet resistance may develop in some cases⁵. In the light of these complexities, natural compounds have been given an ever-growing interest as remedies to HCC. Sourced from plant, animal, or microbial origins, these substances contain multiple active components and present diverse pharmacological activities. Compared to conventional therapies, natural products tend to be less toxic, have broader target profiles, and are less prone to drug resistance⁶. Therefore, exploring the integration of natural products into HCC management shows great potential in delivering more efficient and safer treatment alternatives for patients.

Resveratrol, as a typical substance that is both food-derived and medicinal, reflecting the traditional Chinese medicine concept of "food and medicine sharing the same origin". This concept refers to natural substances that can be consumed as daily food while also possessing definite pharmacological activities and therapeutic value. Resveratrol is widely present in foods such as grapes, red wine, peanuts, and blueberries. The long history of human consumption of these foods provides strong evi-

* Corresponding author.

E-mail addresses: summertree9126@163.com (R. Xia); zouqinghua318@tmmu.edu.cn (Q. Zou)^Δ These authors contributed equally to this work.

ence for its safety⁷. It exhibits various pharmacological effects, including antioxidant, anti-inflammatory, anti-tumor, anti-aging, and cardiovascular protective properties^{8,9}. Owing to its broad biological activities and promising applications in medicine and health products, resveratrol has shown therapeutic potential in various diseases, such as cardiovascular diseases, neurodegenerative disorders, and diabetes^{9,10}. Of special note is its strong anti-tumor activity, which is accomplished through mechanisms including suppression of tumor cell proliferation, induction of apoptosis, and regulation of cell signaling pathways¹¹. Over the last several years, there have been major advances in resveratrol research in several directions. Through structural modification, researchers have created several derivatives, including resveratrol-3-O-β-D-glucoside, dihydroresveratrol, and resveratrol dimer, using chemical methods such as hydroxylation, methylation, and acetylation. Such alterations have largely enhanced its stability and biological activity. Resveratrol has been reported to enhance anti-tumor efficacy synergistically in combination therapy with traditional chemotherapeutic drugs, including sorafenib, oxaliplatin, and 5-fluorouracil, while diminishing chemotherapy-induced toxicity. To address its inadequate bioavailability, researchers have designed a variety of nanocarriers, including liposomes, polymer nanoparticles, solid lipid nanoparticles, and self-emulsifying drug delivery systems. The systems can greatly enhance the therapeutic efficacy of resveratrol by enhancing solubility, increasing half-life, and accomplishing targeted delivery. Its antioxidant, anti-inflammatory, and anti-apoptotic properties render it useful in the management of liver diseases, such as liver fibrosis, cirrhosis, and HCC^{12,13}.

This study explores, in a pioneering manner, the multifaceted influence of resveratrol in various liver diseases, encompassing chronic hepatitis, liver fibrosis, cirrhosis, and HCC. It points out the promise of resveratrol not just in its ability to prevent these liver diseases but also in its ability to slow down their development. The projected findings of this study are expected to offer foundational preclinical evidence for the therapeutic and preventive potential of resveratrol in the context of liver disorders, with notable implications for clinical translation (Fig. 1).

2. Transformation of HCC trilogy

Chronic hepatitis often marks the beginning of the complex and dynamic process leading to HCC. Chronic hepatitis is an inflammatory disease of the liver that may be induced by viruses, alcohol, or drugs, and it can result in progressive injury as time passes¹⁴. With ongoing progression of chronic hepatitis, the liver may develop fibrosis characterized by the replacement of normal hepatic parenchyma by fibrotic tissue, leading to dysfunction of the organ. In the absence of timely management, fibrosis may advance to cirrhosis, characterized by considerable alterations in liver structure and function, with eventual progression to liver failure being possible. The progressive loss of normal regulatory control over hepatocyte differentiation and proliferation at this stage leads to the formation of precancerous lesions that advance into HCC¹⁵. HCC cells have a high capacity for invasion and metastasis, facilitating their rapid spread to distant organs. Timely identification and management of chronic hepatitis, liver fibrosis, and cirrhosis are therefore crucial for reducing the risk that HCC will develop (Fig. 2).

Inflammation together with oxidative stress is frequently seen in various liver diseases¹⁶. According to multiple *in vitro* and *in vivo* studies, resveratrol possesses prominent antioxidant and anti-inflammatory activities that allow it to effectively modulate inflammatory and oxidative stress responses¹⁷. Among its pharmacological properties, the anti-angiogenic and anti-tumor effects of resveratrol make its potential role in HCC prevention and treatment especially noteworthy.

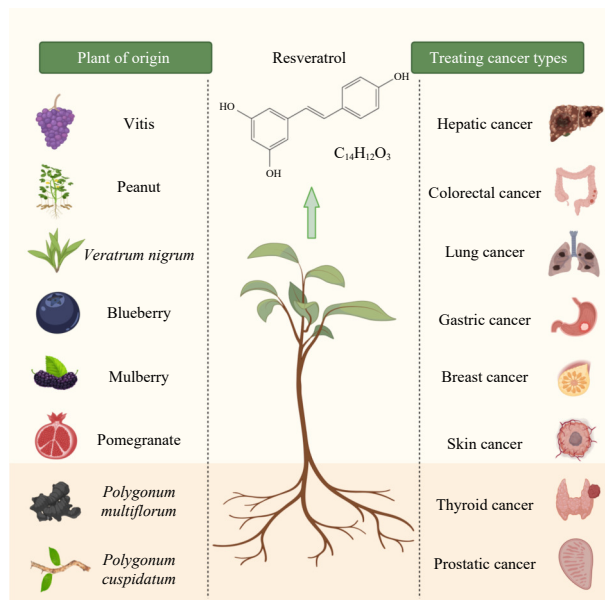


Fig. 1 Natural sources of resveratrol and its therapeutic effects in various cancers

Inflammation is involved throughout the entire sequence of hepatocarcinogenesis. A persistent inflammatory environment promotes hepatocyte injury and degeneration, resulting in decreased liver function. Following hepatitis virus infection, inflammatory responses recruit immune cells like leukocytes and macrophages to the liver. These cells release toxic factors that harm hepatocytes, thereby promoting hepatocellular degeneration and contributing to fibrosis and cirrhosis^{18,19}. Resveratrol has been shown to inhibit abnormal hepatocyte proliferation and induce apoptosis through modulation of the PI3K/Akt signaling pathway, thereby mitigating further liver injury²⁰. In addition, the development of HCC is closely associated with inflammatory cell infiltration and ongoing hepatocyte death. Inflammatory signaling pathways, including JNK, can regulate the expression of cancer-promoting genes like *c-Myc* and *COX-2*, as well as tumor suppressor genes like *p53* and *PTEN* in hepatocytes²¹. Such regulatory disruption can drive the malignant transformation of hepatocytes and contribute to the onset and progression of HCC. Inflammatory cells and cytokines arising from persistent inflammation can activate various signaling mechanisms, including nuclear factor-κB (NF-κB), STAT3, and Wnt/β-catenin, thereby driving tumor cell proliferation, survival, and metastasis²². Furthermore, persistent inflammation contributes to the accumulation of tumor-associated macrophages (TAMs) and regulatory T cells (Tregs) in the tumor microenvironment, dampening the anti-tumor immune response and impairing immune-mediated tumor clearance²³.

Oxidative stress is another principal driver of HCC progression and contributes importantly to each stage of the disease. It is marked by disequilibrium between the production and elimination of reactive oxygen species (ROS), leading to oxidative damage to cellular components. In early-stage hepatitis, hepatocytes can be damaged by viral infections, drugs, and alcohol, which then trigger an inflammatory response and oxidative stress. This stress prolongs inflammation, leading to additional hepatocyte damage. As it persists, it disrupts the functions of hepatocytes, hepatic stellate cells (HSCs), and immune cells and activates profibrotic signaling pathways such as TGF-β1 and Wnt/β-catenin²⁴. The activation of these pathways drives excessive extracellular matrix (ECM) production by fibrotic cells, which in turn leads to liver structural changes and cirrhosis²⁵. The role of oxidative stress in advanced liver cancer is dual, as it contributes to both tumorigenesis and progression. It can induce gene mutations and DNA repair impairment, thereby driving hepatocarcino-

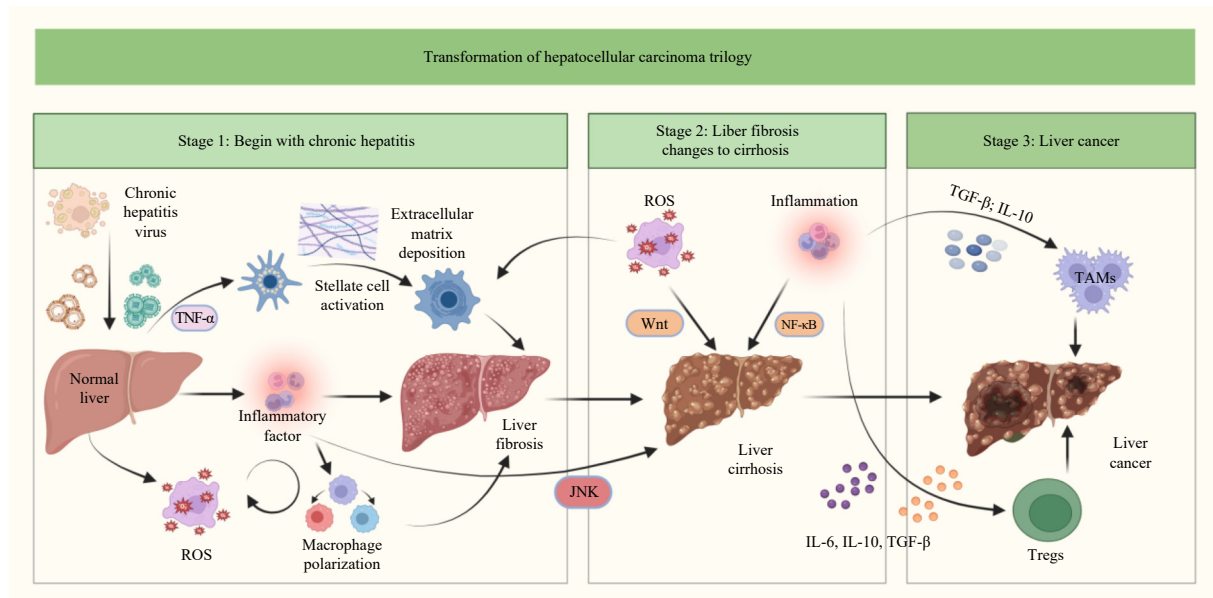


Fig. 2 Progression from chronic hepatitis to liver fibrosis/cirrhosis and HCC. ROS, Reactive oxygen species; TNF- α , Tumor necrosis factor alpha; NF- κ B, Nuclear factor kappa-light-chain-enhancer of activated B cells; TGF- β , Transforming growth factor beta; IL-6, Interleukin-6; IL-10, Interleukin-10.

genesis and promoting tumor cell growth, invasion, and metastasis.

A close relationship exists between inflammation and oxidative stress during liver cancer progression, and together they act synergistically to drive disease advancement. Cytokines and chemokines released during inflammatory responses activate immune cells, including neutrophils and macrophages. These immune cells then generate elevated ROS levels at inflammation sites, thereby increasing oxidative stress. By further damaging hepatocytes, excessive ROS leads to cell dysfunction and necrosis and promotes the release of more inflammatory mediators. These mediators recruit additional immune cells and drive a self-sustaining cycle that worsens liver injury²⁶. In addition, inflammation and oxidative stress both target pathways including NF- κ B, JNK, TGF- β 1, which are pivotal to the evolution of fibrosis and cirrhosis into HCC²⁷.

The interplay between inflammatory and oxidative stress pathways is a condition that is critical for amplifying the development of liver diseases. In particular, the persistent inflammatory response stimulates the NF- κ B pathway, resulting in increased release of pro-inflammatory cytokines such as TNF- α and IL-6. Further activation of the TGF- β 1/Smad pathway in HSCs by these cytokines promotes collagen synthesis and drives fibrosis progression. Meanwhile, ROS arising from inflammatory processes activates the JNK and p38 MAPK pathways. Besides worsening oxidative stress injury, these pathways also shape the balance between apoptosis and proliferation by regulating p53 and Wnt/ β -catenin signaling. During the progression of fibrosis into HCC, altered Hippo pathway regulation leads to aberrant activation of YAP/TAZ, which works together with the PI3K/AKT pathway to suppress apoptosis and induce angiogenic factor expression, including VEGF. This interplay reinforces the pathological sequence of inflammation, fibrosis, and carcinogenesis. Resveratrol may regulate multiple stages of this process through coordinated modulation of these key points of intersection.

3. Mechanisms of resveratrol in inhibiting chronic hepatitis

Chronic hepatitis is a persistent inflammatory liver disease characterized by sustained hepatic inflammation and hepatocellular injury. It can stem from multiple causes, such as viral infection, alcohol consumption, exposure to drugs or toxins, autoimmune disorders, and other metabolic conditions²⁸. Viral infec-

tion, particularly that caused by hepatitis B virus (HBV), stands out among these factors as a leading cause of chronic hepatitis²⁹. Following hepatocyte infection by HBV, viral replication takes place and an immune response is induced. Immune responses against infected hepatocytes give rise to liver cell injury and inflammation³⁰. Ongoing viral infection coupled with chronic immune activation can cause hepatocellular injury, inflammation, and fibrosis, which ultimately escalate to cirrhosis and HCC. Therefore, the cornerstone of chronic hepatitis management lies in suppressing viral replication and limiting immune-mediated hepatic injury³¹. Numerous natural products have demonstrated therapeutic potential at this stage³² and resveratrol has attracted particular attention because it can inhibit viral replication, reduce inflammation, and provide antioxidant properties.

HBV is an enveloped DNA virus with a genome consisting of S, C, and P coding regions. Within virions, the viral genome exists as covalently closed circular DNA (ccDNA), which enables persistent viral residence in hepatocytes³³. Even if the immune system eliminates part of the viral population, HBV can continue to replicate and reinfect liver cells. Additionally, the high genetic variability of HBV promotes the formation of multiple surface antigen variants³⁴, which further contributes to persistent inflammatory infection.

The antiviral effect is the primary mechanism of resveratrol in the treatment of chronic hepatitis B. Studies have found that resveratrol not only prevents the synthesis of viral DNA by inhibiting HBV DNA polymerase activity, but also regulates multiple signaling pathways involved in viral replication, such as PI3K/Akt, STAT3, NF- κ B and MAPK. For example, inhibition of the PI3K/Akt signaling pathway reduces the synthesis of HBV RNA and HBV DNA³⁵. Resveratrol also regulates host gene expression; for instance, it suppresses nuclear miR-155 activity, thereby reducing HBV replication³⁶. In addition, inhibition of p38 MAPK activity may contribute to the suppression of viral replication and apoptosis and protect hepatocytes from virus- and inflammation-induced injury³⁷.

Anti-inflammatory effects also play an important role in the protective effects of resveratrol against chronic hepatitis B. Resveratrol reduces the inflammatory response of the liver by inhibiting inflammation-related signaling pathways, such as NF- κ B and MAPK³⁸. NF- κ B is a key regulator of inflammatory responses, and its inhibition by resveratrol reduces the production of pro-inflammatory cytokines.³⁹ Specifically, resveratrol suppresses the

production of inflammatory factors such as IL-1 β , IL-6 and TNF- α , thereby alleviating liver inflammation⁴⁰. Resveratrol also inhibits MAPK signaling, including ERK, JNK and p38 MAPK, thereby reducing the inflammatory response⁴¹. Experimental studies have demonstrated that resveratrol can decrease the production of inflammatory factors IL-1 β and IL-18 by inhibiting the activation of the NLRP3 inflammasome⁴². Prolonged inflammatory responses can worsen oxidative stress and promote excessive production of ROS that further exacerbate inflammation. Resveratrol scavenges various free radicals, including superoxide anions, hydroxyl radicals, and hydrogen peroxide, thereby reducing oxidative stress-induced damage to the liver⁴³.

HBV surface antigen (HBsAg) may bind to certain receptors on hepatocytes, thereby reducing immune recognition⁴⁴. In addition, HBV can reduce the activation of virus-specific T cells by affecting the antigen presentation process, facilitating immune escape⁴⁵. Resveratrol has been shown to inhibit the expression of HBsAg and HBeAg, thus reducing the spread of the virus within the host. This effect is thought to be linked to the down-regulation of HBx protein expression in infected cells. Lin et al. reported that resveratrol (30 mg·kg⁻¹·d⁻¹) had a therapeutic effect on the inflammatory response in HBx-induced liver injury, reduced intracellular ROS levels, and transiently stimulated hepatocyte proliferation⁴⁶. In addition, resveratrol can also regulate host immunity and enhance resistance to HBV infection. Research has confirmed that resveratrol can promote the activation and proliferation of dendritic cells and T cells, thereby enhancing both cellular and humoral immune responses. Resveratrol can also increase the levels of IL-2 and IFN- γ while reducing the levels of TNF- α and IL-6, which may further contribute to antiviral activity^{47,48} (Fig. 3).

4. Analysis of the mechanisms by which resveratrol inhibits liver fibrosis (sclerosis)

Liver fibrosis is a dynamic pathological process character-

ized by excessive accumulation of ECM proteins (especially collagen), leading to the destruction of normal liver structure and function⁴⁹. It represents a key stage in the continuum of chronic liver disease and is often caused by chronic toxic hepatitis, alcohol abuse, non-alcoholic fatty liver disease (NAFLD), and autoimmune diseases⁵⁰. This process is often accompanied by persistent liver injury and chronic inflammation. At the same time, HSCs become activated, which play a key role in the progression of fibrosis through the synthesis and deposition of ECM components^{51,52}. If left unmanaged, liver fibrosis can progress to cirrhosis, portal hypertension, and ultimately life-threatening liver failure. Therefore, targeting the molecular mechanisms underlying liver fibrosis is essential for slowing the progression of chronic liver disease⁵³. Recent research indicates that resveratrol may effectively inhibit liver fibrosis through diverse mechanisms (Fig. 4).

4.1. Resveratrol inhibits HSC activation

HSCs resident liver cells that play a central role in liver fibrosis through the synthesis and secretion of collagen and other ECM components⁵⁴. Under normal conditions, HSCs remain in a quiescent state and primarily function in the storage of vitamin A, regulation of vasoactive mediators, and maintenance of hepatic microcirculatory homeostasis^{54,55}. However, in response to liver injury or inflammation, quiescent HSCs become activated and undergo phenotypic transformation into myofibroblast-like cells. This transition is accompanied by enhanced collagen synthesis and accumulation of ECM proteins, thereby driving fibrotic progression. Resveratrol has been proven to inhibit HSC activation, thereby slowing down and preventing the development of liver fibrosis⁵⁶⁻⁵⁸.

ShamsEldeen AM and colleagues discovered that resveratrol suppresses HSC activation and collagen production through inhibition of the TGF- β 1/Smad3/miR-21 pathway. Specifically, resveratrol inhibits TGF- β receptor kinase activity, thereby blocking

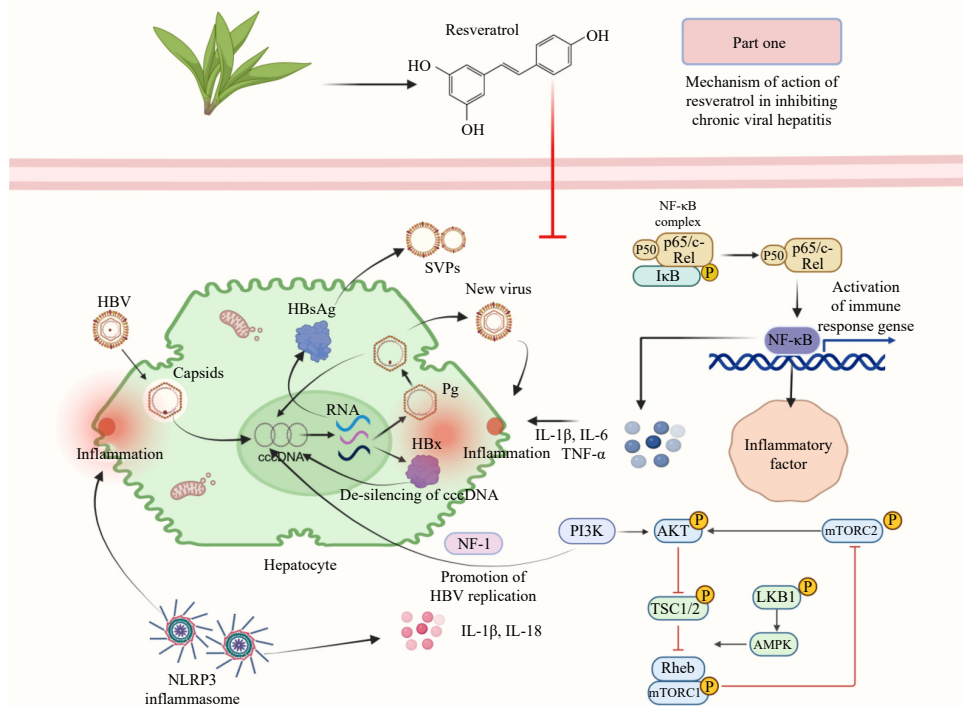


Fig. 3 Resveratrol inhibits viral replication and regulates inflammation and oxidative stress to combat chronic hepatitis. IL-6, Interleukin-6; IL-10, Interleukin-10; TNF- α , Tumor necrosis factor alpha; HBV, Hepatitis B virus; HBeAg, Hepatitis Be antigen; cccDNA, Covalently closed circular DNA; NF- κ B, Nuclear factor I; PI3K, Phosphoinositide 3-kinase; JNK, c-Jun N-terminal kinases; AMPK, AMP-activated protein kinase; mTORC1, Mechanistic target of rapamycin complex 1.

phosphorylation of Smad2 and Smad3 and preventing formation of the active Smad complex. This effect reduces profibrotic transcriptional activity and limits ECM accumulation during fibrosis⁵⁹. Decreased Smad nuclear translocation also suppresses the expression of fibrosis-related genes involved in HSC activation, including α -smooth muscle actin (α -SMA) and collagen. As a result, the transition of quiescent HSCs into myofibroblasts is inhibited, leading to reduced hepatic ECM deposition. In addition, resveratrol has been reported to suppress HSC activation through activation of the Hippo pathway, an effect associated with upregulation of Bax and downregulation of Bcl-2⁵⁶.

4.2. Resveratrol suppresses inflammatory responses

Inflammation is a key factor in the progression of liver fibrosis, and resveratrol shows potent anti-inflammatory effects that hinder this process. NF- κ B is an important transcription factor involved in the regulation of the expression of various cytokines, adhesion molecules, and inflammatory mediators⁶⁰. When the liver is impaired, the NF- κ B pathway is activated, promoting inflammatory cell infiltration and the release of inflammatory factors, such as TNF- α and IL-1 β , which further activate HSCs. Previous studies have shown that resveratrol inhibits NF- κ B activation and reduces TNF- α expression by blocking NF- κ B nuclear translocation in HSCs⁵⁷. The NLRP3 inflammasome is a multi-protein complex composed of NLRP3, ASC and cysteine protease-1 (CASP1), which is one of the important mechanisms of inflammatory signal transduction in the cells. During liver fibro-

genesis, the abnormal activation of the NLRP3 inflammasome triggers the secretion of proinflammatory cytokines such as IL-1 β and IL-6, thereby sustaining inflammation and accelerating fibrosis⁶¹. Animal experiments have shown that resveratrol can significantly reduce the levels of inflammatory factors such as IL-1 β , which is closely related to the Sirtuin pathway regulated by resveratrol⁶². The specific mechanism is that resveratrol suppresses the expression and activity of NAD⁺-hydrolase CD38, which in turn activates the expression and activity of SIRT1⁶³.

Cyclooxygenase-2 (COX-2), an enzyme involved in prostaglandin synthesis and inflammation, is significantly upregulated in patients with liver fibrosis, and the use of COX-2 inhibitors reduces the severity of liver fibrosis⁶⁴. Resveratrol suppresses COX-2 expression by inhibiting activation of the transcription factors NF- κ B and activator protein-1 (AP-1), thereby reducing their binding to the COX-2 promoter⁶⁵. Several members of the MAPK family, including extracellular signal-regulated kinase (ERK), c-Jun N terminal kinase (JNK), and p38 MAPK, activate transcription factors like AP-1. AP-1 then binds to the promoter region of the COX-2 gene, enhancing its transcription and resulting in increased COX-2 expression. Resveratrol has been found to inhibit the activation of ERK, JNK, and p38 MAPK. By disrupting MAPK signaling, resveratrol hinders the activation of transcription factors such as AP-1, leading to a reduction in COX-2 gene expression⁶⁶. Research demonstrates that resveratrol regulates the JAK/STAT pathway and impacts IL-6 expression, potentially inhibiting liver fibrosis by reducing the release of inflammatory factors⁶⁷.

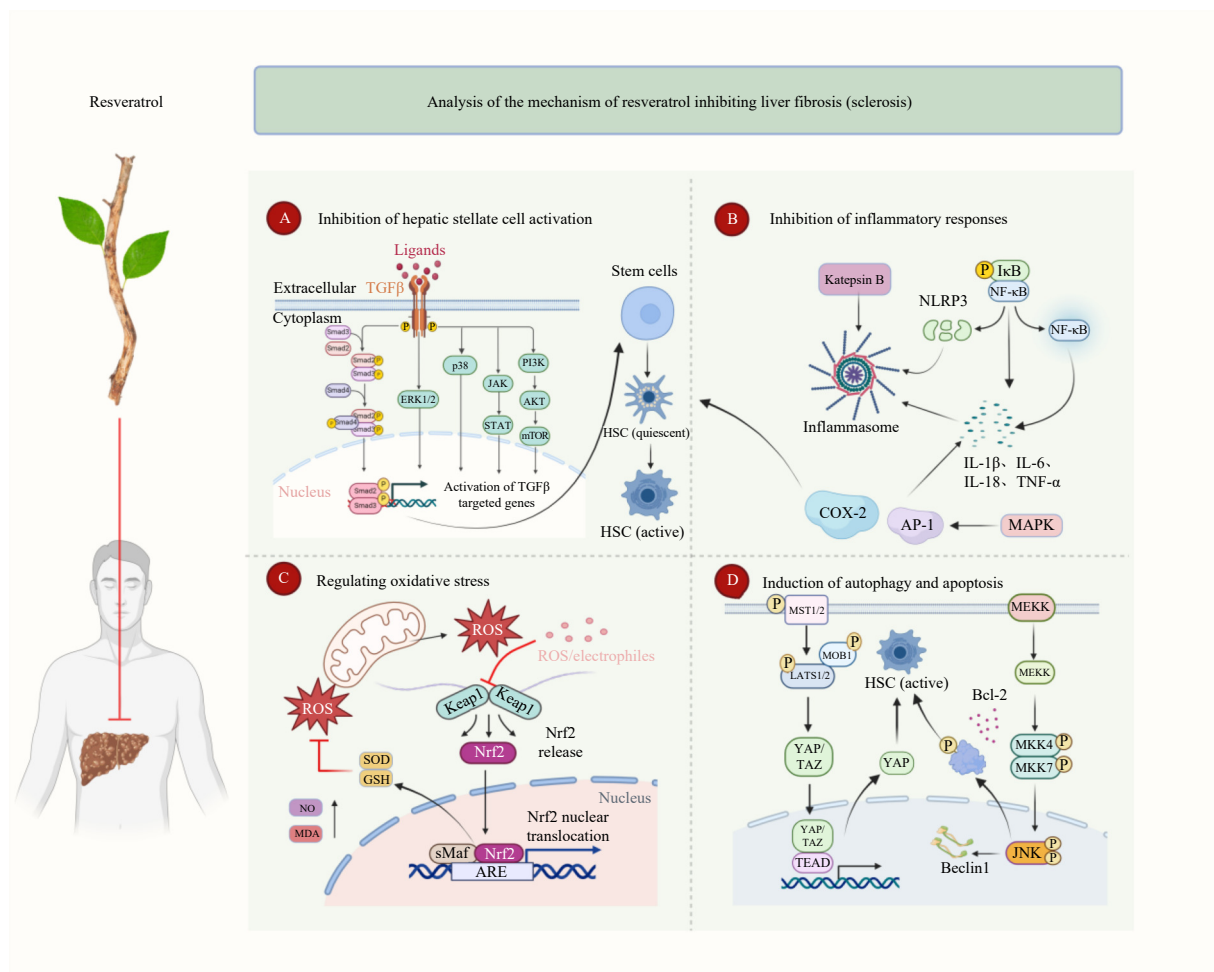


Fig. 4 Mechanisms of resveratrol in liver fibrosis and cirrhosis. ROS, Reactive oxygen species; YAP, Yes-associated protein; TAZ, Transcription coactivator with PDZ-binding motif; JNK: c-Jun N-terminal kinases; IL-6, Interleukin-6; IL-10, Interleukin-10; IL-18, Interleukin-18; IL-1 β , Interleukin-1 β ; COX-2, Cyclooxygenase-2; STAT, Signal transducer and activator of transcription.

4.3. Resveratrol modulates oxidative stress

Oxidative stress plays an important role in the development of liver fibrosis. It promotes fibrotic progression by amplifying inflammatory responses, damaging cell membranes and intracellular structures, and activating fibrosis-related signaling pathways⁶⁸. Therefore, inhibition of excess oxidative stress may be an important therapeutic tool to suppress liver fibrosis.

As a natural polyphenolic compound, resveratrol exhibits potent antioxidant activity, largely attributable to its chemical structure⁶⁹. Free radicals are highly active chemicals that can interact with intracellular lipids, proteins, and nucleic acids, causing damage to cellular structure and function. The hydroxyl and phenyl ring structures of resveratrol confer high electron density and enable it to act as electron donors, thereby scavenging free radicals and reducing oxidative injury⁷⁰. In the process of liver fibrosis, resveratrol can not only remove large free radicals but also reduce malondialdehyde (MDA) and nitric oxide (NO) levels while significantly increasing catalase (CAT), superoxide dismutase (SOD), and prototype liver glutathione (GSH) levels to reduce the oxidative stress in liver tissue⁷¹. Resveratrol also regulates several signaling pathways in oxidative stress. Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor that mainly regulates antioxidant gene expression. Under normal conditions, Nrf2 is located in the cytoplasm and inhibited by the Keap1 protein. Under oxidative stress, Nrf2 is released and enters the nucleus to regulate the expression of downstream genes, thereby enhancing antioxidant capacity. By downregulating the expression of Keap1, resveratrol reduces the inhibition of Nrf2 by Keap1 and promotes nuclear translocation of Nrf2, thereby enhancing expression of antioxidant enzymes^{72, 73}. Studies have also shown that resveratrol can enhance the expression and activity of SIRT1, leading to increased deacetylation of substrates. Activation of SIRT1 signaling can inhibit NF- κ B activity, decrease the production of inflammatory factors (such as TNF- α and IL-1 β), and reinforcing cycle between inflammation and oxidative stress, ultimately slowing the progression of liver fibrosis⁷⁴.

4.4. Resveratrol induces autophagy and apoptotic process

In addition to the above mechanisms, resveratrol has also been shown to inhibit liver fibrosis by inducing autophagy and apoptosis. The Hippo pathway is an important signaling pathway involved in apoptosis regulation. Yes-associated protein (YAP) is an important nuclear transcription regulatory protein, a key member of the Hippo signaling pathway, and its activity is regulated by the Hippo pathway⁷⁵. During liver fibrosis, the activation of the Hippo pathway is usually inhibited, resulting in increased YAP activity in HSCs. Elevated YAP activity promotes the activation and transformation of HSCs into fibroblasts and increase the synthesis and release of collagen and other ECM proteins⁷⁶. Studies have shown that resveratrol activates the Hippo pathway and suppresses nuclear translocation of YAP in HSCs, thereby inhibiting HSC activation. This effect is accompanied by upregulation of Bax and downregulation of Bcl-2⁵⁶.

Experimental studies examining the effects of different concentrations of resveratrol on cellular autophagy have shown that resveratrol can promote autophagy at higher concentrations. For example, resveratrol can significantly increase the expression of the cellular autophagy marker LC3BII at 0.1 and 1 $\mu\text{mol}\cdot\text{L}^{-1}$, but not at 100 $\mu\text{mol}\cdot\text{L}^{-1}$ ⁷⁷. SIRT1 and JNK both regulate autophagy-related processes, and resveratrol appears to modulate the balance between these pathways⁷⁸. Interestingly, upregulation of SIRT1 and suppression of JNK signaling reduce the phosphorylation of Bcl-2/Bcl-xL, thereby releasing Beclin-1 and promoting auto-

phagy. At the same time, the downregulation of the JNK signaling pathway counteracts the antiapoptotic activity of Bcl-2/Bcl-xL through a Bid-Bax-dependent mechanism⁷⁷.

5. Inhibitory effects of resveratrol on HCC

HCC is one of the three leading causes of cancer-related death in 46 countries, according to a new global analysis. It is predicted that by 2040, 1.4 million cases will be diagnosed and the number of new cases of HCC will increase by 55% from 2020; 1.3 million people will die by 2040, with a 56.4% increase from 2020⁷⁹. Therefore, the treatment of HCC is an urgent problem to be solved worldwide. However, the efficacy of traditional therapeutic methods in combating HCC is not ideal. The potential of natural products as an effective adjunct to the treatment of HCC is valued for their lower pharmacological toxicity and fewer side effects. Among these compounds, resveratrol, as a natural compound with a variety of biological activities, has shown great potential in HCC treatment (Fig. 5).

5.1. Resveratrol inhibits the growth and proliferation of HCC cells

A large body of evidence indicates that resveratrol suppresses HCC progression by regulating cell cycle progression, various signaling pathways, and tumor cell proliferation and migration processes. A study on Sprague-Dawley rat liver cancer models discovered a positive correlation between the incidence and total number of hepatocyte nodules with resveratrol administration at doses of 50, 100, or 300 $\text{mg}\cdot\text{kg}^{-1}$ body weight/day. In a distinct trial involving varied resveratrol concentrations tested on HepG2 cells, it was noted that resveratrol at 6.25 $\mu\text{mol}\cdot\text{L}^{-1}$ effectively reduced the migratory and invasive capacities of human HCC cells by suppressing the activity of miR-186-5p and upregulating E-cadherin expression¹³. The DLC1/TCTP/Cdc42 pathway is one of the important pathways in the process of HCC cell proliferation. *DLC1* is a tumor suppressor gene, which is involved in a variety of cellular activities, including matrix attachment, cell proliferation, and migration. TCTP is a cytoplasmic protein that regulates the progression of cell growth and differentiation. It is found that resveratrol can inhibit HCC cell migration by regulating the DLC1/TCTP axis, and the specific mechanism is the upregulation of DLC1 and the inhibition of TCTP expression⁸⁰. The aryl hydrocarbon receptor (AHR), a multifunctional transcription factor within the nuclear receptor superfamily, plays a crucial role in regulating the carcinogen activation pathway. Activation of AHR can induce transcription of the CYP1A1 gene in liver cancer⁸¹. Researchers employed HepG2 cells to analyze CYP1A1 expression levels and AHR function using a variety of tests such as RT-PCR, CAT/ β -GAL, EROD, and EMSA. The results indicated that resveratrol successfully obstructed the translocation of AHR to the nucleus, thereby impeding its ability to bind DNA, and also diminished the rise in CYP1A1 enzyme activity, consequently restraining the growth of liver cancer cells⁸².

In addition, resveratrol also regulates the cell cycle in HCC cells. The cell cycle is the process of cell growth, division and reproduction, which includes G₁, S, M and other stages⁸³. In HepG2 cells, resveratrol suppressed cell proliferation in a time- and dose-dependent manner, possibly through enhancement of p53 activity. Additionally, resveratrol was found to inhibit the growth of HepG2 cells at the S/G₁ phase⁸⁴. Animal experiments showed that resveratrol significantly increased the inhibitory rate in H22 tumor-bearing mice by suppressing expression of cyclin B1 and p34cdc2⁸⁵. In addition, resveratrol upregulates the cyclin-dependent kinase inhibitors p21 and p27, thereby suppressing cyclin-dependent kinase activity and inducing G₁-phase arrest⁸⁶. Through these mechanisms, resveratrol inhibits HCC cell growth and proliferation.

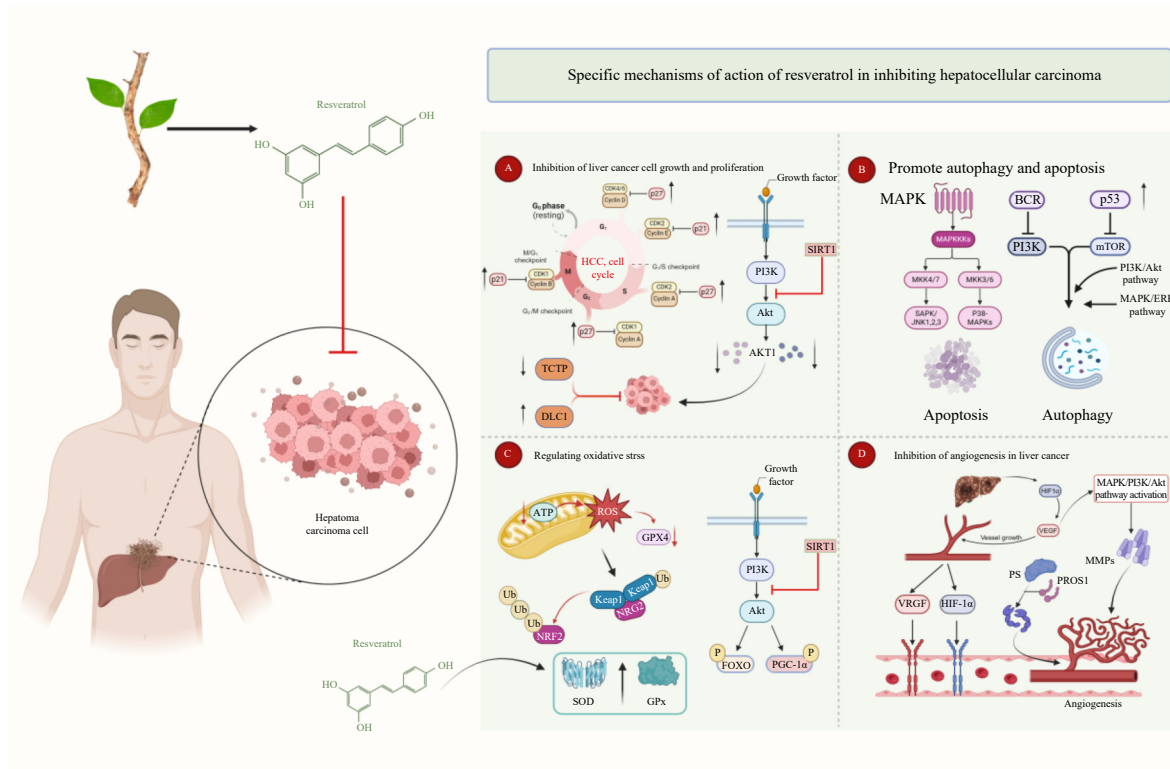


Fig. 5 Resveratrol inhibits HCC progression by regulating the cell cycle, apoptosis, and autophagy, oxidative stress, and angiogenesis. HCC, Hepatocellular carcinoma; VEGF, Vascular endothelial growth factor; HIF-1 α , Hypoxia-inducible factor 1-alpha; Keap1, Kelch-like ECH-associated protein 1; GPx, Glutathione peroxidase; SOD, Superoxide dismutase; PI3K, Phosphoinositide 3-kinase.

5.2. Resveratrol promotes autophagy and apoptosis process in HCC cells

5.2.1. Resveratrol promotes autophagy in HCC cells

Autophagy functions as a quality control mechanism that facilitates the elimination of damaged organelles and proteins, ultimately contributing to the maintenance of cellular homeostasis. Nevertheless, the involvement of autophagy in HCC is complex and context-dependent⁸⁷. Resveratrol promotes autophagy in hepatoma cells through complex molecular pathways. The process is initiated by the activation of AMP-activated protein kinase (AMPK), which serves as a crucial cellular energy sensor⁸⁸. AMPK activation by resveratrol suppresses the mechanistic target of rapamycin complex 1 (mTORC1), thereby relieving an important inhibitory checkpoint on autophagy. This promotes autophagic flux and the formation of autophagosomes that enclose damaged organelles and cytoplasmic components⁸⁹. By enhancing autophagy, resveratrol may facilitate the clearance of aberrant cellular constituents and disrupt survival mechanisms in HCC cells. Another study has shown that the promoting effect of resveratrol on the autophagy process in HCC cells is also associated with activation of the p53 pathway and the PI3K/AKT pathway⁹⁰. The p53 pathway is involved in the control of cell cycle progression, DNA repair, and apoptosis⁹¹, while the PI3K/AKT pathway plays a crucial role in cell growth and metabolism⁹². Experimental evidence indicates that 60 $\mu\text{mol}\cdot\text{L}^{-1}$ resveratrol treatment activates the p53 pathway, increases p53 protein levels, and enhances transcription of p53 target genes, thereby contributing to the induction of autophagy and inhibition of HCC cell growth. Furthermore, resveratrol treatment inhibited the PI3K/AKT pathway, leading to the inhibition of cell survival signaling and the enhancement of autophagy⁹³. It is worth noting that resveratrol-induced autophagy exhibits a dual effect in liver cancer cells: at the early stage of cellular stress, autophagy acts as a protective mechanism by eliminating damaged organelles, whereas excessive or

sustained autophagy, particularly when coupled with apoptosis, may promote cell death.

5.2.2. Resveratrol induces apoptosis in HCC cells

In addition to autophagy, the regulation of apoptosis by resveratrol has attracted much attention. Resveratrol can promote the apoptotic process of HCC cells by regulating the mitochondrial apoptosis pathway, targeting the AMPK/mTOR signaling pathway, and inducing endoplasmic reticulum (ER) stress⁹⁴. For example, resveratrol upregulates the pro-apoptotic protein Bax and downregulates the anti-apoptotic protein Bcl-2, thus affecting the mitochondrial membrane permeability and activating the Caspase-dependent apoptotic pathway^{95, 96}. In addition, resveratrol activates the p53 signaling pathway, which increases the expression of proapoptotic proteins such as Bax and PUMA, promotes cytochrome C release from mitochondria, and triggers the apoptotic process⁹⁷. Resveratrol has also been shown to induce ER stress, resulting in the increased expression of ER stress-related proteins such as GRP 78 and CHOP. As ER stress is closely related to cell apoptosis, modulation of these proteins may contribute to resveratrol-induced cell death⁹⁸. A study in human SK-HEP-1 hepatoma cells showed that apoptosis was positively correlated with resveratrol concentration. Mechanistically, resveratrol promoted apoptosis by increasing reactive oxygen species production and DNA single-strand breaks, upregulating Rab37, and downregulating peroxiredoxin-2⁹⁹. MARCH1 is a membrane-associated RING-CH E3 ubiquitin ligase. Knockout of MARCH1 has been shown to suppress apoptosis development¹⁰⁰. In a study by Hanhan Dai, it was found that resveratrol decreased the levels of MARCH1 protein expression by activating the PTEN/AKT signaling pathway, leading to increased apoptosis in HCC cells¹⁰¹.

In conclusion, there is a complex mutual regulatory relationship between autophagy and apoptosis in the anti-HCC effects of resveratrol. Beclin-1, as a key regulatory factor of autophagy, is simultaneously negatively regulated by the apoptosis-related protein Bcl-2. Resveratrol promotes autophagy by activating the

AMPK/mTOR pathway while also releasing Beclin-1 by down-regulating the expression of Bcl-2, forming a synergistic effect of autophagy and apoptosis. In addition, excessive autophagy may ultimately trigger an apoptotic cascade reaction by depleting cellular ATP and inducing mitochondrial dysfunction, thereby effectively killing HCC cells.

5.3. Resveratrol regulates oxidative stress to inhibit HCC progression

Oxidative stress plays a crucial role in the intricate progression of HCC. The liver, being a center of diverse metabolic functions, is particularly susceptible to oxidative harm¹⁰². ROS are generated as a result of cellular processes, and when their production surpasses the capacity of cellular antioxidant defenses, oxidative stress develops. In HCC, prolonged exposure to risk factors like viral infection, alcohol consumption, and NAFLD can further intensify oxidative stress⁶⁸.

Resveratrol, a natural polyphenol compound, has been demonstrated in numerous studies to significantly inhibit the progression of liver cancer. This inhibitory effect is primarily attributed to the antioxidant properties of resveratrol⁷¹. It enhances the activity of endogenous antioxidant enzymes, such as glutathione peroxidase (GPx) and superoxide dismutase (SOD), thereby mitigating the impact of ROS on cellular components⁸⁸. Moreover, resveratrol activates the Nrf2/Keap1 pathway, a crucial regulator of cellular antioxidant defense, by enhancing Nrf2 nuclear translocation through inhibiting Keap1-mediated degradation¹⁰³. Once in the nucleus, Nrf2 binds to the antioxidant response element (ARE) in the promoter of antioxidant genes, facilitating the expression of phase II detoxification enzymes (heme oxygenase-1) and antioxidant protein¹⁰⁴. SIRT1 is an NAD⁺-dependent deacetylase, plays a vital role in combating oxidative stress by modulating transcription factors like FOXO, p53, and hypoxia-inducible factor 1 α (HIF-1 α)¹⁰⁵. Resveratrol activates SIRT1, leading to deacetylation and activation of targets such as PGC-1 α and FOXO, which in turn regulate antioxidant enzymes, mitochondrial biogenesis, and DNA repair capacity¹⁰⁶.

The deleterious effects of oxidative stress on hepatocytes are not limited to direct DNA damage¹⁰⁷. Oxidative stress and inflammation form a reciprocal cycle that sustains the progression of HCC. Under oxidative stress, the activation of NF- κ B triggers the release of proinflammatory cytokines and chemokines, thereby creating an environment conducive to tumor growth and survival¹⁰⁸. It is noteworthy that oxidative stress can activate transcription factors, such as NF- κ B, thus promoting the pro-inflammatory microenvironment¹⁰⁹. This intricate interplay between oxidative stress and the inflammatory response creates a favorable environment for the development and progression of HCC. As ROS-induced damage accumulates, it contributes to genetic mutations, promotes cell survival mechanisms, and promotes inflammatory responses that jointly drive the malignant transformation of hepatocytes¹¹⁰. Resveratrol suppresses NF- κ B activation by inhibiting I κ B kinase activity, thereby reducing the expression of pro-inflammatory cytokines and chemokines and attenuating oxidative stress associated with chronic inflammation¹¹¹.

5.4. Resveratrol inhibits angiogenesis in HCC tissues

HCC is a highly vascularized malignant tumor, and its generation and development strongly dependent on neovascularization¹¹². Therefore, inhibiting the angiogenesis becomes an important strategy to prevent the progression of HCC. Several studies have shown that resveratrol exerts anti-HCC effects by inhibiting angiogenesis^{113,114}. One major mechanism involves inhibition of vascular endothelial growth factor (VEGF), a key mediator of tumor angiogenesis that promotes vascular formation and main-

tenance in tumors¹¹⁵. HIF-1 α is a key transcription factor driving the expression of VEGF, and an *in vitro* experiment has shown that resveratrol suppresses VEGF transcription through the downregulation of HIF-1 α ^{116,117}. Studies in human HepG2 cells treated with resveratrol at concentrations of 10, 20, and 40 μ mol·L⁻¹ showed a significant time-dependent reduction in cancer cell growth accompanied by decreased VEGF protein expression. This effect was reported to be associated with modulation of NF- κ B signaling¹¹⁸. Furthermore, it has been shown that resveratrol significantly reduces VEGF mRNA expression in a concentration-dependent manner, further supporting its anti-angiogenic activity^{114,119,120}. Previous research has shown that resveratrol can suppress HSC-induced angiogenesis in HepG2 cells by reducing Gli-1 expression, inhibiting ROS production, and decreasing the expression of IL-6 and CXCR4 receptors¹²¹.

Resveratrol has a regulatory effect on the expression of a variety of specific target proteins and genes involved in tumor angiogenesis and endothelial cell function, including matrix metalloproteinases (MMPs) and protein S¹²². MMPs are zinc-dependent proteolytic enzymes that promote tumor angiogenesis¹²³. Resveratrol suppresses gelatinolytic activity derived from MMP-2 secreted by human umbilical vein endothelial cells, thereby limiting tumor growth¹²⁴. Protein S is a widespread phospholipid-binding protein found in the blood circulation¹²⁵. It is mainly synthesized by the liver and is able to bind to coagulation factors. In HepG2 cells, protein S is considered as a factor to promote the growth of liver cancer cells¹²⁶. Experiments by Yoshie Hiroto and colleagues found that resveratrol significantly inhibited the promoter activity of the *PROS1* gene and downregulated the expression of protein S, thereby suppressing HCC progression¹²⁷.

6. Summary of the multistep effects of resveratrol in the treatment of HCC

Resveratrol, a natural polyphenolic compound, has demonstrated exceptional therapeutic efficacy in the prevention and treatment of hepatic disorders. In the context of chronic hepatitis B, resveratrol effectively inhibits HBV replication by targeting the PI3K/Akt and STAT3 signaling axes while alleviating hepatocyte damage mediated by suppressing inflammatory signaling pathways, such as NF- κ B and MAPK. Moreover, its antioxidant properties significantly reduce oxidative stress-induced liver damage by activating an antioxidant enzyme system, including CAT, SOD, and GSH. During the progression of liver fibrosis, resveratrol mitigates the deposition of ECM by inhibiting the activation and collagen synthesis of HSCs. It also enhances cellular adaptive responses through the modulation of the Hippo pathway and antioxidant pathways such as Nrf2/Keap1 and SIRT1. In HCC, resveratrol exhibits antitumor activity through various mechanisms. It suppresses tumor cell proliferation, induces apoptosis, and inhibits migration, invasion, and angiogenesis. These effects are mediated through regulation of several signaling pathways, including PI3K/AKT, JNK, NF- κ B, and Wnt/ β -catenin. Resveratrol also modulates the p53 signaling pathway, enhancing the stability and transcriptional activity of p53, thereby countering the malignant transformation of HCC cells. In summary, resveratrol provides new strategies for the treatment of hepatic disorders through a series of finely tuned molecular mechanisms, and its potential in clinical applications is promising.

7. Key considerations

7.1. Pharmacokinetics analysis of resveratrol

The oral bioavailability of resveratrol is markedly limited due to poor aqueous solubility and extensive first-pass metabo-

olism¹²⁸. As a Biopharmaceutics Classification System (BCS) class II compound, resveratrol exhibits extremely low water solubility (0.03–0.05 mg·mL⁻¹), which restricts its dissolution in the gastrointestinal tract and limits intestinal absorption. In addition, resveratrol undergoes rapid phase II metabolism following absorption. After entering the portal circulation, it is extensively conjugated by uridine diphosphate glucuronosyltransferases (UGT1A1, UGT1A6, UGT1A9) and sulfotransferases (SULT1A3), forming glucuronide and sulfate conjugates that are readily excreted but exhibit reduced biological activity. As a result, the oral bioavailability of resveratrol is typically less than 1%, significantly limiting its clinical efficacy.

However, absorbed resveratrol is widely distributed to multiple tissues, including the liver and heart¹²⁹. Hepatic metabolism further involves cytochrome P450 enzymes, such as CYP1A1, CYP1B1, and CYP3A4, generating additional metabolites¹³⁰. Elimination occurs predominantly via biliary excretion into the intestine, with a minor fraction excreted through the kidneys. To enhance its oral availability, several strategies have been developed. Nanocarrier-based delivery systems, including liposomes, polymeric nanoparticles, and solid lipid nanoparticles, improve solubility, protect resveratrol from gastrointestinal degradation, and enable sustained release. Solid-state modification approaches, such as eutectic and co-amorphous systems, enhance intrinsic solubility. Prodrug strategies aim to bypass first-pass metabolism and enable site-specific activation. In addition, combined administration with metabolic enzyme inhibitors (such as piperine) has also been proven to significantly prolong the *in vivo* retention time of resveratrol¹³¹⁻¹³³. These approaches highlight the importance of thoroughly understanding and effectively utilizing resveratrol.

7.2. Safety and toxicological analysis of resveratrol

Resveratrol is generally considered to have low toxicity, with high doses not exhibiting obvious toxic effects in animal experiments¹³⁴. This indicates that resveratrol is relatively safe when consumed in large amounts over the short term. Long-term toxicity studies have revealed that continuous intake of resveratrol may impact the metabolism of certain drugs, especially those metabolized by hepatic cytochrome P450 enzymes¹³⁵. Consequently, resveratrol may interact with these medications, potentially altering their efficacy or increasing the risk of side effects. Common side effects observed in clinical trials include headache, diarrhea, and rash, although these were generally mild¹³⁶.

At elevated doses, resveratrol may induce mild to moderate gastrointestinal symptoms like nausea, vomiting, and diarrhea. Regarding chronic toxicity, current research suggests that prolonged use of resveratrol within a specific dose range is generally safe for healthy individuals. However, extended use at high doses could potentially impact liver and kidney function¹³⁷. Despite its relatively low toxicity and minimal side effects as per existing research, ongoing monitoring and further studies are necessary to explore its potential toxicity in clinical settings. Particularly with high doses or prolonged usage, vigilance towards potential liver and kidney effects is crucial, alongside the evaluation of other chronic health risks. Current research suggests that resveratrol has low toxicity and minimal side effects, making it a promising, safe, and effective candidate drug for liver cancer.

7.3. Advantages of resveratrol: multi-target and multi-pathway regulation

HCC treatment is complicated by various biological features and fast disease advancement, which frequently restrict the efficacy of treatments that target a single factor. Resveratrol exhibits a multi-target mode of action, enabling simultaneous modulation of

multiple signaling pathways involved in HCC progression. An important aspect in comprehending the substance's foundation and operation mechanism is network pharmacology, which involves the mapping of component-target-signaling pathways^{138, 139}. Network pharmacology analyses have identified key pathways regulated by resveratrol, including PI3K/Akt, SIRT1, JNK, p53, Hippo, and VEGF signaling pathways, highlighting its broad regulatory capacity across the hepatitis-fibrosis-HCC axis. Furthermore, when combined with berberine, bisartemisinin, and other drugs, resveratrol can achieve synergistic multi-target therapeutic effects. For example, co-administration with matrine, there was a synergistic effect observed in the inhibition of liver cancer cell proliferation. Matrine specifically enhanced the activation of caspase-9 and caspase-3 by resveratrol, leading to an up-regulation of the Bax/Bcl ratio.

Recent advances have underscored resveratrol's potent immunomodulatory effects in HCC¹⁴⁰. It reshapes the tumor immune microenvironment by suppressing immunosuppressive CD8⁺CD122⁺ regulatory T cells and M2-polarized tumor-associated macrophages, increasing IFN- γ -expressing CD8⁺ cytotoxic T cells, and shifting the cytokine balance from IL-10/TGF- β toward TNF- α /IFN- γ ^{141, 142}. These changes not only dampen tumor-promoting inflammation but also enhance antigen presentation and effector T cell activity.

Resveratrol also enhances the efficacy of standard chemotherapeutic agents. In combination with sorafenib, it amplifies anti-tumor efficacy by targeting signaling pathways such as PKA/AMPK/eEF2K. It has also been reported to enhance the cytotoxicity of oxaliplatin while alleviating chemotherapy-induced hepatotoxicity¹⁴³. Preclinical and mechanistic studies also indicate that resveratrol-induced macrophage polarization toward an M1 phenotype and suppression of Tregs may augment the effectiveness of immune checkpoint inhibitors, suggesting its potential as an adjuvant in immunotherapy¹⁴⁴. Altogether, these findings highlight resveratrol as a multi-faceted agent that extends beyond direct cytotoxicity—acting systemically to enhance anti-tumor immunity and potentiate combination regimens to overcome drug resistance and improve therapeutic outcomes in HCC.

Network-based analyses have also identified key target genes, including *AKT1*, *Bcl-2*, *TP53*, and *IL-6*, which are involved throughout the progression from hepatitis to HCC. This finding underscores the presence of inflammation and oxidative stress across all stages of liver disease progression (Fig. 6).

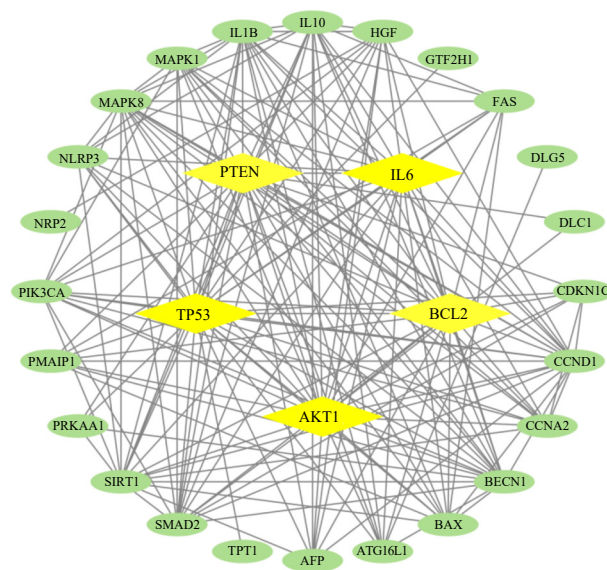


Fig. 6 Target pathway network in the HCC trilogy.

8. Conclusion

This study delves into the multi-step mechanism of resveratrol in treating liver cancer, confirming its significant impact on preventing and treating HCC. Resveratrol targets various signaling pathways and molecular targets, showcasing its broad biological activities, including anti-inflammatory, antioxidant, antiviral, anti-fibrotic, and anti-tumor effects. In chronic hepatitis, resveratrol effectively inhibits HBV replication and reduces liver cell damage through key signaling pathway regulation. Its antioxidant properties mitigate oxidative stress by activating the endogenous antioxidant enzyme system. In liver fibrosis, resveratrol hinders HSC activation and collagen synthesis, bolstering cell self-protection mechanisms by modulating the Hippo pathway and antioxidant pathways like Nrf2/Keap1 and SIRT1. For HCC treatment, resveratrol demonstrates anti-tumor effects by impeding tumor cell proliferation, promoting apoptosis, limiting migration and invasion, and inhibiting angiogenesis. These effects are mediated through the regulation of multiple signaling pathways, including PI3K/AKT, JNK, NF- κ B, and Wnt/ β -catenin, as well as activation of the p53 signaling pathway, thereby inhibiting malignant progression.

Existing research indicates that resveratrol has dual effects in treating viral hepatitis, particularly in cases of hepatitis B and hepatitis C, demonstrating unique properties. Resveratrol not only inhibits viral replication but also boosts the host's antiviral immune responses through the regulation of various signaling pathways, thereby enhancing virus clearance and safeguarding liver function. However, early studies suggest that resveratrol may paradoxically facilitate viral replication under certain conditions, as seen in research on hepatitis C virus models that rely on cell division for replication^{145, 146}. Although subsequent studies have largely refuted these findings, the potential bidirectional effects of resveratrol on viral replication should be carefully considered in clinical applications. Therefore, individualized therapeutic strategies may be required based on disease context. Further investigation is necessary to unravel the precise mechanism of action of resveratrol and optimize its therapeutic benefits while minimizing potential adverse effects.

In summary, the multi-target and multi-pathway mechanism of action of resveratrol provides a new strategy for the treatment of HCC, and its clinical application prospects are broad. Future studies need to further evaluate the pharmacokinetic properties, potential toxicity, and synergy with other drugs of resveratrol to optimize its application in the treatment of liver cancer.

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Declaration of Competing Interest

These authors have no conflict of interest to declare.

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