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REVIEW

WILEY

Therapeutic potential of PPARγ natural agonists in liver diseases

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Abstract

Peroxisome proliferator-activated receptor gamma (PPARγ) is a vital subtype of the PPAR family. The biological functions are complex and diverse. PPARγ plays a significant role in protecting the liver from inflammation, oxidation, fibrosis, fatty liver and tumours. Natural products are a promising pool for drug discovery, and enormous research effort has been invested in exploring the PPARγ-activating potential of natural products. In this manuscript, we will review the research progress of PPARγ agonists from natural products in recent years and probe into the application potential and prospects of PPARγ natural agonists in the therapy of various liver diseases, including inflammation, hepatic fibrosis, non-alcoholic fatty liver and liver cancer.

KEYWORDS

liver diseases, natural agonists, PPARγ

1 | MOLECULAR STRUCTURE OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA (PPARγ)

The PPARs belongs to the superfamily of nuclear hormone receptors and is named for its activation, which is regulated by the peroxisome proliferators. There are three subtypes of PPARs (PPARα, PPARβ and PPARγ). These three subtypes of PPARs are expressed differently in different tissues. PPARα is mainly manifested in cardiomyocytes, hepatocytes, intestinal epithelial cells and renal tubule epithelial cells; PPARβ is found in many tissues, with the higher expression in the intestine, kidney and heart; and PPARγ is mainly expressed in adipose tissue.[1]

PPARs always consist of four domains (A/B, C, D and E/F, Figure 1)The A/B region, located at the N end of the receptor protein, is the active functional region and differs among the subtypes and is independent of ligands. Region C is the DNA binding domain containing two zinc finger structures. Area D is the hinge domain. Region E/F, located at the end of C, is the ligand binding domain and contains a ligand-dependent transcriptional activation functional region.[2] The PPARγ gene can be transcribed into different PPARγ mRNAs and translated into two isoforms [PPAR γ1 and PPAR γ2].[3]

After binding to ligands, PPARγ is activated and combines with retinoids X receptor (RXR) to form a heterodimer. Then, a series of synergistic factors are recruited and combined with the heterodimer to take part in regulating transduction. Typical endogenous ligands for PPARγ include prostaglandins, eicosanoids and fatty acids. At the same time, PPARγ can also directly activate specific genes or conduct gene transduction through DNA-independent patterns (Figure 2).

2 | FUNCTION AND CELLULAR ROLES OF PPARγ

The biological functions of PPARγ are complex and diverse, including regulation of lipid and carbohydrate metabolism, energy balance,

inhibiting inflammation, inducing tumour cell differentiation and apoptosis, inhibiting tumour angiogenesis, anti-fibrosis and anti-atherosclerosis, reducing blood fat and blood pressure, improving heart failure and participating in ventricular remodelling. Thus, PPARγ is a current focus of research present. And indeed, there are a number of researchers, who have written review articles to shed more light on the power of PPARγ.

Semple reviewed the function of PPARγ and its variants in metabolic syndrome.[1] In addition, Jia,[4] Chigurupati[5] and Vallée[6] analysed therapeutic potential of PPARγ agonists in diabetes. PPARγ agonists improve insulin sensitivity and treat complications of diabetes. PPARγ can stimulate the differentiation of pre-adipocytes into mature adipocytes and is closely related to adipogenesis in mature adipocytes.[7] The beneficial role of PPARγ in regulation immunity was summarized by Samuel Philip Nobs,[8] Chung,[9] Abdelrahman,[10] Giaginis[11] and Staels.[12] PPARγ inhibits pro-inflammatory responses by macrophages, DCs, and T cells. Reka,[13] Lecarpentier[14] and Heudobler[15] reviewed the implications for PPARγ in cancer therapy and prevention. Activation of PPARγ by agonists has the ability to inhibit cell proliferation and growth based on the ability to induce differentiation. A number of in vitro and in vivo experiments have shown that PPARγ is expressed in tumour cells and can inhibit the growth of cancer cells after activation, such as breast cancer,[16,17] pancreatic cancer,[18] colon cancer[19,20] and gastric cancer.[21] Additional results confirmed that decreased expression of PPARγ was found in activated hepatic stellate cells (HSCs), suggesting that the increased expression and activity of PPARγ promoted the recovery of activated HSCs to a resting state.[22-25] Among the multiple biological responses involved, PPARγ plays a corresponding role by regulating the expression of signalling pathways, including JAK-STAT, NF-kB, nuclear factor of activated T cell, AP-1, PI3K, leptin and adiponectin. Therefore, PPARγ is of vital importance when making a diagnosis and selecting treatment for related diseases.

3 | PPARγ AGONISTS FROM NATURAL PRODUCTS

Because of the significant role of PPARγ in diseases, the identification of PPARγ agonists is regarded as targets of numerous drug development works. Large amounts of fatty acids and fatty acid derivatives can activate PPARγ. Among the PPARγ activators, long-chain polyunsaturated fatty acids always show better effects, such as eicosanoids [8-S-hydroxyeicosatetraenoic acid and leukotriene B4]. Also, PPARγ can be activated by several prostanoids, such as 15-deoxy-Δ12, 14-prostaglandin J2 (15d-PGJ2) and 15-hydroxyeicosatetraenoic acid. The effect of 15d-PGJ2 has been widely recognized.[11] Thiazolidinediones (TZDs) are synthetic ligands of PPARγ and are well-known for excellent potency in regulating blood glucose levels and insulin sensitivity.[26] However, the undesirable side effects, such as fluid retention, weight gain, cardiac hypertrophy and hepatotoxicity, have limited the clinical use of TZDs.[5] Thus, searching for drugs with a similar clinical function, but fewer side effects has become a new direction of effort. Natural products are rich sources of drug discovery; thus, natural products are a focus of research.[27,28]

Previous studies have successfully demonstrated various PPARγ agonists from natural resources by using reporter gene assays, pharmacophore models, silicon screening and virtual screening approaches. A cell-based luciferase reporter system may become a suitable method to detect bioavailability of nuclear receptors, including PPARs.[29] Rasmus[30] demonstrated that the pharmacophore model can be used to select novel PPARs agonists. In addition, Jang and Peng[31,32] identified promising PPARγ agonists on the basis of structure analyses. Since the first time that virtual screening (VS) was used to identify novel PPARγ agonists by Salam et al,[33] more and more researchers have begun using in silico methods alone or combined with other approaches, such as in vivo or in vitro experiments,[34,35] structure analyses[36,37] and some databases,[36] to find novel agonists as potential candidates to treat diseases.[38] The functionality of some approaches has been verified.

To review PPARγ agonists from natural products we checked the database, DrugBank (www.drugbank.ca), which combines bio- and chem-informatics. Table 1 shows our results. Resveratrol, curcumin, isoflavone, cannabidiol, nabiximols and medical cannabis have been confirmed to have the agonist role.

Not surprisingly, an abundance of research efforts has been undertaken to explore the potential applications of full or partial PPARγ natural agonists. Table 2 exhibits the natural agonists and their functions, which have been discussed in recent years. After reviewing the reported agonists, we found that the majority are flavonoids or isoflavonoids. Most of the other agonists are stilbenes, polyacetylenes, amorfrutins, sesquiterpene lactones and derivatives

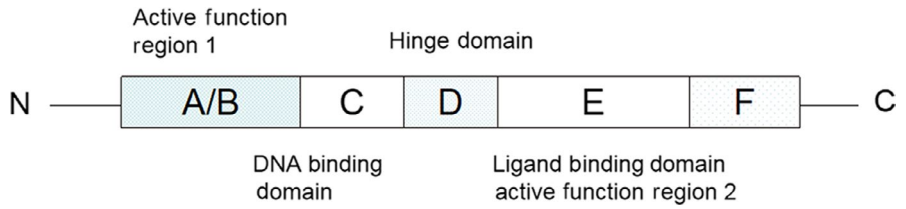


FIGURE 1 PPARγ structure. The A/B region, located at the N end of the receptor protein, is the active functional region. Region C is the DNA binding domain. Area D is the hinge domain. Region E/F, located at the end of C, is the ligand binding domain and contains a ligand-dependent transcriptional activation functional region

of diterpenequinone. The diversity of agonists depends on the large size of the LBD binding pocket and its flexibility.

Meanwhile, there are new trends in the treatment of liver disease which are using dual PPARα/γ or PPAR δ/γ agonists and pan agonists to enhance treatment efficacy.[39,40] Of note, synthetic dual or pan PPAR agonists were discontinued due to adverse events.[41] It has been showed that resveratrol,[42] carvacrol,[43] osthole,[44] dark tea extracts,[45] isoprenols,[46] pseudolaric acid B,[47] mulberry leaf water extract, Korean red ginseng, banaba leaf water extract,[48] and cannabinoids[49] activate two or three isotypes of PPARs, and can therefore be used for regulate metabolism. And the compound functions are discussed below.

The liver is the centre of bio-transformation and detoxification of numerous metabolites and toxicants. Exposure to high levels of exogenous or endogenous toxins may lead to liver damage, which ranges from a transient elevation of liver enzymes to hepatic inflammation, fibrosis, cirrhosis and cancer. Although the expression of PPARγ is always at a low level in liver, PPARγ agonists exhibit various PPARγ-dependent or PPARγ-independent effects in liver.[50] In addition, researches on our team have focused on the prevention and therapy of liver diseases in recent years. We also have published some reports on the effects of PPARs in liver diseases. The protective effects of many Chinese herbal medicines, such as quercetin,[51-53] oleanolic acid,[54] proanthocyanidin B2,[55] epigallocatechin-3-gallate,[56] isorhamnetin[57] and genistein,[58] in liver diseases have been confirmed by our studies.

In fact, some of the Chinese herbal medicines or plants extracts have been reported to have a close relationship with PPARs, and a range of PPARγ activating natural products were recently recognized that possess a great potential to be further explored for the therapeutic effectiveness in liver diseases; but it has not thoroughly reviewed, and its natural agonists have been evaluated even less. Even, few reviews of the effects of PPARγ natural agonists in liver disease have been published. Understanding the role natural products play, as well as their therapeutic potential for fighting liver diseases, including hepatitis, fibrosis, fatty liver and liver cancer, is critical for future progress. Therefore, our present review summarizes the latest research progress of PPARγ agonists from natural products in recent years and explores the application prospect of PPARγ natural agonists in the treatment of liver diseases.

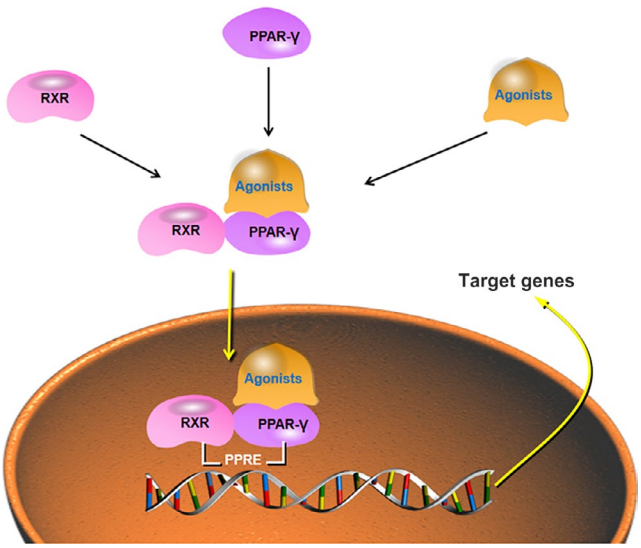


FIGURE 2 PPARγ activation. In normal cells, the PPARγ is located in the cytoplasm. After combining with its agonists and retinoid X receptor (RXR), the PPARγ complex translocates to the nucleus where it recognizes specific DNA sequence elements (peroxisome proliferator response element, PPRE) in promoters of target genes

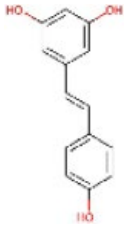
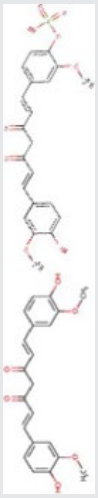
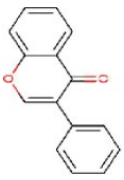
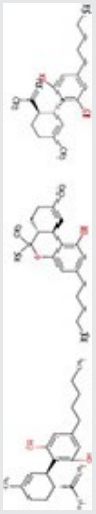
4 | PPARγ NATURAL AGONISTS AND LIVER DISEASES

4.1 | PPARγ natural agonists in hepatitis-associated inflammation

Inflammation is provoked by pathogenic agents, physical or chemical harm, and ischaemic or autoimmune injury, and it is a vital response for protection. The role of PPARγ in the regulation of inflammatory responses has received particular attention. PPARγ appears to be expressed in many cell types of the immune system, such as macrophages, dendritic cells, platelets, T cells and B cells.[59] In addition, PPARγ has been shown in numerous studies to affect the expression of pro-inflammatory, anti-inflammatory and pro-resolving cytokines.[60-63] (Figure 3).

Feng reported that apigenin activates PPARγ and ameliorates inflammation via regulation of macrophage polarization.[64] Apigenin (4,5,7-trihydroxyflavone) is a plant flavonoid abundant in fruits and vegetables that acts as a PPARγ modulator by binding and activating the PPARγ. Moreover, PPARγ is regarded as a modulator of macrophage polarization. Apigenin activates PPARγ and inhibits p65 translocation into the nucleus, favouring M2 macrophage polarization. The ability of apigenin in reversing M1 macrophages into M2 macrophages was confirmed based on in vivo experiments in mice.[65] Apigenin decreased the secretion levels of interleukin(IL)-1β, IL-6, IL-12 and TNF-α both in vitro and in vivo. Hesperidin is a flavanone glycoside in citrus fruits. When detecting the effect of hesperidin in diethylnitrosamine-induced hepatocarcinogenesis, Mahmoud found that hesperidin ameliorates oxidative stress and inflammation, dramatically up-regulates the expression of PPARγ, and significantly prevents liver damage.[66,67] The anti-inflammatory effect of curcumin, a natural polyphenolic compound, was reported by El-Naggar et al.[68] In streptozotocin-induced diabetic rats, the up-regulation of alanine aminotransferase, aspartate aminotransferase, cyclooxygenase, transforming growth factor-β1 and nuclear factor kappa B were reversed by curcumin via its promotion of PPARγ expression. In an investigation of the jellyfish-derived fungus, *Penicillium chrysogenum* J08NF-4, researchers described a new meroterpene derivative, chrysogenester, which has been defined as a PPARγ agonist. In this study, Lius found that chrysogenester activates PPARγ in Ac2F liver

TABLE 1 PPARγ natural agonists in DrugBank

DrugBank ID	Name	Structure	Function description	References
DB02709	Resveratrol		Antioxidant, anti-inflammatory, anti-cancer	42,95,112–114,116
DB11672,14635	Curcumin, Curcumin sulphate		Anti-inflammatory, antioxidant, metabolic regulation	68,72,73,118,119,123–125
DB12007	Isoflavone		Anti-inflammatory, antioxidant, anti-cancer	108,126,127
DB14009(09061,14011)	Medical Cannabis (Cannabidiol, Nabiximols)		Antioxidant, anti-inflammatory, neuroprotective	123–135

cells and increases nuclear PPARγ protein in RAW 264.7 macrophages. Chrysogenester inhibits phosphorylation of the NF-κB and suppressed the expression of pro-inflammatory cytokines, including NO, TNF-α, IL-1β and IL-6.[69]

These reports confirmed the function of PPARγ natural agonists in liver inflammation. The anti-inflammatory properties of betulin, biochanin A, epigallocatechin gallate, harpagoside, madecassic acid, monascin, resveratrol, rhizoma dioscoreae nipponicae polysaccharides and ursolic acid, which can increase the expression of PPARγ, have been explored by many other scientists. These findings provide evidence for the application prospect of PPARγ natural agonists in inflammatory liver diseases.

4.2 | PPARγ natural agonists in liver fibrosis

Liver fibrosis is a chronic and dynamic pathophysiological process, and commonly, excessive secretion and deposition of matrix proteins by HSCs is a pivotal step. Liver fibrosis is closely connected with hepatitis virus infection, alcohol and lipids. The expression of PPARγ is high expression in quiescent HSCs; however, PPARγ is suppressed during fibrosis process. Studies have shown that PPARγ activation blocks HSCs activation and reduces collagen deposition during hepatic fibrogenesis. Thus, PPARγ is an effective target in anti-fibrosis therapy.[70] Also, most PPARγ agonists from nature are partial agonists and always play a biological role by regulating the expression of a variety of genes, resulting in achieving better results. Thus, more and more authorities believe PPARγ agonists could become available therapeutic agents (Figure 4).

Curcumin, for acid polyphenols, is a yellow pigment in turmeric. Zheng and Chen have verified curcumin function inducing PPARγ expression in activated HSCs and suppressing extracellular matrix production (ECM). They found that curcumin could stimulate the trans-activation activity of PPARγ, and thus reduce HSC proliferation, induce apoptosis, down-regulate the expression of ECM gene expression and regulate pathways of TGF-β and connective tissue growth factor.[71,72] Guo et al described the anti-fibrotic role of puerarin, an active ingredient from kudzu root. Puerarin effectively attenuated liver damage by up-regulating PPARγ expression in CCl_4-induced hepatic fibrosis. Puerarin can reverse the changes in serum hepatic enzyme activity, reduce ECM deposition and regulate the expression of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinase (TIMPs).[73] Monascin is derived from monascus-fermented secondary metabolites. It has been shown that monascin rescues the inhibited expression of PPARγ. In HSCs from carboxymethyllysine-induced fibrosis, monascin attenuates α-smooth muscle actin and reactive oxygen species generation. Monascin may slow or even block the progression of liver fibrosis through activation of PPARγ.[74] Chois reported that capsaicininhibits liver fibrosis by restraining the TGF-β1 pathway expression via activation of PPARγ. This report described the protective effect of capsaicin. The mechanism of action of capsaicin includes the reduction of oxidative stress and inflammatory response, induction of HSCs apoptosis and repression of ECM production.[75]

TABLE 2 Discussed natural agonists of PPARγ (from 2010 to 2019)

Functions	Agonists	Years	References
Anti-cancer	*Chromolaena odorata*, Luteolin, Stereoisomers ginsenosides	2012	136–140
	Turbinaria ornata and *Padina pavonica*	2015	141
	Resveratrol	2016, 2019	42,95,113,115
Anti-fibrosis	Puerarin	2013, 2017	74
	Piperine	2017	143
	Berberine	2018	144
Anti-inflammation	Monascin	2011, 2014	145–147
	Astaxanthin, Ankaflavin, Biochanin A, Cullin-3, Danhong, Daidzein	2012	148–153
	Ursolic acid, Epigallocatechin gallate, Monascin	2013	154–156
	Rhizoma Dioscoreae Nipponicae polysaccharides, Harpagoside, Tectorigenin, Chrysin	2015	157–160
	Huangkui, Tripchlorolide, *Kochia scoparia* and *Rosa multiflora*, Resveratrol, Chrysin, Daidzein	2016	115,121,161–164
	Astragalus, Fraglide-1, Madecassic acid, Epigallocatechin Gallate, Hesperetin	2017	66
	Isoprenylated flavonoid, chrysogenum J08NF-4, *Portulaca oleracea* L., Betulin, *Terminalia arjuna*, Naringin	2018	69,169–173
	Beta-caryophyllene, Wogonin, Resveratrol, Hesperetin	2019	113,174–176
Metabolism regulation	Cerco-A, Mycophenolic acid, Fructus Schisandrae, Monascin	2011	156,177–179
	Ankaflavin, Astaxanthin, Danhong	2012	149,150,152
	Amorfrutin, Honokiol, Monascin	2013	156,180,181
	Chebulagic acid, Monascin	2014	145,147,182
	Kaempferol, *Lonicera japonica* Thunb, Quercetin, Tectorigenin	2015	160,183,184
	Osthole, Isorhamnetin, Huangkui, Saponins and sapogenins, Resveratrol, quercetin	2016	95,162,185–188
	ZINC13408172, 4292805, 44179 and 901461, Lycium, Astragalus, Tetrahydrocannabinolic acid, Astragaloside IV	2017	168,189–192
	Betulin, Chlorogenic acid, Isoprenylated flavonoid, Gentiopicroside, Geranylgeraniol, Moringa concanensis Nimmo, *Terminalia arjuna*, Saponins and sapogenins	2018	169,170,172,193–196
	Kaempferia parviflora, Moringa concanensis Nimmo, Resveratrol	2019	42,95,197,198

4.3 | PPARγ natural agonists in liver cancer

More than one decade ago, PPARγ was reported to be closely related to the formation of liver tumours in animals. Researchers found that oestrogen can activate PPARγ by inducing the formation of the metabolite of prostaglandin D2, then activated PPARγ can promote the proliferation of peroxidase bodies, finally causing oxidative DNA damage. This process is closely related to the formation of hepatic tumours.[76] However, with the deepening of research, people have different definitions about the role of PPARγ in the development of liver cancer.[77,78] Koga[79] reported that the expression of PPARγ in liver cancer was very similar to that in surrounding non-tumorous cirrhotic liver; however, the number of cases was small. Schaefer[80] and Lin[81] found that PPARγ is highly expressed in hepatic cancer tissues and in HCC cell lines, and the inhibition of PPARγ function could cause HCC cell death. At the same time, other papers analysed the expression of PPARγ in human HCC tissues and adjacent non-tumorous liver tissue, and found a significant decrease in HCC tissues, thus showing us that PPARγ ligands, including thiazolidinediones. TZDs and 15-deoxy-Δ12,14-prostaglandin J2 inhibit growth and induce apoptosis of liver cancer cells.[82-87]

When scientists shifted their perspective to natural agonists of PPARγ, the potential in HCC therapy was shown. Avicularin is a bioactive flavonoid from various plants. Researchers use Huh7 cells to investigate the effect of avicularin in HCC. The results indicated that avicularin treatment decreased cell proliferation, inhibited cell migration and invasion in HCC and induced cell apoptosis via inhibiting the G0/G1-phase cells and decreasing the accumulation of S-phase cells. Moreover, the demonstrated anti-cancer efficacy of avicularin was at least partly dependent on its activation of PPARγ activities.[88] Another flavonoid, hispidulin, exhibits potent cytotoxicity towards a variety of human cancers. Hans confirmed the protective effect of hispidulin on HCC both in vitro and in vivo. Hispidulin triggered apoptosis, inhibited cell migration and invasion, and activated PPARγ

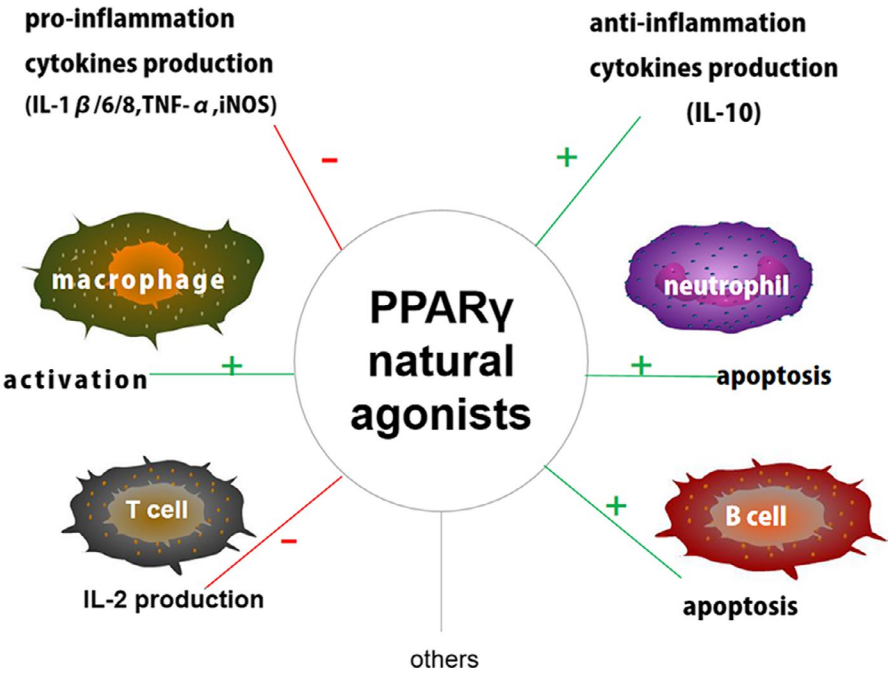


FIGURE 3 PPARγ natural agonists and inflammation. PPARγ natural agonists can regulate inflammatory responses. PPARγ natural agonists promote the activation of macrophages, the apoptosis of neutrophils and B cells, and the expression of some anti-inflammatory cytokines. In addition, PPARγ suppresses the function of T cells and decreases the expression of some pro-inflammatory cytokines

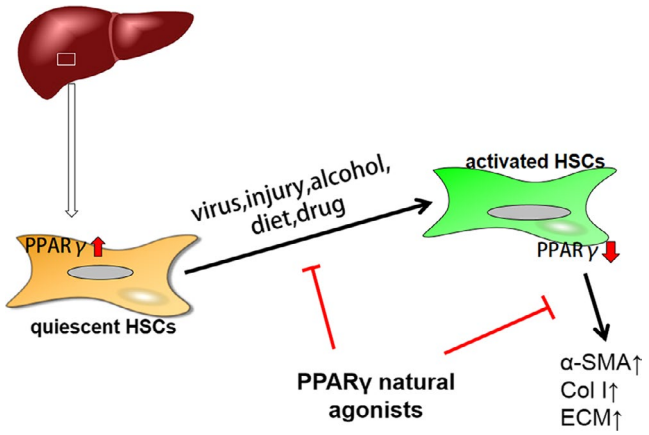


FIGURE 4 PPARγ natural agonists and liver fibrosis. Activation of HSCs is closely connected with viral infections, injury alcohol, diet and drugs. PPARγ is highly expressed in quiescent HSCs; however, PPARγ is suppressed during the process of fibrosis. PPARγ natural agonists block HSC activation and reduce collagen deposition during hepatic fibrogenesis

signalling. The animal experiments showed that hispidulin administration could suppress tumour growth and lung metastasis.[89] Huangs studied the combined effects of chrysin and apigenin, both of which are found in *Morinda citrifolia*, in liver cancer. These two drugs were used in both in vivo and in vitro experiments, and authors found they could inhibit cancer cell growth, disorganize cell cycle distributions and suppress cancer cell migration. The combined effects were better, compared with either alone.[90] Vara team detected the anti-proliferative effects of cannabinoids in hepatocellular carcinoma on HepG2 and HUH-7 cell lines in vitro and in vivo. Δ9-tetrahydrocannabinol and JWH-015 are two famous cannabinoids, and they could inhibit cancer cell proliferation and induce autophagy. The activity and intracellular level of PPARγ were increased by them, and the effects can be abolished by a PPARγ inhibitor.[91]

The studies on the favourable effects of PPARγ natural agonists for HCC were few, and researches for several other types of cancer are listed in Table 3.[16,92-94] To some extent, they can also demonstrate the potential of PPARγ natural agonists as anti-liver cancer agents.

4.4 | PPARγ natural agonists in non-alcoholic fatty liver disease (NAFLD)

Fatty liver disease, due to input/output imbalance of hepatic free fatty acid(FFA) metabolism, is regarded as one of the most common chronic liver diseases worldwide. Insulin resistance and oxygen stress are regarded as the central to development. The multi-layer and multi-angle function of PPARγ have been confirmed by many researchers.[95,96] As we mentioned above, PPARγ activation down-regulate inflammatory response,[97] inhibit HSCs activation,[98] increase energy expenditure[99] and increase insulin sensitivity.[100] PPARγ activation could stimulate fatty acid oxidation in the liver.[101,102] These are positive roles of PPARγ. At the same time, in vivo experiments for deletion or overexpression of PPARγ exhibited its prosteatotic role in the development of NAFLD or NASH.[103-105] PPARγ also regulates lipid deposition in liver and other tissues.[106] Utilizing the positive effects of PPARγ while limiting its negative effects by targeting other PPARs has paved the way for the development of a new batch of dual and pan agonists. Some researchers have set their sights to natural dual and pan PPAR agonists. There are some cell studies showing that soy isoflavones exhibit antidiabetic and hypolipidemic effects by activating both PPARα and PPARγ.[107] Guozhu[42] reported that resveratrol suppresses oleate-induced total cholesterol accumulation in macrophages by activating PPARα/γ signalling pathway, and it was confirmed that resveratrol could prevent

TABLE 3 Anti-cancer effect of PPARγ natural agonists

Agonists	Cancer type	Function	References
Cladosporol A	Colorectal cancer cell	Inhibit proliferation, up-regulate 3 p21waf1/cip1 gene expression, inactivate β-catenin/TCF pathway	94
Morusin	Breast cancer cell	Inhibit proliferation, induce adipogenic differentiation, apoptosis and lipoapoptosis of cancer cells, up-regulate expressions of C/EBPβ	16
Carotenoids	Leukaemia K562 cells	Inhibit proliferation, decrease the viability, induced G0/G1 cell cycle arrest, up-regulate the expression of Nrf2	93
Chrysin	Breast cancer cell	Inhibit proliferation, decrease the viability, inhibit epithelial-mesenchymal transition	91
6-Shogaol	Breast and colon cancer cell	Inhibit proliferation, induced G2/M cell cycle arrest	19
Bitter gourd seed	Colon cancer cell	Inhibit proliferation, induce apoptosis and up-regulate GADD45, p53	20
Deoxyelephantopin	Hela cells	Inhibit proliferation, induce apoptosis and cell cycle arrest at G(2)/M phase	199
Dihydroartemisinin	Colon cancer cell	Inhibit proliferation, induce apoptosis	200
isoprenols	Colon cancer cell	Induce apoptosis	201
Hydroxysafflor-Yellow A	Gastric carcinoma cell	Inhibit proliferation, induce apoptosis and cell cycle arrest at G0/G1 phase	202
Luteolin	Colorectal cancer cell	Luteolin-mediated OCTN2 expression and activity potentiate the sensitivity of cancer cells to oxaliplatin	203
Lycopene	Prostate cancer cell	Inhibit proliferation	204

hepatic steatosis in NAFLD.[108] Polyphenolic compounds from different sources showed apparent effects on PPAR expression and affect lipid accumulation in high-fat-fed mice.[109] Bavachinin is a natural pan PPAR agonist that increase effectiveness of TZDs or fibrates when regulating carbohydrate and lipid metabolism in diet-induced obese mice.[110]

5 | CONCLUSION

Natural products have been and continue to be rich sources for drug discovery. Natural agonists of PPARγ have confirmed anti-inflammatory, antioxidant properties, anti-fibrosis, anti-tumour and metabolism regulation effects. These beneficial effects may be partly due to the role of PPARγ in pathophysiological processes. Both experimental and clinical research results have indicated PPARγ agonists from natural products play vital roles in their protective effects in liver diseases. Besides, dual PPARα/γ or PPAR δ/γ agonists and pan agonists have draw researchers' attention, and sometimes they have better curative effects.

However, the limitation of this review is that there are few studies on the treatment of liver diseases with PPARγ natural agonists. Because PPARγ and the target genes of natural products are diverse, it is likely that many other mechanisms contribute to their beneficial effects in these and other disease models. A lot of ongoing research efforts are trying to broaden our horizons to better understand the role of PPARγ systematically.

CONFLICT OF INTERESTS

The authors report no conflicts of interest in the present study.

AUTHOR CONTRIBUTION

Liwei Wu wrote the manuscript and made the original tables and figures. Chuanyong Guo and Jianye Wu revised the manuscript and tables and figures. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

All data included in this study are available.

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