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Peroxisome Proliferator-Activated Receptor-Gamma as a therapeutic target for hepatocellular carcinoma: Experimental and Clinical scenario

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Abstract

Hepatocellular carcinoma (HCC) is the most common type of liver cancer worldwide. Viral hepatitis is a significant risk factor for HCC, although metabolic syndrome and diabetes are more frequently associated with the HCC. With increasing prevalence, the number of cases is expected to be more than one million annually by 2025. Therefore, there is an urgent need to establish the potential therapeutic targets to cure disease. Peroxisome-proliferator-activated receptor gamma (PPAR γ) is a ligand-activated transcription factor that plays a crucial role in the pathophysiology of HCC. Many of the synthetic agonists of PPAR γ were well explored to suppress HCC in experimental studies and clinical trials. The synthetic agonist has shown promising results by inducing cell cycle arrest and apoptosis in HCC cells and preventing the invasion and metastasis of HCC. However, some synthetic agonists also pose severe side effects in addition to their therapeutic efficacy. Thus natural PPAR γ agonist could be an alternative to exploit this potential target for HCC treatment. In this review, the regulatory role of PPAR γ in the pathogenesis of HCC is elucidated. Further, the experimental and clinical scenario of both synthetic and natural PPAR γ agonists against HCC is discussed. Most of the available literature advocates PPAR γ as a potential therapeutic target for the treatment of HCC.

Key Words: Anticancer; Hepatocellular carcinoma; Natural agonists; Peroxisome proliferator-activated receptor- γ ; Thiazolidinediones

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Core Tip: Hepatocellular carcinoma (HCC) is the most common type of liver cancer worldwide. Viral infections and metabolic syndrome are the major risk factors for HCC, and its incidence is expected to increase by >1 million individuals annually by 2025. The crucial role of the Peroxisome-proliferator-activated receptor gamma (PPAR γ) in HCC pathophysiology makes it a potential target for its treatment. Along with the synthetic agonists, the natural PPAR γ agonists provide alternative and safer options for HCC treatment; however, they need to be validated clinically. This review discusses the regulatory role of PPAR γ in HCC pathogenesis and experimental and clinical scenario of PPAR γ agonists in HCC treatment.

INTRODUCTION

Liver cancer is the sixth most common cause of cancer death worldwide, with a higher prevalence in men than women. Recently, hepatocellular carcinoma (HCC) incidence was expected to increase by more than one million individuals annually by 2025 [1]. Hepatocellular carcinoma (HCC), a primary subtype of liver cancer, primarily occurs in Asia and Africa due to the high prevalence of hepatitis B virus (HBV), hepatitis C virus (HCV), and diabetes [2]. These conditions are linked with the inflammatory response in the liver leading to the development of HCC. Furthermore, other conditions such as obesity, dietary mycotoxin exposure, and excessive alcohol consumption are also among the risk factors for the development of HCC. These factors lead to the development of cirrhosis in 70-80% of HCC patients. Liver transplantation is the best option for curing HCC now, but there is a limitation to the availability of donors [3]. During the last two decades, understanding and management of HCC have changed dramatically due to the extensive basic and clinical research, which may further help to reveal potential targets for the treatment of HCC. Sorafenib is the first-line defense therapy approved by the United States Food and Drug Administration (US-FDA) in the advanced stages of HCC. It is a type of multikinase inhibitor that shows tumor-suppressing activity *via* targeting vascular endothelial growth factor receptor (VEGFR), adenosine monophosphate-activated protein kinase (AMPK), and platelet-derived growth factor receptor (PDGFR) [4]. Apart from their therapeutic potential, sorafenib showed acquired resistance in HCC cells. The low response rate implies that patients sensitive to sorafenib during the treatment will develop resistance within six months. These negative impacts of approved drugs prompted many researchers to find novel drugs or targets to cure HCC [5].

Peroxisome proliferator-activated receptor gamma (PPAR γ) is a ligand-activated nuclear receptor activated by synthetic and natural agonists [6]. It is highly expressed in adipose tissue, where it plays a central role in regulating adipose tissue function. Many studies established the role of PPAR γ in the pathophysiology of HCC. Increasing *in vivo*

and *in vitro* pieces of evidence showed the inhibitory role of PPAR γ activation on tumor cell growth, migration, and invasion suggesting its therapeutic role in the growth regulation of HCC [7,8]. The anti-tumor effect of PPAR γ is fulfilled by various mechanisms, including the induction of cell cycle arrest and activation of genes/proteins involved in immune and inflammatory responses [9]. Previous reports revealed the mechanism behind the development of HCC and suggested the presence of PPAR γ in human HCC tissues, which showed a dose-dependent decrease in the cell growth of HCC cell lines [10]. Thus, molecules modulating PPAR γ signaling pathways will provide a novel solution for the effective treatment of HCC. This review focuses on the role of PPAR γ in the HCC pathophysiology and the experimental and clinical status of PPAR γ agonists in the treatment of HCC.

THE MOLECULAR ARRANGEMENT OF PPAR γ

The peroxisome-proliferator-activated receptors (PPARs) protein belongs super-family of nuclear hormone factors containing 48 members. PPARs were mainly recognized for their proficiency in promoting peroxisome proliferation in the liver, and their expression is mainly regulated in response to ligand binding [11]. Three isoforms of PPARs, namely PPAR α , PPAR γ , and PPAR δ , are elucidated to a large extent. Out of these isoforms, PPAR γ is highly expressed in adipose tissue, and it plays a vital role in regulating lipid homeostasis, energy balance, adipogenesis, and inflammation. Due to the presence of different promotor regions and 5' exons, PPAR γ has three distinct mRNAs (PPAR γ 1, PPAR γ 2, and PPAR γ 3). The translation products of PPAR γ 1 and PPAR γ 3 yield identical proteins; however, PPAR γ 2 resulted in the product with an additional N-terminal region [12]. PPAR γ 1 and PPAR γ 3 are biologically expressed in different tissues (hepatocytes, muscles, and endothelial cells), while PPAR γ 2 is only widely expressed in adipose tissue [9,13]. PPAR γ plays a significant role in maintaining metabolic alterations, inflammation, glucose homeostasis, cell cycle regulation, differentiation, and migration, making it a potential therapeutic target for treating metabolic disorders and cancers [14]. The structural arrangement of PPARs is similar to steroid and thyroid hormone receptors. Its ligand-binding cavity is 3 to 4 times higher

than the other nuclear receptors. They can be activated by various natural and synthetic agonists, such as essential fatty acids (EFA) [15,16]. The three-dimensional structure of PPAR γ consists of a canonical domain shared with other nuclear receptors, named A-E from N to C terminus (Figure 1). These domains include the amino-terminal AF-1 domain, a DNA-binding domain with two zinc finger motifs, and a ligand-binding domain (LBD or E/F domain) at C-terminus responsible for specific ligand binding at the peroxisome proliferator response elements (PPRE) [16,17]. After the interaction with specific ligands, LBD facilitates the heterodimerization of PPARs with retinoid X receptor (RXR), which subsequently binds with PPRE of the target gene. RXR is activated by the natural ligand 9-cis-retinoic acid receptor and synthetic retinoids receptors. However, in the absence of specific ligands, heterodimers bind with co-repressors, ultimately inhibiting the gene [12]. This complex subsequently recruits coactivation or co-repressors to regulate the expression of targets genes related to lipid glucose metabolisms and inflammation (Figure 1) [6].

ROLE OF PPAR γ IN HCC

PPAR γ plays a multifunctional role in many tissues and cell types such as adipocytes, pancreas, macrophages, liver, kidney, and skeletal muscle. It plays a regulatory role in adipocytes differentiation, lipid metabolism, and insulin sensitivity via downregulating leptin concentration [7]. Despite the low expressions in the healthy liver, PPAR γ plays a significant role in several hepatic conditions such as fatty liver, fibrosis, and HCC. Many *in vitro* and *in vivo* studies reported that natural and synthetic PPAR γ agonists inhibited tumor growth and cell migration in HCC [18]. The activation of PPAR γ inhibits cell growth by inducing G0/G1 cell cycle arrest in HCC cells. The cell cycle arrest was suggested to be associated with p21, p27, and p18 upregulation (Figure 2). Further, p27 upregulation downregulates Skp2 in HCC, an F-box protein component of the SCF ubiquitin-ligase complex. p27 was demonstrated to play a vital role in G0/G1 arrest instead of p21 [10,19]. The direct overexpression of PPAR γ in the hepatic cancerous cells also inhibited the cell growth; however, the cells were arrested in the G2/M phase instead of the G0/G1 phase after the PPAR γ agonist treatment. The G2/M

phase arrest in PPAR γ overexpression is attributed to activating Cdc25C phosphatase by Ser216 phosphorylation and preventing premature mitosis [20]. Compared to wild-type mice, another study on PPAR γ deficient mice showed increased hepatocarcinogenesis after treatment of diethylnitrosamine (DEN). GDF15 (Growth Differentiation Factor 15) was identified as a target gene of PPAR γ and induced by its activation. GDF 15 overexpression in many cancers was associated with an anti-tumorigenic response as it was suggested to reduce cancer cell viability and induce cell apoptosis. PPAR γ activation by agonist or direct overexpression induces apoptosis by intrinsic and extrinsic pathways [21]. The activation of the extrinsic apoptosis pathway by PPAR γ overexpression is attributed to the induction of tumor necrosis factor α (TNF α) and Fas, leading to the activation of downstream caspases (Figure 2). In the intrinsic pathway, PPAR γ overexpression stimulates Bax transcription and release into the cytosol, activating apoptotic protease activating factor 1 (APAF-1) and caspase-9 complex, which further triggers caspase 3 and 7 to induce apoptosis. [6,21] The anti-tumorigenic effect of PPAR γ in HCC is also suggested *via* modulation of the PI3K/Akt pathway [22]. PPAR γ activation attenuates p85 activation, which is essential for Akt induction, thus inhibiting PI3K/Akt signaling and inducing apoptosis [23].

Hepatic inflammation is crucial in the progression of HCC, and PPAR γ plays a central role in regulating inflammation. PPAR γ inhibits the inflammation by interfering with NF κ B and suppressing the production of proinflammatory cytokines (TNF α and IL-1 β). Activation of PPAR γ by specific ligands in T cell differentiation prompts an inflammatory response, thereby playing a significant role in the adaptive immune response. Thus, PPAR γ act as an important therapeutic target for regulating inflammatory markers (TNF α , IL-2, IL-1 β , and IL-6) against the progression of several diseases [7,16]. Hepatic stellate cells (HSC) activation and fibrogenic factor significantly contribute to the development of HCC (Figure 2). PPAR γ is highly expressed in the quiescent HSCs and has a role in their trans-differentiation. HSC activation and PPAR γ are inversely related as increased expression of PPAR γ inhibits HSC proliferation and induces apoptosis in activated HSCs [24]. Further, it also reduces the expressions of

α SMA and hydroxyproline to inhibit hepatic fibrosis. Hepatic injury induces microvascular complications in the liver, stimulating various sinusoidal cells like HSCs, liver sinusoidal endothelial cells, and kupffer cells. PPAR γ regulates the role of these cells in liver inflammation and fibrosis. The deactivation of HSCs by the PPAR γ agonists further reduces the ECM deposition and expressions patterns of MMP/TIMP. The expressions of MMP (9 and 13), TIMP, heparinase, and E-cadherin are associated with cancer cell migration and metastasis [25]. The expression patterns of these markers are directly linked to the PPAR γ activation. Reports also linked the PPAR γ activation with autophagy in hepatocellular carcinoma. Autophagy was suggested to be inhibited after autophagosome formation in the absence of PPAR γ resulting in increased LC3 protein expression and accumulation of p62 in the autophagosome [26,27]. Therefore, induction of autophagy in HCC is linked to the activation of PPAR γ in HCC. A recent study elucidated the role of PPAR γ Coactivator-1 α (PGC1 α) in suppressing HCC metastasis. The levels of PGC1 α were found downregulated in human HCC and were associated with poor prognosis, large tumor size, and vascular invasion [28]. However, PGC1 α overexpression in the HCC cells inhibited tumor cell migration and invasion. The suppression of metastasis by PGC1 α overexpression was suggested due to PPAR γ dependent down-regulation of pyruvate dehydrogenase kinase isozyme 1 and inhibition of aerobic glycolysis through Wnt/ β -catenin/PDK1 axis regulation [29].

Zinc finger protein 746 (ZNF746) is recognized as a Parkinson-interacting substrate (PARIS), acting as a transcriptional regulator of PPAR γ co-activator 1 alpha (PGC1 α) which further regulates the activity of PPAR γ and is involved in the onset of HCC. The elevated levels of insoluble parkin with PARIS accretion in the hepatic cells of diethylnitrosamine (DEN)-injected mice were observed with the downregulation of PGC1 α and NRF1. Moreover, Chang liver cells treated with hydrogen peroxide showed the PARIS accretion and alleviation of PGC1 α . Being the co-activator, PGC1 α is directly linked to PPAR γ regulation, further monitoring the oncogenic stresses promoting cancer development. Thus, the modulation of PPAR γ and its co-activators can be a promising therapeutic target for HCC [30]. In a clinical study, it was subsequently

observed that the expression of PGC1 α was negatively associated with tumor size and vascular influx. The increased expressions of PGC1 α could elevate the degree of oxidative phosphorylation, further slowing down the rate of metastasis and the Warburg effect of HCC cells [31]. Rapid proliferation is the prime feature of cancerous cells for which cells need to meet high energy demand through the aerobic glycolysis pathway rather than the pyruvate oxidation pathway. The canonical Wnt/ β -catenin signaling was also targeted to observe the expression of PDK1 in the PGC1 α knockdown model by employing two popular inhibitors of this signaling pathway (XAV-939 and ICG-001). The GSEA analysis indicated that these inhibitors alleviated the overexpression of extracellular lactate, suggesting the possible role of PGC1 α in the inhibition of aerobic glycolysis *via* Wnt/ β -catenin signaling. The dual-luciferase reporter assays showed that transcriptional actions of PPAR γ were significantly increased **in** HCCLM3 and MHCC97H cells with PGC1 α augmentation. These results advocate that the tumor-suppressive activity of PGC1 α depends on PPAR γ , which makes PPAR γ **a** key regulator of HCC [29,32]. One of the earlier reports also unveiled the role of PPAR γ in HCC **by** analyzing mRNA and protein expression in 20 patients with cirrhosis and chronic hepatitis. The results indicated a statistically pronounced drop in levels of PPAR γ in HCC compared to the conjoined liver tissue [33]. A report has confirmed that miR-130b aids cell aggressiveness by suppressing PPAR γ in human HCC [34]. Similarly, the evidence on the oncogenic role of miR-1468 in HCC *via* activating the PPAR γ /AKT pathway was also confirmed recently. The increased levels of miR-1468 elevated the malignant prognostic features and improved survival. Also, CITED2 and UPF1 were identified as the downstream targets for miR-1468, which regulates the PPAR γ /AKT pathway activation. The restoration of the expression of these targets partially abolished the effects of miR-1468, explaining the regulation *via* PPAR γ /AKT signaling [35].

EXPERIMENTAL AND CLINICAL SCENARIOS

Many studies explored the therapeutic effect of synthetic and natural PPAR γ agonists against HCC in preclinical and clinical trials. The activation of PPAR γ has

shown significant suppression of HCC progression and invasion. Several findings have identified PPAR γ as a target for tumour suppression, a mediator of apoptosis, a suppressor of carcinogenesis and metastasis *via* triggering intrinsic pathways, and mainly inhibiting the PI3K/AKT survival pathway [8,21,36]. The various synthetic and natural PPAR γ agonist used for HCC are given in Table 1.

SYNTHETIC PPAR γ AGONISTS IN HCC

PPAR- γ itself and its agonists have anti-cancer activities, such as growth inhibition, induction of apoptosis, and cell differentiation. Thiazolidinediones (TZD) is a class of synthetic PPAR γ agonists, and many compounds of this class were studied for their efficacy in experimental models and clinical trials. These compounds were used as a bio-regulatory remedial approach to target the communicative framework of HCC in patients with non-curative HCC [37]. The TZD was also found effective for glycaemic control and the likelihood of HCC and hepatic manifestations in diabetic patients with chronic hepatitis B (CHB). Out of 28,999 patients with CHB, 3963 patients developed HCC at a median follow-up of 7.1 years, while 1153 patients were administered with TZD during the follow-ups. The findings showed the co-relation of TZD use with lowering the risk of poor hepatic manifestations in diabetic patients with CHB [38]. A population-based case-control study performed on 23,580 diabetic patients demonstrated the negative relation between the risk of HCC and the use of TZDs. There is a time-dependent effect of TZD use on the risk of hepatocellular carcinoma. Longer the duration of TZDs use, the lower the risk of HCC [39,40,41]. Many other reports also suggested that the administration of PPAR γ agonists ameliorates several types of cancers, *viz.* colorectal cancer, bladder cancer, lung cancer, and liver cancer. The effects were more substantial on higher cumulative dosages with longer durations [42].

Pioglitazone

Pioglitazone (PGZ), a PPAR γ ligand, works by improving the insulin sensitivity of tissues and is known to exhibit anti-cancerous activity. It selectively stimulates PPAR γ *via* modulating transcriptional alterations of genes involved in glucose metabolism and insulin resistance and further decreasing the gluconeogenesis and

levels of glycated hemoglobin in the bloodstream [43]. PGZ treatment inhibited fibrosis progression and HCC development and reduced the tumor size in DENA-induced rats (at 3 mg/kg dose) and mice (at 10 mg/kg dose). PGZ is suggested to exhibit a protective effect by reducing the MAPK and upregulating adiponectin levels, resulting in the activation of the hepatoprotective AMPK pathway [44].

The anti-cancer activity of PGZ was attributed to the pathological receptors for advanced glycation end products (RAGE). HCC tissues from 75 subjects demonstrated a profound expression of RAGE in HCC tissues which was closely linked with the pathological staging and lymph-vascular space influx. However, PGZ treatment suppressed the cellular proliferation, ameliorated apoptosis, and cell cycle arrest, which further elevated the PPAR γ expression and alleviated RAGE, NF κ B, HMGB1, p38MAPK Ki-67, MMP-2, and CyclinD1 expressions. The results demonstrated that PGZ as a PPAR γ agonist possibly slows down the growth and invasion of HCC cells by blocking the RAGE signaling [45]. Another prospective study confirmed the effect of PGZ on HCC by investigating 85 patients with HCC and hepatitis C virus infection to investigate recurrence-free survival. The spline-model analysis showed the lessened risk of HCC recurrence associated with the increased body weight and body mass index ≥ 23 . Pioglitazone was also observed to alleviate insulin resistance and serum adiponectin levels [46]. A lifetime Markov model was employed among the population of Thailand to study the life expectancy, quality-adjusted life years, lifetime costs, and the incremental cost-effectiveness ratios in HCC patients. The weight reduction program with the administration of PGZ demonstrated that PGZ could lessen the number of HCC cases [47]. These therapeutic potentials are backed up with various limitations too. Unlike the beneficiary effects, pioglitazone also showed adverse effects like body weight gain, peripheral edema, bone loss and heart failure. Additionally, the risk of bladder cancer significantly limits the use of this agonist in the medical field. [48]

Rosiglitazone

Rosiglitazone is a member of the thiazolidinediones (TZDs) class of insulin-sensitizing PPAR- γ agonists. An inhibitory effect of PPAR γ was reported on the

invasive and metastatic potential of HCC *in vitro* (MHCC97L and BEL-7404 cell lines) and *in vivo* (orthotopic HCC mouse model). A pronounced expression of PPAR γ was demonstrated in HCC cell lines treated with Ad-PPAR γ (Adenovirus expressing mouse PPAR γ 1), rosiglitazone (50 μ M), or Ad-PPAR γ plus rosiglitazone. The induction of PPAR γ markedly repressed HCC cell migration, invasiveness, levels of pro-metastatic genes (MMP9, MMP13, HPSE), and hepatocyte growth factor (HGF). However, elevated the levels of cell adhesion genes (E-cadherin and SYP), extracellular matrix regulator tissue inhibitors of metalloproteinase (TIMP) 3, and tumor suppressor gene retinoblastoma 1. Additionally, the direct transcriptional regulation of the genes TIMP3, MMP9, MMP13, and HPSE regulating PPAR γ levels was also validated by ChIP-PCR [25]. Bcl-2 is a well-known family of anti-apoptotic proteins regulating endogenous apoptotic pathways and are highly expressed in carcinomas. (-)-gossypol ((-)-G) is the (-) enantiomer of gossypol that acts as a small molecule to induce apoptosis in several types of cancers *via* inhibiting Bcl-2 proteins. In a study, rosiglitazone was employed to sensitize (-)-G to induce apoptosis at different concentrations, viz. .1, 1, 10, 100 μ M. The (-)-G induced Mcl-1 (Myeloid cell leukemia-1) stability was the prime concern for its apoptotic activity. However, rosiglitazone attenuated this stability *via* JNK-phosphorylation, further repressing the cancer growth. These results suggest that rosiglitazone can reduce cancer growth and sensitize the other apoptotic factors for performing a similar activity. The study also provides insights into the novel cancer therapeutic activity of BH3 mimetics in the case of carcinomas based on the combination of PPAR γ agonists and BH3 mimetics [49]. Rosiglitazone (80 μ M) was also observed to inhibit HCC cell growth by restricting the oncogenic activity of septin 2 (SEPT2) [50].

A long-term clinical trial was conducted in which 53 patients underwent liver biopsies and were further treated with rosiglitazone (8 mg/day) for the next two years. Forty-four patients fulfilled the criteria of the extension period and underwent another biopsy. During the extension phase, serum insulin and ALT (Alanine aminotransferase) levels were decreased by 26 % and 24 %, respectively. The NASH activity, ballooning,

and fibrotic stage decreased but not on a significant scale. The treatment was carried forward for another two years, but no significant results were obtained, showing that rosiglitazone does attenuate the insulin sensitivity and transaminase levels but might not significantly improve the other histopathological parameters. However, additional targets were suggested to be explored [51]. However, there is increasing evidence of bone fractures in females medicated with rosiglitazone after menopause, limiting its use. In September 2010, US Food and Drug Administration (FDA) restricted the use of rosiglitazone on the bases of meta-analyses of mostly short-term randomized controlled trials, which showed evidence of myocardial infection (MI) risk. However, these restrictions were removed in 2013 based on other large clinical trials by Duke Clinical Research Institute, which showed no complications regarding heart failure [52].

Telmisartan

Telmisartan (TEL) is an angiotensin II receptor blocker with a high affinity for the angiotensin II receptor type 1, whose impromptu link with HCC has been discovered; however, the underlying mechanism is not very clear. TEL shows basal resemblance with a well-known PPAR γ agonist, pioglitazone. TEL (at concentrations of 10, 50, or 100 μ M) inhibits the proliferation and the G0 to G1 cell cycle transition leading to G0/G1 cell cycle arrest in hepatic cancer cells (HLF, HLE, HuH-7, PLC/PRF/5, and HepG2) in a dose-dependent manner. The cell cycle arrest was accompanied by reduced cell cycle-related proteins, including cyclin D1 and cyclin E. Further TEL was suggested to increase the activity of AMPK and inhibit the mTOR pathway [53]. Another study used the diethylnitrosamine (DENA) induced HCC mice model to evaluate the effects of TEL (15 mg/kg), Sorafenib SRF (30 mg/kg), and a combination of these two agonists. The treatment downregulated the mRNA expressions of NF- κ BP65, AFP, TNF α , and TGF β 1 resulting in the reversion of malignant anomalies and suppression of ERK1/2 activation. SRF and TEL showed anti-proliferative, anti-metastatic, and anti-angiogenic effects by improving the expressions of hepatic cyclin D1, MMP-2, and VEGF. However, only TEL has exhibited agonistic activity for PPAR γ receptors, as indicated by the elevated PPAR γ DNA binding activity, mRNA expressions of CD36, HO-1, and

enhanced hepatic anti-oxidant capacity. Moreover, TEL and SRF both ameliorated phosphorylation-induced activation of TAK1 (TGF-beta-activated kinase 1) and advocated that TAK1 might act as the core mediator for the interaction between ERK1/2 and NF- κ B. It was also observed that TEL exerts its anti-cancerous action by modulating the ERK1/2, TAK1, and NF- κ B signaling axis from the perspective of its PPAR γ agonistic activity. Thus, TEL could prove to be an encouraging PPAR γ agonist for further clinical studies in the context of HCC treatment [54]. Despite these potentials, it showed adverse effects, including headaches, dizziness, fatigue, upper respiratory tract or stomach-related infections, sinusitis, nonspecific pain, and diarrhea [55].

Troglitazone

It is a member of the thiazolidinediones class of drugs and acts as a PPAR γ agonist. The anti-proliferative and anti-tumorigenic effects of troglitazone (TGZ) were studied in the BEL-7402 HCC cell line at 5, 10, and 25 μ M concentrations. TGZ induced cell death in a concentration-dependent manner resulting in the increased presence of the fragmented DNA and TUNEL positive cells. TGZ enhanced the cell cycle arrest at G0/G1 phase and caspase activities (caspase 3, 6, 7, and 9), indicating the elevated cell apoptosis [56]. In another study, the HepG2 cell line treated with TGZ showed significant growth inhibition in a dose-dependent manner. TUNEL assay and immunohistochemistry showed apoptosis induction and elevated expressions of apoptotic proteins like caspase 3 and survivin [57]. The PPAR γ was functionally expressed in hepatic cancer cell lines (Hep G2, HuH-7, KYN-1, and KYN-2) with troglitazone treatment. This was followed by the profound inhibition of cellular proliferation, DNA synthesis, cell cycle growth, and α -fetoprotein levels [58]. Similar results have also been deduced by other groups that used many other HCC cell lines like PLC/PRF/5, HuH-7 [59], HLF, HAK-1A, HAK-1B, and HAK-5 with TGZ [10,19]. The reduction in cell proliferation and increased apoptosis in most of the studies altogether advocated the usefulness of TGZ for chemoprevention in HCC. Some recent studies showed the hepatotoxic role of TGZ in diabetic patients. There is a significant elevation in liver enzymes level (ALT and AST) in 1.9 % of patients with diabetes treated with

TGZ for 24 to 48 wk. Furthermore, the cost of TGZ is much higher than that of other oral anti-hyperglycemic agents or insulin, which also limits the use of TGZ [60].

Saroglitazar

Saroglitazar is a first-class drug that acts as a dual PPAR α / γ agonist. It is indicated for enhanced diabetic dyslipidemia, inflammation, steatosis, ballooning, and fibrosis progression. The conjoined agonism of this drug has a favorable impact on insulin resistance and lipid profile. A report suggested the amelioration of high-fat diet-induced aberrations by saroglitazar treatment. The improvements were observed in hepatic lobular inflammation, hepatocellular ballooning, steatosis, and fibrosis. The effect of saroglitazar was found more pronounced compared to pioglitazone. The transcriptomic analysis revealed the elevated expressions of PPAR γ in hepatic tissue with the anti-inflammatory effects of saroglitazar treatment [61]. Similarly, saroglitazar improved liver function parameters, degenerative changes, glucose and insulin levels, and lipid profile in high-fat emulsion plus LPS treated rats. The positive effects on serum leptin, TNF α , and adiponectin levels were also observed. The multiple protective roles of PPAR α / γ agonists in liver disorders advocate the use of saroglitazar in managing liver cancer [62].

In a prospective observational study, 30 diabetic patients with liver fibrosis were enrolled and treated with 4 mg saroglitazar daily for six months. A profound improvement in glycaemic index, liver stiffness, and serum TG levels of the patients was observed with no significant adverse side effects [63]. Another study conducted on 90 NAFLD patients who underwent liver biopsies, fibrosis scores, and other non-invasive parameters concluded that treatment of saroglitazar had significantly improved the serum biomarker levels and fibrosis score in the patients. The study concluded the reversal effect of saroglitazar on fibrosis and advocated its use in treating HCC [64]. However, the most common adverse events associated with saroglitazar included asthenia, gastritis, chest discomfort, peripheral edema, dizziness, and tremors [65].

NATURAL PPAR γ AGONISTS IN HCC

Natural PPAR γ agonists were reported to have many beneficial properties, including antioxidant, anti-inflammatory, anti-fibrotic, and anti-tumor. In addition to therapeutic effects, the synthetic drugs manifested many adverse effects due to full PPAR- γ activation. Therefore, researchers are exploring potential natural PPAR γ modulators with high specificity in terms of their binding at the active site and improving drug safety. The PPAR γ activating effect of natural products is recognized as having great potential in developing anticancer therapy. There are many reports on the natural PPAR γ agonist against HCC in various experimental models.

Cannabinoids

The hemp plant *Cannabis sativa* L. produces approximately 60 unique compounds known as cannabinoids, of which Δ 9-tetrahydrocannabinol (THC) is the most important owing to its high potency and abundance in cannabis. Various studies reporting the fair safety profile of cannabinoids, in accord with its probable anti-proliferative activity on cancerous cells, may set the basis for future trials to evaluate the potential anti-tumoral activity of cannabinoids. Vara *et al* (2013) reported that cannabinoids THC and JWH-015 increased the intracellular mRNA and protein levels of PPAR γ in HCC cells, and inhibition of PPAR γ decreased the cannabinoid-induced cell death and apoptosis. Further, increased PPAR γ levels were correlated with the endoplasmic reticulum stress and autophagy in HCC cells suggesting the anti-proliferative effect of cannabinoids through PPAR γ -dependent pathways [66]. The anti-tumoral activity of THC was evaluated in patients who had failed standard therapy norms. *In vitro* studies showed the suppression of tumor cells proliferation, and Ki67 immunostaining exhibited a reduced number of tumor cells [67]. THC was suggested to induce transcriptional modulation of the PPAR γ pathway, and the activation is much more potent by cannabinoid acids than its decarboxylated products. Thus, the study revealed a correlation between the cannabinoids as a PPAR γ agonist [68]. *Cannabis* contains some psychoactive agents that increase sociability and exert the euphoric effects. Repeated use of *cannabis* has been linked to short-term and long-term side effects, including respiratory and cardiovascular disorders, cognitive alterations, psychosis,

schizophrenia, and mood disorders [69]. One of the recent studies highlighted the side effects of using a common preparation from *Cannabis sativa* named *marijuana*. This study gave the putative association of the use of *cannabis* with a higher risk of gingival and periodontal diseases, oral infection, and cancer of the oral cavity [70]. Given the growing popularity of cannabinoid-based drugs for recreational and medical purposes and their potentially harmful effects, there is a need for further investigation in this field.

Capsaicin

Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is a vital constituent of chili peppers belonging to the family of Capsicums. These phytoconstituents are known to possess anti-inflammatory and chemo-preventive. They have been shown to counter various compounds' mutagenic properties and exert anti-cancer properties on the breast, colon, prostate, and hepatic cancer. The DENA-induced models of HCC in rats and hepatic stellate cell lines were used to study the effect of capsaicin. Capsaicin was observed to inhibit hepatic injury, NF κ B activation, and collagen deposition. It has also ameliorated the levels of α -SMA, collagen type I, MMP-2, TGF- β 1, and TNF- α . Further, the TGF- β 1 expression and the phosphorylation of Smad2/3 were also inhibited through induction of PPAR γ expression. The findings showed that CPS attenuates hepatic fibrosis *via* activating PPAR γ expressions [71]. In addition, the limitations of this natural PPAR γ agonist cannot be left unnoticed. Capsaicin is a well-known irritant responsible for producing a painful, burning sensation when applied to the skin. Exposure to the eyes is painful and causes tearing, conjunctivitis, and blepharospasm [72]. Capsaicin is also a tussive agent, and inhaled capsaicin can be used to induce cough under experimental conditions. In humans, inhaled capsaicin induced a cough response immediately upon administration [73, 74]. Interestingly, there is evidence that topical capsaicin can exacerbate ACE inhibitor-induced cough. A patient taking an ACE inhibitor for several years with no complaint of coughing reported coughing associated with applying a 0.075% capsaicin cream [75]. Additionally, oral administration of the ACE inhibitor captopril was found to cause a shift in the dose-response curve of inhaled capsaicin-induced cough in a trial with healthy adults [76].

Curcumin

Curcumin is a polyphenol compound present in the *Curcuma longa* and is well known for its multiple therapeutic effects. One of our studies reported the effect of curcumin and piperine in DENA-induced HCC in rats. Curcumin prevented the HCC progression by improving hepatic pathology, apoptosis induction, and inhibiting cell proliferation. However, the synergistic effect on HCC suppression was observed in the curcumin and piperine combination [77]. Similarly, another study also reported the inhibition of cell proliferation, tumor growth, and apoptosis induction by curcumin treatment in HCC. The effect was suggested to decrease the VEGF expression and PI3K/AKT signaling [78]. A study on transgenic mice (expressing double HBV oncoproteins; HBx and pre-S2 in the liver) model of HBV-related hepatocellular carcinoma reported the protective effects of phytosomal curcumin *via* targeting PPAR γ as a key regulator. Curcumin decreased the HCC formation and reduced the tumor size. Moreover, considerably more potent effects were observed on activation of PPAR γ and inhibition of NF κ B. The report suggested that curcumin plays the role of an agonist for PPAR γ , upregulating the genes involved in lipid metabolism, anti-cell proliferation, and anti-inflammation. Further, PPAR γ activation regulated the suppression of NF κ B and subsequent pro-inflammatory cytokines. In addition, curcumin also suggested the act of repressing mTOR [79]. Recently, the antitumor effect of curcumin in HCC was suggested due to the involvement of miR-21 targeting TIMP3 and inhibition of the TGF- β 1/smad3 signaling pathway. The inhibition of TGF- β 1/smad3 signaling by curcumin was reported to be linked with the activation of the PPAR γ gene [80, 81]. It was further suggested to suppress the cell proliferation through long non-coding RNAs (lincROR) downregulation and inhibition of Wnt/ β -catenin signaling [82]. The major disadvantage of this medication is the usage of high doses, which ultimately leads to liver injury in humans and experimental animals. A study showed that curcumin supplementation with paracetamol at the dose of 50 and 100 mg/kg/day in experimental rabbits showed elevation in liver injury markers (AST, ALT, ALP, total protein, and albumin level) in plasma. Furthermore, levels of red blood cells and platelets were raised [83]. Also, the

poor bioavailability of curcumin leads to its combined usage with other drugs like piperine, which is reported to cause adverse drug reactions [84].

Hesperidin

Hesperidin is a flavanone glycoside found in the rind of citrus fruits like oranges, lemon, *etc.* It possesses several pharmacological activities, including antioxidant, anti-inflammatory, and anti-cancerous. The chemo-preventive efficacy of hesperidin was evaluated in DENA-induced HCC in rats. The hesperidin significantly reduced hepatic serological and tumor biomarkers along with TNF α . Further, it has also reduced the hepatic degenerative changes, oxidative stress, collagen deposition, TGF β 1, and NF κ B expressions. However, up-regulated expressions of Nrf2, HO-1 and PPAR γ suggested the effect of hesperidin *via* suppressing TGF β signaling and subsequently activating PPAR γ [85]. Another study investigated the efficacy of hesperidin *via* PI3K/Akt pathway as a probable mechanism for curing HCC. The treatment of hesperidin elevated the protein levels of PI3K, AKT and CDK-2 and ameliorated the HCC progression [86]. In addition, hesperidin was also reported to alter the Wnt3a/ β -catenin signaling in preventing HCC [87]. There are minimal reports on the bioavailability and solubility of hesperidin. Ameer *et al* reported that hesperidin is absorbed across the gastrointestinal tract on oral administration, but cumulative recovery indicates low bioavailability. The factors which limit the bioavailability of hesperidin are poor water solubility and its precipitation in an acidic environment [88].

Hispidulin

Hispidulin, a phenolic flavonoid, exhibits anticancer activity against several types of cancers. The effect of hispidulin on HCC was studied in tumor cell lines (SMMC7721 and Bel7402) and mouse tumor xenograft models. Hispidulin activates caspase 3, triggers apoptosis, and inhibits cell migration *via* PPAR γ activation, further linked to escalated phosphorylation of AMPK, ERK, and JNK *in vitro*. Specifically, GW9662 (a PPAR γ inhibitor), compound C (an AMPK inhibitor), and PD98059 (a MEK inhibitor) negated the protective effects of hispidulin on PPAR γ signaling. However, no pronounced changes in PPAR γ levels were noted with pre-treatment of SP6000125 (a

JNK inhibitor) *in vitro*, while it attenuated the anticancer activity of hispidulin. The suppression of Bel7402 xenograft tumor growth was successfully achieved by hispidulin *via* PPAR γ activation, indicating the cardinal role of PPAR γ signaling in HCC cell growth [89]. Recently, Lv *et al* (2020) suggested that induction ROS-mediated apoptosis through activation of the ER stress pathway is also responsible for the anticancer effect of Hispidulin [90]. Some shreds of evidence link hispidulin to its limited large-scale preparation. Studies showed the lack of a single-dose design of hispidulin, which further limits the bioavailability [91,92].

Isoflavones

Isoflavones are the group of some potential phytochemicals, a type of naturally occurring isoflavonoids. Studies have shown the anticancer effects of different isoflavones in the case of HCC [93]. A combination of two well-known isoflavones, Biochanin A and SB590885, was evaluated for anticancer activities in HCC. The combination showed synergistic inhibition of cell growth and induced cell cycle arrest and apoptosis *in vitro*. The inhibition of cellular proliferation and tumor suppression was attributed to the aberration of ERK MAPK and the PI3K/AKT pathways. *In vivo*, a profound reduction in the size and volumes of HCC tumors was noted, indicating combination therapy of isoflavones as a potential lead for the management and treatment of advanced HCC [94]. The anti-tumorigenic and anti-proliferative role of genistein (GE) was also studied on HCC *in vitro*. The isoflavone suppressed the proliferation of Hepa 1-6 cells and caused apoptosis in a time-dependent and dose-dependent manner [95]. In another study, genistein treatment suppressed aerobic glycolysis and increased the apoptotic rate in the HCC cell lines. Additionally, GE exhibited an inhibitory effect on tumor progression and aerobic glycolysis. This may be identified as an effective treatment for advanced HCC [96]. Studies have reported the PPAR γ modulating effect of isoflavones and inhibition of the HCC through inhibition of PI3K/AKT pathways and aerobic glycolysis further validates the involvement of PPAR γ signaling. Clinical studies also suggested that the more the dietary intake of flavonoids, the lesser the risk of developing HCC. In the Japanese population, a

correlation between the isoflavone-rich diet and the risk of HCC was observed [97,98]. Despite the therapeutic potential, some contentious health issues are associated with their intake. Soy proteins rich in isoflavones showed unfavorable effects at a higher dose, including gastrointestinal upset, constipation, nausea, allergic reactions, and loss of appetite. In animals, the intake of isoflavone (genistein) was reported to impact the fertility and morphogenesis of ovaries. In addition, long-term use of soy extract may result in abnormal tissue growth in the uterus [99].

Oroxyloside

Oroxyloside (OAG), a flavonoid, was explored as a new dual agonist of PPAR γ / α , which acts as a potent cell proliferation inhibitor in HCC-based metabolic transition. It regulates the glycolipid metabolic enzymes (PPAR-dependent or independent), inhibits the breakdown of glucose, and promotes fatty acid oxidation, which generates acetyl-CoA for the TCA cycle and oxidative phosphorylation. The metabolic transition produced by OAG exhibits a profound generation of reactive oxygen species (ROS), leading to G1 cell cycle arrest and growth repression of HCC cells. OAG requires pyruvate dehydrogenase kinase 4 (PDK4) and β -Oxidation to inhibit the cell proliferation explaining its PPAR γ agonistic behavior. The report projected OAG as a new PPAR γ / α agonist drug candidate and an effective therapeutic approach for HCC based on metabolic reprogramming [100]. Although many bioactive flavones' sources are very well-known, the information on their bioavailability and their active forms *in vivo* are limited. In particular, most flavonoid agents' absorption, metabolism, and blood delivery are poorly understood. Due to limited literature, it is difficult to elucidate the whole molecular mechanism. Hence further studies are required to uncover their therapeutic potential against liver diseases.

Resveratrol

Resveratrol is a popular natural polyphenolic PPAR γ agonist, well-known for its anticancer properties, and has been recognized as the alternate mode in cancer treatment. A study revealed the effect of resveratrol against alcohol-aflatoxin B1-induced HCC. During the progression of HCC, a decline in the antioxidant markers was

effectively restored by resveratrol treatment. Resveratrol modulated the activity of the SIRT1 enzyme in HCC by negatively regulating the levels of NFκB, and a cross-talk between this PPARγ agonist and SIRT1 signaling was observed [101]. A nano-formulation of resveratrol using liposomes was developed to establish a specific drug delivery system for managing HCC. *In vitro* studies revealed the increased internalization and enhanced anticancer activity of liposomal formulation (RL5) compared to naïve resveratrol. A profound reduction in the liver injury markers, hepatocyte nodules, and degenerative changes in the liver was observed in the *in vivo* HCC model. The results implied the promising action of nano-formulation of resveratrol and its substantial activity **in controlling** the severity of HCC [102]. **Earlier, similar approaches were** briefly reviewed by Santos *et al* to study the pharmacokinetics of RS-loaded nanoparticles (RS-NPs) and study their effect on cancer tissue. A comprehensive analysis was carried out in various *in vivo* models, which revealed the markedly enhanced anticancer activity of RS-NPs in every [103]. **However, the poor bioavailability and rapid metabolism restricted the successful translation of resveratrol to clinical form. The *in vivo* efficacy of resveratrol is affected due to its low solubility and low bioavailability. Oral intake of 25 mg of resveratrol showed extremely low bioavailability; only a trace** amount of unmetabolized resveratrol was detected in plasma. The GI tract absorbs approximately 70 percent of resveratrol, but it is further metabolized by three distinct metabolic pathways leading to low bioavailability [104].

Miscellaneous

Avicularin (quercetin-3-α L arabinofuranoside), a glycoside related to quercetin, has been reported to reduce obesity, inflammation, and drug resistance [105,106]. It is also reported to induce cytotoxicity in cancerous cells by promoting intrinsic **apoptosis pathways**. One of the studies aimed to investigate the activity of avicularin in HCC by employing HuH-7 cell lines. Avicularin inhibited cell proliferation in a dose-dependent manner and markedly decreased the cell migration and invasiveness of the cancerous cells. The gene and protein expression studies revealed reduced levels of NFκB, COX-2,

and PPAR γ . Avicularin has been suggested to have the potential to modulate PPAR γ to induce anti-neoplastic activity in HCC [107].

Honokiol (C₁₈H₁₈O₂) is a bioactive, biphenolic phytoconstituent derived from the bark and leaves of *Magnolia Officinalis*. Honokiol exhibits various protective activities like anti-carcinogenic, anti-inflammatory, anti-angiogenic, anti-oxidative, and a repressive potency towards the malignant conversion of papillomas to carcinomas without any noticeable toxicity effects. A group of researchers employed a great blend of *in silico*, *in vitro*, and *in vivo* techniques to pinpoint and validate honokiol as a potent lead for being a PPAR γ agonist. The binding of honokiol into the ligand-binding pocket of PPAR γ was anticipated *via* various *in silico* techniques. The luciferase reporter assay confirmed this binding and advocated that honokiol could act as a partial PPAR γ agonist. Further, using 3T3-L1 and mouse embryonic cell lines, it was observed that honokiol stimulated basal glucose uptake but did not induce adipogenesis. However, the oral administration of honokiol resulted in reduced hyperglycemia and weight gain [108]. Various studies suggest that honokiol acts as an RXR agonist forming RXR dimers and activating PPAR γ /RXR heterodimers. Additionally, it also potentiates the activation of PPAR γ /RXR heterodimers induced by rosiglitazone [109,110,111]. Also, no peer-reviewed papers proving the abuse, misuse, or dependence on or addiction to avicularin and honokiol have been retrieved yet.

Chrysin is a dihydroxyflavone belonging to the family of flavonoids. A study revealed that chrysin reduced cell viability and promoted apoptosis in all the cell lines *via* inhibiting the Skp2 (S-phase kinase-associated protein-2) and LRP6 (low-density lipoprotein receptor-related protein 6) protein expressions. However, reduced MMP2, MMP9, and fibronectin levels were observed [112]. Despite these interesting bioactivities, the clinical applications of chrysin have been constrained by its hydrophobicity, poor bioavailability, and degradation at alkaline pH [113]. Similarly, quercetin (QE) is a classic flavonoid and a yellow crystalline pigment present in plants, used as a food supplement to reduce allergic responses or boost immunity. It has been known to inhibit the development of various types of cancer hepatic conditions [114,115]. QE was suggested to

effectively suppress HCC due to its close interaction with the STAT3 pathway ^[116,117]. It has inhibited the cell proliferation, cell cycle regulation, and invasiveness of the cancer cells by promoting the autophagy of HCC ^[118]. However, the bioavailability of quercetin is very low due to its poor aqueous solubility and instability, challenging its therapeutic application in the pharma sector ^[119].

CONTRADICTIONARY ROLE OF PPAR γ

The cancerous tissues display metabolic and thermodynamic aberrations with dysregulated cellular growth. Although the role of PPAR γ and its agonists in HCC and other cancers have been extensively studied, as discussed above, several conflicting reports exist concerning the PPAR γ expression in cancers. It is **unclear** whether PPAR γ induction promotes or suppresses tumor growth and viability. In the case of several cancers, PPAR γ **mainly** exhibits the down-regulated expressions while activating several other pathways like the canonical Wnt/beta-catenin pathway, PI3K-AKT pathway, STAT3 pathway, *etc.* ^[82,87,118]. The activation of Wnt/ β -catenin signaling leads to the up-regulated pyruvate dehydrogenase kinase-1 (PDK1), which leads to aerobic glycolysis and mitochondrial stress ^[29]. A recent report by Galbraith *et al* revealed that the activation of PPAR γ , in turn, induced AKT serine/threonine kinase 3 (AKT3), which eventually led to the more **aggressive** form of cancer. AKT3 enhanced the PGC1 α localization to the nuclear space by repressing CRM1 (chromosome maintenance region 1), while the latter served as the downstream target for PGC1 α . All these led to mitochondrial biogenesis, which fueled the progression of the tumor ^[120]. Previous studies have also reported such inconsistent findings for PPAR γ in HCC. Koga *et al* tested five patients with cirrhotic livers and found no significant change in the PPAR γ expressions compared to the surrounding non-cancerous tissue ^[10]. Another study reported the consistently overexpressed PPAR γ in HCC tissue having null expression in the surrounding tissues, even though all the patients were infected with viral hepatitis (B or C) ^[121]. Although the well-known inhibitory effects of PPAR γ agonists are reported, they are also suggested to have PPAR γ -independent effects on cancers. Troglitazone, as discussed above, has a prominent anti-tumorigenic role in HCC.

However, there are reports of it exhibiting PPAR γ -independent activity. Palakurthi *et al* studied troglitazone and ciglitazone on both PPAR γ ^{-/-} and PPAR γ ^{+/+} mouse embryonic stem cells considering various concentrations. Both the agonists could inhibit cellular proliferation in a dose-dependent manner by suppressing the G1-S transition [122]. This evidence demonstrated that the anti-proliferative effect was induced by suppressing the translation initiation. More similar reports back up the PPAR γ -independent anti-tumorigenic property of PPAR γ agonists [123,124]. One of the studies focused on the HCC progression in HBV-transgenic mice demonstrated that the anti-cancerous, anti-proliferative, and apoptotic effects of TZD were more significant in PPAR γ -deficient mice in comparison with the control mice, exhibiting normal PPAR γ levels [125]. It is well-understood that PPAR γ could potentially affect various pathways, so it is vital to understand the underlying mechanisms critically. This understanding is an absolute requirement as PPAR γ may be inconsistent. However, it highlights its crucial role in tumor development, suggesting that targeted biomedical research against PPAR γ could provide a highly efficacious avenue for treating and managing of HCC and various other cancers.

CONCLUSION

The majorities of current studies support the fact that PPAR γ may be a potential target against the progression of HCC. They have extensively explored the various signaling cascades through which PPAR γ exerted inhibitory against HCC using synthetic and natural agonists in preclinical and clinical trials. PPAR γ was suggested as a potential target as it suppresses cell proliferation, migration, and invasion in HCC cells through different signaling pathways. Thiazolidinediones (TZD), a class of synthetic PPAR γ agonists, were extensively studied for their efficacy against HCC. TZD showed significant results against the progression of HCC; however, due to their adverse effect on different organs, these drugs are not approved for any cancer treatment. Therefore, increased focus was employed to identify natural and endogenous PPAR γ agonists having high bioavailability and specificity in terms of their binding at the active site.

Several studies reported the safety profiles and therapeutic role of natural agonists against HCC in various experiment modals. Natural agonists are also effectively reported to mediate apoptosis and inhibit cell proliferation, tumor growth, and metastasis in HCC. Few reports also highlighted the contradictory role of PPAR γ in HCC. These contradictions might be due to some unidentified link between PPAR γ and cancer. With the well-established role of PPAR γ in the progression of HCC, better efficacy of its agonists may be achieved by a complete understanding of underlying mechanisms through which PPAR γ showed therapeutic effects. Future studies should be focused on developing novel PPAR γ targeting therapy for the treatment of HCC.

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