**Review Article**

**15-Deoxy-Δ-12,14-Prostaglandin J2 (15d-PGJ2), an Endogenous Ligand of PPAR-γ: Function and Mechanism**

**Jingjing Li**, **Chuanyong Guo**, and **Jianye Wu**

*1Department of Gastroenterology, Putuo People’s Hospital, Tongji University School of Medicine, Shanghai 200060, China*

*2Department of Gastroenterology, Shanghai Tenth People’s Hospital, Tongji University School of Medicine, Shanghai 200072, China*

Correspondence should be addressed to Jianye Wu; wijmail@163.com

Received 29 March 2019; Accepted 14 July 2019; Published 1 August 2019

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15-Deoxy-Δ-12,14-prostaglandin J2 (15d-PGJ2), a natural peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist, has been explored in some detail over the last 20 years. By triggering the PPAR-γ signalling pathway, it plays many roles and exerts anti-tumour, anti-inflammatory, antioxidation, antifibrosis, and antiangiogenesis effects. Although many synthetic PPAR-γ receptor agonists have been developed, as an endogenous product of PPAR-γ receptors, 15d-PGJ2 has beneficial characteristics including rapid expression and the ability to contribute to a natural defence mechanism. In this review, we discuss the latest advances in our knowledge of the biological role of 15d-PGJ2 mediated through PPAR-γ. It is important to understand its structure, synthesis, and functional mechanisms to develop preventive agents and limit the progression of associated diseases.

**1. Introduction**

Prostaglandins are lipid signalling molecules with multiple functions that are produced from arachidonic acid by cyclooxygenase [1]. Most prostaglandins activate a variety of intracellular signalling pathways and stimulate various biological activities by activating specific G protein-coupled receptors on cell membranes [2, 3]. Most prostaglandins exert proinflammatory effects, but cyclopentenone prostaglandins reportedly exert anti-inflammatory effects. 15-Deoxy-Δ-12,14-prostaglandin J2 (15d-PGJ2), the most widely studied cyclopentenone prostaglandin, was also the first endogenous ligand of peroxisome proliferator-activated receptor-γ (PPAR-γ) to be identified [4]. However, PPAR-γ plays an important role in lipid and carbohydrate metabolism, inflammation, and the proliferation and differentiation of many cell types in different tissues [5, 6]. The present review summarises the health benefits of 15d-PGJ2 related to various diseases and the PPAR-γ signalling pathway.

**1.1. Structure of 15d-PGJ2.** 15d-PGJ2 is a prostaglandin derived from arachidonic acid. It is an unsaturated carboxylic acid composed of a 20-carbon skeleton that includes a five-membered ring. It has highly active alpha- and beta-unsaturated carbonyl groups that can covalently bind to mercaptan groups of various proteins, thereby altering their functions. 15d-PGJ2 is a cyclopentenone prostaglandin with broad biologically activity that generally exists in liquid form (Figure 1). The molecular formula of 15d-PGJ2 is C20H28O3, and the molecular mass is 316.4 kDa.

**1.2. Biosynthesis of 15d-PGJ2.** 15d-PGJ2 is the most widely studied metabolite of the prostatic family of PGJ2 compounds. It can react rapidly with important cell nucleophiles such as cysteine sulphydryl groups of proteins via the MELK addition reaction, thereby altering biological activity [7]. First, arachidonic acid in membrane phospholipids is induced by phospholipase A, and unstable endoperoxide prostaglandin H2 (PGH2) is produced by cyclooxygenase 1 and 2 (COX-1 and -2). In the presence of sulphydryl complexes, PGD2 synthase catalyses the isomerisation of PGH2 to PDGD2, PGF2α, PGJ2, and thromboxane A2 that interact with specific receptors. PGD2 can spontaneously release water molecules to form PGJ2, partly dependent on serum albumin, resulting in Δ12PGJ2 and other molecules,
1.3. 15d-PGJ2 Regulation of PPAR-\(\gamma\). The N-terminal functional region of PPAR-\(\gamma\) contains a phosphorylation site mitogen-activated protein kinase (MAPK). After 15d-PGJ2 enters cells and binds to PPAR-\(\gamma\), activation results in the formation of heterodimers with retinoid X receptor alpha (RXR\(\alpha\)) and subsequent binding to specific DNA sequences to activate expression of target genes [8]. This specific DNA sequence, found in genes encoding hexanoyl coenzyme A synthase, lipoprotein lipase (LPL), insulin receptor substrate-2 (IRS-2), leptins, and tumour necrosis factor-alpha (TNF-\(\alpha\)), is known as the peroxisome proliferator response element (PPRE) [9]. Simultaneously, PPAR can also affect nuclear factor-kappa B (NF-\(\kappa\)B), activator protein-1 (AP-1), and JAK/STAT, which further regulates the expression of downstream related genes and plays an important role in fat formation, glycolipid metabolism, inflammatory responses and immunity (Figure 3) [10–13].

2. Bioavailability of 15d-PGJ2 Related to PPAR-\(\gamma\)

PPAR-\(\gamma\) is the main target of many natural compounds and is closely related to cancer, inflammation, hypertension, type 2 diabetes, and other diseases [14–16]. 15d-PGJ2 is one of the most well defined PPAR-\(\gamma\) ligands, and its anticancer and anti-inflammatory effects may or may not be dependent on PPAR-\(\gamma\). This review summarises recent findings regarding the functions and mechanisms of 15d-PGJ2 related to PPAR-\(\gamma\).

2.1. Antitumour Activity. Studies have shown that the natural PPAR-\(\gamma\) agonist 15d-PGJ2 exerts anticancer activity by promoting apoptosis, resisting angiogenesis, and inhibiting migration and stem cell activity [6]. As a PPAR-\(\gamma\) ligand, 15d-PGJ2 can induce terminal differentiation and inhibit the growth of lung and colon cancer cells by inhibiting DNA synthesis [17, 18]. Its functions can be divided into PPAR-\(\gamma\)-dependent and semi-dependent types. One group suggested that 15d-PGJ2 can regulate the myc/mad/max network via PPAR-\(\gamma\) to promote cell apoptosis by inhibiting the expression of human telomerase reverse transcriptase (hTERT) and telomerase activity in colon cancer cells [19]. Another group demonstrated that 15d-PGJ2 may play an anticancer role in gastric cancer [20] and oral squamous cell carcinoma cells [21] by promoting cell apoptosis. Although 15d-PGJ2 is an endogenous ligand of PPAR-\(\gamma\), it promotes apoptosis of cancer cells, and this is not entirely dependent on PPAR-\(\gamma\). Han and colleagues found that 15d-PGJ2 enhanced TRAIL-induced apoptosis by downregulating AKT expression and phosphorylation. The sensitivity of 15d-PGJ2 to TRAIL-induced apoptosis was not completely blocked by PPAR-\(\gamma\) inhibitor GW9662, suggesting that 15d-PGJ2 is not completely dependent on PPAR-\(\gamma\) [22]. In addition, 15d-PGJ2 sensitises cancer cells to TNF-like weak activators through a reactive oxygen species (ROS)-dependent cell death pathway and may have chemotherapeutic effects as an apoptotic enhancer [23]. Consistent with this proposal, Fulzele and colleagues (2007) confirmed that the mechanisms of 15d-PGJ2 (combined with docetaxel) on apoptotic induction in lung cancer are both PPAR-\(\gamma\)-dependent and -independent [24]. These results suggest that PPAR-\(\gamma\) activation may be a key factor in inducing apoptosis of cancer cells. Therefore, 15d-PGJ2 may promote apoptosis of cancer cells in a PPAR-\(\gamma\)-dependent manner, and the PPAR-\(\gamma\) ligand may be a new anticancer agent worthy of further study.

Neovascularisation is a key mechanism of tumorigenesis, development, and rapid metastasis. Therefore, inhibiting angiogenesis is a crucial factor in cancer treatment. It has been reported that 15d-PGJ2 has antineovascularisation effects. Fu and Yuan found that angiogenesis is inhibited by 15d-PGJ2 via downregulation of angiopoietin-1 [25] and vascular endothelial growth factor [26] in gastric and renal cancer. 15d-PGJ2 inhibits overexpression of COX-2 and alters the expression of important angiogenesis regulators in various human malignant tumours [27].

The specificity of 15d-PGJ2 for proliferation and invasion of cancer cells also plays an important role in cancer therapy [28]. The PPAR-\(\gamma\) ligand 15d-PGJ2 can inhibit the growth of oesophageal adenocarcinoma cells by inducing cell cycle arrest, combined with promoting apoptosis and reducing ornithine decarboxylase activity [29]. Furthermore, cell cycle arrest at the G2/M phase and apoptosis of human endothelial cells induced by 15d-PGJ2 result in growth arrest of a uterine cancer cell line [30]. Another study showed that 15d-PGJ2 is a microtubule protein binding agent that can disrupt the stability of microtubules and induce mitotic arrest, leading to breast cancer cell death [31]. In terms of migration and invasion, 15d-PGJ2 is believed to reduce the expression of matrix metalloproteinase (MMP)-2 and MMP-9, thereby inhibiting the invasiveness of breast cancer [32] and pancreatic cancer cells [33, 34]. In addition, 15d-PGJ2 inhibits the proliferation and invasiveness of colon cancer cell lines via a mechanism related to G1 cell cycle arrest, and downregulation of MMP-7 synthesis [35] and CXCR4 via PPAR-\(\gamma\) and NF-kappa B [10]. Together, these studies have
shown that 15d-PGJ2 can simultaneously promote apoptosis and inhibit migration, which can comprehensively inhibit tumour progression.

Recent studies have shown that cancer stem cells play an important role in the initiation and maintenance of tumour growth, and 15d-PGJ2 can control proliferation to a certain extent [36]. However, research on the effect of 15d-PGJ2 on the proliferation of cancer stem cells is in its infancy. First, PPAR-γ agonists have been identified as markers of the inhibition of growth and progression of brain cancer stem cells [37]. However, the effect of 15d-PGJ2 on cancer stem cells and its application to anticancer therapy require further exploration, as do potential therapeutic applications. The antineoplastic effects of 15d-PGJ2 are summarised in Table 1.

2.2. Anti-Inflammatory and Antioxidant Activity. PPAR-γ is expressed in human endothelial cells, vascular smooth muscle cells, and monocytes [38, 39]. 15d-PGJ2 can effectively regulate T-cell activation, expression of surface proteins, and related inflammatory cytokines by enhancing PPAR-γ transcriptional activity [40]. Similar to most other PGs, 15d-PGJ2 displays anti-inflammatory and antioxidative activities, e.g., via inhibition of NF-kappa B and JAK-STAT pathways [41, 42]. This section of the review focuses on the anti-inflammatory and antioxidative effects of 15d-PGJ2.

Activation of macrophages leads to the production of various proinflammatory mediators, such as IL-6, TNF-α, IL-1β, and inducible nitrate oxide synthase (iNOS), among which the activation of PPAR-γ plays a negative regulatory role [43, 44]. Meng and colleagues used the natural PPAR-γ ligand 15d-PGJ2 to stimulate mouse-derived RAW264.7 macrophage cell line and found that angiotensin-II-induced expression of EGR-1, ROS, and inflammatory factors (IL-1β, TNF-α, TGF-β, MCP-1, and ICAM-1) was significantly reduced, while macrophage migration and proliferation were inhibited [45]. In chronic liver injury, 15d-PGJ2 decreases the number and activation of bone marrow (BM)-derived macrophages (BMMs) in damaged liver tissue and inhibits the expression of inflammatory cytokines such as MIP-1β, TNF-α, and NOS2 [46]. Endothelial cells also express large quantities of PPAR-γ, and Marcone et al. (2016) suggested that 15d-PGJ2 may modify proteasomes in human endothelial cells and inhibit the NF-κB inflammation-mediated pathway [47]. Similarly, 15d-PGJ2 can protect brain endothelial cells from apoptosis induced by hypoxia by inhibiting the
transcription of p22phox [48]. In human retinal pigment epithelial cells, 15d-PGJ2 also inhibits lipopolysaccharide (LPS)-stimulated inflammation by enhancing the activity of platelet-activating factor acetyl hydrolase in conjunction with PPAR-γ [49].

The accumulated evidence suggests that, in animal models, 15d-PGJ2 plays an indispensable anti-inflammatory and antioxidative role. Firstly, 15d-PGJ2 can prevent concanavalin A-induced autoimmune hepatitis by reducing the release of proinflammatory cytokines, which is related to the activation of PPAR-γ and decreased NF-κB activity [50]. This mechanism was validated in a HepG2 cell model in vitro [51]. It was also demonstrated that 15d-PGJ2 downregulates the activin receptor and Smad pathways [52]. In an endotoxin-induced lung injury model, 15d-PGJ2 has been shown to reduce the levels of TNF-α and ICAM-1 by inhibiting the activity of NF-κB [53]. In other studies, 15d-PGJ2 protected rat lung tissue from gastric inhalation injury and reduced infection or allergy-induced pulmonary inflammation by inhibiting the production of proinflammatory cytokines (TNF-α and IL-10) [54, 55] and gene expression of chemokines (CCL2, CCL3, CCL4, and CXCL10) [56]. During protection of the nervous system, 15d-PGJ2 is important. M2 microglia can promote neurogenesis and oligogenesis of nerve stem/progenitor cells through the PPAR-γ signalling pathway [57, 58]. PPAR-γ agonists can control inflammation and protect neurons from degenerative diseases of the central nervous system such as Alzheimer’s disease, Parkinson’s disease, and multiple sclerosis by inhibiting activated microglia and via PPAR-γ. Huang et al. found that 15d-PGJ2, a recognised endogenous ligand of PPAR-γ, is increased in the supernatant of M2 phenotype cells. After cerebral perfusion of 15d-PGJ2, expression of TNF-α and IL-1β decreases, the proportion of apoptotic cells decreases, cerebral infarction and brain oedema decrease, and neurological deficits decrease, suggesting that it regulates the neuroprotective effects of microglia [59]. Similarly, pretreatment with 15d-PGJ2 also inhibits the activation of nitrogen oxides and ROS in a PPAR-γ-dependent manner [60], thereby alleviating neuronal damage [61]. Another viewpoint is that 15d-PGJ2 exerts neuroprotective effects by mediating neuronal autophagy following cerebral ischemia-reperfusion injury [62]. In addition, in gouty arthritis, 15d-PGJ2 inhibits

| Tumour type               | Mechanism               | Cell type                  | Dosage       | References |
|---------------------------|-------------------------|----------------------------|--------------|------------|
| Lung cancer               | Apoptosis               | H841, A549, PC14           | 1–40 μM      | [17]       |
| Colon cancer              | Apoptosis               | HT-29                      | 0–100 μM     | [18]       |
| Colon cancer              | Apoptosis               | Caco-2                     | 10–45 μM     | [19]       |
| Gastric cancer            | Apoptosis, Cell cycle(G1) | MKN-7, MKN-28, MKN-45, AGS | 0.1–10 μM    | [20]       |
| Oral squamous cell cancer | Apoptosis, Cell cycle(G2/M) | SCCa                     | 10 μM, 20 μM | [21]       |
| Lung cancer               | Drug combination        | A549, H460, female athymic nu/nu mice | 0–40 μM      | [24]       |
| Colon cancer              | Apoptosis               | HT-29, Caco-2              | 10 μM        | [23]       |
| Leukemic                  | Apoptosis               | HL-60, K562, SNU-C4        | 0–20 μM      | [22]       |
| Gastric cancer            | Inhibition of Ang-1     | MKN45, HUVEC               | 0–10 μM      | [25]       |
| Renal cancer              | Apoptosis, Inhibition of VEGF | SMKT-R-1, R-2, R-3, and R-4 | 0–50 μM    | [26]       |
| Lymphoma                  | Inhibition of COX-2     | U937, BAEC                 | 0–10 μM      | [27]       |
| Oesophageal cancer        | Apoptosis, Cell Cycle(G1) | TE-7                      | 0–10 μM      | [29]       |
| Endometrial cancer        | Apoptosis, Cell Cycle(G2/M) | HHUA, HEC-59             | 0–20 μM      | [30]       |
| Breast cancer             | Apoptosis, Cell Cycle(G2/M) | MCF-7                     | 0–10 μM      | [31]       |
| Breast cancer             | Invasion                | MDA-MB-231                 | 5 μM         | [32]       |
| Pancreatic cancer         | Invasion                | BxPC-3, Mia PaCa-2, Panc-1 | 0–25 μM    | [33, 34]   |
| Colon cancer              | Cell Cycle(G1), Invasion | SW480, L5174T             | 0–40 μM      | [35]       |
| Colon cancer              | Invasion                | HT-29                      | 0–30 μM      | [10]       |
| Brain tumour              | Inhibition of stem cells | U87MG, T98G               | 0–10 μM      | [37]       |
inflammation by reducing the release and oxidative stress levels of IL-1β, TNF-α, IL-6, IL-17, and IL-33 [9]. 15d-PGJ2 can also inhibit the prostaglandin synthesis pathway in activated chondrocytes and regulate the anti-inflammatory circuit by regulating heat shock 70 (HSP70) to reduce the levels of NF-kB, COX-2, and oxidative stress in chondrocytes [63]. Furthermore, 15d-PGJ2 can significantly reduce eosinophil production and migration in the abdominal cavity, via IL-23/IL-17 and IL-33, and exert therapeutic effects on eosinophil-induced diseases [64]. In acute pancreatitis, 15d-PGJ2 also attenuates the expression of TLR4 in acinar cells and inflammatory responses and reduces the severity of acute pancreatitis [65].

In summary, 15d-PGJ2 was the first endogenous ligand of PPAR-gamma to be discovered. It plays anti-inflammatory, antioxidative, and protective roles in brain injury induced by stress, acute pancreatitis, drug-induced lung injury, and ischemia-reperfusion in animal models of monocyes, endothelial cells, macrophages, and other inflammatory diseases. The anti-inflammatory and antioxidant effects of 15d-PGJ2 are summarised in Table 2.

2.3. Antifibrotic Activity. Organ fibrosis has always been a difficult problem for the scientific community to address, because it can lead to progressive dysfunction of various organs [66, 67]. The main pathological mechanism is excessive activation of TGF-β. Ligands of PPAR-γ may depend on activating PPAR-γ to block TGF-β signalling and inhibit tissue and organ fibrosis [68, 69]. Of course, some mechanisms may also play an antifibrotic role independent of PPAR-γ activation. Herein, we systematically review studies on the antifibrosis mechanism of 15d-PGJ2.

In studies on pulmonary fibrosis, 15d-PGJ2 was found to inhibit the differentiation of myofibroblasts driven by TGF-β and the production of type I collagen, and its effects are both dependent on and independent of PPAR-γ [70]. PPAR-γ activation leads to the transformation of hepatic stellate cells (HSCs) from an activated to a stationary state. 15d-PGJ2 can strongly inhibit the proliferation of HSCs, and the expression of connective tissue growth factor (CTGF) in HSCs induced by TGF-β1, and inhibition can be significantly (but not completely) eliminated by pretreatment with PPAR-γ inhibitor GW9662. This indicates that PPAR-γ mediates the inhibition [71]. In the process of renal fibrosis, many kinds of cells participate together, including mesangial cells and fibroblasts, renal tubular epithelial cells, monocytes and macrophages, and lymphocytes [72]. Guo et al. (2004) proposed that 15d-PGJ2 may inhibit the activation of AP-1 and MAPKs by inhibiting TGF-β1, and it may inhibit the expression of fibronectin in mouse mesangial cells, thereby acting via dual mechanisms both dependent on and independent of PPAR-γ activation [73]. Wang et al. demonstrated that 15d-PGJ2 could reverse the TGF-β1/Smads signalling pathway and inhibit the activation of renal fibroblasts, CTGF expression, and extracellular matrix (ECM) synthesis in rat renal interstitial fibroblasts (NRK/49F) [74]. Finally, 15d-PGJ2 can also prevent the loss of the epithelial phenotype induced by TGF-β1 by activating PPAR-γ, and it can inhibit oxidative stress. Interestingly, specific knockout of PPAR-γ cannot play an effective role 15 days later. This indicates that targeting of PPAR-γ plays an important role in maintaining normal epithelial phenotype and fighting fibrosis in renal tubular epithelial cells [75]. In addition, 15d-PGJ2 also plays an important role in many other systems. For example, 15d-PGJ2 blocks TGF-β1-induced elevation of CTGF in cat corneal fibroblasts [76]. In skin fibroblasts, PPAR-γ activation can also eliminate the stimulation of collagen gene expression induced by TGF-β1, as well as Smads-dependent promoter activity in myofibroblast differentiation and normal fibroblasts, revealing a new method for controlling scoloderma fibrosis [77]. Fu et al. (2001) also found that 15d-PGJ2 significantly inhibits CTGF production induced by TGF-β1 in human aortic smooth muscle cells in a dose-dependent manner, and activation of PPAR-γ was achieved by directly interfering with the Smad3 signalling pathway [78].

Due to the broad tissue distribution and complex functions of PPAR-γ, its agonists play important physiological roles. Strong antifibrosis effects caused by inhibiting the TGF-β signalling pathway are clearly important [79]. In conclusion, evidence suggests that TGF-β is a key mediator of fibrous tissue. As a PPAR-γ agonist, 15d-PGJ2 has a significant inhibitory effect on TGF-β signal transduction and is an effective antifibrosis drug. The antifibrotic effects of 15d-PGJ2 are summarised in Table 3.

2.4. Other Biological Activities. 15d-PGJ2 also plays an important role in other diseases. During the development of osteoporosis, 15d-PGJ2 may inhibit the expression of osteoblast marker genes in bone marrow cells by activating PPAR-γ transcriptional activity, which may be one of the reasons for 15d-PGJ2 involvement in age-related osteoporosis [80]. During vascular remodelling, the PPAR-γ agonist 15d-PGJ2 inhibits Ang II-induced cell proliferation and expression of KLF5 and cyclin D1 in vascular smooth muscle cells with growth arrest in dose-dependent manner, which provides new evidence for the beneficial vascular effects of PPAR-γ activation [81]. Additionally, 15d-PGJ2 inhibits activation of signal transducers and STAT3 in neuronal cells (SH-SY5Y-Ob-Rb cells) induced by leptin through the PPAR-γ pathway [82].

3. Other Molecular Targets of 15d-PGJ2

The effect of 15d-PGJ2 can be achieved independently of PPAR-γ. For example, in cancer research, Shin et al. demonstrated that 15d-PGJ2 can induce apoptosis in leukaemia and colorectal cancer cells through inactivation of AKT mediated by reactive oxygen species, further verifying its antitumour activity in vivo [83]. Ho and his colleagues proposed that 15d-PGJ2 induces vascular endothelial cell apoptosis through JNK signalling and p38 MAPK-mediated p53 activation both in vitro and in vivo [84]. In addition, 15d-PGJ2 plays an antitumour role by upregulating death receptor 5 expression in HCT116 cells [85]. In the treatment of inflammation, 15d-PGJ2 can rapidly induce the transcription of cytokine signal transduction inhibitors (SOCS) 1 and 3 and inhibit the activity of JAK in activated glial cells, thereby performing an anti-inflammatory role [86]. Additionally, inflammatory
**Table 2: Anti-inflammatory and antioxidant activities of 15d-PGJ2.**

| Type           | Mechanism                        | Cell type                        | Dosage       | References |
|----------------|----------------------------------|----------------------------------|--------------|------------|
| macrophage     | IL-1β, TNF-α, TGF-β, MCP-1, ICAM-1 | RAW264.7                         | 5 μM         | [45]       |
| macrophage     | MIP-1β, TNF-α, NOS2               | Primary liver macrophages        | 0.5–2.5 μM   | [46]       |
| endothelial cells | NF-κB, TNF-α, VCAM-1, ICAM-1    | Aortic endothelial cells (CECs)   | 10 μM        | [47]       |
| endothelial cells | ROS, Apoptosis                  | Cerebral endothelial cells       | 1 μM         | [48]       |
| endothelial cells | IL-6, MCP-1, ICAM-1              | Human ARPE19 retinal pigment epithelial cells | 10–20 μM | [49]       |
| Liver          | NF-κB, IL-1β, IL-6, IL-8, COX-2   | LO2 and RAW264.7 cells, mice     | 2 μM, 30 μg/mL | [50]      |
|                |                                  | HepG2 cells                      | 5 μM, 10 μM  | [51]       |
|                |                                  | HepG2 cells                      | 2 μM, 5 μM   | [52]       |
| Lung           | TNF-α, NF-κB, ICAM-1, CINC-1     | Mice                             | 1 mg/kg      | [53]       |
|                | TNF-α, CINC-1, IL-10, NF-κB      | Rats                             | 0.3 mg/kg    | [54]       |
|                | IL-6, TNF-α, CCL2, CCL3, CCL4, CCL10 | Rats                             | 250 μg/kg    | [56]       |
|                | ROS, NOX                         | Primary cortical neurons         | 1 μM         | [61]       |
| Nervous system | TNF-α, IL-1β, ROS, NOX           | Rats                             | 200 μg/kg/10 μL  | [59]       |
|                |                                  | Primary neurons cells             | 5 μM         | [60]       |
| Gout arthritis | IL-1β, NF-κB, IL-6, IL-17, IL-33 | Mice                             | 10 μM        | [64]       |
| Cartilage      | IL-1β, NF-κB, COX-2              | Chondrocytes                      | 10 μM        | [63]       |
| Chronic eosinophilia | IL-33, IL-17, IL-23     | Mice                             | 100, 300 or 1000 μg/kg | [64] |
| Acute pancreatitis | TLR4, CCL2                  | Pancreatic acini cells            | 10 μM        | [65]       |

**Table 3: Anti-fibrotic activity of 15d-PGJ2.**

| Organ       | Mechanism                      | Cell type            | Dosage      | References |
|-------------|--------------------------------|----------------------|-------------|------------|
| Lung        | TGF-β1, α-SMA                  | Human lung fibroblasts | 10 μM       | [70]       |
| Liver       | TGF-β1, CTGF                   | Rat hepatic stellate cells | 1–20 μM  | [71]       |
| Renal       | TGF-β1, MAPKs, AP-1            | murine mesangial cells (SV40 MES 13) | 20 μM     | [73]       |
|             | TGF-β1, CTGF, α-SMA            | rat renal interstitial fibroblasts (NRK/49F) | 10 μM | [74] |
|             | TGF-β1, ROS                    | Human kidney-2 cells (HK-2) | 10 μM     | [75]       |
| Eye         | TGF-β1, α-SMA                  | Cat corneal fibroblasts   | 5 μM        | [76]       |
| Skin        | TGF-β1, α-SMA, COL1A2          | human dermal fibroblasts   | 10 μM        | [77]       |
| Aorta       | TGF-β1, CTGF                   | Human Aortic Smooth Muscle Cells | 1–10 μM  | [78]       |

Factors such as IL-6, IL-8, and IFN-γ can be inhibited by 15d-PGJ2 through NF-κB, Nrf2, and JAK/STAT pathways rather than PPAR-γ [87–89]. Furthermore, 15d-PGJ2 plays a key role in the homeostasis of BMSCs via a mechanism dependent on ROS-induced damage of liver, but not PPAR-γ, which may represent a new strategy for the treatment of liver fibrosis [90]. 15d-PGJ2 inhibits the expression of chemokines in a PPAR-γ-independent manner, which is related to blocking the NF-κB pathway. PPAR-γ agonists may therefore represent a key drug target for improving inflammation-related tubulointerstitial fibrosis [91]. In pulmonary fibrosis, 15d-PGJ2 regulates the extracellular signal-regulated kinase pathway by inhibiting the expression of TG2 rather than PPAR-γ [92]. Finally, 15d-PGJ2 can also play a potential role in lowering blood lipid by regulating the specific molecules of lipid metabolism, such as PPAR-δ, liver X receptor (LXR), farnesoid X receptor (FXR), and SIRT1. Its effect in different tissues may be related to the distribution of the above antibodies in tissues and the differences in affinity of 15d-PGJ2 [93–95].
4. Conclusion and Future Perspectives

15d-PGJ2 is a metabolic product of the PGJ2 prostate family. Two studies in 1995 showed that it can activate the transcription factor PPAR-γ [96, 97]. Although many new alternative drugs have been developed over the years, as an endogenous ligand, 15d-PGJ2 has advantages, including rapid expression. 15d-PGJ2 has been extensively explored in recent studies, which proves that it can prevent various harmful pathological changes in vivo, such as tumors, inflammation, oxidative stress, fibrosis, vascular remodelling, and lipid metabolism, and reveals its protective role related to PPAR-γ signalling pathways [4–6]. Herein, the structure, synthesis, and biological effects of 15d-PGJ2 are reviewed based on the latest literature, but there remain gaps in our knowledge. For example, 15d-PGJ2 produced in vivo is not sufficient to regulate most physiological processes, and external replenishment requires more stable carriers. Moreover, 15d-PGJ2 has a variety of pharmacological effects, many of which are antagonistic toward each other, as exemplified by the dual characteristics of inducing the synthesis of vascular endothelial growth factor and antiangiogenesis [71, 95]. Therefore, it is also very important to explore the conditions under which a certain pharmacological action takes place. Work is clearly needed to elucidate the biological effects of 15d-PGJ2 and related compounds in order to develop improved drug treatment regimens and therapies.

Conflicts of Interest

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

Acknowledgments

This work was supported by China Foundation for Hepatitis Prevention and Control WBN Liver Disease Research Fund (grant No. CFHPC2019031), Innovation Plan of Health System of Science and Technology Commission of Putuo District, Shanghai (grant No. ptkwsw201901).

References

[1] H. Peng and F. Chen, “Recent advances in asymmetric total synthesis of prostaglandins,” Organic & Biomolecular Chemistry, vol. 15, no. 30, pp. 6281–6301, 2017.
[2] R. S. Peebles, “Prostaglandins in asthma and allergic diseases,” Pharmacology & Therapeutics, vol. 193, pp. 1–19, 2019.
[3] Y. Singh and P. Mikrou, “Use of prostaglandins in duct-dependent congenital heart conditions,” Archives of disease in childhood - Education & practice edition, vol. 103, no. 3, pp. 137–140, 2018.
[4] T. Behl, I. Kaur, H. Goel, and A. Kotwani, “Implications of the endogenous PPAR-gamma ligand, 15-deoxy-delta-12, 14-prostaglandin J2, in diabetic retinopathy,” Life Sciences, vol. 153, pp. 93–99, 2016.
[5] J. U. Scher and M. H. Pillinger, “15d-PGJ2: the anti-inflammatory prostaglandin?” Clinical Immunology, vol. 114, no. 2, pp. 100–109, 2005.
[6] Q. Bie, H. Dong, C. Jin, H. Zhang, and B. Zhang, “15d-PGJ2 is a new hope for controlling tumor growth,” American Journal of Translational Research, vol. 10, no. 3, pp. 648–658, 2018.
[7] N. Ueno, M. Murakami, T. Tanioka et al., “Coupling between Cyclooxygenase, Terminal Prostanoid Synthase, and Phospholipase A2,” The Journal of Biological Chemistry, vol. 276, no. 37, pp. 34918–34927, 2001.
[8] S. Álvarez-Almañán, M. Bello, F. Tamay-Cach et al., “Study of new interactions of glitazone's stereoisomers and the endogenous ligand 15d-PGJ2 on six different PPAR gamma proteins,” Biochemical Pharmacology, vol. 142, pp. 168–193, 2017.
[9] K. W. Ruiz-Miyazawa, L. Stauergno-Ferrari, F. A. Pinho-Ribeiro et al., “15d-PGJ2-loaded nanocapsules ameliorate experimental gout arthritis by reducing pain and inflammation in a PPAR-gamma-sensitive manner in mice,” Scientific Reports, vol. 8, no. 1, Article ID 13979, 2018.
[10] C. L. Richard, E. L. Lowthers, and J. Blay, “15-Deoxy-A12,14-prostaglandin J2 down-regulates CXCR4 on carcinoma cells through PPARY- and NFκB-mediated pathways,” Experimental Cell Research, vol. 313, no. 16, pp. 3446–3458, 2007.
[11] M. Turgut, V. Cinar, R. Pala et al., “Biotin and chromium histidine-nate improve glucose metabolism and proteins expression levels of IRS-1, PPAR-γ, and NF-kB in exercise-trained rats,” Journal of the International Society of Sports Nutrition, vol. 15, no. 1, pp. 45, 2018.
[12] L. Shi, Q. Lin, X. Li et al., “Alliin, a garlic organosulfur compound, ameliorates gut inflammation through MAPK-NF-xB/AP-1/STAT-1 inactivation and PPAR-γ activation,” Molecular Nutrition & Food Research, vol. 61, no. 9, Article ID 1601013, 2017.
[13] J. S. Wang, W. W. Xiao, Y. S. Zhong et al., “Galec tin-3 deficiency protects lipopolysaccharide-induced chondrocytes injury via regulation of TLR4 and PPAR-γ-mediated NF-kB signaling pathway,” Journal of Cellular Biochemistry, vol. 120, no. 6, pp. 10195–10204, 2018.
[14] P. J. Blair, S. J. Hwang, M. C. Shonnard et al., “The Role of Prostaglandins in Disrupted Gastric Motor Activity Associated With Type 2 Diabetes,” Diabetes, vol. 68, no. 3, pp. 637–647, 2019.
[15] K. Kobayashi, K. Omori, and T. Murata, “Role of prostaglandins in tumor microenvironment,” Cancer and Metastasis Reviews, vol. 37, no. 2-3, pp. 347–354, 2018.
[16] S.-H. Yun, S.-H. Han, and J.-I. Park, “Peroxisome proliferator-activated receptor γ and PGC-1α in cancer: dual actions as tumor promoter and suppressor,” PPAR Research, vol. 2018, Article ID 6727421, 12 pages, 2018.
[17] T. Shimada, K. Kojima, Y. Yoshiura, H. Hiraishi, and A. Terano, “Characteristics of the peroxisome proliferator activated receptor γ (PPARγ) ligand induced apoptosis in colon cancer cells,” Gut, vol. 50, no. 5, pp. 658–664, 2002.
[18] C. Toaldo, S. Pizzimenti, A. Cerbone et al., “PPARγ ligands inhibit telomerase activity and hTERT expression through modulation of the Myc/Mad/Max network in colon cancer cells,” Journal of Cellular and Molecular Medicine, vol. 14, no. 6 A, pp. 1347–1357, 2010.
[19] H. Sato, S. Ishihara, K. Kawashima et al., “Expression of peroxisome proliferator-activated receptor (PPARγ) in gastric
cancer and inhibitory effects of PPARγ agonists," *British Journal of Cancer*, vol. 83, no. 10, pp. 1394–1400, 2000.

[21] N. G. Nikitakis, H. Siavash, C. Hebert, M. A. Reynolds, A. W. Hamburger, and J. J. Saut, "15-PG(2), but not thiazolidinediones, inhibits cell growth, induces apoptosis, and causes downregulation of Stat3 in human oral SCCa cells," *British Journal of Cancer*, vol. 87, no. 12, pp. 1396–1403, 2002.

[22] H. Han, S.-W. Shin, C.-Y. Seo et al., "15-Deoxy-Delta(12,14)-prostaglandin J2 (15d-PGJ2) sensitizes human leukemic HL-60 cells to tumor necrosis factor-related apoptosis-inducing lig- (and TRAIL)-induced apoptosis through Akt downregulation," *Apoptosis*, vol. 12, no. 11, pp. 2101–2114, 2007.

[23] S. Dionne, E. Levy, D. Levesque, and E. G. Seidman, "PPARγ ligand 15-deoxy-delta 12,14-prostaglandin J2 sensitizes human colon carcinoma cells to TWEAK-induced apoptosis," *Anticancer Research*, vol. 30, no. 1, pp. 157–166, 2010.

[24] S. V. Fulzele, A. Chatterjee, M. S. Shaik, T. Jackson, N. Ichite, and M. Singh, "15-Deoxy-Delta(12,14)-prostaglandin J2 enhances doctexal anti-tumor activity against A549 and H460 non-small-cell lung cancer cell lines and xenograft tumors," *Anti-Cancer Drugs*, vol. 18, no. 1, pp. 65–78, 2007.

[25] Y. Fu, J. Sung, K. Wu et al., "Inhibition of gastric cancer cells associated angiogenesis by 15d-prostaglandin J2 through the downregulation of angiopoietin-1," *Cancer Letters*, vol. 243, no. 2, pp. 246–254, 2006.

[26] J. Yuan, A. Takahashi, N. Masumori et al., "Ligands for peroxisome proliferator-activated receptor gamma have potent antitumor effect against human renal cell carcinoma," *Urology*, vol. 65, no. 3, pp. 594–599, 2005.

[27] H. Inoue, T. Tanabe, and K. Umesono, "Feedback control of cyclooxygenase-2 expression through," *The Journal of Biological Chemistry*, vol. 275, no. 36, pp. 28028–28032, 2000.

[28] A. R. Diers, B. P. Dranka, K. C. Ricart et al., "Modulation of mammary cancer cell migration by 15-deoxy-Δ12,14-prostaglandin J2: implications for anti-metastatic therapy," *Biochemical Journal*, vol. 430, no. 1, pp. 69–78, 2010.

[29] T. Takashima, Y. Fujitani, K. Higuchi et al., "PAPR-gamma ligands inhibit growth of human esophageal adenocarcinoma cells through induction of apoptosis, cell cycle arrest and reduction of ornithine decarboxylase activity," *International Journal of Oncology*, vol. 19, no. 3, pp. 465–471, 2001.

[30] H. Li and H. Narahara, "15-Deoxy-Delta(12,14)-prostaglandin J(2) induces growth inhibition, cell cycle arrest and apoptosis in human endometrial cancer cell lines," *International Journal of Molecular Medicine*, vol. 31, no. 4, pp. 778–788, 2013.

[31] C. Cocca, J. Dorado, E. Calvo, J. A. López, A. Santos, and A. Perez-Castillo, "15-Deoxi-Delta(12,14)-prostaglandin J2 is a tubulin-binding agent that destabilizes microtubules and induces mitotic arrest," *Biochemical Pharmacology*, vol. 78, no. 10, pp. 1330–1339, 2009.

[32] H. Liu, C. Zang, M. H. Fenker, K. Possinger, and E. Elstner, "PPARγ ligands and ATRA inhibit the invasion of human breast cancer cells in vitro," *Breast Cancer Research and Treatment*, vol. 79, no. 1, pp. 63–74, 2003.

[33] B. Farrow, K. L. O’Connor, K. Hashimoto, T. Iwamura, and B. M. Evers, "Selective activation of PPARγ inhibits pancreatic cancer invasion and decreases expression of tissue plasminogen activator," *Surgery*, vol. 134, no. 2, pp. 206–212, 2003.

[34] K. Hashimoto, R. T. Ethridge, and B. M. Evers, "Peroxisome proliferator-activated receptor γ ligand inhibits cell growth and invasion of human pancreatic cancer cells," *International Journal of Gastrointestinal Cancer*, vol. 32, no. 1, pp. 7–22, 2002.

[35] D. Shen, C. Deng, and M. Zhang, "Peroxisome proliferator-activated receptor γ agonists inhibit the proliferation and invasion of human colon cancer cells," *Postgraduate Medical Journal*, vol. 83, no. 980, pp. 414–419, 2007.

[36] Y. Li, K. Atkinson, and T. Zhang, "Combination of chemotherapy and cancer stem cell targeting agents: Preclinical and clinical studies," *Cancer Letters*, vol. 396, pp. 103–109, 2017.

[37] W. Chearwae and J. J. Bright, "PPARγ agonists inhibit growth and expansion of CD133+ brain tumour stem cells," *British Journal of Cancer*, vol. 99, no. 12, pp. 2044–2053, 2008.

[38] R. B. Clark, "The role of PPARs in inflammation and immunity," *Journal of Leukocyte Biology*, vol. 71, no. 3, pp. 388–400, 2002.

[39] S. A. Degrelli, H. Shaoito, and T. Fournier, "New transcriptional reporters to quantify and monitor PPARγ activity," *PPAR Research*, vol. 2017, Article ID 613907, 7 pages, 2017.

[40] P. Illés, A. Grycsová, K. Krasulová, and Z. Dvořák, "Effects of flavored nonalcoholic beverages on transcriptional activities of nuclear and steroid hormone receptors: proof of concept for novel reporter cell line PAZ-PPARγ," *Journal of Agricultural and Food Chemistry*, vol. 66, no. 45, pp. 12066–12078, 2018.

[41] J. U. Scher and M. H. Pillingar, "The anti-inflammatory effects of prostaglandins," *Journal of Investigative Medicine*, vol. 57, no. 6, pp. 703–708, 2015.

[42] V. Carregaro, M. H. Napimoga, R. S. Peres et al., "Therapeutic treatment of arthritic mice with 15-Deoxy-Δ12,14-Prostaglandin J3 (15d-PGJ3) ameliorates disease through the suppression of TH17 cells and the induction of CD4+CD25 Foxp3+ cells," *Mediators of Inflammation*, vol. 2016, Article ID 9626427, 13 pages, 2016.

[43] M. Ricote, A. C. Li, T. M. Willson, C. J. Kelly, and C. K. Glass, "The peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation," *Nature*, vol. 391, no. 6662, pp. 79–82, 1998.

[44] A. F. Valledor and M. Ricote, "Nuclear receptor signaling in macrophages," *Biochemical Pharmacology*, vol. 67, no. 2, pp. 201–212, 2004.

[45] Y. Meng, C. Chen, C. Tian, J. Du, and H. H. Li, "Angiotensin II-induced Egfr-1 expression is suppressed by peroxisome proliferator-activated receptor-gamma ligand 15d-PGJ(2) in macrophages," *Cellular Physiology and Biochemistry*, vol. 35, no. 2, pp. 689–698, 2015.

[46] W. Li, N. Chang, L. Tian et al., "miR-27b-3p, miR-181a-1-3p, and miR-326-5p are involved in the inhibition of macrophage activation in chronic liver injury," *Journal of Molecular Medicine*, vol. 95, no. 10, pp. 1091–1105, 2017.

[47] S. Marcone, P. Evans, and D. J. Fitzgerald, "15-Deoxy-Δ12,14-Prostaglandin J2 modifies components of the proteasome and inhibits inflammatory responses in human endothelial cells," *Frontiers in Immunology*, vol. 7, p. 459, 2016.

[48] J.-S. Wu, H.-D. Tsai, C.-Y. Huang, J.-J. Chen, and T.-N. Lin, "15-Deoxy-Δ12,14-PGJ2, by activating peroxisome proliferator-activated receptor-gamma, suppresses p22phox transcription to protect brain endothelial cells against hypoxia-induced apoptosis," *Molecular Neurobiology*, vol. 50, no. 1, pp. 221–238, 2014.

[49] W.-K. Jung, C.-M. Lee, D.-S. Lee et al., "The 15-deoxy-Δ12,14-prostaglandin J2 inhibits LPS-stimulated inflammation via enhancement of the platelet-activating factor acetylhydrolase activity in human retinal pigment epithelial cells," *International Journal of Molecular Medicine*, vol. 33, no. 2, pp. 449–456, 2014.
[50] K. Chen, J. Li, J. Wang, Y. Xia et al., “15-Deoxy- gamma 12,14-prostaglandin J2 reduces liver impairment in a model of ConA-induced acute hepatic inflammation by activation of PPAR gamma and reduction in NF- kappa B activity,” PPAR Research, vol. 2014, Article ID 215631, 10 pages, 2014.

[51] S. Tsujimoto, M. Kishina, M. Koda et al., “Nimesulide, a cyclooxygenase-2 selective inhibitor, suppresses obesity-related non-alcoholic fatty liver disease and hepatic insulin resistance through the regulation of peroxisome proliferator-activated receptor-?,” International Journal of Molecular Medicine, vol. 38, no. 3, pp. 721–728, 2016.

[52] S.-W. Park, C. Cho, B.-N. Cho, Y. Kim, T. W. Goo, and Y. I. Kim, “15-deoxy- gamma -prostaglandin J down-regulates activin-induced activin receptor, smad, and cytokines expression via suppression of NF- B and MAPK signaling in HepG2 Cells,” PPAR Research, vol. 2013, Article ID 751261, 7 pages, 2013.

[53] D. Liu, Z. Geng, W. Zhu, H. Wang, Y. Chen, and J. Liang, “15-deoxy-Delta(1)/2, (1/2)-prostaglandin J 2 ameliorates endotoxin-induced acute lung injury in rats,” Chinese Medical Journal, vol. 127, no. 5, pp. 815–820, 2014.

[54] J. Zhou, L. Jiang, X. Long et al., “Bone-marrow-derived mesenchymal stem cells inhibit gastric aspiration lung injury and inflammation in rats,” Journal of Cellular and Molecular Medicine, vol. 20, no. 9, pp. 1706–1717, 2016.

[55] T. Maehara, T. Nakamura, S. Maeda, K. Aritake, M. Nakamura, and T. Murata, “Epithelial cell-derived prostaglandin D 2 inhibits chronic allergic lung inflammation in mice,” The FASEB Journal, vol. 33, no. 7, pp. 8202–8210, 2019.

[56] A. Cloutier, I. Marois, D. Cloutier, C. Verreault, A. M. F. Xu, J. Li, W. Ni, Y. W. Shen, and X. P. Zhang, “PPAR-gamma agonist 15d-PGJ2 mediates neuronal autophagy after cerebral ischemia-reperfusion injury,” PLoS ONE, vol. 8, no. 1, Article ID e55080, 2013.

[57] A. Bianchi, D. Moulin, S. Hupont et al., “Oxidative stress-induced expression of HSP70 contributes to the inhibitory effect of 15d-PGJ2 on inducible prostaglandin pathway in chondrocytes,” Free Radical Biology & Medicine, vol. 76, pp. 114–126, 2014.

[58] T. S. Farnesi-de-Assunção, C. F. Alves, V. Carregaro et al., “PPAR-y agonists, mainly 15d-PGJ2, reduce eosinophil recruitment following allergen challenge,” Cellular Immunology, vol. 273, no. 1, pp. 23–29, 2012.

[59] A. Mateu, L. Ramudo, M. A. Manso, and I. De Dios, “Cross-talk between TLR4 and PPARy pathways in the arachidonic acid-induced inflammatory response in pancreatic acini,” The International Journal of Biochemistry & Cell Biology, vol. 69, pp. 132–141, 2015.

[60] R. Weiskirchen, S. Weiskirchen, and F. Tacke, “Organ and tissue fibrosis: Molecular signals, cellular mechanisms and translational implications,” Molecular Aspects of Medicine, vol. 65, pp. 2–15, 2019.

[61] T. A. Wynn, “Cellular and molecular mechanisms of fibrosis,” The Journal of Pathology, vol. 214, no. 2, pp. 199–210, 2008.

[62] X. M. Meng, D. J. Nikolic-Paterson, and H. Y. Lan, “TGF-? the master regulator of fibrosis,” Nature Reviews Nephrology, vol. 12, no. 6, pp. 325–338, 2016.

[63] H. H. Hu, D. Q. Chen, Y. N. Wang et al., “New insights into TGF-beta/Smad signaling in tissue fibrosis,” Chemico-Biological Interactions, vol. 292, pp. 76–83, 2018.

[64] H. A. Burgess, L. E. Daugherty, T. H. Thatcher et al., “PPAR agonists inhibit TGF-? induced pulmonary myofibroblast differentiation and collagen production: implications for therapy of lung fibrosis,” American Journal of Physiology-Lung Cellular and Molecular Physiology, vol. 288, no. 6, pp. L1146–L1153, 2005.

[65] K. Sun, Q. Wang, and X.-H. Huang, “PPAR gamma inhibits growth of rat hepatic stellate cells and TGF beta induced connective tissue growth factor expression,” Acta Pharmacologica Sinica, vol. 27, no. 6, pp. 715–723, 2006.

[66] S. Djudjaj and P. Boor, “Cellular and molecular mechanisms of kidney fibrosis,” Molecular Aspects of Medicine, vol. 65, pp. 16–36, 2019.

[67] B. Guo, D. Koya, M. Isono, T. Sugimoto, A. Kashiwagi, and M. Haneda, “Peroxisome proliferator-activated receptor-gamma ligands inhibit TGF-beta 1-induced fibronectin expression in glomerular mesangial cells,” Diabetes, vol. 53, no. 1, pp. 200–208, 2004.

[68] W. Wang, F. Liu, and N. Chen, “Peroxisome proliferator-activated receptor-gamma (PPAR-gamma) agonists attenuate the profibrotic response induced by TGF-beta in renal interstitial fibroblasts,” Mediators of Inflammation, vol. 2007, Article ID 062641, 7 pages, 2007.

[69] M. Zhao, Y. Chen, G. Ding et al., “Renal tubular epithelium-targeted peroxisome proliferatoractivated receptor-? maintains the epithelial phenotype and antagonizes renal fibrogenesis,” Oncotarget, vol. 7, no. 40, pp. 64690–64701, 2016.

[70] K.-I. Jeon, R. P. Phipps, J. C. Oud, and K. R. Huxlin, “Inhibitory effects of PPARy ligands on TGF-? induced CTGF expression in cat corneal fibroblasts,” Experimental Eye Research, vol. 138, pp. 52–58, 2015.

[71] A. K. Ghosh, S. Bhattacharyya, G. Lakos, S.-J. Chen, Y. Mori, and J. Varga, “Disruption of transforming growth factor-? signaling and profibrotic responses in normal skin fibroblasts by peroxisome proliferator-activated receptor-?,” Arthritis & Rheumatism, vol. 50, no. 4, pp. 1305–1318, 2004.

[72] M. Fu, J. Zhang, X. Zhu et al., “Peroxisome Proliferator-activated Receptor-? Inhibits Transforming Growth Factor
β-induced Connective Tissue Growth Factor Expression in Human Aortic Smooth Muscle Cells by Interfering with Smad3,” The Journal of Biological Chemistry, vol. 276, no. 49, pp. 45888–45894, 2001.

[79] D. Fanale, V. Amodeo, and S. Caruso, “The interplay between metabolism, PPAR signaling pathway, and cancer,” PPAR Research, vol. 2017, Article ID 1830626, 2 pages, 2017.

[80] M. H. Napimoga, A. P. Demasi, J. P. Bossonaro, V. C. de Araújo, J. T. Clemente-Napimoga, and E. F. Martinez, “Low doses of 15d-PGJ2 induce osteoblast activity in a PPAR-gamma independent manner,” International Immunopharmacology, vol. 16, no. 2, pp. 131–138, 2013.

[81] D. Gao, G. Hao, Z. Meng et al., “Rosiglitzone suppresses angiotensin II-induced production of KLF5 and cell proliferation in rat vascular smooth muscle cells,” PLoS ONE, vol. 10, no. 4, Article ID e0123724, 2015.

[82] T. Hosoi, S. Matsuzaki, T. Miyahara, K. Shimizu, Y. Hasegawa, and K. Ozawa, “Possible involvement of 15-deoxy-Δ12,14-prostaglandin J2 in the development of leptin resistance,” Journal of Neurochemistry, vol. 133, no. 3, pp. 343–351, 2015.

[83] S. W. Shin, C. Y. Seo, H. Han et al., “15d-PGJ2 induces apoptosis by reactive oxygen species-mediated inactivation of akt in leukemia and colorectal cancer cells and shows in vivo antitumor activity,” Clinical Cancer Research, vol. 15, no. 17, pp. 5414–5425, 2009.

[84] T. C. Ho, S. L. Chen, Y. C. Yang et al., “15-deoxy-Delta(12,14)-prostaglandin J2 induces vascular endothelial cell apoptosis through the sequential activation of MAPKS and p53,” The Journal of Biological Chemistry, vol. 283, no. 44, pp. 30273–30288, 2008.

[85] R.-Y. Su, K.-H. Chi, D.-Y. Huang, M.-H. Tai, and W.-W. Lin, “15-Deoxy-Δ12,14-prostaglandin J2 up-regulates death receptor 5 gene expression in HCT116 cells: Involvement of reactive oxygen species and C/EBP homologous transcription factor gene transcription,” Molecular Cancer Therapeutics, vol. 7, no. 10, pp. 3429–3440, 2008.

[86] E. J. Park, S. Y. Park, E.-H. Joe, and I. Jou, “15d-PGJ2 and rosiglitazone suppress Janus kinase-STAT inflammatory signaling through induction of suppressor of cytokine signaling 1 (SOCS1) and SOCS3 in glia,” The Journal of Biological Chemistry, vol. 278, no. 17, pp. 14747–14752, 2003.

[87] S. K. Seo, D. I. Seo, W. S. Park et al., “Attenuation of IFN-γ-induced B7-H1 expression by 15-deoxy-delta12,14-prostaglandin J2 via downregulation of the Jak/STAT/IRF-1 signaling pathway,” Life Sciences, vol. 112, no. 1-2, pp. 82–89, 2014.

[88] X. Li, B. Luo, L. Wang, W. Zhang, and Z. Liu, “15-Deoxy-prostaglandin J2 anti-inflammation in a rat model of chronic obstructive pulmonary disease and human bronchial epithelial cells via Nrf2 activation,” Genetics and Molecular Research, vol. 14, no. 4, pp. 14037–14042, 2015.

[89] W. K. Jung, I. S. Park, and S. J. Park, “The 15-deoxy-Delta12,14-prostaglandin J2 inhibits LPS-stimulated AKT and NF-κappaB activation and suppresses interleukin-6 in osteoblast-like cells MC3T3E-1,” Life Sciences, vol. 85, pp. 46–53, 2009.

[90] X. Liu, S. Jia, W. Li et al., “15-Deoxy-Δ12,14-Prostaglandin J2 inhibits homing of bone marrow-derived mesenchymal stem cells triggered by chronic liver injury via redox pathway,” PPAR Research, vol. 2015, Article ID 876160, 11 pages, 2015.

[91] Y. Lu, Q. Zhou, F. Zhong et al., “15-Deoxy-Δ12,14-Prostaglandin J2 Modulates Lipopolysaccharide-Induced Chemokine Expression by Blocking Nuclear Factor-κB Activation via Peroxisome Proliferator Activated Receptor-γ-Independent Mechanism in Renal Tubular Epithelial Cells,” Nephron Experimental Nephrology, vol. 123, no. 1-2, pp. 1–10, 2013.

[92] K. C. Olsen, A. P. Epa, A. A. Kulkarni et al., “Inhibition of transglutaminase 2, a novel target for pulmonary fibrosis, by two small electrophilic molecules,” American Journal of Respiratory Cell and Molecular Biology, vol. 50, no. 4, pp. 737–747, 2014.

[93] X. Xu, Y. Lu, L. Chen, J. Chen, X. Luo, and X. Shen, “Identification of 15d-PGJ2 as an antagonist of farnesoid-X receptor: molecular modeling with biological evaluation,” Steroids, vol. 78, no. 9, pp. 813–822, 2013.

[94] I. H. Tae, E. Y. Park, P. Dey et al., “Novel SIRT1 inhibitor 15-deoxy-Δ12,14-prostaglandin J2 and its derivatives exhibit anticancer activity through apoptotic or autophagic cell death pathways in SKOV3 cells,” International Journal of Oncology, vol. 53, no. 6, pp. 2518–2530, 2018.

[95] A. T. Reddy, S. P. Lakshmi, A. Banno, and R. C. Reddy, “Identification and Molecular Characterization of Peroxisome Proliferator-ACTivated Receptor δ as a Novel Target for Covalent Modification by 15-Deoxy-Δ12,14-prostaglandin J 2,” ACS Chemical Biology, vol. 13, no. 12, pp. 3269–3278, 2018.

[96] J. M. Lehmann, L. B. Moore, T. A. Smith-Oliver, W. O. Wilkison, T. M. Willson, and S. A. Kliewer, “An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor γ (PPARγ),” The Journal of Biological Chemistry, vol. 270, no. 22, pp. 12953–12956, 1995.

[97] B. M. Forman, P. Tontonoz, J. Chen, R. P. Brun, B. M. Spiegelman, and R. M. Evans, “15-deoxy-Δ12,14-prostaglandin J2 is a ligand for the adipocyte determination factor PPARγ,” Cell, vol. 83, no. 5, pp. 803–812, 1995.