Journal of Hepatocellular Carcinoma

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REVIEW

Natural Bioactive Compounds Targeting the Wnt/β-Catenin Pathway for the Treatment of Hepatocellular Carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide, with limited treatment options and poor prognosis. The Wnt/β-catenin signaling pathway is a key regulator of cellular proliferation, differentiation, and stem cell maintenance, and is frequently dysregulated in HCC, contributing to tumor progression, metastasis, and drug resistance. Natural bioactive compounds (NBCs) have emerged as promising treatments due to their multi-targeted mechanisms, low toxicity, and ability to modulate key oncogenic pathways. This review examines the potential of NBCs to target the Wnt/β-catenin pathway in HCC. Compounds such as curcumin, emodin, gallic acid, and ginsenosides exhibit anti-tumor effects by inhibiting β-catenin nuclear translocation, inducing autophagy, suppressing angiogenesis, and modulating the tumor microenvironment. For example, curcumin inhibits HCC cell proliferation and invasion by downregulating lncRNA expression and EMT markers, thereby inactivating the Wnt/β-catenin signaling pathway. Additionally, alkaloids like tetrandrine and toosendanin reduce metastasis through pathway-specific inhibition and epigenetic modulation. These compounds demonstrate potential as standalone therapies, and also in combination with conventional treatments like sorafenib by enhancing the effectiveness and overcoming resistance. However, challenges such as limited bioavailability, stability, and the intricate interplay of the Wnt/β-catenin pathway with other signaling pathways highlights the need for advanced delivery systems and combination strategies. In conclusion, future research should prioritize clinical validation, precision medicine approaches, and exploration of the role of NBCs in cancer stem cell regulation. Collectively, NBCs targeting the Wnt/β-catenin pathway offer a novel, safer, and multi-faceted approach for improving HCC treatment outcomes, paving the way for their integration into standard therapeutic regimens.

Keywords: hepatocellular carcinoma, Wnt/β-catenin signaling, natural bioactive compounds, cancer therapeutics, pathway modulation

Introduction

Hepatocellular carcinoma (HCC) is the most prevalent primary liver malignancy, and ranks as the third leading cause of cancer-related death worldwide.[1] Despite advances in treatment methods, including surgical resection, liver transplantation, and targeted therapies, the prognosis of HCC is poor with a 5-year overall survival (OS) rate below 20%.[2,3] Current systemic treatments like sorafenib and lenvatinib have limited effectiveness and serious side effects.[4,5] This highlights the urgent need for novel therapeutic strategies.

The Wnt/β-catenin signaling pathway plays a crucial role in cell proliferation, differentiation, and stem cell maintenance.[6] Aberrant activation of this pathway occurs in approximately 30–40% of HCC cases, leading to enhanced tumor growth, metastasis, and drug resistance.[7] Dysregulation typically results from mutations in pathway components or altered expression of Wnt ligands and receptors.[8]

Natural bioactive compounds (NBCs) that are derived from plants, marine organisms, and microorganisms have emerged as promising therapeutic agents due to their diverse molecular targets and generally lower toxicity profiles.[9]

Received: 19 February 2025
Accepted: 11 July 2025
Published: 23 July 2025

These compounds exhibit various anti-cancer properties including anti-proliferative, pro-apoptotic, and anti-metastatic effects through affecting multiple signaling pathways.[10]

Given the critical role of Wnt/β-catenin signaling in HCC progression, and the therapeutic potential of NBCs, investigating bioactive molecules that target this pathway represents a promising strategy for HCC treatment. This review summarizes current knowledge of NBCs that modulate Wnt/β-catenin signaling in HCC, discussing their mechanisms of action and therapeutic potential.

An Overview of Wnt/β-Catenin Signaling

Wnt/β-Catenin Signaling in Normal Physiology and Malignancy

The Wnt/β-catenin signaling pathway plays a crucial role in normal physiology and in various diseases, including malignancies. In normal physiology, Wnt proteins act as growth factors that regulate cell proliferation, tissue patterning, and the maintenance of tissue architecture, especially through their effects on stem cells. The core mechanism of Wnt signaling involves the stabilization and nuclear translocation of β-catenin. In the absence of Wnt signals, β-catenin is targeted for degradation by a destruction complex composed of axin, the adenomatous polyposis coli (APC) tumor suppressor protein, and kinases like GSK3 and CK1. When Wnt proteins bind to their cell-surface receptors (Frizzled and LRP5/6), the destruction complex is inhibited, allowing β-catenin to accumulate and enter the nucleus, where it activates Wnt target gene expression through interaction with T-cell factor (TCF) transcription factors. Mutations in key components of the pathway, such as APC, β-catenin, and axin, are frequently observed in colorectal and other carcinomas, and Wnt pathway inhibitors like RNF43 and ZNRF3 contribute to tumorigenesis by increasing Wnt signaling.[7]

Dysregulation of Wnt/β-catenin signaling is associated with malignancies and other diseases. Activation of Wnt/β-catenin signaling (Wnt ligands binding to Frizzled receptors and LRP5/6 co-receptors) leads to inhibition of the β-catenin destruction complex (axin, APC, CK1α, GSK3β) and subsequent accumulation of β-catenin. This accumulated β-catenin translocates to the nucleus, where it activates genes regulating cell proliferation, survival, and invasion. In cancers, this pathway plays a crucial role in maintaining cancer stem cells, enabling epithelial-mesenchymal transition (EMT), and promoting tumor growth, chemoresistance, and metastasis. Therapeutic strategies targeting Wnt ligands, Frizzled receptors, and β-catenin, including natural products and small-molecule inhibitors, show promise for treatment of HCC.[8–12]

Wnt/β-Catenin Signaling in HCC

The Wnt/β-catenin signaling pathway plays a pivotal role in HCC by contributing to its development and progression. As a well-conserved and tightly regulated signaling cascade, Wnt/β-catenin signaling is crucial for liver homeostasis, tissue regeneration, and metabolic zonation. However, aberrant activation of this pathway is a key driver of hepatocarcinogenesis.

The canonical Wnt/β-catenin pathway is activated when Wnt ligands bind to Frizzled receptors and LRP5/6 co-receptors, resulting in the inactivation of the β-catenin destruction complex, which includes axin, APC, GSK3β, and CK1α. This allows β-catenin to accumulate in the cytoplasm and translocate to the nucleus, where it interacts with TCF/lymphoid enhancer factor (LEF) transcription factors to activate genes involved in cell proliferation and survival. In HCC, this pathway is frequently upregulated due to mutations in CTNNB1 (encoding β-catenin) or components of the degradation complex, such as AXIN1 and APC, leading to stabilization and nuclear accumulation of β-catenin. This dysregulation promotes tumorigenic processes, including cancer stem cell maintenance, drug resistance, tumor progression, and immune evasion.

The Wnt/β-catenin pathway is an attractive target for HCC treatment. Strategies under investigation include inhibitors that block β-catenin nuclear translocation or disrupt its interaction with transcriptional co-activators. However, the development of effective treatments is challenging due to the pathway's complexity and its interplay with other oncogenic signals. Further research is needed to refine these approaches and develop more precise treatments.

Overall, dysregulation of the Wnt/β-catenin pathway is a hallmark of HCC, contributing to tumor heterogeneity and a poor prognosis, and because of these characteristics it remains a key focus for development of new treatments for HCC.[13–17]

NBCs for HCC Treatment

Natural bioactive compounds (NBCs) are promising for the treatment of HCC because they can target key molecular pathways and have reduced adverse effects that are associated with conventional treatments.

Targeting the STAT3 Pathway

The STAT3 signaling pathway is pivotal in HCC progression by promoting tumor cell survival, proliferation, and metastasis. Bioactive compounds like terpenes, alkaloids, carotenoids, and phenols inhibit STAT3 activation. For example, curcumin prevents STAT3 phosphorylation, thereby reducing tumor growth and invasion.

Chemoprevention and Current Therapies

Conventional HCC treatments such as sorafenib and lenvatinib can have serious side effects and the development of drug resistance is not uncommon. Natural compounds like resveratrol and curcumin serve as potential chemo-preventive agents due to their anti-oxidant, anti-proliferative, and anti-inflammatory properties. These compounds modulate critical pathways, including JAK/STAT, Wnt/β-catenin, and vascular endothelial growth factor (VEGF) to inhibit cancer progression.

Immune Microenvironment Modulation

The HCC tumor microenvironment is characterized by immunosuppressive mechanisms that limit the effectiveness of immunotherapies. Natural compounds can improve the microenvironment by reducing the numbers of regulatory T-cells and tumor-associated macrophages, and thus enhance immune responses. For instance, icaritin decreases immunosuppressive factors and promotes T-cell activation, improving anti-tumor immunity.

Oxidative Stress and Signaling Pathways

Oxidative stress contributes significantly to HCC progression through pathways such as VEGF, MAPK, and mTOR. Anti-oxidant-rich bioactive compounds, like flavonoids and saponins, mitigate oxidative damage, reduce angiogenesis, and inhibit tumor growth. Compounds targeting angiogenesis, such as VEGF inhibitors, highlight the importance of addressing tumor vascularization.

NBCs hold potential as safer, multi-targeted therapies that may complement or replace existing HCC treatments, offering improved efficacy and reduced toxicity. Further research is needed to translate these findings into clinical applications.[18–21]

Targeting Wnt/β-Catenin Signaling with NBCs in HCC

NBCs targeting the Wnt/β-catenin signaling pathway in HCC can be broadly classified into 3 categories: direct Wnt/β-catenin inhibitors, autophagy modulators, and epigenetic modifiers. Direct inhibitors include compounds that specifically inactivate or modulate the Wnt/β-catenin pathway. Autophagy modulators, such as curcumin and certain alkaloids, impact autophagic processes relevant to tumor progression. Epigenetic modifiers are NBCs that influence epigenetic factors, including EZH2 and long non-coding RNAs (lncRNAs). These compounds are further categorized based on their chemical class. Figure 1 illustrates the mechanistic roles of all NBCs discussed below in the relevant pathways.

Flavonoids

Flavonoids are polyphenolic compounds found in a variety of fruits, vegetables, and plants, and have shown potential as anti-cancer agents. They act by modulating various cellular signaling pathways, including the Wnt/β-catenin pathway. Flavonoids can interfere with Wnt/β-catenin signaling by inhibiting key components like β-catenin, thereby suppressing

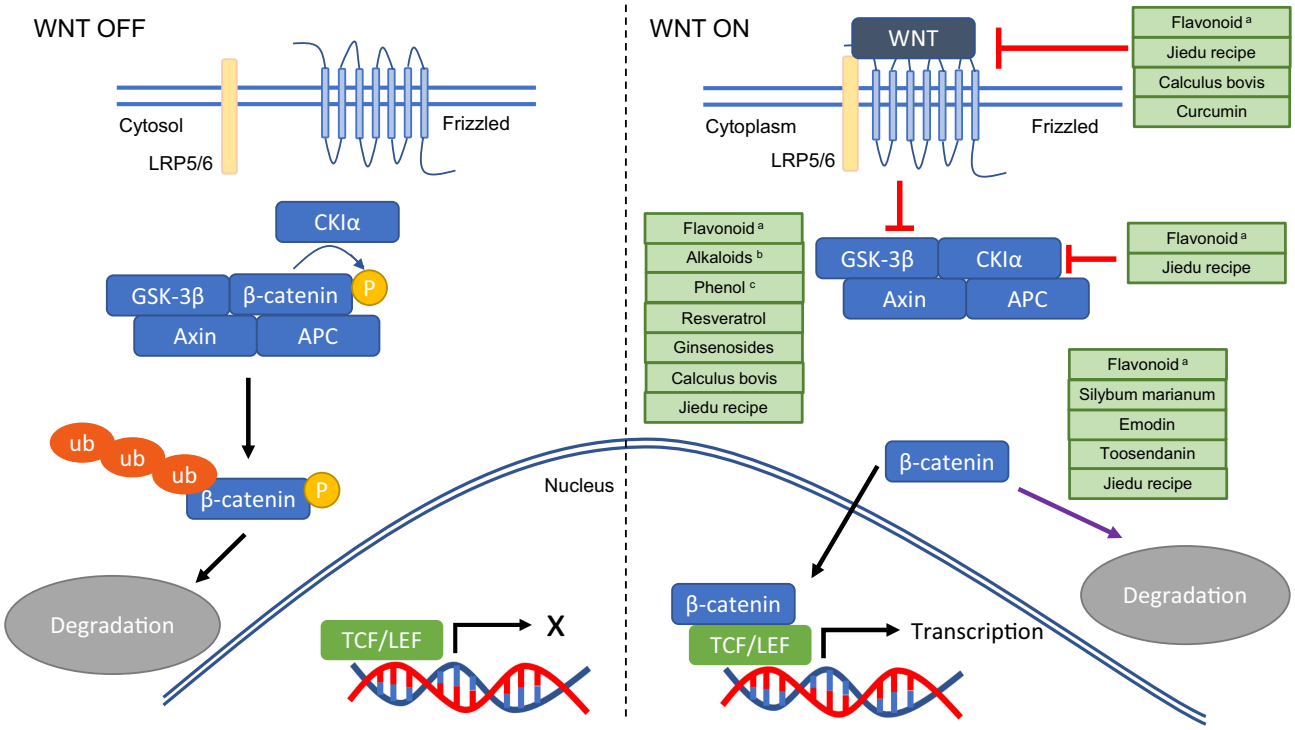

Figure 1 Illustrates the mechanistic roles of all NBCs discussed below in the relevant pathways.
Notes: [a]Fquercetin, Genistein, Apigenin, 6-CEPN. [b]Tetrandrine, Sempervirine, Berberine, Evodiamine. [c]Gallic acid.

cancer cell proliferation, inducing apoptosis, and preventing metastasis. Examples of flavonoids with such effects include quercetin, genistein, and apigenin.[22]

Among flavonoids, 6-C-(E-phenylethenyl)naringenin (6-CEPN) is a semi-natural derivative of naringenin (chemically synthesized by modifying the naturally occurring naringenin to enhance its bioactivity), a flavonoid commonly found in citrus fruits and other plants. The Wnt/β-catenin signaling pathway is suppressed by 6-CEPN through the degradation of β-catenin, inhibition of its nuclear translocation, and upregulation of GSK3β, which facilitates β-catenin phosphorylation and degradation. 6-CEPN attenuates cancer cell "stemness" by reducing cell viability, colony formation, and self-renewal capacity, as well as decreasing the expression of stemness-associated transcription factors such as SOX2, OCT4, and NANOG. Pretreatment with 6-CEPN sensitizes HCC cells to cisplatin and sorafenib, leading to increased apoptosis. Additionally, 6-CEPN has been shown to suppress EMT in vitro, reducing the migratory and invasive capabilities of HCC cells, and effectively inhibit tumor growth and metastasis in animal models. By targeting the Wnt/β-catenin pathway, 6-CEPN presents a promising treatment for HCC, offering potential for both reducing cancer stem cell -driven progression and enhancing drug efficacy.[23]

Curcumin

Curcumin is a bioactive compound derived from Curcuma longa, and has been shown to have potent anti-cancer activity in HCC by modulating the Wnt/β-catenin signaling pathway through multiple mechanisms. It inhibits HCC cell proliferation by inducing cell cycle arrest and apoptosis, achieved in part by downregulating the lncRNA lincROR, which in turn inactivates Wnt/β-catenin signaling. This regulatory mechanism is responsible for the tumor-suppressive effects of curcumin, making it a promising treatment for HCC with aberrant Wnt/β-catenin pathway activation.[24]

Curcumin also exerts its anti-cancer effects by downregulating the glypican-3 (GPC3)/Wnt/β-catenin signaling pathway. By reducing GPC3 expression, which normally promotes HCC cell proliferation and survival, curcumin leads to decreased cancer cell growth and enhanced apoptosis. In addition, autophagy amplifies the effects of curcumin;

blocking autophagy partially negates GPC3 downregulation, highlighting a potential synergy between curcumin and autophagy pathways.[25]

Additionally, the combination of curcumin and N-n-butyl haloperidol iodide enhances the inhibitory effects of curcumin on HCC proliferation and migration. This combination suppresses the Wnt/β-catenin pathway by downregulating EZH2 and its associated lncRNA H19, contributing to epigenetic modifications that reduce tumorigenic capabilities. These findings suggest that curcumin-based combination therapies may improve treatment efficacy in HCC.[26]

Curcumin also inhibits invasion and EMT in HCC cells via the TET1/Wnt/β-catenin signaling axis. By downregulating EMT markers and components of the Wnt/β-catenin pathway, curcumin reduces cancer cell migration and invasion and thus may help control metastasis and tumor progression.[27]

Alkaloids

Tetrandrine is a bisbenzylisoquinoline alkaloid derived from the Chinese herb Stephania tetrandra, and has been shown to have marked anti-cancer properties in HCC by targeting the Wnt/β-catenin signaling pathway. Tetrandrine inhibits HCC cell invasion, migration, and EMT through an autophagy-dependent mechanism. Tetrandrine suppresses Wnt/β-catenin activity by preventing β-catenin nuclear translocation, reducing Wnt3a levels, and modulating key downstream targets like CyclinD1 and c-Myc. Additionally, tetrandrine downregulates metastatic tumor antigen 1 (MTA1), a molecule closely linked to cancer aggressiveness and Wnt pathway activation, further inhibiting EMT and metastasis. Preclinical studies have shown that tetrandrine effectively reduces tumor growth and lung metastasis in vivo. The compound's dual action, inducing autophagy and inhibiting Wnt/β-catenin signaling, makes it a promising candidate for treating HCC.[28]

The alkaloid sempervirine, derived from Gelsemium elegans, exhibits anti-tumor properties in HCC by modulating the Wnt/β-catenin signaling pathway. Sempervirine inhibits HCC cell proliferation and promotes apoptosis, causing cell cycle arrest in the G1 phase. This action is associated with increased p53 expression and the downregulation of cyclin D1, cyclin B1, and CDK2. The mechanism involves the suppression of β-catenin nuclear translocation, and reduced expression of downstream oncogenes like c-Myc and survivin. Sempervirine also exhibits a synergistic effect with sorafenib, enhancing its anti-tumor efficacy in vivo by inhibiting β-catenin and inducing tumor cell apoptosis.[29]

Berberine is another alkaloid derived from several plant species, including Berberis species (such as Berberis vulgaris, commonly known as barberry), Coptis chinensis (golden thread), and Hydrastis canadensis (goldenseal). These plants have a long history of use in traditional medicine, particularly in Chinese and Ayurvedic systems, for their antimicrobial, anti-inflammatory, and hepatoprotective properties. It has a synergistic anti-cancer effect against HCC when combined with HMQ1611. This combination impairs cell proliferation and migration by regulating the Wnt/β-catenin signaling pathway. It induces G1 phase cell cycle arrest and downregulates key proteins like cyclin D1 and cyclin E. Additionally, the combination inhibits the nuclear translocation of β-catenin, decreases phosphorylation of LRP5/6, and suppresses the expression of MMPs and c-Myc, key mediators of cancer cell migration and invasion. The combination has been shown to markedly suppress tumor growth in xenograft models.[30]

Evodiamine is an alkaloid derived from Euodia rutaecarpa that exhibits potent anti-tumor effects against HCC through inhibition of angiogenesis mediated by the Wnt/β-catenin signaling pathway. It suppresses β-catenin-mediated transcriptional regulation of VEGFa, a key factor in angiogenesis, leading to decreased vascular formation in vivo and reduced tube formation in endothelial cell assays. In a subcutaneous H22 xenograft model, evodiamine treatment significantly reduced tumor volume and weight, decreased angiogenesis markers CD31 and CD34, and lowered serum levels of tumor markers such as α-fetoprotein (AFP) and tumor-specific growth factor (TSGF). Evodiamine also inhibits the viability, migration, and invasion of HCC cells in a dose- and time-dependent manner. Mechanistically, it reduces β-catenin and VEGFa levels while blocking the nuclear translocation of β-catenin, thereby impairing Wnt/β-catenin signaling. By targeting angiogenesis and tumor growth via this pathway, evodiamine holds promise as a therapeutic agent for HCC, offering the potential to inhibit tumor progression and metastasis while decreasing blood vessel formation.[31]

Resveratrol

Resveratrol is a natural polyphenol that has been shown to have anti-tumor activity against HCC by modulating exosome secretion and key signaling pathways. In HCC cells (Huh7), resveratrol reduces exosome secretion in a dose-dependent manner by downregulating Rab27a, leading to impaired proliferation, migration, and EMT. This reduction in exosome release alters their composition, notably increasing lncRNA SNHG29, which inhibits the nuclear translocation of β-catenin and blocks autophagy. The inhibition of exosome secretion by resveratrol suppresses HCC cell viability and EMT, with a concurrent upregulation of E-cadherin expression. These findings indicate the potential of resveratrol as a therapeutic agent for HCC, leveraging its ability to disrupt exosome-mediated signaling and modulate critical oncogenic pathways.[32]

Phenols

Gallic acid (GA) is a natural phenolic compound found in various plants that exhibits marked anti-tumor effects in HCC by targeting the Wnt/β-catenin signaling pathway through 2 distinct mechanisms: suppression of proliferation and metastasis, and induction of ferroptosis. GA inhibits HCC cell proliferation and metastasis by downregulating the lncRNA MALAT1, a critical regulator of the Wnt/β-catenin pathway. This results in reduced β-catenin expression, inhibition of its nuclear translocation, and decreased expression of downstream oncogenic targets such as cyclin D1 and VEGF. These effects have been demonstrated in vitro and in vivo, indicating the potential of GA as a chemo-preventive and therapeutic agent for HCC by disrupting the MALAT1-Wnt/β-catenin axis. GA also induces ferroptosis, a form of iron-dependent cell death, by inactivating the Wnt/β-catenin pathway. It downregulates key ferroptosis-related proteins, including SLC7A11 and GPX4, leading to increased reactive oxygen species (ROS) production and mitochondrial damage. This effect is attributed to GA's inhibition of β-catenin nuclear transport, which in turn diminishes β-catenin's involvement in promoting ferroptosis resistance. Activation of the Wnt/β-catenin pathway with lithium chloride (LiCl) was shown to attenuate GA-induced ferroptosis, confirming the pathway's central role in this process.[33,34]

Emodin

Emodin, a natural anthraquinone extracted from traditional Chinese medicinal plants of the Rheum species, exhibits anti-tumor effects in HCC by inhibiting cell proliferation, migration, and invasion. These effects are mediated by modulating the Wnt/β-catenin signaling pathway, and promoting autophagy. Emodin suppresses the proliferation of HepG2 cells in a dose- and time-dependent manner, induces cell cycle arrest at the S and G2/M phases, and promotes apoptosis. Emodin also reduces HCC cell migration and invasion by downregulating EMT markers, including N-cadherin, Snail, and β-catenin, while increasing E-cadherin expression. Importantly, emodin promotes autophagy, which facilitates the degradation of Snail and β-catenin, thereby inhibiting EMT. This effect is associated with the downregulation of the PI3K/AKT/mTOR and Wnt/β-catenin signaling pathways. Additionally, emodin reduces phosphorylation levels of PI3K, AKT, and mTOR while inhibiting β-catenin activity by modulating GSK3β, a key component of the Wnt/β-catenin pathway. As such, emodin has potential as a therapeutic agent for HCC, offering multi-targeted anti-cancer effects through the interplay of autophagy and signaling pathway modulation.[35]

Ginsenosides

20(S)-Ginsenoside Rh2 is a bioactive compound derived from ginseng that exhibits potent anti-tumor effects in HCC by targeting angiogenesis and the GPC3/Wnt/β-catenin signaling pathway. Rh2 has been shown to inhibit angiogenesis of human umbilical vein endothelial cells (HUVECs) stimulated by HepG2 cells by reducing cell viability, migration, and tube formation, effects mediated by the downregulation of pro-angiogenic factors such as VEGF and matrix metalloproteinase-2 (MMP-2). Additionally, it suppresses the GPC3/Wnt/β-catenin pathway by decreasing glypican-3 (GPC3) expression, limiting β-catenin nuclear translocation, and downregulating oncogenes such as c-Myc and cyclin D1. Notably, GPC3 silencing enhances the anti-tumor effects of Rh2. Rh2 also induces apoptosis and causes cell cycle arrest at the G0/G1 phase in HCC cells, contributing to its anti-proliferative activity. These findings suggest that Rh2 is

a promising treatment for HCC due to its dual mechanism of action, targeting angiogenesis and the Wnt/β-catenin pathway.[36]

Silybum Marianum

The active components of Silybum marianum (milk thistle), silymarin and silibinin, exhibit anti-cancer effects in HCC by targeting key signaling pathways including HGF/c-Met, Wnt/β-catenin, and PI3K/Akt/mTOR. These compounds reduce tumor growth and proliferation by downregulating the expression of the proliferation marker Ki-67 and inhibiting the activation of oncogenic pathways. Suppression of Wnt/β-catenin signaling decreases β-catenin levels and downstream oncogene expression, promoting apoptosis and limiting cancer progression. In addition to their anti-cancer effects, silymarin and silibinin provide anti-oxidant and hepatoprotective effects by reducing oxidative stress, enhancing anti-oxidant enzyme activity, lowering lipid peroxidation, and increasing hepatic glutathione content. Histopathological improvements have been observed after treatment with silymarin and silibinin, including restored liver architecture and reduced necrosis and cancer-related alterations. These findings suggest that the derivatives of Silybum marianum are promising therapeutic agents for HCC, offering a dual benefit of anti-tumor activity and liver protection.[37]

Calculus Bovis

Calculus bovis (CB) is a traditional Chinese medicine derived from dried bovine gallstones that has been shown to have therapeutic potential against HCC by modulating the Wnt/β-catenin signaling pathway and regulating the tumor microenvironment. CB inhibits the tumor-promoting M2 polarization of tumor-associated macrophages (TAMs) through Wnt/β-catenin signaling, thereby reducing the supportive environment for cancer cells and suppressing tumor growth and invasiveness.[38,39] Key active compounds in CB include oleanolic acid, ergosterol, and ursolic acid, and they exhibit activity against HCC by enhancing apoptosis, preventing tumor invasion, and regulating the proliferation of cancer stem cells and tumor cells.[40] Furthermore, CB induces ferroptosis in cancer cells, blocks pathways such as the SLC7A11-GSH -GPX4 axis, and influences cell cycle regulators and anti-apoptotic proteins to exert protective and anti-tumor effects.[40] Preclinical studies in animal models and in vitro systems demonstrated that CB reduces tumor size and impedes cell migration and invasion by modulating immune functions and apoptosis-related pathways.[38,39] The potential of CB as a complementary treatment for HCC is promising, with future research needed to assess its clinical efficacy and safety, as well as its potential use in combination with other therapies such as kinase inhibitors.[39,40]

Jiedu Recipe

Jiedu recipe (JR) is a traditional Chinese herbal formula composed of Cremastrae Pseudobulbus Pleiones Pseudobulbus (Shancigu), Actinidia valvata Dun (Maorenshen), Salvia chinensis Benth (Shijianchuan), and Galli Gigerii Endothelium Corneum (Jineijin).[41] It exhibits anti-cancer effects against HCC by inhibiting cancer stemness and blocking progression under hypoxic conditions via the Wnt/β-catenin signaling pathway. JR downregulates the expression of stemness-related transcription factors (NANOG, OCT-4, SOX-2) and EMT markers (vimentin, α-SMA), while upregulating E-cadherin expression. Furthermore, JR alleviates hypoxic stress in HCC cells by decreasing intracellular hypoxia levels, as evidenced by reduced expression of hypoxia-inducible factor-1α (HIF-1α) at both the protein and mRNA levels. In vitro studies demonstrated that JR suppresses HCC cell proliferation, migration, and invasion under hypoxic conditions. In vivo experiments using a nude mouse model confirmed the tumor-suppressive effects of JR, demonstrating reduced hypoxia and decreased expression of Wnt/β-catenin signaling components.[41] The role of the Wnt/β-catenin pathway in the mechanism of action of JR has been confirmed through studies utilizing pathway agonists (LiCl) and inhibitors (IWR-1-endo).[41]

Toosendanin

Toosendanin (TSN), a natural compound extracted from the bark of Melia toosendan and Melia azedarach (plants commonly used in traditional Chinese medicine), has demonstrated potent therapeutic potential for hepatocellular carcinoma (HCC). It acts as an agonist of the tumor suppressor gene WWOX, enhancing its tumor-suppressive functions. By upregulating WWOX, TSN suppresses key oncogenic pathways, including JAK2/STAT3 and Wnt/β-catenin, thereby

inhibiting cancer progression and metastasis. TSN reduces the phosphorylation and nuclear translocation of STAT3, a critical driver of tumor growth and invasion, by increasing SOCS3 expression, a negative regulator of the JAK2/STAT3 signaling pathway. Furthermore, TSN disrupts Wnt/β-catenin signaling by inhibiting upstream molecules like DVL2 and activating the β-catenin degradation complex (APC, AXIN1, CK1, GSK3β). This dual action promotes β-catenin degradation, preventing its accumulation and nuclear translocation, effectively halting cancer progression. In vitro study has shown that TSN exhibits anti-metastatic effects by reducing cell migration and invasion, as well as decreasing metastatic lung nodules in mouse models. These effects are accompanied by reduced expression of metastasis-related proteins, including MMP2, MMP9, and c-Myc. These findings position TSN as a promising therapeutic agent for targeting HCC by modulating critical signaling pathways and suppressing metastasis.[42]

Conclusion and Future Perspectives

NBCs targeting the Wnt/β-catenin signaling pathway offer a promising therapeutic avenue for HCC. The pathway's central role in HCC progression, along with its frequent dysregulation, makes it an attractive target for intervention. Compounds such as curcumin, emodin, GA, and ginsenosides have demonstrated significant anti-tumor effects through diverse mechanisms, including suppression of β-catenin nuclear translocation, inhibition of angiogenesis, induction of autophagy, and modulation of the tumor microenvironment. These compounds exhibit multi-targeted effects that inhibit cancer proliferation and metastasis, as well as enhancing sensitivity to existing therapies and improving immune responses.

Despite their potential, several challenges must be addressed before NBCs can be widely adopted in clinical practice. First, the bioavailability and stability of many natural compounds are limited, necessitating the development of improved delivery systems, such as nanoparticles or liposomal formulations. Second, the intricate crosstalk between the Wnt/β-catenin pathway and other oncogenic signaling pathways, such as JAK/STAT and PI3K/Akt, underscores the need for combination therapies that target multiple pathways simultaneously. Third, rigorous preclinical and clinical studies are essential to validate the safety, efficacy, and optimal dosing of these compounds in HCC patients.

Future research should focus on translating preclinical findings into clinical applications. The integration of advanced drug delivery systems, precision medicine approaches, and high-throughput screening methods can aid in identifying synergistic combinations of NBCs with conventional treatments like sorafenib or immune checkpoint inhibitors. Additionally, studies exploring the potential of NBCs in overcoming drug resistance and targeting cancer stem cells could pave the way for more effective and durable therapeutic strategies. Furthermore, the liver functional reserve is also important to assess the prognosis and recommend the treatment.[43]

In conclusion, NBCs represent a promising class of therapeutic agents for HCC, offering a safer and more holistic approach to targeting key oncogenic pathways. Continued exploration of their mechanisms, coupled with technological advancements and clinical validation, may establish these compounds as integral components of future HCC treatment regimens.

Data Sharing Statement

All data and information reviewed in this article are derived from previously published studies and are available within the cited references. No new data were generated or analyzed in this review.

Author Contributions

All authors made substantial contributions to the work reported, whether in study design, execution, data acquisition, analysis, or interpretation; have drafted, revised, or critically reviewed the article; have agreed on the journal to which the article will be submitted; have reviewed and approved all versions of the article prior to submission, during revision, and at the proofing stage; and agree to take full responsibility and be accountable for the contents of the article.

Funding

This work was supported by the [National Natural Science Foundation of China] under Grant [number 82372070, 82072037] and [National Key Research and Development Program of China] under Grant [number 2024YFC2417802].

Disclosure

The authors report no conflicts of interest in this work.

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