ACCSCIENCE PUBLISHING

Journal of Clinical and Translational Research

REVIEW ARTICLE

Propranolol: Repurposing an old drug to modulate tumor growth, angiogenesis, and immunity in hepatocellular carcinoma

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Abstract

Background: Hepatitis B virus (HBV) and hepatitis C virus (HCV) are the key risk determinants for hepatocellular carcinoma (HCC), which is a significant public health issue worldwide. Molecular mechanisms of HBV- and HCV-related hepatocarcinogenesis are reviewed here, together with the therapeutic potential of propranolol against HCC. HBV and HCV promote HCC development through chronic inflammation, oxidative stress, and dysregulation of signaling pathways involved in proliferation, apoptosis, and immunity. Propranolol demonstrates promise in inhibiting tumor growth, angiogenesis, and metastasis in HCC by modulating adrenergic receptors and the immune response. Evidence suggests propranolol reduces inflammatory cytokines, enhances natural killer cell activity, and decreases the expression of immune checkpoint proteins such as programmed cell death protein 1 and T cell immunoglobulin and mucin domain-containing protein-3 in HCC cells. Clinical studies indicate that propranolol may lower HCC incidence and improve survival in cirrhotic patients. However, optimal dosing, long-term safety, and efficacy require further research through large randomized controlled trials. **Aim:** This paper aims to review the potential of propranolol as an adjuvant therapy for HBV/HCV-induced HCC by examining its antitumor, anti-angiogenic, and immunomodulatory effects. **Conclusion:** Propranolol represents a prospective adjuvant therapy for HBV/HCV-induced HCC that warrants continued investigation to fully elucidate its therapeutic potential against this disease. **Relevance for patients:** Propranolol may improve outcomes in HBV/HCV-related HCC by reducing tumor growth, angiogenesis, and immune evasion, offering a potential adjunct therapy to enhance patient survival and prognosis.

Keywords: Hepatocellular carcinoma; Hepatitis B virus; Hepatitis C virus; Propranolol; Cirrhosis

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Citation: Owliaee I, Khaledian M, Ramezani F, Shojaeian A. Propranolol: Repurposing an old drug to modulate tumor growth, angiogenesis, and immunity in hepatocellular carcinoma. *J Clin Transl Res*. 2025;11(4):18-29. doi: 10.36922/JCTR025080010

Received: February 18, 2025

Revised: April 29, 2025

Accepted: May 28, 2025

Published online: June 19, 2025

1. Introduction

1.1. General overview of hepatocellular carcinoma (HCC)

Globally, HCC ranks fifth in the frequency of new occurrences, with 500,000 – 1,000,000 cases reported yearly. Up to 80% of HCC cases are found in developing nations, with sub-Saharan Africa and Southeast Asia having the most significant incidence rates.[1,2] HCC has been the Taiwan region's primary source of cancer-related fatalities since 1984. In the Taiwan region, 8,000 new instances of HCC are discovered each year, and about 7,000 HCC deaths occur annually.[3] Around the world, hepatitis B virus (HBV) infections account for over half of all HCC cases, whereas hepatitis C virus (HCV) infections account for roughly one-third. However, the proportion of HCC caused by these viruses varies significantly by demographic, and there is evidence that the prevalence of HCV globally is significantly underreported.[4] Developed Western countries have a low prevalence of HCC, although there has been a rising trend over the past 20 years. These two viruses account for over 80% of all HCC cases worldwide, making them the two main risk factors for developing HCC. Non-viral variables, such as alcohol use as well as aflatoxin B1, and other chronic liver disorders, are less frequently associated with HCC risk.[2,5] Although several Asian and African nations are known to have a high incidence of HCC, there has been a more recent rise in the condition in nations such as the United States. Environmental pollutants, alcohol and drug abuse, autoimmune diseases, genetics, obesity, high hepatic iron levels, and infections with hepatotropic viruses have all been associated with HCC development.[5] Regardless of the condition's cause, patients with chronic viral infections are likely to develop liver cirrhosis, a significant risk factor for carcinogenesis.[6]

Finding effective HCC therapies is critical. Effective medical interventions can vastly enhance patient outcomes, increase survival rates, and improve the quality of life for patients suffering from this condition.[7] Furthermore, improvements in HCC treatment will lessen the strain on health-care systems by eliminating the requirement for costly interventions such as palliative care or liver transplantation. Finding successful HCC treatments will also give patients and their families hope and provide them with a chance to battle this terrible enemy. In addition, it would open the door for more investigation into the biology of liver cancer, allowing researchers to identify new therapeutic targets and create groundbreaking strategies to fight HCC.[8] In this paper, we aim to examine propranolol's potential as a treatment for HCC by thoroughly examining the available literature and research findings as part of our aspiration to contribute to the ongoing efforts of identifying novel therapeutics for this aggressive kind of liver cancer.

2. Molecular mechanisms of HBV in the development of HCC

2.1. HBV

HBV, a small pathogenic enveloped virus, belongs to the Hepadnaviridae family. Among DNA viruses, HBV is distinct since an RNA intermediate is utilized as an intermediate in its DNA genome replication.[9,10] The reverse transcriptase (the enzyme for DNA replication by reverse transcription), three envelope glycoproteins, and the C protein of the viral core (the chief component of the viral nucleocapsid) are all translated from the four open reading frames (ORFs) of the small, 3.2 kb HBV DNA genome. HBV is transmitted by contact with infected blood or body fluids in the same manner as HIV. In comparison to HIV, HBV is 50 – 100 times more infectious.[11] Malaise, exhaustion, jaundice, and skin and sclera discoloration are common symptoms of hepatitis, an inflammation of the liver which is brought on by liver malfunction and high blood bilirubin levels.[5] It is estimated that 350 million people globally have chronic HBV. Up to 40% of these people will experience problems from HCC and cirrhosis. Chronic HBV carriers have an annual risk of <1%, but individuals who also have cirrhosis have an annual risk of 2 – 3%. About 70 – 80% of HBV-related HCC develops in cirrhotic livers, whereas the remainder of HCC develops in livers that do not have cirrhosis. The formation of HCC in people with chronic hepatitis B is a multistage, complex process that involves the interaction of the host and the environment. HBV is not immediately cytopathic. Gender, age, cigarette smoking, alcohol use, chemical carcinogens, hormones, and genetic vulnerability are among the chronic HBV-associated risk factors for HCC.[6]

2.2. Overview of HBV replication

The Hepadnaviridae family of viruses, of which HBV is a part, can result in persistent liver infections. Each hepadnavirus appears to have a restricted host range dictated by intracellular signaling components and a cell-surface receptor.[5] The hepadnavirus known as HBV reproduces by use of RNA. The 3.2 kb partially double-stranded relaxed circular DNA (rcDNA) of HBV is converted into covalently closed circular DNA (cccDNA) after it enters hepatocytes. All viral mRNAs are transcriptionally transcribed from the cccDNA, which is organized as a minichromosome by both viral and cellular histone and non-histone proteins. Recurrence of the disease is possible even after successful treatment and HBsAg removal since HBV replication would still

continue after the intake of nucleoside analogs.[9] Upon entry into the nucleus of the partially double-stranded circular DNA, single-stranded DNA gaps are closed, and the HBV genome is transformed into a covalently closed circular, double-stranded DNA (cccDNA). cccDNA serves as a template for viral mRNA transcription and synthesis rather than replication. HBV genome is small and contains four overlapping ORFs encoding HBx protein, envelope (S antigen), reverse transcriptase/polymerase (Pol), and capsid (core). Pre-genomic RNA (pgRNA), the largest HBV transcript, is a terminally redundant viral replication intermediate. The viral reverse-transcriptase/polymerase of the infected hepatocyte cytoplasm replicates by reversing the pgRNA to the DNA genome. The HBsAg proteins either secrete the replicating, encapsulated viral genome to the nucleus to enhance the nuclear reservoir of cccDNA or sequester it as capsid buds within the endoplasmic reticulum. The encapsulated virion is released from the cell; numerous studies have demonstrated that HBV release from cells is regulated by multivesicular body components.[5] Three stages may be distinguished in the hepadnaviral genome replication process. First, the icosahedral core of the infectious virions contains rcDNA, which is a circular, partly double-stranded DNA molecule of around 3.2 kb. Second, within the host cell's nucleus, the rcDNA transforms into a plasmid-like cccDNA upon infection. Finally, pgRNA, which is preferentially packed into progeny capsids and reverse-transcribed by the co-packaged P protein into new rcDNA genomes, is one of the genomic and subgenomic RNAs produced by the cccDNA.[12]

2.3. Mechanisms of HBV-induced HCC

Prevention of HBV infection and early detection of HCC are crucial for reducing the disease's burden. Vaccination against HBV has proven to be highly effective at preventing new infections, and efforts should be made to increase global vaccination rates. Regular screening for HBV infection can assist in identifying individuals at risk for HCC, enabling early intervention and treatment.[13] Public health campaigns should emphasize the significance of vaccination and screening, especially among high-risk populations such as those with a family history of HBV or in areas with a high prevalence rate.[14] In HBV-related HCC, angiogenesis is critically regulated by vascular endothelial growth factor A (VEGFA), whose post-transcriptional control by HBV remains unclear. It has been revealed that HBV increases m6A methylation of VEGFA mRNA, thereby upregulating the RNA-binding protein IGF2BP3, stabilizing VEGFA in an m6A-dependent manner, and enhancing endothelial cell migration and tube formation. Knockdown of IGF2BP3 in an HBV-associated HCC xenograft model reduced VEGFA levels and tumor growth, identifying the IGF2BP3-VEGFA axis as a potential therapeutic target for antiangiogenic therapy in HBV-related HCC.[15]

Another major oncogenic mechanism involves HBV integration into the host genome, which subsequently disrupts essential cellular regulatory functions required for cell survival and proliferation. Interacting with different cellular proteins and regulating their functions, the HBV X protein (HBx) is a key molecule in promoting the development of HCC.[16] HBx can activate multiple signaling pathways involved in cell proliferation and survival, such as the PI3K/Akt and MAPK/ERK pathways. HBx can also disrupt DNA repair mechanisms, leading to genomic instability and mutation accumulation. Another essential mechanism is the induction of chronic inflammation by HBV infection, which creates a microenvironment conducive to the initiation and progression of tumors. During chronic inflammation, inflammatory cytokines stimulate cell proliferation, angiogenesis, and tissue remodeling.[17] By releasing pro-inflammatory mediators, HBV-induced immune responses can also contribute to liver injury and promote the development of HCC. These pro-inflammatory mediators exacerbate the inflammatory response, thereby perpetuating liver injury and promoting the development of HCC.[18] In addition, HBV infection can interfere directly with cellular processes involved in DNA repair and replication, resulting in genomic instability and an increased risk of mutations. These mutations contribute to the progression of HCC.[19] Furthermore, immune responses elicited by HBV are also capable of recruiting immune cells such as macrophages and lymphocytes, which produce other pro-inflammatory cytokines that lead to tissue damage and tumor development. This vicious cycle between chronic inflammation, immune response, genomic instability, and mutagenesis represents the complexity of HBV-induced HCC formation. All these processes should be unveiled to develop targeted therapies to prevent this complicated sequence and improve the prognosis of HBV-related HCC patients.[17]

3. Molecular mechanisms of HCV in the development of HCC

3.1. HCV

HCV is a member of the Flaviviridae family of enveloped RNA viruses. The 9 kb long, positive-strand, single-stranded RNA genome of HCV, similar to other flaviviruses, is translated as a polyprotein, which is processed by proteases into four functional proteins at the C-terminus. They comprise non-structural proteins involved in the replication of the virus, two envelope glycoproteins (E1

and E2), and a single capsid (C) protein. Like HBV, HCV is transmitted by blood and body fluids.[2,11] Despite having no known DNA form during its life cycle or latent stage, HCV commonly causes recurrent liver infections. Unlike HBV infections, the probability of developing a chronic HCV infection is between 55% and 85%, and it does not change much with age.[11] Worldwide, there are over 170 million HCV-infected people, and 20% of them will develop cirrhosis. Unlike patients with chronic hepatitis B, those with chronic hepatitis C nearly invariably develop HCC in the context of cirrhosis. Annually, 1 – 4% of chronic hepatitis C patients with cirrhosis are prone to developing HCC, whereas 1 – 3% of patients with a chronic HCV infection will do so within 30 years. Similar to HBV, the association between HCV and HCC likely involves both the indirect effect of cirrhosis and HCV's direct role in promoting hepatocarcinogenesis.[2] Because of the expression of the entry receptors needed for viral replication and host liver-enriched cellular factors (miRNA-122), HCV infects mainly hepatocytes. Extrahepatic manifestations were, however, observed in kidneys, peripheral nervous system, epithelial cells, and mononuclear blood cells.[20]

The livers of HCV-infected individuals have higher amounts of the hepatic low-density lipoprotein (LDL) receptor, which is crucial for assessing blood cholesterol levels. This suggests that in HCV patients, viral infection directly causes decreased LDL levels.[6] The combination of environmental, host, and viral variables is one of the processes behind HCV-induced HCC. HCV does not incorporate into the host genome such as HBV does. However, like HBV, HCV may cause chromosomal instability by directly affecting genes that control how centrosomal processes and mitotic spindles are arranged during the cell cycle.[21]

The attachment of HCV to cells marks the start of its life cycle. HCV particle entrance into hepatocytes is facilitated by a variety of cellular components, including proteins, lipids, and glycans. HCV first binds to surface proteoglycans, including the tetraspanin CD81 and the scavenger receptor class B type I. Following their relocation to tight junctions, occluding proteins and claudin-1 become essential for HCV penetration.[22]

3.2. Mechanisms of HCV-induced HCC

The mechanisms of HCV-induced HCC involve a complex interplay of numerous factors. Through its persistent infection, the virus causes chronic inflammation in the liver. This inflammatory response activates multiple signaling pathways, including the JAK/STAT and NF-κB pathways, which promote cell survival and proliferation.[23] Key factors include genetic mutations (e.g., TP53 and CTNNB1), dysregulated signaling pathways (e.g., Wnt/β-catenin and PI3K/AKT/mTOR), and epigenetic modifications that drive uncontrolled hepatocyte proliferation. The tumor microenvironment, comprising immune cells, fibroblasts, and extracellular matrix components, further promotes HCC by fostering immune evasion, angiogenesis, and metastasis. Chronic inflammation due to hepatitis B/C infection, metabolic disorders (e.g., non-alcoholic fatty liver disease), and oxidative stress also contribute to HCC pathogenesis by sustaining pro-tumorigenic conditions.[24] In addition, HCV proteins, notably core and NS5A, directly contribute to hepatocarcinogenesis by interfering with essential cellular processes. NS5A enhances cell proliferation and inhibits apoptosis,[25] whereas the core protein disrupts cell cycle regulation and promotes genomic instability. Moreover, HCV-induced oxidative stress and DNA damage play essential roles in the progression of HCC. The virus induces the production of reactive oxygen species and impairs antioxidant defense mechanisms, resulting in DNA lesions and genomic modifications.[26] These alterations can activate oncogenes and inactivate tumor suppressor genes, further promoting hepatocarcinogenesis. Furthermore, persistent inflammation in the liver brought on by HCV infection creates an environment that is favorable for tumor development and progression. Pro-inflammatory cytokines and chemokines are released by the virus, drawing immune cells that produce growth factors and encourage angiogenesis.[27] This sustained inflammatory response also contributes to the activation of cell proliferation and survival signaling pathways. In addition, HCV proteins interact with host factors to dysregulate cellular signaling pathways, such as those associated with cell proliferation, apoptosis, and immune responses. These interactions disrupt normal cellular functions and foster the growth of cancer. Individuals infected with HCV develop hepatocarcinogenesis due to the complex effects of HCV on critical cellular processes, including oxidative stress-induced DNA damage, chronic inflammation, and dysregulation of signaling pathways.[28] Moreover, HCV infection affects hepatocytes and the microenvironment surrounding the liver. Chronic inflammation triggered by HCV recruits immune cells, such as macrophages and lymphocytes, which release pro-inflammatory cytokines and chemokines.[29] This disruption permits unrestrained cell proliferation and survival, thereby fostering the development of HCC. Taken together, the complex interplay between chronic inflammation, oxidative stress-induced DNA damage, and dysregulated signaling pathways underlie the pathogenesis of HCV-associated hepatocarcinogenesis. Understanding these

mechanisms is crucial for developing targeted therapies to prevent or treat HCC in patients with chronic HCV infection.[30]

4. Propranolol

4.1. Properties of propranolol

Propranolol (Figure 1) is a non-selective beta-adrenergic receptor antagonist first developed by Sir James Black in 1962 and approved for clinical use in 1964.[31] It blocks both β1 and β2 receptors, leading to reduced heart rate, myocardial contractility, and blood pressure.[32] Beyond its cardiovascular applications, propranolol demonstrates anti-angiogenic, anti-inflammatory, and immunomodulatory properties. These characteristics form the basis of its emerging role in oncology, including HCC.[33,34]

Due to its high lipophilicity, propranolol readily crosses the blood-brain barrier and undergoes extensive first-pass hepatic metabolism, with approximately 25% bioavailability.[35] While it binds to plasma proteins at a high rate (>90%), propranolol's distribution across tissues, including the liver, supports its potential therapeutic use in hepatic malignancies.[35]

Research has shown that propranolol can inhibit β-adrenergic receptor-mediated signaling pathways, which are implicated in tumor cell proliferation, migration, and angiogenesis.[36] The drug suppresses the production of vascular endothelial growth factor (VEGF) and hypoxia-inducible factor-1 alpha (HIF-1α), key regulators of angiogenesis in tumors.[37,38] It also induces apoptosis in endothelial cells, thereby disrupting tumor vascularization.[39]

Propranolol's immunomodulatory effects are also noteworthy. It reduces the release of pro-inflammatory cytokines and enhances the activity of natural killer cells, which play a vital role in antitumor immunity.[40,41] These combined effects suggest that propranolol may be effective in preventing tumor progression and recurrence in HBV- and HCV-associated HCC.[42]

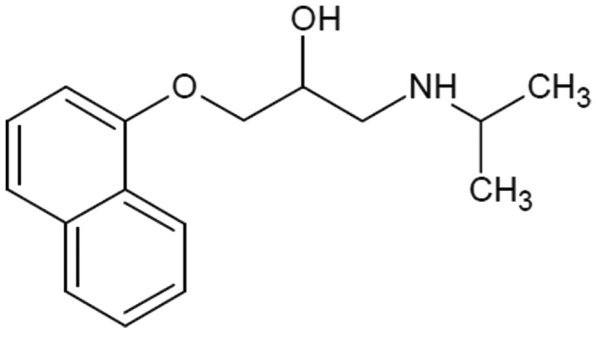

Figure 1. Chemical structure of propranolol

5. Role of propranolol in the prevention of HCC

Propranolol has been found to suppress the growth and proliferation of HCC cells by blocking beta-adrenergic receptors, which were found to be a key regulator for cancer development.[36] In addition, propranolol was said to regulate the immune system by blocking the secretion of pro-inflammatory cytokines and inducing anti-tumor immunity.[43] This dual mechanism of action makes propranolol an attractive treatment option for HCC patients infected with HBV and HCV. In addition, clinical investigations have shown that propranolol can increase overall survival rates and decrease tumor recurrence in these patients.[42] Furthermore, propranolol's anti-angiogenic effects contribute to its anticancer activity. By suppressing VEGF and HIF-1α expression, it effectively reduces neovascularization required for tumor growth and metastasis.[38,44,45] These properties have shown promise not only in HCC but also in other malignancies such as breast, lung, and colorectal cancers.[41] Propranolol effectively starves cancer cells and inhibits their ability to proliferate by targeting this critical phase of tumor development. This anti-angiogenic effect has been observed in breast, lung, and colorectal cancers. Propranolol has demonstrated immunomodulatory effects that extend beyond cytokine suppression. Notably, it has been shown to enhance the activity of natural killer cells – key components of the innate immune system responsible for targeting and eliminating cancer cells. By activating natural killer cells and boosting their cytotoxic function, propranolol strengthens the body's antitumor response, offering a promising mechanism for its potential efficacy in cancer therapy.[40,41,46] This discovery sheds light on the potential of propranolol as an adjunct therapy for various cancers, including breast, lung, and colorectal cancers. With its multiple effects on cytokine production and immune cell activity, propranolol bears promise as a cancer-fighting agent.[47] Propranolol can reduce the expression of programmed cell death protein 1 (PD-1) and T cell immunoglobulin and mucin domain-containing protein-3 (TIM-3) in liver cancer cells. PD-1 and TIM-3 are proteins that help cancer cells evade the immune system. By reducing the expression of these proteins, propranolol can make liver cancer cells more susceptible to attack by the immune system.[48] It has also been found that propranolol can increase the expression of granzyme B and interferon-gamma (IFN-γ) in liver cancer cells. Granzyme B is a protein that helps to kill cancer cells, and IFN-γ is a cytokine that helps to activate the immune system. By increasing the expression of these proteins,

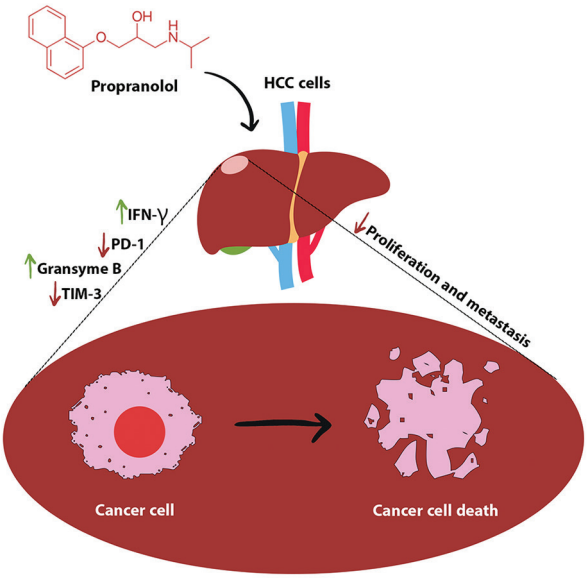

Figure 2. Schematic mechanism of the effect of propranolol on liver cancer cells. The use of propranolol reduces PD-1 and TIM-3, which increases granzyme B and IFN-γ, which ultimately reduces the proliferation and metastasis of cancer cells.
Abbreviations: HCC: Hepatocellular carcinoma; IFN-γ: Interferon-gamma; PD-1: Programmed cell death protein 1; TIM-3: T cell immunoglobulin and mucin domain-containing protein-3.

propranolol can help kill liver cancer cells and boost the immune response against cancer (Figure 2).[49]

Propranolol has been shown to inhibit the formation of new blood vessels essential for tumor growth. This is one potential mechanism for its antitumor activity. Observational studies have yielded promising results; however, randomized controlled trials are required to establish the drug's efficacy and safety profile definitively. This multifaceted mechanism of action makes propranolol a compelling adjunct therapy for HBV- and HCV-associated HCC. However, further studies, including randomized clinical trials, are needed to confirm its efficacy, determine optimal dosing, and evaluate its long-term safety in cancer patients.[42,50]

6. Clinical studies on propranolol's efficacy against HBV/HCV-induced HCC

Several studies have investigated the effect of propranolol on HCC. In 2023, a study by Wu *et al.*[51] showed that propranolol reduced the risk of HCC development in patients with cirrhosis by up to 40% and also improved survival in patients with HCC, with a median survival of 20 months in patients who received propranolol compared to 12 months in patients who did not receive propranolol, but the optimal dose and duration of propranolol treatment for HCC remains unknown. Cheng *et al.*[52] found that propranolol was associated with a decreased risk of HCC death in patients with cirrhosis; however, a significant difference in overall survival between patients who took propranolol and those who did not was not detected. Another study by Nkontchou *et al.*[53] found that long-term propranolol treatment was associated with a significant reduction in the incidence of HCC in patients with HCV-associated cirrhosis. In addition, London and McGlynn showed that patients who took propranolol for an average of 3.5 years were significantly less likely to develop HCC than patients who did not take propranolol, and the risk of HCC was reduced by about 50% in those taking propranolol.[54]

At present, there are four clinical trials on ClinicalTrials.gov investigating the effects of propranolol on HCC. At the time of writing this article, one of these trials was in phase II, while patient enrollment was still ongoing for the remainder of the trials. To determine whether propranolol is a safe and effective treatment for HCC, the outcomes of these trials will be crucial. The status of these trials may alter over time; therefore, it is always advisable to consult the ClinicalTrials.gov website for the most recent information, as summarized in Table 1.

7. Comparison of propranolol with other HCC prevention strategies

7.1. Antiviral therapies

The goals of antiviral treatments for persistent HBV infection are to inhibit viral replication, lessen hepatic inflammation, and stop the development of cirrhosis and HCC. Nucleos(t)ide analogs and IFN are the two main families of antiviral drugs that have shown promise in reducing HBV infection.[55] By inhibiting HBV DNA polymerase, nucleos(t)ide analogs such as entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide provide strong viral suppression while lowering hepatic inflammation and fibrosis.[56] Patients with persistent HBV infection have shown a considerable decrease in their likelihood of developing HCC while receiving long-term nucleos(t)ide analogs.[57] Nonetheless, there is variation in HCC risk reduction between various nucleos(t)ide analogs; research indicates that TDF users could have a lower incidence of HCC than ETV users. However, because these results are observational in nature, they should be interpreted with caution. Furthermore, compared to individuals who were not treated, IFN treatment has demonstrated a 34 – 41% reduced incidence of HCC, indicating its potential advantages despite restrictions on patient eligibility and adverse effects.[58] Direct-acting antivirals (DAAs), which provide sustained virologic response (SVR) rates of 95% across all genotypes,

Table 1. Summarized clinical trials of propranolol therapy for hepatocellular carcinoma

No.	NCT number	Study status	Interventions	Characteristics	Population	Years	Country/ Region
1	NCT01298284	Unknown	Propranolol	Interventional/Phase IV	No.: 60 Age: 18 – 80 years	2009 – 2011	Taiwan region
2	NCT01451658	Unknown	Propranolol	Interventional/Phase IV	No.: 100 Age: 18 – 80 years	2009 – 2020	Taiwan region
3	NCT01970748	Recruiting	Propranolol	Interventional/Phase IV	No.: 200 Age: 20 – 80 years	2009 – 2025	Taiwan region
4	NCT05451043	Not yet recruiting	Propranolol/Cisplatin/ Durvalumab/Tremelimumab Gemcitabine/Nab-paclitaxel	Interventional/Phase II	No.: 62 Age: 18 – 80 years	2023 – 2028	Canada

Abbreviations: HCC: Hepatocellular carcinoma; NCT: National Clinical Trial.

thus corresponding to a virological cure, have completely changed the therapy landscape for chronic HCV infection.[59] Reaching SVR lowers the chance of developing HCC by dramatically reducing hepatic inflammation and stopping the growth of fibrosis.[60] Studies have shown that compared to individuals with an active infection, those who achieve SVR had a much-decreased risk of HCC.[61] Liver stiffness decreased from 12.3 kPa at baseline to 6.6 kPa over 5 years, with the most significant improvement occurring in the 1st year post-treatment.[61] Early concerns about increased HCC incidence and recurrence following DAA-induced SVR, potentially due to disrupted immune surveillance, have been alleviated by recent meta-analyses, which found no evidence of differential HCC risk between DAA and IFN-based therapies.[62]

In addition to antiviral therapies, pharmacological interventions offer promising strategies for HCC prevention, particularly in populations with chronic liver disease, metabolic dysfunction, or other risk factors. Aspirin, for instance, demonstrates chemopreventive effects through the inhibition of cyclooxygenase-2, reducing pro-inflammatory prostaglandins and disrupting platelet–tumor cell interactions that facilitate tumor growth and metastasis.[63] Meta-analyses consistently show that regular aspirin use lowers HCC risk, particularly in individuals with chronic liver disease, though gastrointestinal bleeding and hemorrhagic stroke risks necessitate careful risk–benefit assessments.[64,65] By inhibiting hydroxymethylglutaryl-CoA reductase, statins reduce oncogenic signaling pathways such as Ras/Raf/MEK/ERK and modify the mevalonate pathway, which has anti-inflammatory, immunomodulatory, and antiproliferative effects.[66] Although myopathy or rhabdomyolysis is still a problem, especially in patients with decompensated cirrhosis, lipophilic statins, such as simvastatin and atorvastatin, have stronger protective benefits against HCC than hydrophilic versions.[67]

By activating AMP-activated protein kinase and blocking the mammalian target of the rapamycin pathway, metformin, a medication often used to treat type 2 diabetes, has also shown chemopreventive promise against HCC by reducing the development and proliferation of tumor cells.[68] It also lowers levels of insulin and insulin-like growth factor, both of which are linked to the development of hepatocarcinogenesis.[69] Although lactic acidosis in individuals with renal impairment highlights the need for careful patient selection, clinical data indicates that diabetic patients treated with metformin have a much lower risk of HCC.[70] Similarly, glucagon-like peptide-1 (GLP-1) agonists decrease the risk of HCC by improving insulin sensitivity, reducing hyperinsulinemia, and exhibiting anti-inflammatory qualities.[71] A large cohort study by Wang *et al.*[72] found that GLP-1 agonists were associated with a markedly reduced HCC risk compared to other antidiabetic therapies, though gastrointestinal disturbances and pancreatitis risks warrant careful monitoring.

By enhancing indicators of steatosis and fibrosis, sodium-glucose cotransporter 2 inhibitors, which are mainly used for glycemic management, have the potential to prevent HCC.[73] Angiotensin receptor blockers and angiotensin-converting enzyme inhibitors have anti-inflammatory and anti-fibrotic effects, which lessen liver fibrosis, a significant risk factor for HCC.[74] Known for its immunomodulatory and anti-inflammatory properties, Vitamin D supplements have also been associated with a lower risk of HCC, with a deficit markedly raising the risk of liver cancer.[75] Finally, nutraceuticals and herbal supplements, including curcumin, resveratrol, and silymarin, have shown promise in preclinical studies due to their antioxidant, anti-inflammatory, and anti-proliferative properties.[76] However, cases of drug-induced liver injury and variability in quality and potency highlight the need for regulation and standardization.[77] Collectively, these pharmacological interventions offer

valuable tools for HCC prevention, but their use must be tailored to individual patient profiles to balance efficacy and safety.

8. Potential limitations or challenges in using propranolol for HCC prevention/ treatment

While propranolol is potentially a therapeutic agent in reducing HBV/HCV-induced HCC, several limitations and challenges must be considered. The optimal dosage and treatment duration of propranolol for HCC prevention or treatment remain unclear. Drug interactions with other medications should be carefully evaluated, as propranolol may affect the hepatic metabolism of certain drugs.[78] Individual patient characteristics, such as age, liver function status, and comorbidities, may influence the efficacy and safety profile of propranolol treatment. The effectiveness of propranolol may vary among individuals due to differences in metabolism and genetic factors. Long-term use of propranolol might lead to adverse effects such as fatigue, dizziness, and gastrointestinal disturbances, potentially impacting patient compliance and overall treatment outcomes.[53]

9. Conclusion and future perspectives

HCC caused by HBV and HCV is a significant global health burden. Chronic viral infection results in various molecular alterations that promote the development of liver tumors. Due to its ability to inhibit critical processes involved in hepatocarcinogenesis caused by these viruses, propranolol has emerged as a potential therapeutic option. In conclusion, the prospective benefits of adding propranolol to HCC treatment are encouraging. Studies have demonstrated that it can inhibit tumor growth, angiogenesis, and metastasis, suggesting it could be a valuable addition to existing treatment strategies. However, some constraints and obstacles must be addressed. One such limitation is the requirement for dosage optimization, as the optimal dose of propranolol for treating HCC has yet to be determined. In addition, potential adverse effects associated with the use of propranolol must be monitored and managed with care. Future research should refine the delivery regimen and identify the patient populations most likely to benefit from propranolol therapy. In addition, investigating combination therapies that combine propranolol with other targeted agents may result in even greater efficacy in treating HCC. It is essential to address the current need for more well-defined approaches to enhance the treatment of HCC. In addition, thorough monitoring and effective management of potential side effects associated with propranolol are required.

Future research should prioritize fine-tuning dosing regimens and identify specific patient populations that would experience the most significant benefits from propranolol therapy. We can aim for more effective and individualized strategies to combat this problematic disease by pursuing these avenues. Investigating the use of propranolol in combination with immunotherapeutic agents is a prospective future research direction for exploring the full potential of propranolol in HCC treatment. Combining propranolol with immunotherapies such as immune checkpoint inhibitors or adoptive cell therapies may result in synergistic effects, enhancing treatment outcomes and patient survival rates. In addition, future research could target identifying specific biomarkers or genetic profiles that could predict a patient's response to propranolol therapy. This personalized approach would enable more targeted treatment strategies and maximize the use of propranolol in patients who are most likely to benefit. In addition, it is essential to investigate the optimal dosage and treatment duration of propranolol for HCC. Researchers can identify specific biomarkers or genetic profiles that predict a patient's response to propranolol therapy by conducting additional research. There is a need for large-scale, multicenter clinical trials to provide solid evidence on the long-term outcomes and potential adverse effects of propranolol use in this context. If proven effective, propranolol could be an accessible and cost-effective treatment option for those at high risk for or diagnosed with HBV/HCV-associated HCC.

Acknowledgments

The authors would like to sincerely thank the staff of the Research Center for Molecular Medicine of Hamadan University of Medical Sciences for their cooperation.

Funding

None.

Conflict of interest

The authors declare that they have no conflicts of interest.

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Conceptualization: Ali Shojaeian
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Writing–review & editing: All authors

Ethics approval

This study was approved by the ethics committee of Hamadan University of Medical Sciences (IR.UMSHA.

REC.1404.157).

Consent for publication

Not applicable.

Availability of data

Not applicable.

References

1. Gurtsevitch VE. Human oncogenic viruses: Hepatitis B and hepatitis C viruses and their role in hepatocarcinogenesis. *Biochemistry* (*Mosc*). 2008;73(5):504-513.

   doi: 10.1134/s0006297908050039

2. Fung J, Lai CL, Yuen MF. Hepatitis B and C virus-related carcinogenesis. *Clin Microbiol Infect.* 2009;15(11):964-70.

   doi: 10.1111/j.1469-0691.2009.03035.x

3. Chen CH, Huang GT, Yang PM, *et al.* Hepatitis B- and C-related hepatocellular carcinomas yield different clinical features and prognosis. *Eur J Cancer.* 2006;42(15):2524-2529.

   doi: 10.1016/j.ejca.2006.06.007

4. Dondog B, Lise M, Dondov O, Baldandorj B, Franceschi S. Hepatitis B and C virus infections in hepatocellular carcinoma and cirrhosis in Mongolia. *Eur J Cancer Prev*. 2011;20(1):33-39.

   doi: 10.1097/cej.0b013e32833f0c8e

5. Bouchard MJ, Navas-Martin S. Hepatitis B and C virus hepatocarcinogenesis: lessons learned and future challenges. *Cancer Lett.* 2011;305(2):123-143.

   doi: 10.1016/j.canlet.2010.11.014

6. Haberl EM, Weiss TS, Peschel G, *et al.* Liver lipids of patients with hepatitis B and C and associated hepatocellular carcinoma. *Int J Mol Sci*. 2021;22(10):5297.

   doi: 10.3390/ijms22105297

7. Gordan JD, Kennedy EB, Abou-Alfa GK, *et al.* Systemic therapy for advanced hepatocellular carcinoma: ASCO guideline. *J Clin Oncol.* 2020;38(36):4317-4345.

   doi: 10.1200/JCO.20.02672

8. Llovet JM, Kelley RK, Villanueva A, *et al*. Hepatocellular carcinoma. *Nat Rev Dis Primers*. 2021;7(1):6.

   doi: 10.1038/s41572-020-00240-3

9. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science*. 1989;244(4902):359-362.

   doi: 10.1126/science.2523562

10. Manns MP, Buti M, Gane E, *et al.* Hepatitis C virus infection. *Nat Rev Dis Primers*. 2017;3:17006.

    doi: 10.1038/nrdp.2017.6

11. Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. *Int J Med Sci*. 2006;3(2):47-52.

    doi: 10.7150/ijms.3.47

12. Beck J, Nassal M. Hepatitis B virus replication. *World J Gastroenterol*. 2007;13(1):48-64.

    doi: 10.3748/wjg.v13.i1.48

13. Kwok AJ, Mentzer A, Knight JC. Host genetics and infectious disease: New tools, insights and translational opportunities. *Nat Rev Genet*. 2021;22(3):137-153.

    doi: 10.1038/s41576-020-00297-6

14. Elgendy MO, Abdelrahim MEA. Public awareness about coronavirus vaccine, vaccine acceptance, and hesitancy. *J Med Virol*. 2021;93(12):6535-6543.

    doi: 10.1002/jmv.27199

15. Xu X, Zhang Y, Wu S, *et al*. Hepatitis B virus promotes angiogenesis in hepatocellular carcinoma by increasing m6A modification of VEGFA mRNA via IGF2BP3. *J Med Virol*. 2025;97(5):e70356.

    doi: 10.1002/jmv.70356

16. Levrero M, Zucman-Rossi J. Mechanisms of HBV-induced hepatocellular carcinoma. *J Hepatol*. 2016;64(1 Suppl):S84-S101.

    doi: 10.1016/j.jhep.2016.02.021

17. Jiang Y, Han Q, Zhao H, Zhang J. The mechanisms of HBV-induced hepatocellular carcinoma. *J Hepatocell Carcinoma*. 2021;8:435-450.

    doi: 10.2147/JHC.S307962

18. Li TY, Yang Y, Zhou G, Tu ZK. Immune suppression in chronic hepatitis B infection associated liver disease: A review. *World J Gastroenterol*. 2019;25(27):3527-37.

    doi: 10.3748/wjg.v25.i27.3527

19. Sommers Smith SK, Smith DM. Beta blockade induces apoptosis in cultured capillary endothelial cells. *In Vitro Cell Dev Biol Anim*. 2002;38(5):298-304.

    doi: 10.1290/1071-2690(2002)038<0298:BBIAIC>2.0.CO;2

20. D'Souza S, Lau KC, Coffin CS, Patel TR. Molecular mechanisms of viral hepatitis induced hepatocellular carcinoma. *World J Gastroenterol*. 2020;26(38):5759-5783.

    doi: 10.3748/wjg.v26.i38.5759

21. Vescovo T, Refolo G, Vitagliano G, Fimia GM, Piacentini M. Molecular mechanisms of hepatitis C virus-induced hepatocellular carcinoma. *Clin Microbiol Infect*. 2016;22(10):853-861.

    doi: 10.1016/j.cmi.2016.07.019

22. Tamai K, Shiina M, Tanaka N, *et al.* Regulation of hepatitis C virus secretion by the Hrs-dependent exosomal pathway.

Virology. 2012;422(2):377-385.

doi: 10.1016/j.virol.2011.11.009

23. Goossens N, Hoshida Y. Hepatitis C virus-induced hepatocellular carcinoma. *Clin Mol Hepatol*. 2015;21(2):105-114.

doi: 10.3350/cmh.2015.21.2.105

24. Yuan H, Xu R, Li S, *et al.* The malignant transformation of viral hepatitis to hepatocellular carcinoma: Mechanisms and interventions. *MedComm* (*2020*). 2025;6(3):e70121.

doi: 10.1002/mco2.70121

25. He Y, Staschke KA, Tan SL. HCV NS5A: A multifunctional regulator of cellular pathways and virus replication. In: Tan SL, editor. *Hepatitis C Viruses: Genomes and Molecular Biology.* Norfolk (UK): Horizon Bioscience; 2006.

26. Rebbani K, Tsukiyama-Kohara K. HCV-induced oxidative stress: Battlefield-winning strategy. *Oxid Med Cell Longev*. 2016;2016:7425628.

doi: 10.1155/2016/7425628

27. Li H, Huang MH, Jiang JD, Peng ZG. Hepatitis C: From inflammatory pathogenesis to anti-inflammatory/hepatoprotective therapy. *World J Gastroenterol*. 2018;24(47):5297-5311.

doi: 10.3748/wjg.v24.i47.5297

28. Zhao H, Wu L, Yan G, *et al.* Inflammation and tumor progression: Signaling pathways and targeted intervention. *Signal Transduct Target Ther*. 2021;6(1):263.

doi: 10.1038/s41392-021-00658-5

29. Zampino R, Marrone A, Restivo L, *et al.* Chronic HCV infection and inflammation: Clinical impact on hepatic and extra-hepatic manifestations. *World J Hepatol*. 2013;5(10):528-540.

doi: 10.4254/wjh.v5.i10.528

30. Dong Y, Tu R, Liu H, Qing G. Regulation of cancer cell metabolism: Oncogenic MYC in the driver's seat. *Signal Transduct Target Ther*. 2020;5(1):124.

doi: 10.1038/s41392-020-00235-2

31. Srinivasan AV. Propranolol: A 50-year historical perspective. *Ann Indian Acad Neurol*. 2019;22(1):21-26.

doi: 10.4103/aian.AIAN_201_18

32. Frishman WH. A historical perspective on the development of β-adrenergic blockers. *J Clin Hypertens*. 2007;9(S4):19-27.

doi: 10.1111/j.1524-6175.2007.06633.x

33. Roozendaal B, Hahn EL, Nathan SV, de Quervain DJ, McGaugh JL. Glucocorticoid effects on memory retrieval require concurrent noradrenergic activity in the hippocampus and basolateral amygdala. *J Neurosci*. 2004;24(37):8161-8169.

doi: 10.1523/JNEUROSCI.2574-04.2004

34. Dobarro M, Orejana L, Aguirre N, Ramírez MJ. Propranolol restores cognitive deficits and improves amyloid and Tau pathologies in a senescence-accelerated mouse model. *Neuropharmacology*. 2013;64:137-44.

doi: 10.1016/j.neuropharm.2012.06.047

35. Kao J, Luu B. Can propranolol prevent progression of melanoma? *JAAPA*. 2019;32(6):1-5.

doi: 10.1097/01.JAA.0000558241.84003.91

36. Xie Y. Hepatitis B virus-associated hepatocellular carcinoma. *Adv Exp Med Biol*. 2017;1018:11-21.

doi: 10.1007/978-981-10-5765-6_2

37. Storch CH, Hoeger PH. Propranolol for infantile haemangiomas: Insights into the molecular mechanisms of action. *Br J Dermatol*. 2010;163(2):269-274.

doi: 10.1111/j.1365-2133.2010.09848.x

38. Ji Y, Li K, Xiao X, *et al*. Effects of propranolol on the proliferation and apoptosis of hemangioma-derived endothelial cells. *J Pediatr Surg*. 2012;47(12):2216-2223.

doi: 10.1016/j.jpedsurg.2012.09.008

39. Wołowiec Ł, Grześk G, Osiak J, *et al*. Beta-blockers in cardiac arrhythmias-Clinical pharmacologist's point of view. *Front Pharmacol*. 2022;13:1043714.

doi: 10.3389/fphar.2022.1043714

40. Solernó LM, Sobol NT, Gottardo MF, *et al*. Propranolol blocks osteosarcoma cell cycle progression, inhibits angiogenesis and slows xenograft growth in combination with cisplatin-based chemotherapy. *Sci Rep.* 2022;12(1):15058.

doi: 10.1038/s41598-022-18324-3

41. Fjæstad KY, Rømer AMA, Goitea V, *et al*. Blockade of beta-adrenergic receptors reduces cancer growth and enhances the response to anti-CTLA4 therapy by modulating the tumor microenvironment. *Oncogene*. 2022;41(9):1364-1375.

doi: 10.1038/s41388-021-02170-0

42. Pasquier E, Ciccolini J, Carre M, *et al.* Propranolol potentiates the anti-angiogenic effects and anti-tumor efficacy of chemotherapy agents: Implication in breast cancer treatment. *Oncotarget*. 2011;2(10):797-809.

doi: 10.18632/oncotarget.343

43. Tu Z, Zhong Y, Hu H, *et al.* Design of therapeutic biomaterials to control inflammation. *Nat Rev Mater*. 2022;7(7):557-574.

doi: 10.1038/s41578-022-00426-z

44. Afify EA, Andijani NM. Potentiation of morphine-induced antinociception by propranolol: The involvement of dopamine and GABA systems. *Front Pharmacol.* 2017;8:794.

doi: 10.3389/fphar.2017.00794

45. Admani S, Feldstein S, Gonzalez EM, Friedlander SF.

Beta blockers: An innovation in the treatment of infantile hemangiomas. *J Clin Aesthet Dermatol*. 2014;7(7):37-45.

46. Musumeci M, Maccari S, Sestili P, *et al*. Propranolol enhances cell cycle-related gene expression in pressure overloaded hearts. *Br J Pharmacol*. 2011;164(8):1917-1928.

doi: 10.1111/j.1476-5381.2011.01504.x

47. Björkström NK, Strunz B, Ljunggren HG. Natural killer cells in antiviral immunity. *Nat Rev Immunol*. 2022;22(2):112-123.

doi: 10.1038/s41577-021-00558-3

48. Lin Y, Liu Y, Gao Z, *et al*. Beta-adrenergic receptor blocker propranolol triggers anti-tumor immunity and enhances irinotecan therapy in mice colorectal cancer. *Eur J Pharmacol*. 2023;949:175718.

doi: 10.1016/j.ejphar.2023.175718

49. Rousalova I, Krepela E. Granzyme B-induced apoptosis in cancer cells and its regulation (review). *Int J Oncol*. 2010;37(6):1361-1378.

doi: 10.3892/ijo_00000788

50. Kum JJ, Khan ZA. Mechanisms of propranolol action in infantile hemangioma. *Dermatoendocrinol*. 2014;6(1):e979699.

doi: 10.4161/19381980.2014.979699

51. Wu YL, van Hyfte G, Özbek U, *et al*. Outcomes of beta blocker use in advanced hepatocellular carcinoma treated with immune checkpoint inhibitors. *Front Oncol*. 2023;13:1128569.

doi: 10.3389/fonc.2023.1128569

52. Cheng HY, Lin HC, Lin HL, Uang YS, Keller JJ, Wang LH. Association between nonselective beta-blocker use and hepatocellular carcinoma in patients with chronic hepatitis B without cirrhosis and decompensation. *Front Pharmacol*. 2021;12:805318.

doi: 10.3389/fphar.2021.805318

53. Nkontchou G, Aout M, Mahmoudi A, *et al*. Effect of long-term propranolol treatment on hepatocellular carcinoma incidence in patients with HCV-associated cirrhosis. *Cancer Prev Res (Phila)*. 2012;5(8):1007-1014.

doi: 10.1158/1940-6207.CAPR-11-0450

54. London WT, McGlynn KA. Can propranalol prevent hepatocellular carcinoma? *Cancer Prev Res* (*Phila*). 2012;5(8):989-991.

doi: 10.1158/1940-6207.CAPR-12-0247

55. Kaewdech A, Sripongpun P. Challenges in the discontinuation of chronic hepatitis B antiviral agents. *World J Hepatol*. 2021;13(9):1042.

doi: 10.4254/wjh.v13.i9.1042

56. Lampertico P, Agarwal K, Berg T, *et al.* EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol*. 2017;67(2):370-398.

doi: 10.1016/j.jhep.2017.03.021

57. Papatheodoridis GV, Chan HLY, Hansen BE, Janssen HL, Lampertico P. Risk of hepatocellular carcinoma in chronic hepatitis B: Assessment and modification with current antiviral therapy. *J Hepatol*. 2015;62(4):956-67.

doi: 10.1016/j.jhep.2015.01.002

58. Ren H, Huang Y. Effects of pegylated interferon-α based therapies on functional cure and the risk of hepatocellular carcinoma development in patients with chronic hepatitis B. *J Viral Hepat*. 2019;26:5-31.

doi: 10.1111/jvh.13150

59. Pawlotsky JM. New hepatitis C therapies: The toolbox, strategies, and challenges. *Gastroenterology*. 2014;146(5):1176-1192.

doi: 10.1053/j.gastro.2014.03.003

60. Kanwal F, Kramer J, Asch SM, Chayanupatkul M, Cao Y, El-Serag HB. Risk of hepatocellular cancer in HCV patients treated with direct-acting antiviral agents. *Gastroenterology*. 2017;153(4):996-1005.

doi: 10.1053/j.gastro.2017.06.012

61. Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: A meta-analysis of observational studies. *Ann Intern Med*. 2013;158(5_Part_1):329-337.

doi: 10.7326/0003-4819-158-5-201303050-00005

62. Reig M, Mariño Z, Perelló C, *et al.* Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. *J Hepatol*. 2016;65(4):719-726.

doi: 10.1016/j.jhep.2016.04.008

63. Cervello M, Montalto G. Cyclooxygenases in hepatocellular carcinoma. *World J Gastroenterol*. 2006;12(32):5113.

doi: 10.3748/wjg.v12.i32.5113

64. Bian W, Bian W, Li Q, Li Y. Aspirin in patients with viral hepatitis: Systematic review and meta-analysis of observational studies. *J Gastrointest Cancer*. 2024;55(2):638-651.

doi: 10.1007/s12029-024-01027-5

65. Zhou X, Zhang T, Sun Y, *et al.* Systematic review and meta-analysis: Association of aspirin with incidence of hepatocellular carcinoma. *Front Pharmacol*. 2022;13:764854.

doi: 10.3389/fphar.2022.764854

66. Mullen PJ, Yu R, Longo J, Archer MC, Penn LZ. The interplay between cell signalling and the mevalonate pathway in cancer. *Nat Rev Cancer*. 2016;16(11):718-731.

doi: 10.1038/nrc.2016.76

67. Simon TG, Duberg AS, Aleman S, *et al*. Lipophilic statins and risk for hepatocellular carcinoma and death in patients with chronic viral hepatitis: Results from a nationwide Swedish population. *Ann Intern Med*. 2019;171(5):318-327.

doi: 10.7326/M18-2753

68. Memmott RM, Mercado JR, Maier CR, Kawabata S, Fox SD, Dennis PA. Metformin prevents tobacco carcinogen-induced lung tumorigenesis. *Cancer Prev Res* (*Phila*). 2010;3(9):1066-1076.

doi: 10.1158/1940-6207.CAPR-10-0055

69. Zi F, Zi H, Li Y, He J, Shi Q, Cai Z. Metformin and cancer: An existing drug for cancer prevention and therapy. *Oncol Lett*. 2018;15(1):683-690.

doi: 10.3892/ol.2017.7412

70. Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK. Metformin in patients with type 2 diabetes and kidney disease: A systematic review. *JAMA*. 2014;312(24):2668-2675.

doi: 10.1001/jama.2014.15298

71. Zhao X, Wang M, Wen Z, *et al*. GLP-1 receptor agonists: Beyond their pancreatic effects. *Front Endocrinol*. 2021;12:721135.

doi: 10.3389/fendo.2021.721135

72. Wang L, Berger NA, Kaelber DC, Xu R. Association of GLP-1 receptor agonists and hepatocellular carcinoma incidence and hepatic decompensation in patients with type 2 diabetes. *Gastroenterology*. 2024;167(4):689-703.

doi: 10.1053/j.gastro.2024.04.029

73. Bica IC, Stoica RA, Salmen T, *et al*. The effects of sodium-glucose cotransporter 2-inhibitors on steatosis and fibrosis in patients with non-alcoholic fatty liver disease or steatohepatitis and type 2 diabetes: A systematic review of randomized controlled trials. *Medicina*. 2023;59(6):1136.

doi: 10.3390/medicina59061136

74. Barone M, Viggiani MT, Losurdo G, Principi M, Di Leo A. Systematic review: Renin-angiotensin system inhibitors in chemoprevention of hepatocellular carcinoma. *World J Gastroenterol*. 2019;25(20):2524.

doi: 10.3748/wjg.v25.i20.2524

75. Yi Z, Wang L, Tu X. Effect of vitamin D deficiency on liver cancer risk: A systematic review and meta-analysis. Asian *Pac J Cancer Prev*. 2021;22(4):991.

doi: 10.31557/APJCP.2021.22.4.991

76. Kunnumakkara AB, Hegde M, Parama D, *et al*. Role of turmeric and curcumin in prevention and treatment of chronic diseases: Lessons learned from clinical trials. *ACS Pharmacol Transl Sci*. 2023;6(4):447-518.

doi: 10.1021/acsptsci.2c00012

77. Halegoua-DeMarzio D, Navarro V, Ahmad J, *et al*. Liver injury associated with turmeric-A growing problem: Ten cases from the Drug-Induced Liver Injury Network [DILIN]. *Am J Med*. 2023;136(2):200-206.

doi: 10.1016/j.amjmed.2022.09.026

78. Ding Q, Li Z, Liu B, Ling L, Tian X, Zhang C. Propranolol prevents liver cirrhosis by inhibiting hepatic stellate cell activation mediated by the PDGFR/Akt pathway. *Hum Pathol*. 2018;76:37-46.

doi: 10.1016/j.humpath.2018.02.018