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REVIEW

Peroxisome proliferator-activated receptor gamma as a therapeutic target for hepatocellular carcinoma: Experimental and clinical scenarios

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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, there is expected to be > 1 million cases annually by 2025. Therefore, there is an urgent need to establish potential therapeutic targets to cure this disease. Peroxisome-proliferator-activated receptor gamma (PPARγ) is a ligand-activated transcription factor that plays a crucial role in the patho-physiology of HCC. Many synthetic agonists of PPARγ suppress HCC in experimental studies and clinical trials. These synthetic agonists have 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 PPARγ agonists can be an alternative to exploit this potential target for HCC treatment. In this review, the regulatory role of PPARγ in the pathogenesis of HCC is elucidated. Furthermore, the experimental and clinical scenario of both synthetic and natural PPARγ agonists against HCC is discussed. Most of the available literature advocates PPARγ as a potential therapeutic target for the treatment of HCC.

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

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 to > 1 million cases annually by 2025. The crucial role of peroxisome-proliferator-activated receptor gamma (PPARγ) in HCC pathophysiology makes it a potential therapeutic target. Along with synthetic agonists, natural PPARγ agonists provide alternative and safer options for HCC treatment; however, they need to be validated clinically. This review discusses the regulatory role of PPARγ in HCC pathogenesis and experimental and clinical scenarios of PPARγ agonists in HCC treatment.

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INTRODUCTION

Liver cancer is the sixth most common cause of cancer-related death worldwide, with a higher prevalence in men than women. Hepatocellular carcinoma (HCC) incidence was expected to increase to > 1 million individuals annually by 2025[1]. 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, and diabetes [2]. These conditions are linked to 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 currently the best option for curing HCC, but there is a limitation to the availability of donors[3]. During the last two decades, the 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 (FDA) for the advanced stages of HCC. It is a type of multikinase inhibitor that shows tumor-suppressing activity *via* targeting vascular endothelial growth factor receptor, adenosine monophosphate-activated protein kinase (AMPK), and platelet-derived growth factor receptor[4]. Apart from their therapeutic potential, sorafenib shows acquired resistance in HCC cells. The low response rate indicates that patients sensitive to sorafenib during the treatment will develop resistance within 6 mo. These negative impacts of approved drugs prompted many researchers to find novel drugs or targets to cure HCC[5].

Peroxisome proliferator-activated receptor gamma (PPARγ) 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 have established the role of PPARγ in the pathophysiology of HCC. *In vitro* and *in vivo* data have shown the inhibitory role of PPARγ activation in tumor cell growth, migration, and invasion suggesting its therapeutic role in the growth regulation of HCC[7,8]. The antitumor effects of PPARγ are 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 have revealed the mechanism underlying the development of HCC and suggested the presence of PPARγ in human HCC tissues, which shows a dose-dependent decrease in the growth of HCC cell lines[10]. Thus, molecules modulating PPARγ signaling pathways will provide a novel solution for the effective treatment of HCC. This review focuses on the role of PPARγ in the HCC pathophysiology and the experimental and clinical status of PPARγ agonists in the treatment of HCC.

MOLECULAR ARRANGEMENT OF PPARγ

The PPARs protein belong to the superfamily 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 PPARα, PPARγ, and PPARδ, have been studied to a large extent. Of these isoforms, PPARγ is highly expressed in adipose tissue, where 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, PPARγ has three distinct mRNAs (PPARγ1, PPARγ2, and PPARγ3). The translation products of PPARγ1 and PPARγ3 yield identical proteins; however, PPARγ2 results in a product with an additional N-terminal region[12]. PPARγ1 and PPARγ3 are biologically expressed in different tissues (hepatocytes, muscles, and endothelial cells), whereas PPARγ2 is only widely expressed in adipose tissue[9,13]. PPARγ 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 that of the other nuclear receptors. They can be activated by various natural and synthetic agonists, such as essential fatty acids[15,16]. The three-dimensional structure of PPARγ 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 the C-terminus responsible for specific ligand binding at the peroxisome proliferator response element (PPRE)[16,17]. After interaction with specific ligands, the LBD facilitates the heterodimerization of PPARs with retinoid X receptor (RXR), which subsequently binds to the 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 PPARγ IN HCC

PPARγ 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 adipocyte differentiation, lipid metabolism, and insulin sensitivity *via* downregulating leptin concentration[7]. Despite the low expression in the healthy liver, PPARγ plays a significant role in several hepatic conditions such as fatty liver, fibrosis, and HCC. Many *in vitro* and *in vivo* studies have reported that natural and synthetic PPARγ agonists inhibit tumor growth and cell migration in HCC[18]. The activation of PPARγ inhibits cell growth by inducing G0/G1 cell cycle arrest in HCC cells, which is suggested to be associated with p21, p27, and p18 upregulation (Figure 2). Furthermore, p27 upregulation downregulates S-phase kinase-associated protein-2 (Skp2) in HCC, an F-box protein component of the Skp, Cullin, F-box ubiquitin-ligase complex. p27 plays a vital role in G0/G1 arrest instead of p21[10,19]. The direct overexpression of PPARγ in hepatic cancerous cells also inhibits cell growth; however, the cells are arrested in the G2/M phase instead of the G0/G1 phase after PPARγ agonist treatment. G2/M phase arrest in PPARγ overexpression is attributed to activating cell division cycle 25C phosphatase by Ser216 phosphorylation and preventing premature mitosis[20]. Compared to wild-type mice, another study on PPARγ-deficient mice showed increased hepatocarcinogenesis after treatment of diethylnitrosamine (DENA). Growth differentiation factor 15 (GDF 15) is a target gene of PPARγ and is induced by its activation. GDF 15 overexpression in many cancers is associated with an antitumorigenic response, as it was suggested to reduce cancer cell viability and induce cell apoptosis. PPARγ activation by agonist or direct overexpression induces apoptosis by intrinsic and extrinsic pathways[21]. Activation of the extrinsic apoptosis pathway by PPARγ overexpression is attributed to the induction of tumor necrosis factor α (TNFα) and Fas, leading to the activation of downstream caspases (Figure 2). In the intrinsic pathway, PPARγ overexpression stimulates B-cell lymphoma 2 (Bcl-2)-associated X protein transcription and release into the cytosol, activating apoptotic protease activating factor 1 and caspase-9 complex, which further triggers caspase 3 and 7 to induce apoptosis[6,21]. The antitumorigenic effect of PPARγ in HCC is also suggested *via* modulation of the phosphoinositide 3-kinase (PI3K)/Akt pathway [22]. PPARγ 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 PPARγ plays a central role in regulating inflammation. PPARγ inhibits inflammation by interfering with nuclear factor-kappa B (NF-κB) and suppressing the production of proinflammatory cytokines (TNFα and interleukin 1 beta [IL-1β]). Activation of PPARγ by specific ligands in T-cell differentiation promotes an inflammatory response, thereby playing a significant role in the adaptive immune response. Thus, PPARγ act as an important therapeutic target for regulating inflammatory markers (TNFα, IL-2, IL-1β, and IL-6) against the progression of several diseases[7,16]. Hepatic stellate cell (HSC) activation and fibrogenic factor significantly contribute to the development of HCC (Figure 2). PPARγ is highly expressed in quiescent HSCs and has a role in their transdifferentiation. HSC activation and PPARγ are inversely related as increased expression of PPARγ inhibits HSC proliferation and induces apoptosis in activated HSCs[24]. It also reduces the expression of alpha-smooth muscle actin (αSMA) and hydroxyproline to inhibit hepatic fibrosis. Hepatic injury induces microvascular complications in the liver, stimulating various sinusoidal cells such as HSCs, liver sinusoidal endothelial cells, and Kupffer cells. PPARγ regulates the role of these cells in liver inflammation and fibrosis. The deactivation of HSCs by PPARγ agonists further reduces extracellular matrix deposition and expression patterns of matrix metalloproteinase (MMP)/tissue inhibitors of MMPs (TIMP). The expression of MMP9 and MMP13, TIMP, heparinase, and E-cadherin is associated with cancer cell migration and metastasis[25]. The expression patterns of these markers are directly linked to PPARγ activation. Reports also link PPARγ activation with autophagy in HCC. Autophagy is thought to be inhibited after autophagosome formation in the absence

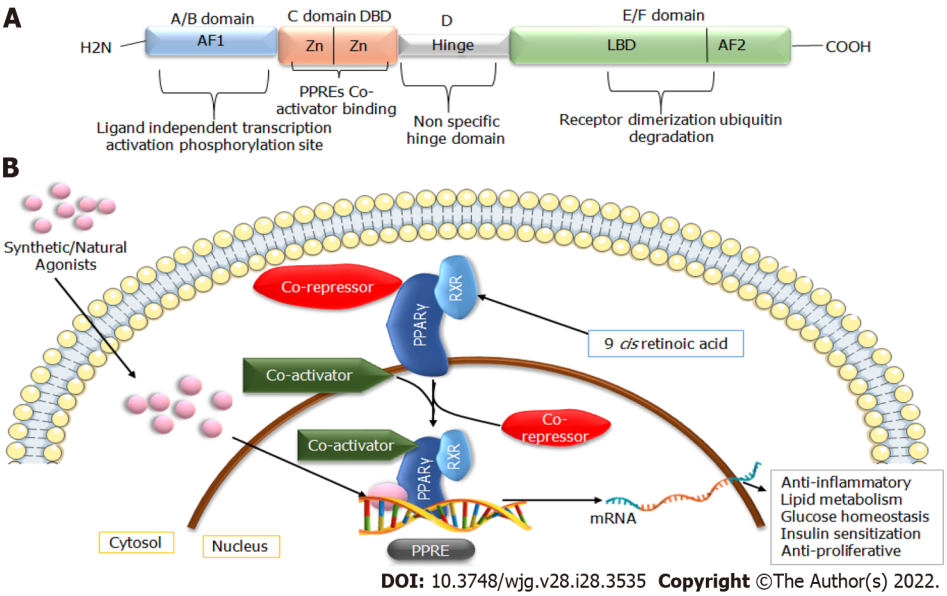

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Figure 1 General structure and ligand-activated transcription of peroxisome proliferator-activated receptor-gamma. A: Peroxisome proliferator-activated receptor (PPAR) structure includes four distinct structural domains A/B, C, D, and E/F; B: Ligand-activated transcription of PPARγ, which includes heterodimerization with nuclear receptor retinoid X receptor (RXR) and binding with peroxisome proliferator response elements located in the target genes through the DNA-binding domain (DBD). In the absence of ligand, PPAR is linked with the corepressor complex, whereas, in the presence of ligand, it is associated with the coactivator complex. LBD: Ligand-binding domain; PPRE: Peroxisome proliferator response element.

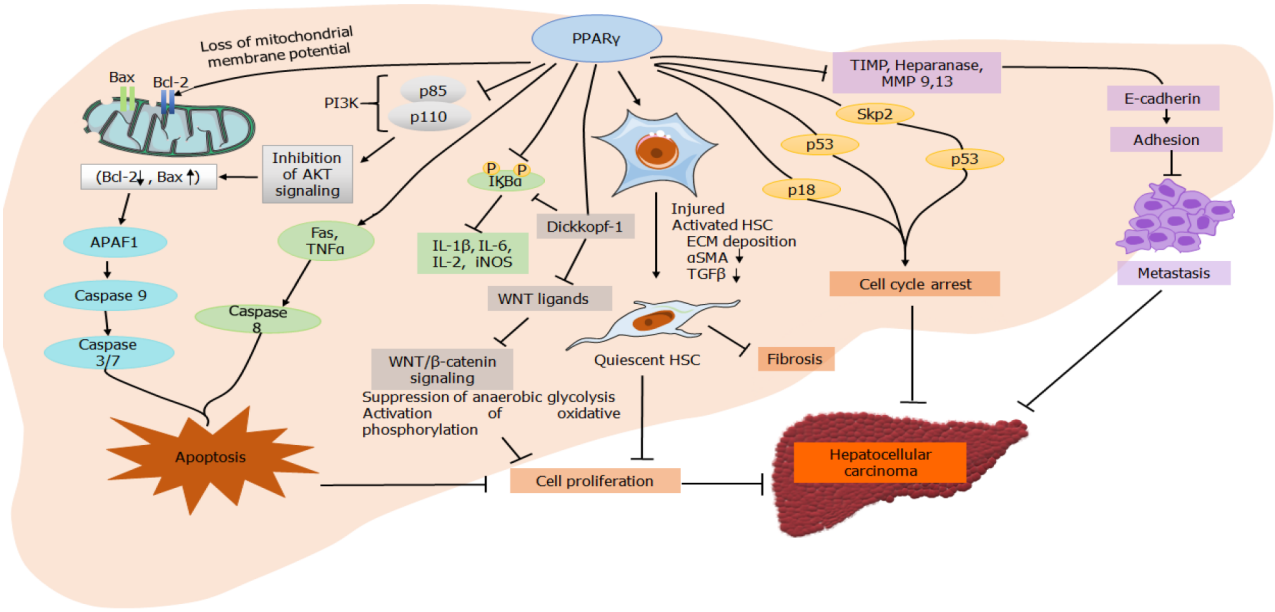

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Figure 2 Schematic diagram showing the protective effect of peroxisome proliferator-activated receptor γ against the progression of hepatocellular carcinoma. Activated peroxisome proliferator-activated receptor γ (PPARγ) interacts with multiple pathways, leading to cell cycle arrest, apoptosis, inhibition of cell proliferation, and cell metastasis in hepatocellular carcinoma. BAX: B-cell lymphoma 2 (Bcl-2)-associated X protein; IκBα: Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibition alpha; IL: Interleukin; TIMP: Tissue inhibitor of metalloproteinases; MMP: Matrix metalloproteinase; ECM: Extracellular matrix; αSMA: Alpha-smooth muscle actin; TGFβ: Transforming growth factor beta; iNOS: Inducible nitric oxide synthase; TNFα: Tumor necrosis factor alpha; APF1: Apoptotic protease activating factor 1.

of PPARγ, resulting in increased light chain 3 protein expression and accumulation of p62 in the autophagosome[26,27]. Therefore, induction of autophagy in HCC is linked to the activation of PPARγ in HCC. A recent study elucidated the role of PPARγ coactivator-1α (PGC1α) in suppressing HCC metastasis. The levels of PGC1α were downregulated in human HCC and associated with a poor prognosis, large tumor size, and vascular invasion[28]. However, PGC1α overexpression in the HCC cells inhibited tumor cell migration and invasion. The suppression of metastasis by PGC1α overex-

pression was suggested due to PPARγ-dependent downregulation of pyruvate dehydrogenase kinase isozyme 1 and inhibition of aerobic glycolysis through Wnt/β-catenin/pyruvate dehydrogenase kinase-1 (PDK1) axis regulation[29].

Zinc finger protein 746 (ZNF746) is a Parkin-interacting substrate (PARIS), acting as a transcriptional regulator of PPARγ co-activator 1 alpha (PGC1α) which further regulates the activity of PPARγ 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 PGC1α and NRF1. Moreover, Chang liver cells treated with hydrogen peroxide showed PARIS accretion and alleviation of PGC1α. As the co-activator, PGC1α is directly linked to PPARγ regulation, further monitoring the oncogenic stress promoting cancer development. Thus, the modulation of PPARγ 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 PGC1α is negatively associated with tumor size and vascular influx. The increased expression of PGC1α 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 the 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 PGC1α knockdown model by employing two popular inhibitors of this signaling pathway (XAV-939 and ICG-001). Gene Set Enrichment Analysis indicated that these inhibitors alleviate the overexpression of extracellular lactate, suggesting the possible role of PGC1α in the inhibition of aerobic glycolysis *via* Wnt/β-catenin signaling. Dual-luciferase reporter assays showed that the transcriptional actions of PPARγ are significantly increased in HCCLM3 and MHCC97H cells with PGC1α augmentation. These results show that the tumor-suppressive activity of PGC1α depends on PPARγ, which makes PPARγ a key regulator of HCC[29,32]. An earlier report revealed the role of PPARγ in HCC by analyzing the mRNA and protein expression in 20 patients with cirrhosis and chronic hepatitis. The results indicated a statistically pronounced drop in levels of PPARγ in HCC compared to the non-tumorous liver tissue[33]. A report confirmed that miR-130b aids cell aggressiveness by suppressing PPARγ in human HCC[34]. Similarly, evidence on the oncogenic role of miR-1468 in HCC *via* activating the PPARγ/Akt pathway was also recently confirmed. The increased levels of miR-1468 elevated the malignant prognostic features and improved survival. Carboxy-terminal domain 2 and UPF1 RNA Helicase And ATPase were identified as the downstream targets for miR-1468, which regulate PPARγ/Akt pathway activation. Restoration of the expression of these targets partially abolished the effects of miR-1468, explaining the regulation *via* PPARγ/Akt signaling[35].

EXPERIMENTAL AND CLINICAL SCENARIOS

Many studies have explored the therapeutic effects of synthetic and natural PPARγ agonists against HCC in preclinical and clinical trials. The activation of PPARγ significantly suppresses HCC progression and invasion. Several findings have identified PPARγ as a target for tumor suppression, a mediator of apoptosis, and a suppressor of carcinogenesis and metastasis by triggering intrinsic pathways and mainly inhibiting the PI3K/Akt survival pathway[8,21,36]. The various synthetic and natural PPARγ agonists used for HCC are listed in Table 1.

SYNTHETIC PPARγ AGONISTS IN HCC

PPARγ itself and its agonists have anticancer activities, such as growth inhibition, induction of apoptosis, and cell differentiation. Thiazolidinediones (TZDs) are a class of synthetic PPARγ agonists, and many compounds of this class have been studied for their efficacy in experimental models and clinical trials. These compounds were used as a bioregulatory remedial approach to target the communicative framework of HCC in patients with non-curative HCC[37]. TZDs are also effective for glycemic control and the likelihood of HCC and hepatic manifestation in diabetic patients with chronic hepatitis B (CHB). Of the 28999 patients with CHB, 3963 patients developed HCC at a median follow-up of 7.1 years, whereas 1153 patients were administered 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 in 23580 diabetic patients demonstrated the negative relationship between the risk of HCC and use of TZDs. There is a time-dependent effect of TZD use on the risk of HCC. The longer the duration of TZD use, the lower the risk of HCC[39-41]. Many other reports have also suggested that the administration of PPARγ agonists ameliorates several types of cancers, *i.e.* colorectal, bladder, lung, and liver cancers. The effects are more substantial at higher cumulative dosages with longer durations[42].

Table 1 Various synthetic and natural peroxisome-proliferator-activated receptor gamma agonist used in experimental and clinical trials for hepatocellular carcinoma

Agonist name	Drug bank/ PubChem ID	Model	Concentration/dose of agonist	Effects	Ref.
Synthetic agonists					
Pioglitazone	DB01132	*In vivo* (Rats, and Mice)	3 mg/kg; 10 mg/kg	Reduced HCC progression and decreased tumor size and volume	[44]
Rosiglitazone	DB00412	*In vivo* (Orthotopic Mice) *In vitro* (MHCC97L, and BEL-7404)	50 μmol/L	Decreased HCC migration, and invasiveness	[25]
		In vitro (HepG2 and PC3)	0.1, 1, 10, 100 μmol/L	Reduced cancer growth, Increased apoptosis	[49]
		In vitro (HepG2 and Hep3B)	80 μmol/L	Restricted the oncogenic activity of SEPT2	[50]
Telmisartan	DB00966	*In vitro* (HLF, HLE, HuH-7, PLC/PRF/5, and HepG2)	10, 50 or 100 μmol/L	Inhibit proliferation, induce cell cycle arrest	[53]
		In vivo (Mice)	15 mg/kg	Reversed malignant anomalies, antioxidant, anti-inflammatory	[54]
Troglitazone	DB00197	*In vitro* (Hep G2, HuH-7, KYN-1, and KYN-2)	5, 10, 25 μmol/L	Reduced cell proliferation and increased apoptosis	[56]
		In vitro (HepG2)	5, 10, 20, 40, 80, and 100 μmol/L	Apoptosis and growth inhibition	[57]
		In vitro (Hep G2, HuH-7, KYN-1, and KYN-2)	5, 10, and 25 μmol/L	Inhibited DNA synthesis, cell cycle growth, and α-fetoprotein levels	[58]
		In vitro (PLC/PRF/5, and HuH-7)	5, 10, 20, 40, 60, 80, and 100 μmol/L	Reduced cell proliferation and increased apoptosis	[59]
		In vitro (HLF, HAK-1A, HAK-1B, and HAK-5)	10, 20, 30, 40, and 50 μmol/L	Reduced cell proliferation and increased apoptosis	[19]
Saroglitazar	DB13115	*In vivo* (Mice)	4 mg/kg	Reduced inflammation in hepatic lobules, hepatocellular ballooning, and steatosis	[61]
		In vivo (Rats)	4 mg/kg	Improved lipid profile, and histopathological changes	[62]
Natural agonists					
Cannabinol, Cannabinoids	DB14737	*In vitro* (HepG2 and HUH-7); *In vivo* (Mice)	8 μmol/L; 15 mg/kg	Increased apoptosis, autophagy, anti-proliferative	[66]
		In vitro (HEK-293T and Neuro-2a); *In vivo* (Mice)	1, 5, 10, 25 μmol/L; 20 mg/kg	Antitumor, antioxidant, anti-inflammatory	[68]
Capsaicin	DB06774	*In vivo* (Rats)	0.5 and 1 mg/kg	Inhibit hepatic injury, and collagen deposition, anti-inflammatory	[71]
Curcumin	DB11672	*In vivo* (Rats)	20 mg/kg	Attenuated histopathological, serological, proliferative, and apoptotic parameters	[77]
		In vitro (H22); *In vivo* (Mice)	5, 10, 20, 40, and 80 μmol/L; 50, 100 mg/kg	Antiproliferative, decrease tumor growth, induce apoptosis	[78]
		In vivo (Mice)	150 mg/kg	Reduced inflammation, and tumor size	[79]
		In vivo (Rats)	0.5, 1, 2, 5, 10, 15, and 20 ng/mL	Interrupted TGFβ signaling, activated hepatic stellate cells	[80]
		In vitro (SMMC7721 and Huh-7)	10, 20, 40, 80, and 160 μmol/L	Suppressed cellular proliferation	[82]
Hesperidin	DB04703	*In vivo* (Rats)	50 and 100 mg/kg	Suppressed TGFβ signaling and hepatocarcinogenesis	[85]
		In vivo (Rats)	200 mg/kg	Inhibited PI3K/Akt pathway, Antioxidant	[86]

		In vitro (HepG2); *In vivo* (Rats)	100 μmol/L; 150 mg/kg	Inhibited Wnt3a/5a signaling pathway, anti-inflammatory	[87]
Hispidulin	DB14008	*In vitro* (SMMC7721 and Bel7402); *In vivo* (mouse tumor xenograft)	10 and 20 μmol/L; 20 and 40 mg /kg	Anticancerous, inhibited cell migration	[89]
		In vitro (NCI-H460 and A549)	4, 8, 15, 30, and 60 μmol/L	Induced ROS-mediated apoptosis, anti-cancerous	[90]
Isoflavone	DB12007	*In vivo* (Bel-7402 and SK-Hep-1)*In vivo* (Mice)	75 and 12 μmol/L resp.; 25 and 7.5 mg/kg resp.	Anti-inflammatory, anti-tumorigenic, reduced the size and volume of tumor	[94]
		In vitro (Hepa 1-6 cells)	1, 5, 10, 15, 20, 25, 50, 75, and 100 μmol/L	Antitumorigenic and antiproliferative	[95]
		In vitro (HCC-LM3, SMMC-7721, Hep3B, Bel-7402, and Huh-7)*In vivo* (Mice)	40, 60, and 80 μmol/L; 20, 40, and 80 mg/kg	Suppressed aerobic glycolysis and increased apoptotic rate	[96]
Oroxyloside	14655551	*In vitro* (HepG2) and SMMC-7721); *In vivo* (Mice)	100, 200, and 300 μmol/L; 90 mg/kg	Cell cycle arrest and growth repression	[100]
Resveratrol	DB02709	*In vivo* (Rats)	100 mg/kg	Antioxidant, anti-inflammatory, anticancer	[101]
		In vitro (HepG2); *In vivo* (Rats)	7.81, 15.63, 31.25, 62.5, 125, and 250 μg/mL; 20 mg/kg	Attenuated histopathological, serological, proliferative, and apoptotic parameters	[102]
Miscellaneous					
Avicularin	5490064	*In vitro* (HuH-7)	25, 50, and 100 μg/mL	Decreased the cell migration and invasiveness	[107]
Honokiol	72303	*In vitro* (HEK-293 and 3T3-L1); *In vivo* (Mice)	1, 3, and 10 μmol/L; 100 mg/kg	Activated PPARγ/RXR heterodimers; Reduced hyperglycemia	[108]
Chrysin	DB15581	*In vitro* (MDA-MB-231 and HepG2)*In vivo* (Mice)	10 μmol/L; 10 mg/kg	Increased apoptosis	[112]
Quercetin	DB04216	*In vitro* (HepG2 and SMCC-7721); *In vivo* (Mice)	0.05, 0.1, and 0.15 mmol/L; 40 mg/kg	Promoted the autophagy	[114]
		In vitro (PATU-8988 and PANC-1)	20, 40, 80, and 160 μmol/L	Suppressed HCC *via* STAT3 pathway	[117]
		In vitro (LM3); *In vivo* (Mice)	40, 80, and 120 μmol/L; 100 mg/kg	Reduced invasiveness, Cell cycle regulation	[118]
Clinical trials					
		Population type	No. of patients		
Thiazolidinediones	NA	Hongkong	1153	Reduce the synergistic effect of diabetes with liver disorders; Reduced risk of HCC	[38],[39], [40],[41]
		Taiwanese	77396		
			32891		
			76349		
Pioglitazone	DB01132	Chinese	75	Blocked RAGE signaling; Reduced HCC	[45]
		Japanese	85	Reduced growth and invasion of HCC cells	[46]
		Thai	10000	Reduced risk of HCC	[47]
Rosiglitazone	DB00412	French	44	Reduced NASH activity and ballooning score, Ameliorated histopathological aberrations	[51]
Saroglitazar	DB13115	Indian	30	Improved glycemic index and liver stiffness	[63]
			90	Improved fibrosis score	[64]

Isoflavone	DB12007	Japanese	302	Antioxidant, reduced risk of HCC	[97]
			191	Antioxidant, reduced risk of HCC	[98]

Akt/PKB: Protein kinase B; HCC: Hepatocellular carcinoma; NASH: Non-alcoholic steatohepatitis; PI3K: Phosphoinositide 3-kinase; PPARγ: Peroxisome proliferator-activated receptor gamma; RAGE: Receptor for advanced glycation end products; ROS: Reactive oxygen species; RXR: Retinoid X receptor; SEPT2: Septin 2; STAT3: Signal transducer and activator of transcription 3; TGFβ: Transforming growth factor beta; Wnt: Wingless-related integration site.

Pioglitazone

Pioglitazone (PGZ), a PPARγ ligand, works by improving the insulin sensitivity of tissues and exhibits anticancer activity. It selectively stimulates PPARγ *via* modulating the 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 inhibits fibrosis progression and HCC development and reduces tumor size in DENA-induced rats at 3 mg/kg and mice at 10 mg/kg. PGZ is suggested to exhibit protective effects by reducing mitogen-activated protein kinase (MAPK) and upregulating adiponectin levels, resulting in activation of the hepatoprotective AMPK pathway[44].

The anticancer activity of PGZ is attributed to the pathological receptors for advanced glycation end products (RAGE). HCC tissues from 75 patients showed high expression of RAGE in HCC tissues, which was closely linked to pathological staging and lymph-vascular space influx. However, PGZ treatment suppressed cellular proliferation, ameliorated apoptosis, and cell cycle arrest, which further elevated PPARγ expression and decreased the expression of RAGE, NF-κB, high mobility group box 1, p38MAPK Ki-67, MMP2, and cyclin D1. The results demonstrated that PGZ as a PPARγ agonist possibly slows down the growth and invasion of HCC cells by blocking 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 that the lessened risk of HCC recurrence is associated with increased body weight and body mass index ≥ 23. PGZ 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 can reduce the number of HCC cases[47]. These therapeutic potentials also have limitations. PGZ has adverse effects such as 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 TZD class of insulin-sensitizing PPARγ agonists. An inhibitory effect of PPARγ 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 PPARγ was demonstrated in HCC cell lines treated with adenovirus-expressing mouse PPARγ1 (Ad-PPARγ), rosiglitazone (50 μmol/L), or Ad-PPARγ plus rosiglitazone. The induction of PPARγ markedly repressed HCC cell migration, invasiveness, levels of pro-metastatic genes (MMP9, MMP13, heparanase [HPSE]), and hepatocyte growth factor. However, the levels of cell adhesion genes (E-cadherin and SYP), extracellular matrix regulator TIMP3, and tumor suppressor gene retinoblastoma 1 were elevated. Additionally, direct transcriptional regulation of the genes TIMP3, MMP9, MMP13, and HPSE regulating PPARγ levels was also validated by chromatin immunoprecipitation-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 by inhibiting Bcl-2 proteins. In a study, rosiglitazone was employed to sensitize (-)-G to induce apoptosis at different concentrations (0.1, 1, 10, 100 μmol/L). The (-)-G induced Mcl-1 (myeloid cell leukemia-1) stability was the prime concern for its apoptotic activity. However, rosiglitazone attenuated this stability *via* Janus kinase phosphorylation, further repressing 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 PPARγ agonists and BH3 mimetics[49]. Rosiglitazone (80 μmol/L) also inhibits HCC cell growth by restricting the oncogenic activity of septin 2[50].

A long-term clinical trial was conducted in which 53 patients underwent liver biopsies and were further treated with rosiglitazone (8 mg/d) for the next 2 years. Forty-four patients fulfilled the criteria of the extension period and underwent another biopsy. During the extension phase, serum insulin and alanine aminotransferase (ALT) levels were decreased by 26% and 24%, respectively. Non-alcoholic steatohepatitis activity, ballooning, and fibrotic stage were decreased but not on a significant scale. The treatment was continued for another 2 years, but no significant results were obtained, showing that rosiglitazone does attenuate insulin sensitivity and transaminase levels but might not significantly

improve 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, the FDA restricted the use of rosiglitazone based on meta-analyses of mostly short-term randomized controlled trials, which showed evidence of myocardial infection 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 clear. TEL shows basal resemblance with a well-known PPARγ agonist, PGZ. TEL (at concentrations of 10, 50, or 100 μmol/L) inhibits the proliferation and 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 mammalian target of rapamycin (mTOR) pathway[53]. Another study used a DENA-induced HCC mouse 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 expression of NF-κBp65, AFP, TNFα, and transforming growth factor beta 1 (TGFβ1) resulting in the reversion of malignant anomalies and suppression of extracellular signalregulated protein kinase 1/2 (ERK1/2) activation. SRF and TEL showed antiproliferative, antimetastatic, and anti-angiogenic effects by improving the expression of hepatic cyclin D1, MMP2, and vascular endothelial growth factor (VEGF). However, only TEL has exhibited agonistic activity for PPARγ receptors, as indicated by the elevated PPARγ DNA-binding activity, mRNA expression of cluster of differentiation 36, heme oxygenase 1, and enhanced hepatic antioxidant capacity. Moreover, TEL and SRF both ameliorate phosphorylation-induced activation of TGFβ-activated kinase 1 (TAK1), suggesting that TAK1 might act as the core mediator for the interaction between ERK1/2 and NF-κB. TEL exerts its anticancer effects by modulating the ERK1/2, TAK1, and NF-κB signaling axis from the perspective of its PPARγ agonistic activity. Thus, TEL may be a useful PPARγ agonist for further clinical studies in the context of HCC treatment[54]. Despite its potential, it has adverse effects including headaches, dizziness, fatigue, upper respiratory tract or stomach-related infections, sinusitis, nonspecific pain, and diarrhea[55].

Troglitazone

Troglitazone (TGZ) is a member of the TZD class of drugs and acts as a PPARγ agonist. The antiproliferative and antitumorigenic effects of TGZ were studied in the BEL-7402 HCC cell line at 5, 10, and 25 μmol/L concentrations. TGZ induced cell death in a concentration-dependent manner resulting in the increased presence of fragmented DNA and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL)-positive cells. TGZ enhanced cell cycle arrest in the G0/G1 phase and increased caspase activities (caspase 3, 6, 7, and 9), indicating increased cell apoptosis[56]. In another study, the HepG2 cell line treated with TGZ showed significant growth inhibition in a dose-dependent manner. The TUNEL assay and immunohistochemistry showed apoptosis induction and elevated expression of apoptotic proteins such as caspase 3 and survivin[57]. PPARγ was functionally expressed in hepatic cancer cell lines (HepG2, HuH-7, KYN-1, and KYN-2) with TGZ 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 shown by other groups that used other HCC cell lines such as 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 these studies demonstrated the usefulness of TGZ for chemoprevention in HCC. Some recent studies showed the hepatotoxic effect of TGZ on diabetic patients. There is a significant elevation in liver enzymes level (ALT and aspartate aminotransferase [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 antihyperglycemic agents or insulin, which also limits the use of TGZ[60].

Saroglitazar

Saroglitazar is a first-class drug that acts as a dual PPARα/γ agonist. It is indicated for enhanced diabetic dyslipidemia, inflammation, steatosis, ballooning, and fibrosis progression. The agonistic effects of this drug have a favorable impact on insulin resistance and lipid profile. Saroglitazar treatment is thought to ameliorate high-fat diet-induced aberrations. The improvements were observed in hepatic lobular inflammation, hepatocellular ballooning, steatosis, and fibrosis. The effects of saroglitazar were more pronounced compared to PGZ. Transcriptomic analyses revealed the elevated expression of PPARγ 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 lipopolysaccharide (LPS)-treated rats. The positive effects on serum leptin, TNFα, and adiponectin levels were also observed. The multiple protective roles of PPARα

/γ agonists in liver disorders suggest the usefulness 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 6 mo. A profound improvement in glycemic index, liver stiffness, and serum triglyceride levels of the patients was observed with no significant adverse side effects[63]. Another study conducted in 90 NAFLD patients who underwent liver biopsies, fibrosis scores, and other non-invasive parameters showed that saroglitazar treatment significantly improved the serum biomarker levels and fibrosis score. The study concluded the reversal effect of saroglitazar on fibrosis and advocated its use in treating HCC[64]. The most common adverse events associated with saroglitazar included asthenia, gastritis, chest discomfort, peripheral edema, dizziness, and tremors[65].

NATURAL PPARγ AGONISTS IN HCC

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

Cannabinoids

The hemp plant *Cannabis sativa L.* produces approximately 60 unique compounds known as cannabinoids, of which ∆9-tetrahydrocannabinol (THC) is the most important due to its high potency and abundance in cannabis. Various studies have reported the fair safety profile of cannabinoids, in accordance with its probable antiproliferative activity on cancerous cells, may set the basis for future trials to evaluate the potential antitumor activity of cannabinoids. Vara *et al*[66] reported that cannabinoids THC and JWH-015 increased the intracellular mRNA and protein levels of PPARγ in HCC cells, and inhibition of PPARγ decreased cannabinoid-induced cell death and apoptosis. Further, increased PPARγ levels were correlated with endoplasmic reticulum stress and autophagy in HCC cells, suggesting the antiproliferative effects of cannabinoids through PPARγ-dependent pathways. The antitumor activity of THC was evaluated in patients who had failed standard therapy norms. *In vitro* studies have shown the suppression of tumor cell proliferation, and Ki67 immunostaining exhibits a reduced number of tumor cells[67]. THC is suggested to induce transcriptional modulation of the PPARγ pathway, and the activation is much more potent by cannabinoid acids than its decarboxylated products, indicating that cannabinoids act as a PPARγ agonist[68]. *Cannabis* contains some psychoactive agents that increase sociability and exert euphoric effects. Repeated use of *cannabis* has been linked to short- and long-term side effects, including respiratory and cardiovascular disorders, cognitive alterations, psychosis, schizophrenia, and mood disorders[69]. A recent study highlighted the side effects of a common preparation from *C. 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 Capsicum. These phytoconstituents possess anti-inflammatory and chemopreventive properties. They counter various compounds' mutagenic properties and exert anticancer effects on breast, colon, prostate, and hepatic cancers. The DENA-induced models of HCC in rats and hepatic stellate cell lines were used to study the effects of capsaicin. Capsaicin was observed to inhibit hepatic injury, NF-κB activation, and collagen deposition. It has also ameliorated the levels of α-SMA, collagen type I, MMP2, TGFβ1, and TNFα. Furthermore, TGFβ1 expression and the phosphorylation of Smad2/3 were also inhibited through induction of PPARγ expression. The findings showed that capsaicin attenuates hepatic fibrosis by upregulating PPARγ expression[71]. The limitations of this natural PPARγ agonist should be mentioned. 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 induces a cough response immediately upon administration[73,74]. Interestingly, there is evidence that topical capsaicin can exacerbate angiotensin-converting enzyme (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 *Curcuma longa* and is well known for its multiple therapeutic effects. Our previous study reported the effect of curcumin and piperine on DENA-induced HCC in rats. Curcumin prevented HCC progression by improving hepatic pathology, apoptosis induction, and inhibiting cell proliferation. However, the synergistic effect on HCC suppression was observed with the combination of curcumin and piperine[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 VEGF expression and PI3K/Akt signaling[78]. A study in a transgenic mouse model (expressing double HBV oncoproteins, HBx and pre-S2 in the liver) of HBV-related HCC reported the protective effects of phytosomal curcumin *via* targeting PPARγ as a key regulator. Curcumin decreased HCC formation and reduced the tumor size. Moreover, considerably more potent effects were observed on activation of PPARγ and inhibition of NF-κB. The report suggested that curcumin is an agonist for PPARγ, upregulating the genes involved in lipid metabolism, antiproliferation, and anti-inflammation. Furthermore, PPARγ activation regulates the suppression of NF-κB and subsequent pro-inflammatory cytokines. In addition, curcumin also is suggested to repress mTOR[79]. Recently, the antitumor effect of curcumin on HCC was suggested due to the involvement of miR-21 targeting TIMP3 and inhibition of the TGFβ1/Smad3 signaling pathway. The inhibition of TGFβ 1/Smad3 signaling by curcumin is reportedly linked to activation of the PPARγ gene[80,81]. It was further suggested to suppress cell proliferation through long non-coding RNA 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 doses of 50 and 100 mg/kg per day in experimental rabbits showed elevation of liver injury markers (ALT, AST, 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 such as piperine, which reportedly causes adverse drug reactions[84].

Hesperidin

Hesperidin is a flavanone glycoside found in the rind of citrus fruits including oranges and lemon. It possesses several pharmacological activities including antioxidant, anti-inflammatory, and anticancer effects. The chemopreventive efficacy of hesperidin was evaluated in DENA-induced HCC in rats. The hesperidin significantly reduced hepatic serological and tumor biomarkers along with TNFα. Furthermore, it also reduced the hepatic degenerative changes, oxidative stress, collagen deposition, TGFβ1, and NF-κB expression. However, the upregulated expression of nuclear factor erythroid 2–related factor 2, HO-1, and PPARγ suggested the effect of hesperidin *via* suppressing TGFβ signaling and subsequently activating PPARγ[85]. Another study investigated the efficacy of hesperidin *via* the PI3K/Akt pathway as a probable mechanism for curing HCC. Treatment with hesperidin elevated the protein levels of PI3K, Akt, and cyclin-dependent kinase 2 and ameliorated HCC progression[86]. In addition, hesperidin reportedly alters Wnt3a/β-catenin signaling in preventing HCC[87]. There are few reports on the bioavailability and solubility of hesperidin. Ameer *et al*[88] reported that hesperidin is absorbed across the gastrointestinal tract on oral administration, but cumulative recovery indicates low bioavailability. The factors limiting the bioavailability of hesperidin are poor water solubility and its precipitation in an acidic environment.

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* PPARγ activation, which is further linked to escalated phosphorylation of AMPK, ERK, and JNK *in vitro*. Specifically, GW9662 (a PPARγ inhibitor), compound C (an AMPK inhibitor), and PD98059 (a MEK inhibitor) negated the protective effects of hispidulin on PPARγ signaling. However, no pronounced changes in PPARγ levels were noted with pre-treatment of SP6000125 (a JNK inhibitor) *in vitro,* whereas it attenuated the anticancer activity of hispidulin. The suppression of Bel7402 xenograft tumor growth was successfully achieved by hispidulin through PPARγ activation, indicating the cardinal role of PPARγ signaling in HCC cell growth[89]. Recently, Lv *et al*[90] suggested that induction of reactive oxygen speciesmediated apoptosis through activation of the endoplasmic reticulum stress pathway is also responsible for the anticancer effect of hispidulin. Some evidence links hispidulin to its limited large-scale preparation. Studies have shown the lack of a single-dose design of hispidulin, which further limits the bioavailability[91,92].

Isoflavones

Isoflavones are a group of 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 their 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 were attributed to the aberration of ERK MAPK and PI3K/Akt pathways. *In vivo*, a profound reduction in the size and volume of HCC tumors was noted, indicating the combination therapy of isoflavones as a potential lead for the management and treatment of advanced HCC[94]. The antitumorigenic and antiproliferative role of genistein was also studied in HCC *in vitro*. The isoflavone suppressed the proliferation of Hepa 1-6 cells and caused apoptosis in time- and dose-dependent manners[95]. In another study, genistein treatment suppressed aerobic glycolysis and increased the apoptotic rate in HCC cell lines. Additionally, genistein exhibited inhibitory effects on tumor progression and aerobic glycolysis. This may be identified as an effective treatment for advanced HCC[96]. Studies have reported the PPARγ-modulating effect of isoflavones and inhibition of HCC through inhibition of the PI3K/Akt pathway, and aerobic glycolysis further validates the involvement of PPARγ signaling. Clinical studies have 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 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) reportedly impacts 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 PPARγ/α, which acts as a potent cell proliferation inhibitor in HCC-based metabolic transition. It regulates the glycolipid metabolic enzymes (PPAR-dependent or PPAR-independent), inhibits the breakdown of glucose, and promotes fatty acid oxidation, which generates acetyl-CoA for the tricarboxylic acid cycle and oxidative phosphorylation. The metabolic transition produced by OAG exhibits a profound generation of reactive oxygen species, leading to G1 cell cycle arrest and growth repression of HCC cells. OAG requires pyruvate dehydrogenase kinase 4 and β-oxidation to inhibit cell proliferation, explaining its PPARγ agonistic behavior. OAG is a new PPARγ/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, information on their bioavailability and their active forms *in vivo* is 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 (RS) is a popular natural polyphenolic PPARγ agonist, well known for its anticancer properties, and has been recognized as the alternate mode in cancer treatment. A study revealed the effect of RS against alcohol-aflatoxin B1-induced HCC. During the progression of HCC, a decline in the antioxidant markers was effectively restored by resveratrol treatment. RS modulated the activity of the sirtuin 1 (SIRT1) enzyme in HCC by negatively regulating the levels of NF-κB, and cross-talk between this PPARγ agonist and SIRT1 signaling was observed[101]. A nano-formulation of RS using liposomes was developed to establish a specific drug delivery system for managing HCC. *In vitro* studies have revealed the increased internalization and enhanced anticancer activity of liposomal formulation (RL5) compared to naïve RS. A profound reduction in liver injury markers, hepatocyte nodules, and degenerative changes in the liver was observed in an *in vivo* HCC model. The results indicated the promising action of nano-formulation of RS and its substantial activity in controlling the severity of HCC[102]. Earlier, similar approaches were briefly reviewed by Santos *et al*[103] to study the pharmacokinetics of RS-loaded nanoparticles (RS-NPs) and study their effects on cancer tissue. A comprehensive analysis was carried out in various *in vivo* models, which revealed the markedly enhanced anticancer activity of RS-NPs. However, the poor bioavailability and rapid metabolism restricted the successful translation of resveratrol to clinical form. The *in vivo* efficacy of RS is affected due to its low solubility and low bioavailability. Oral intake of 25 mg of RS showed extremely low bioavailability; only a trace amount of unmetabolized RS was detected in plasma. The gastrointestinal tract absorbs approximately 70% of RS, 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, reportedly reduces obesity, inflammation, and drug resistance[105,106]. It also induces cytotoxicity in cancer cells by promoting intrinsic apoptosis pathways. One study investigated 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 cancer cells. Gene and protein expression studies revealed reduced levels of NF-κB, cyclooxygenase 2, and PPARγ. Avicularin may have the potential to modulate PPARγ to induce antineoplastic 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 such as anticarcinogenic, anti-inflammatory, anti-angiogenic, antioxidative, and 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 PPARγ agonist. The binding of honokiol into the ligand-binding pocket of PPARγ was anticipated *via* various *in silico* techniques. The luciferase reporter assay confirmed this binding and advocated that honokiol could act as a partial PPARγ 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 have suggested that honokiol acts as an RXR agonist forming RXR dimers and activating PPARγ/RXR heterodimers. Additionally, it also potentiates the activation of PPARγ/RXR heterodimers induced by rosiglitazone[109-111]. 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 cell lines *via* inhibiting the Skp2 and low-density lipoprotein receptor-related protein 6 expression. 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 signal transducer and activator of transcription 3 (STAT3) pathway[116,117]. It inhibits cell proliferation, cell cycle regulation, and invasiveness of the cancer cells by promoting the autophagy of HCC[118]. However, the bioavailability of QE is very low due to its poor aqueous solubility and instability, challenging its therapeutic application in the pharma sector[119].

CONTRADICTORY ROLE OF PPARγ

Cancer tissues display metabolic and thermodynamic aberrations with dysregulated cellular growth. Although the role of PPARγ and its agonists in HCC and other cancers have been extensively studied, as discussed above, several conflicting reports exist concerning the PPARγ expression in cancers. It is unclear whether PPARγ induction promotes or suppresses tumor growth and viability. In the case of several cancers, PPARγ 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 upregulated PDK1, which leads to aerobic glycolysis and mitochondrial stress[29]. A recent report by Galbraith *et al*[120] revealed that the activation of PPARγ, in turn, induced Akt serine/threonine kinase 3 (AKT3), which eventually led to the more aggressive form of cancer. AKT3 enhances PGC1α localization to the nuclear space by repressing chromosome maintenance region 1, while the latter served as the downstream target for PGC1α. All these led to mitochondrial biogenesis, which fueled the progression of the tumor. Previous studies have also reported such inconsistent findings for PPARγ in HCC. Koga *et al*[10] tested five patients with cirrhotic livers and found no significant change in the PPARγ expressions compared to the surrounding non-cancerous tissue. Another study reported the consistently overexpressed PPARγ 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 PPARγ agonists are reported, they are also suggested to have PPARγ-independent effects on cancers. Troglitazone, as discussed above, has a prominent antitumorigenic role in HCC. However, there are reports of it exhibiting PPARγ-independent activity. Palakurthi *et al*[122] studied troglitazone and ciglitazone on both PPARγ-/- and PPARγ+/+ 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. This evidence demonstrated that the antiproliferative effect was induced by suppressing the translation initiation. More similar reports back up the PPARγ-independent antitumorigenic property of PPARγ agonists[123,124]. One of the studies focused on the HCC progression in HBV-transgenic mice demonstrated that the anticancerous, antiproliferative, and apoptotic effects of TZD were more significant in PPARγ-deficient mice in comparison with the control mice, exhibiting normal PPARγ levels[125]. It is well-understood that PPARγ could potentially affect various pathways, so it is vital to understand the underlying mechanisms critically. This understanding is an absolute requirement as PPARγ may be inconsistent. However, it highlights its crucial role in tumor development, suggesting that targeted biomedical research against PPARγ could provide a highly efficacious avenue for treating and managing of HCC and various other cancers.

CONCLUSION

The majority of current studies support the fact that PPARγ may be a potential target against the progression of HCC. They have extensively explored the various signaling cascades through which PPARγ exerted inhibitory against HCC using synthetic and natural agonists in preclinical and clinical trials. PPARγ was suggested as a potential target as it suppresses cell proliferation, migration, and invasion in HCC cells through different signaling pathways. TZD, a class of synthetic PPARγ 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 PPARγ 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 PPARγ in HCC. These contradictions might be due to some unidentified link between PPARγ and cancer. With the well-established role of PPARγ in the progression of HCC, better efficacy of its agonists may be achieved by a complete understanding of underlying mechanisms through which PPARγ showed therapeutic effects. Future studies should be focused on developing novel PPARγ targeting therapy for the treatment of HCC.

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