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Review

Therapeutic Potential and Challenges of Pioglitazone in Cancer Treatment

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Abstract: Pioglitazone (ACTOS) is a thiazolidinedione for peroxisome proliferator-activated receptor γ (PPAR-γ) that has been well established for the second or third line treatment of type 2 diabetes mellitus. Beyond the effects on glucose metabolism, pioglitazone displays positive effects on lipid metabolism, blood pressure, endothelial function, bone density, and apoptosis of cancer cells. In fact, according to in vitro experiments and preclinical studies, PPAR-γ ligand is currently considered a potential target for both chemoprevention and cancer therapy. PPAR-γ ligands are known to inhibit cancer cell proliferation and metastasis through terminal differentiation and underexpression of inflammatory mediators. Despite its anticancer properties, pioglitazone was withdrawn by the national medicine agencies of France and Germany, due to reports of increased incidence of bladder cancer. These reports were associated with European populations undergoing higher doses and longer durations of treatment. In this review, we discuss the pharmacokinetics, therapeutic potential, and limitations regarding the clinical use of pioglitazone, with a focus on cancer treatment.

Keywords: pioglitazone; cancer; type 2 diabetes

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1. Introduction

Thiazolidinediones (TZDs) are a class of oral hypoglycemic agents for the management of diabetes. TZDs are ligands for PPAR α and γ, a member of the nuclear receptor family which regulates glucose and lipid metabolism, inflammation, and cell proliferation [1–3]. PPARs are classified into three subtypes: PPAR-α, PPAR-β/δ, and PPAR-γ. Specifically, PPAR-α receptors are expressed in the heart, liver, and skeletal muscle, while PPAR-γ receptors are expressed in adipose tissue. The former regulate fatty acid oxidation followed by decreased low-density lipoprotein cholesterol (LDL-C) and increased high-density lipoprotein cholesterol (HDL-C) levels, while the latter regulate cell differentiation, leptin expression and insulin sensitivity [4,5]. As a result, TZDs find therapeutic application in the treatment of type 2 diabetes mellitus (T2DM), as well as non-alcoholic fatty liver disease (NASH) and multiple types of cancer [6,7].

Initially approved by the FDA in 1999, pioglitazone is marketed under the brand name ACTOS by Takeda Pharmaceuticals. It has been established as a second- or third-line treatment for the management of T2DM when first-line treatment with metformin is inadequate [8,9]. In this scenario, metformin is combined with sulfonylureas, glinides,

alpha-glucosidase inhibitors, insulin, glucagon-like peptide-1 receptor agonist, dipeptidyl peptidase 4 inhibitors, sodium-glucose co-transporter 2 inhibitors, and thiazolidinediones, such as pioglitazone [10]. Pioglitazone is typically administered orally, with the optimal dose customized based on clinical status. According to the European Medicines Agency (EMA) recommendations, the initial dose ranges from 15 to 45 mg once daily. The dose may be increased if inadequate glycemic control is achieved. Alternatively, it may need to be decreased if the patient is receiving pioglitazone along with other diabetes medications (insulin, chlorpropamide, glibenclamide, gliclazide, and tolbutamide). The tablets should be administered once a day with water, either with or without food. After three to six months, the patients should be evaluated and treatment discontinued if considered non-beneficial [11].

However, despite its effectiveness in enhancing glycemic control, concerns have been raised about its safety profile, one of which regards an increased bladder cancer risk. Notably, indications of a higher incidence of bladder cancer among pioglitazone users prompted the French and German pharmaceutical regulators to withdraw the medication from the market in May 2011. Nevertheless, the medicine remained available throughout the rest of Europe [12].

The aim of this literature review is to thoroughly evaluate pioglitazone's safety profile and efficacy, with an emphasis on its association with bladder cancer. This review summarizes clinical data, epidemiological studies, and regulatory recommendations in an effort to evaluate the risk–benefit ratio of pioglitazone. Its evaluation will shed light into current clinical practice and direct future studies to explore the multiple therapeutic applications of pioglitazone.

2. Overview of Pioglitazone

Pioglitazone, also known as 5-{4-[2-(5-ethyl-2-pyridinyl)ethoxy]benzyl}-1,3-thiazolidine-2,4-dione based on the International Union of Pure and Applied Chemistry (IUPAC), is a TZD compound, as shown in Figure 1, which is derived from a pyridine derivative through a nucleophilic aromatic substitution reaction with a 72% yield [13]. Pioglitazone appears as needles from dimethylformamide and water, while pioglitazone hydrochloride (HCl) appears as colorless prisms from ethanol, with a melting point of 183–184 °C and 193–194 °C, respectively [14]. The solubility of pioglitazone hydrochloride (HCl) increases with increasing temperature [15]. Low aqueous solubility and oral bioavailability can be overcome through temperature increase, cosolvents, and formulation strategies such as cyclodextrins inclusion complexes or nanostructured lipid carriers (NLCs). More specifically, polyethylene glycols (PEGs) are safe cosolvents for oral or parenteral pioglitazone HCl formulations. The additions of PEGs 200, 400, or 600, and a temperature increase significantly enhanced the solubility profile of pioglitazone [15]. Positive results were achieved through the addition of cyclodextrins in ethanol solution or encapsulation of pioglitazone HCl. Cyclodextrins caused a 6-fold increase in dissolution rate of pioglitazone HCl-β-cyclodextrin when compared to the pure drug, while lipid carriers achieved controlled release up to 24 h [16,17]. The latter was also observed during the administration of a newly discovered racemic compound that serves as a more thermodynamically stable and less soluble form of pioglitazone HCl [18].

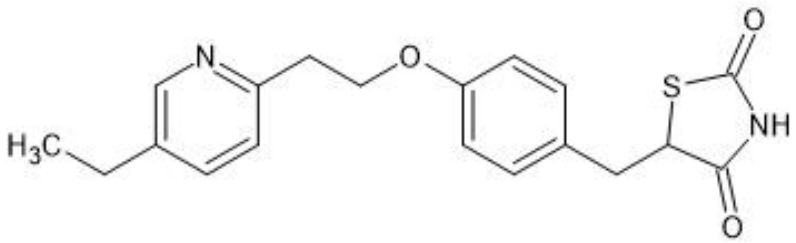

Figure 1. Chemical structure of pioglitazone (created using ACD/ChemSketch, version 2021.2.0 (Advanced Chemistry Development, Inc., (ACD/Labs), Toronto, ON, Canada; Available online: www.acdlabs.com (accessed on 25 January 2025)).

The molecular structure and properties of pioglitazone have been well-characterized, providing a solid foundation for its pharmacological profile. The pharmacological activity of pioglitazone has been attributed to its hydroxy and ketone derivatives during in vivo studies on rats and dogs [13]. Similarly to other thiazolidinediones, pioglitazone activates the PPAR-γ receptor, increasing insulin sensitivity, without inducing insulin release from pancreatic cells. It is typically administered once a day with or without food, metabolized by the cytochrome P450 hepatic enzymes with a half-life of approximately 9 h, and excreted in the urine. The pharmacokinetics of pioglitazone are dose and time-dependent, leading to non-linear changes in plasma concentration and potential toxicity. According to clinical evidence, pioglitazone follows the same pharmacokinetic profile in healthy participants, diabetic patients, and patients with renal failure, irrespective of age, gender, and race. However, dose adjustment is required for patients with hepatic failure due to decreased metabolic function and by extension decreased plasma concentration [19].

3. Therapeutic Use of Pioglitazone

3.1. Diabetes Mellitus Type 2 (T2DM)

Thiazolidinediones (TZDs), also known as glitazones, have been well-established for the treatment of type 2 diabetes mellitus (T2DM) [20]. Given the pathophysiology of T2DM, targeting mechanisms regulating lipid metabolism is a viable option [21]. TZDs are peroxisome-proliferator activated receptor γ (PPAR-γ) agonists which regulate gene expression related to the uptake, distribution, and metabolism of lipids, resulting in reduced lipid levels and sensitization to insulin. However, the use of TZDs has been limited during the past years due to major safety and toxicity concerns, such as edema, cardiovascular disease, weight gain, and carcinogenesis reports, as analyzed below [22].

3.2. Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH)

NASH is characterized as one of the most extreme forms of NAFLD, having the potential to lead to severe and often terminal hepatic disorders such as fibrosis, cirrhosis, and hepatocellular cancer [23]. Considering the association of NASH with T2DM and dyslipidemia, pioglitazone is a reasonable option against NASH in both diabetic and non-diabetic patients [24]. According to the study conducted by Della Pepa et al. (2021), pioglitazone has demonstrated positive effects against NASH, even in relatively small doses. This is achieved through the increase of the peripheral and adipose tissue sensitivity to insulin, leading to the reduction of hepatic inflammation and steatosis in a glucose-independent manner [25]. It is important to note several investigations of combination therapies against NASH, with the most significant one being pioglitazone combined with vitamin E [26,27].

3.3. Cardiovascular Protection

By lowering insulin resistance, TZDs can have cardioprotective and anti-atherosclerotic activity, and prevent ischemic events to an extent in patients with prior history of insulin resistance [28–30]. Additionally, it has been noted that, in murine models and in vitro studies, pioglitazone has demonstrated the capability of limiting cardiac hypertrophy in addition to arresting cardiac fibrosis and providing protection against oxidative stress [31–33].

3.4. Neurodegenerative Diseases (NDs)

There have been promising indications that PPAR-γ agonists, such as pioglitazone, possess the capability of reducing neuroinflammation, as well as the concentration phosphorylated tau protein and synaptophysin. This is complemented by the elevated permeability of the blood–brain barrier [34]. Focusing on Alzheimer's Disease (AD), given that PPAR-γ regulates the expression of key enzymes related to the production and metabolism of amyloid plates, the inhibition of its phosphorylation, and therefore deactivation by pioglitazone, suggests favorable results, as illustrated in Figure 2 [35]. The neuroprotective properties of pioglitazone that mainly stem from the anti-inflammatory effects and the mitochondrial enhancement can also be applied for Parkinson's Disease (PD), as well as amyotrophic lateral sclerosis (ALS), in which case the effects on the muscular tissue are also of significance [36,37]. As such, based on the results of studies conducted in rodents and humans, it is evident that pioglitazone can have a positive impact in the cognition and other neurological functions of patients with NDSs [38–40].

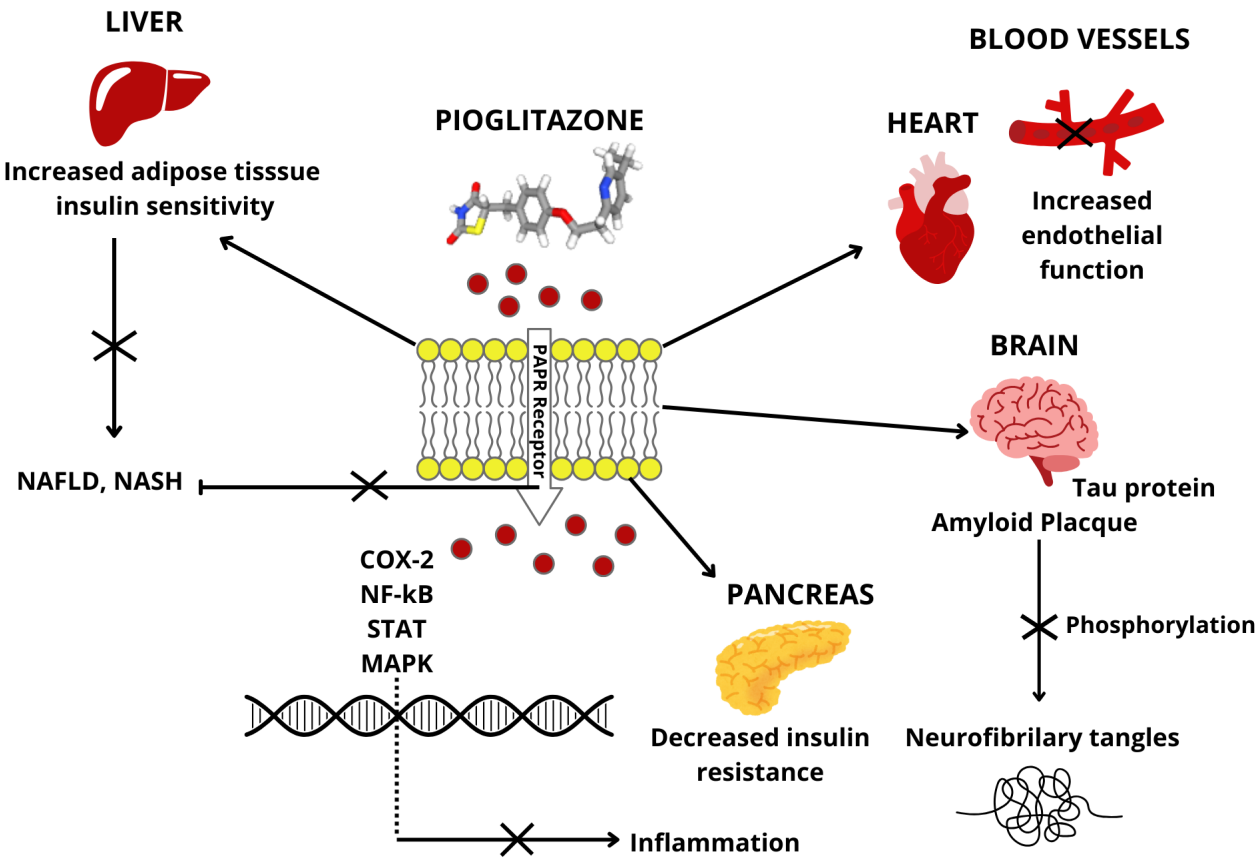

Figure 2. Pharmacological effect of pioglitazone on the cardiovascular and nervous system, as well as hepatic and metabolic function. Effect of pioglitazone on different systems. Pioglitazone enhances insulin sensitivity, which improves endothelial, neuronal, pancreatic and liver cell function (created using https://biorender.com, URL accessed on 25 January 2025).

3.5. Anticancer Properties

3.5.1. Overview

As established, pioglitazone has been associated with elevated risk of bladder cancer, especially in the Caucasian population, to such extend that it has catalyzed its withdrawal from the French, German, and Indian markets, and led the Food and Drug Administration (FDA) to introduce a mandate for the providing of information regarding potential risk [41,42]. However, there have been several reports and studies that point out the antineoplastic properties of pioglitazone and the related biochemical pathways that PPAR-γ is implicated in. Given the pleiotropic effects of PPAR-γ and its agonists, we consider that investigating the exact molecular interactions will contribute to shedding some light on the mechanism of action and toxicity, as well as the interactions and effects of pioglitazone, and potentially suggest new applications and optimalization/personalization of interventions involving TZDs.

3.5.2. Molecular Pharmacology

PPAR-γ is classified as a nuclear receptor which, after binding with its ligand, translocates to the nucleus, heterodimerizes the retinoid X receptor (RXR), and acts as gene regulator via its interaction with the peroxisome proliferator response element (PPRE) of selected genes. The latter is related to metabolism in physiological as well as cancer cells [43]. As such, the receptor possesses the capability of affecting key cancer cell processes related to proliferation, progression, differentiation, metastasis, apoptosis, etc. Activation of PPAR-γ receptors suppresses tumorgenicity through their interaction with insulin growth factor, as illustrated in Figure 3. Additional molecular mechanisms of therapeutic significance are summarized in Table 1.

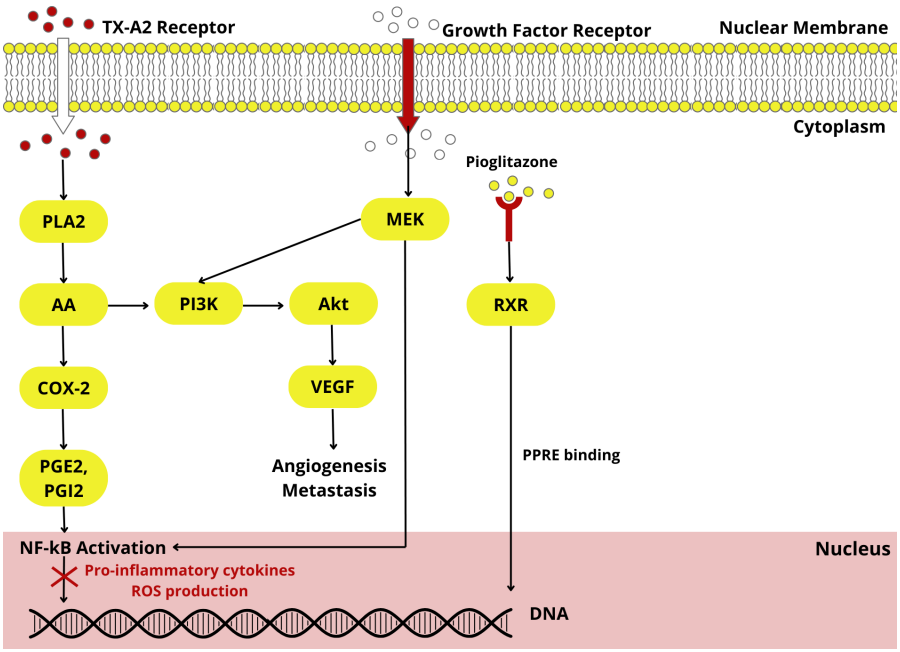

Figure 3. Pharmacological effect of pioglitazone facilitated through the inhibition of thromboxane A2 (TX-A2) and growth factor receptor pathways. The former regulates the expression of phospholipase A2 (PLA2), arachidonic acid (AA), cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2) and prostacyclin I2 (PGI2). The latter regulates the expression of vascular endothelial growth factor (VEGF) through the phosphoinositide 3-Kinase pathway (PI3K) (created using https://biorender.com, URL accessed on 25 January 2025).

Table 1. Molecular mechanisms of pioglitazone.

Process	Mechanism	Cancer Type
Reduced cell proliferation	Increased expression of excitatory amino acid transporter 2 [44].	Neuroblastoma
	Increased activity of p-Akt and p-GSK-3β [44].	
	Redifferentiation of tumor associated adipocytes [44].	
	Inhibited cell growth via mTOR and STAT5 pathway tampering by retinoid X receptor agonists [45].	Glioma
	Inhibited expression of estrogen receptor and aromatase via PGE2 and BRCA1 pathways [46].	Breast cancer
	Inhibition of JAK2/STAT3 pathway [47].	
	Increased expression of p21 and MAPK activity [48].	
	Inhibited CSC proliferation due to decreased STAT5 and HIF-2α levels [49].	Chronic myeloid leukemia
	Downregulated *MAPK*, *RAS*, *MYC* gene expression and phosphorylation of MAPK pathway proteins [50].	Non-small cell lung cancer
Increased apoptosis	Downregulation of BCL2 and SCD1 [44].	Leukemia
	Reduced expression phosphorylation of MEK1 and ERK phosphorylation [51].	
	Downregulation of STAT3 with ERK1/2, NF-κβ and p38MAPK molecules unaffected [49,52].	
	Reduced expression of Survivin [49,52].	
	Increased expression of TRAIL death ligand and apoptosis inducing factor [49,53].	
	Downregulation of BCLXL/BCL2 in a PPAR-γ and caspase-independent manner [51].	Prostate cancer, squamous cell cancer (SCC)
	Induction of apoptosis in a caspase-dependent manner assisted by downregulation of c-FLIP, leading to BCL2 downregulation and instability [54].	Caki cells
	Downregulation of X-linked inhibitor of apoptosis (XIAP) and cyclooxygenase-2 (COX-2) [55].	Colorectal cancer
	Upregulation of cyclinB1, CDC2, p21 and alteration of BAX/BCL2 ratio [55].	
Reduced angiogenesis [44–46,56–58]	Reduced expression of matrix metalloproteinase 2 (MMP2), vascular endothelial growth factor (VEGF), COX-2.	Hepatocellular carcinoma
	Inhibition of fibroblast growth factor 2 (FGF-2) and urokinase plasminogen activator.	
	Apoptosis of endothelial cells.	
	Combined downregulation of COX-2 and VEGF when coupled with clofibric acid [45].	Ovarian cancer
	Reduction of bFGF- and VEGF-initiated angiogenesis [59].	Chick chorioallantoic membrane model

Table 1. *Cont.*

Process	Mechanism	Cancer Type
Drug Sensitization	Reduced expression of metallothionein and endorphin connected to S273 phosphorylation [60].	Pancreatic cancer
	Enhanced type I Interferon activity due to inhibition of the STAT-3 pathway [58].	
	Increased arsenic trioxide induced tumor toxicity through inhibition of the PI3K/AKT pathway [45].	Leukemia
	Doxorubicin sensitization via modulation of P-glycoprotein [56].	Osteosarcoma
	Reduced resistance to cisplatin [46].	
Cell Cycle Modification	Increased cisplatin and oxiplatin efficacy.	Thyroid, lung, prostate, breast, kidney, esophageal and urothelial cancer
	Inhibited EGFR/MDM2 mediated chemoresistance and PPAR-γ degradation [50].	
	Downregulation of cyclin dependent kinase 4 (CDK4).	
	Upregulation of CDK inhibitors including p19, p21, p27 and rho-related GTP binding protein.	
	Activation of Rb protein [51,60].	
	Downregulation of cyclins D, cyclin E, CDK2, CDK4, proliferating nuclear antigen and retinoblastoma protein [58].	Breast and colorectal cancer
	Induction of G1-arrest through the activation of p21 along with the upregulation of FOXO3a [61].	Acute promyelotic leukemia (NB4 cells)
Accelerated differentiation	Induced adipogenesis [57].	Melanoma
Immunomodulation	Increased β3 and α5 integrin expression [57].	Colorectal cancer
	Reduced PD-L1 levels due to autophagy [62].	Lung, colorectal cancer
Bioenergetic disruption	Reduced pyruvate oxidation and glutathione levels.	Hepatocellular carcinoma
	ROS-induced stress mediated by HIF-1 and NF-κβ signaling.	
Reduced metastasis and invasiveness	Downregulation of smad family member 3 (SMAD3), PDK1 and MCT-1.	Breast cancer
	Upregulation of plasminogen activator inhibitor-1 (PAI-1).	
	Downregulation of NF-κβ, eIF2α, MMP9 and fibronectin [46].	Lung cancer
	Upregulation of CXCR4, CXCR7, E-cadherin [47].	
	Downregulation of TGF-β.	Glioma
	Reduced expression and invasiveness of β-cantenin [46].	Breast cancer
	Downregulation of TGFβR1 and SMAD3 associated with epithelial to mesenchymal transition (EMT) [63].	Non-small cell lung cancer
Increased autophagy	Upregulation of HIF-1 and BNIP3 [51].	Breast and prostate cancer
	Activation of PI3K [61].	Acute promyelotic leukemia (NB4 cells)

3.6. Therapeutic Effect on Different Types of Cancer

3.6.1. Breast Cancer

According to retrospective cohort studies, there is insignificant to almost no elevated breast cancer (BC) risk related to the use of pioglitazone [64]. It is important to note that PPAR-γ levels are reduced and methylation of PPAR-γ promoter is increased in BC cells, leading to the indication of its unfavorable role in cancer proliferation. In the example of triple negative breast cancer (TNBC), pioglitazone has proven its value as an adjuvant in the combined use with doxorubicin, as it decreases the invasiveness and tendency for migration,

an issue commonly associated with the use of the latter. Similar findings were also reported for the apoptosis-inducing capabilities of cisplatin during in vitro testing [50,65]. PPAR-γ facilitates major regulatory processes such as the promotion of CXCR4 and CXCR7 genes, inhibition of eIF2α, and intracellular accumulation of glucose-affecting related migration pathways [66,67]. Despite the aforementioned evidence, there is no clinical application yet [68,69].

3.6.2. Lung Cancer

According to clinical evidence, PPAR-γ agonists play a major role lung cancer progression. In fact, PPAR-γ agonists have been associated with differentiation, tumor size, BCL2/BAX ratio and c-MYC expression levels, in cases of non-small cell lung cancer (NSCLC), lung adenocarcinoma, and squamous cell lung cancer (SCLC) [70]. Pioglitazone has demonstrated the ability to reduce NSCLC proliferation and invasiveness through downregulation and altering pathways of major significance in proliferation, apoptosis, angiogenesis, and metastatic potential. Indeed, rodent studies have shown that pioglitazone has the potential to reduce tumor formation and volume [71]. Additionally, inflammation is also affected, as pioglitazone inhibits prostaglandin 2 (PGE2) production while bypassing cyclooxygenase 2 (COX-2) [59]. As a chemopreventive medication, pioglitazone has proven to have little value considering the double-blind clinical trial conducted by Keith et al. (2019), which reported that no significant alterations in the endpoints were noted other than some minor effect on lesions [72]. Chemopreventive studies were also carried out by Seabloom et al. (2017), who noted significant reduction in adenoma formation but no noteworthy alteration to the effect of metformin when combined with it, and by a team of similar composure, who evaluated the effectiveness of pioglitazone in an aerosol form [73]. They concluded from animal tests that a dose of 150–450 μg/kg was tolerable, with limited to no adverse effects, and effective, given the reduction in adenoma formation after biochemical and histological assessments [74]. As with BC, pioglitazone has also been considered for combination therapy along with more established anticarcinogenic agents, as studied in the following cases:

- The use with EGFR Tyrosine Kinase Inhibitors such as gefitinib for NSCLC, as it was found that PPAR-γ mediated upregulation of phosphate, and tensin homolog (PTEN) downregulated the PI3K/Akt pathway that is correlated to resistance to said TKIs [70].
- Combination of pioglitazone with clarithromycin and a relatively small dose of chemotherapeutic agent was compared against nivolumab in the ModuLung trial by Heudobler et al. (2021) [75]. This trial was terminated early due to the approval of checkpoint inhibitors as first line treatment, with the conclusion that nivolumab was superior to this combination therapy; however, with a difference in the overall survival rate and quality of life between the two regimens being similar, the latter seems to be a viable alternative to be assessed in future trials and be considered in cases with few other options [75].

Granted that inactivation of PPAR-γ combined with increased presence of prostaglandins is a dangerous sign, as it leads to loss of control over Ras/Raf/Mek activation and NF-Kβ mediated proliferation, Kiran et al. (2022) tested pioglitazone along with COX-2 specific antagonist celecoxib on rodents. The results were coherent with the hypothesis as decreases in tumor size, alterations to tumor architecture, and increase in lifespan, as well as improvement of its quality, were noted [76].

However, PPAR-γ also possesses tumor promoting effects regarding lung cancer [77], such as the case of increased tumor progression in orthotropic mice after systemic PPAR-γ activation in the cancer cells as well as the tumor microenvironment [59], and, as such,

additional studies regarding the exact effects of pioglitazone in a clinical setting and risk–benefit assessment in the given context are needed.

3.6.3. Renal Cancer

It has been noted that the antidiabetic use of pioglitazone is not associated with elevation in the risk of renal cancer [78]. Pioglitazone itself induced apoptosis in Caki cells, a model used for the study of clear cell renal cell carcinoma, as shown in Table 1 [54]. Such effects are expected, considering the aforementioned, as well as the elevated presence of PPAR-γ receptors in renal carcinoma cells. Another cell line, 769-P cells, was heavily affected in a dose-dependent manner with imminent apoptosis as the application of the molecule led to significant morphological alterations, including cell density. The suggested mechanism of apoptosis, with limited proof, in this case, was mitochondrial with membrane irregularities and release of cytochrome c. This cell line also exhibited increased sensitivity to methotrexate after treatment with pioglitazone, something that was not evident in the Vero cell line [79]. Finally, there is a lot of interest in the combination of pioglitazone with cisplatin, as it showed nephroprotective effects in rodent models HK-2 cells by preventing tissue damage and oxidative stress and it potentiated the latter's effects on renal adenocarcinoma cells inhibiting NF-κB-mediated inflammatory response and activation of Nrf2-mediated antioxidative stress signaling [80].

3.6.4. Hepatocellular Carcinoma

Assessing the preventative potential of pioglitazone, metanalytical results indicate that the use of TZDs in patients with T2DM is associated with protection against liver cancer [81]. Complementary rodent studies indicated prevention of liver fibrosis and carcinogenesis following cirrhosis [82]. Results originating from preclinical studies showcase pioglitazone's anticancer properties. The increased presence of the receptor for advanced glycation end products (RAGE) is deemed as a negative biomarker for the progression of hepatocellular carcinoma which possibly indicates invasion. Pioglitazone decreased the expression of RAGE along with HMGB1, NF-κβ, and p38MAPK, resulting in reduced proliferation, invasion, and metastatic potential [83]. Additionally, it was reported that metabolomic alterations triggered by pioglitazone, mostly regarding the metabolism of lipids, leading to the death of chemically induced hypoxic HepG2 cells from oxidative stress [84].

3.6.5. Colorectal Cancer

Similarly to hepatocellular carcinoma, it has been indicated that TZDs reduce the risk of colorectal cancer occurrence in patients with T2DM after metanalytical assessment of about 2.5 million T2DM patients [85]. Direct effects were reported during in vitro experiments with pioglitazone and its analog, Δ2-pioglitazone treated HCT116 and HT29 cells. There were similarities in the endpoints, such as cell growth arrest and differentiation, in addition to key differences in the ways those were achieved, namely arrest in the S phase when treated with the former and in the G0/G1 phase when treated with the latter [86]. Additionally, xenograft studies on rodents using HT29 and SW480 cell lines indicated antiproliferative and antimetastatic activity towards the liver activity [85]. As an adjuvant, pioglitazone can be used in immunotherapy due to the autophagic degradation of PD-L1 mediated by PPAR-γ whose binding with the immunomodulatory ligand is similarly enhanced by said xenobiotic agent in the case of lung cancer [62]. Investigations in the field of pharmaceutics addressing pioglitazone's poor solubility have shown that its combination with capecitabine, an established chemotherapeutic molecule against colorectal cancer, in the form of nanoparticles, enhances its bioavailability and overall proapoptotic effect on HT29 and HCT119 cells [87].

3.6.6. Thyroid Cancer

The use of pioglitazone has been correlated with neither increased nor decreased risk of thyroid cancer according to a study comprising mostly Eastern Asian individuals [88]. A widely studied finding is the PAX8-PPAR-γ Fusion Protein (PPFP) and how pioglitazone alters its function. PPFP is a result of a fused gene containing the significant majority of the Paired Box Gene 8 (PAX8) transcription factor, related to thyroid development and function, gene, and the entirety of the PPAR-γ gene and, as such, a binding site for TZDs [89]. As evident by the imminent intracellular lipid accumulation and the expression of adipocyte-related biomarkers upon treatment, pioglitazone induces the differentiation of thyroid cancer cells into adipocytes. Moreover, it is accepted that pioglitazone blocks the interaction between PPFP and Thyroid Transcription Factor 1 (TTF-1), which otherwise leads to the severe limiting of the differentiation induction by the former via the suspension of recruitment of synergistic molecules such as coactivators and corepressors [90]. Considering immunity, pioglitazone also advanced the infiltration of T cells and macrophages in the tumor microenvironment when tested on mice, and exhibited favorable properties in a clinical setting [91]. Unfortunately, Giordano et al. (2018), in their examination of 40 thyroid cancer patients, found that only one tested positive for PPFP, potentially indicating that it is a rare phenomenon in these cases [92]. Finally, studies have suggested that pioglitazone and metformin have a synergistic effect against thyroid cancer, especially in the induction of apoptosis [93].

3.6.7. Glioma

As mentioned before, pioglitazone can cross the blood–brain barrier, a capability that can be utilized in the case of glioma, as it is one of the most aggressive brain malignancies. Cytotoxic activity has been confirmed, as it has been reported to reduce glioma cell proliferation in vitro in the U87MG, T98G, and U251MG cell lines, as well as LN-229 cells in a xenograft model [94,95]. However, in another xenograft study using Gl261 cells, pioglitazone seemed to significantly alter the fate of the test subjects only when injected into the cerebrum [96]. Antineoplastic action can be by conventional, PPARγ-dependent and -independent pathways previously mentioned, namely alterations in the levels of cyclin D1, MMP9, N-Cadhenin and caspase 3, in addition to β-catenin inhibition, as revealed by knockout studies [97,98]. Invasiveness is also affected, as it was limited to C6 rat glioma cells [99]. Complimentary to this is the evident increase in the expression of the Excitatory Amino Acid Transporter 2 (EAAT2) in the same cell lines, except T98G. Lack of this transporter is commonly found in glioma cells as the resulting elevation of extracellular glutamate concentration leads to excitotoxicity, assisting in the thriving of malignant cells, as an excitatory neurotransmitter, and sets the field for tumor associated epilepsy (TAE). As such, by increasing EAAT2 levels in glioma cells, pioglitazone worsens the conditions, not favoring the development of glioma and, potentially, the associated symptoms such as TAE [100]. The effect of pioglitazone has been further investigated in glioma stem cells (GSCs), which do not seem to be immune from the effects of pioglitazone either. In vitro tests by Cilibrasi et al. (2016) involving treatment of GSCs revealed that G166, GliNS2, GBM2, and G144 (with latent effects) cells reduced their metabolic rate and alteration in the proteomic profile regarding the expression of markers related to differentiation and stemness. These changes in the behavior of the cells were not accompanied by any alterations in their morphology [101]. Data originating from the clinical data reveal a preventative relationship between pioglitazone and glioma [94]. A synergy between TZDs (with pioglitazone being the most potent of them) and statins has been suggested by Tapia-Perez et al. (2010), as they observed a significant reduction in the population in in vitro tests using the U87 and RG II cell lines, even in hypoxic conditions [102]. Follow-up rodent model tests,

also by Tapia Perez et al. (2016), revealed no significant differences in overall survival rate compared to the controls, and that the only combination displaying reduction in tumor size was lovastatin/atorvastatin + plus pioglitazone [103]. Related to cancer care, pioglitazone has also been found to protect against radiation induced cognitive decline in patients with brain malignancy and is relatively safe for use in radiation treatment [104].

3.6.8. Hematological Malignancies

There is a great amount of interest in the potential of pioglitazone in blood cancers. Studies conducted by Esmaeili et al. (2021) on U937 cells, modeling acute myeloid leukemia (AML) cancer cells, have shown in their results that pioglitazone dampened their survival and development capabilities, led to accumulation of cells in the G1 and pre-G1 cell cycle phases, and induction of apoptosis, as indicated by the increase in the population of cells that test positive for Annexin-V and PI [105]. Similar targeted antiproliferative effects were also observed on HL60 (modeling Acute Pro-myelocytic Leukemia-APL), K562 (modeling Chronic Myeloid Leukemia), and Jurkat (modeling T-cell lymphoma) cells, and the cell cycle of the HL60 line also demonstrated accumulation in the G1 phase and decrease in the G2 and metaphasis populations [106]. Jurkat cells were also assessed with the combination of pioglitazone and valproic acid, with optimistic results as cell cycle deregulation was noted [107–109]. According to in vitro studies in different types of leukemia—AML in U937 cells, APL in Jurkat cells, ALL in SD-1, IM-9, Sup-B15, and NALM-6 cells—the primary mode of action for pioglitazone is cell cycle arrest [110]. Adding to the above are the tests on Philadelphia chromosome positive leukemic cells by Okabe et al. (2017), which reported the antineoplastic effects of pioglitazone on cells bearing the T315I mutation while sparing normal CD34 expressing cells and inducing the phosphorylation of the AMP-activated protein kinase (AMPK) [111]. The combination of pioglitazone with PI3K inhibitors can potentiate its cytotoxic effects, as was observed on NB4 cells (APL) when they were treated with pioglitazone, and PI3K inhibitors CAL-101 and BKM120. The suggested mechanism of synergy is the cell cycle arrest, as analyzed before, mediated by p21 [112]. However, in NALM-6 cell line experiments, where similar synergy was noted, it was found that said effects are interfered with by NF-κβ signaling and autophagy [113]. Potential synergy was also noticed in more conventional chemotherapeutics with a statistically insignificant remission rate being reported for cytarabine and daunorubicin in the clinical study conducted by Ghadiany et al. (2019) [114]. Additionally, as noted in Table 1, pioglitazone is correlated with elevated effectiveness of arsenic trioxide [115]. Adjuvant use of pioglitazone has been proven to positively influence interventions utilizing BCR-ABL1 tyrosine kinase inhibitors (TKIs) in Chronic Myeloid Leukemia (CML). In vitro experiments carried out on K562 cells by Glodkowska-Mrowka et al. (2016) resulted in the eradication of leukemia stem cells (LSCs), progenitors, and differentiated CML cells [116,117]. A small phase II clinical trial by Rousselot et al. (2016) involving 24 subjects treated with imatinib, who were administered pioglitazone at a dosage ranging from 30mg/d to 45mg/d, exhibited that about half of the patients showed response within one year, with no significant adverse effects other than edema, higher than the rate of 23% in monotherapy with imatinib, thus suggesting correlation between the synergy of pioglitazone and favorable outcomes [118]. Additional discontinuation trials such as EDI-PIO in Brazil have raised the issue of alterations in the lipid metabolism and metabolomic profile of the patients, given the effects of pioglitazone on the adipose tissue, and the aspect of mitochondrial dysfunction that influences the proliferation of CML cells [106]. However, results originating from the same study, suggest that pioglitazone does not affect STAT5 expression and, therefore, the levels of downstream molecules to it, such as HIF-2α, contrary to the statements of previous reports [119].

3.6.9. Pancreatic Cancer

There has been contradictory evidence regarding the association between the antidiabetic use of pioglitazone and the elevation of the risk of pancreatic cancer. As such, the effect the molecule has on pancreatic cancer occurrence, and the extent of it, is yet to be determined [120–123]. Nevertheless, antitumor activity has been observed in cell lines modeling pancreatic cancer, including Capan-1, Apsc-1 BxPC-3, PANC-1, and MIApaCa-2. Xenograft studies involving BxPC-3 revealed antiproliferative and antimetastatic properties, as tumor size was limited along with lymph metastasis [124]. Finally, pioglitazone has been reported to enhance the anticancer effects of gemcitabine through inhibition of the NF-κβ, induction of apoptosis, and setting of the platform to include HDAC inhibitors that have proven to be helpful in the activity of PPAR-γ, as illustrated in Figure 4 [125].

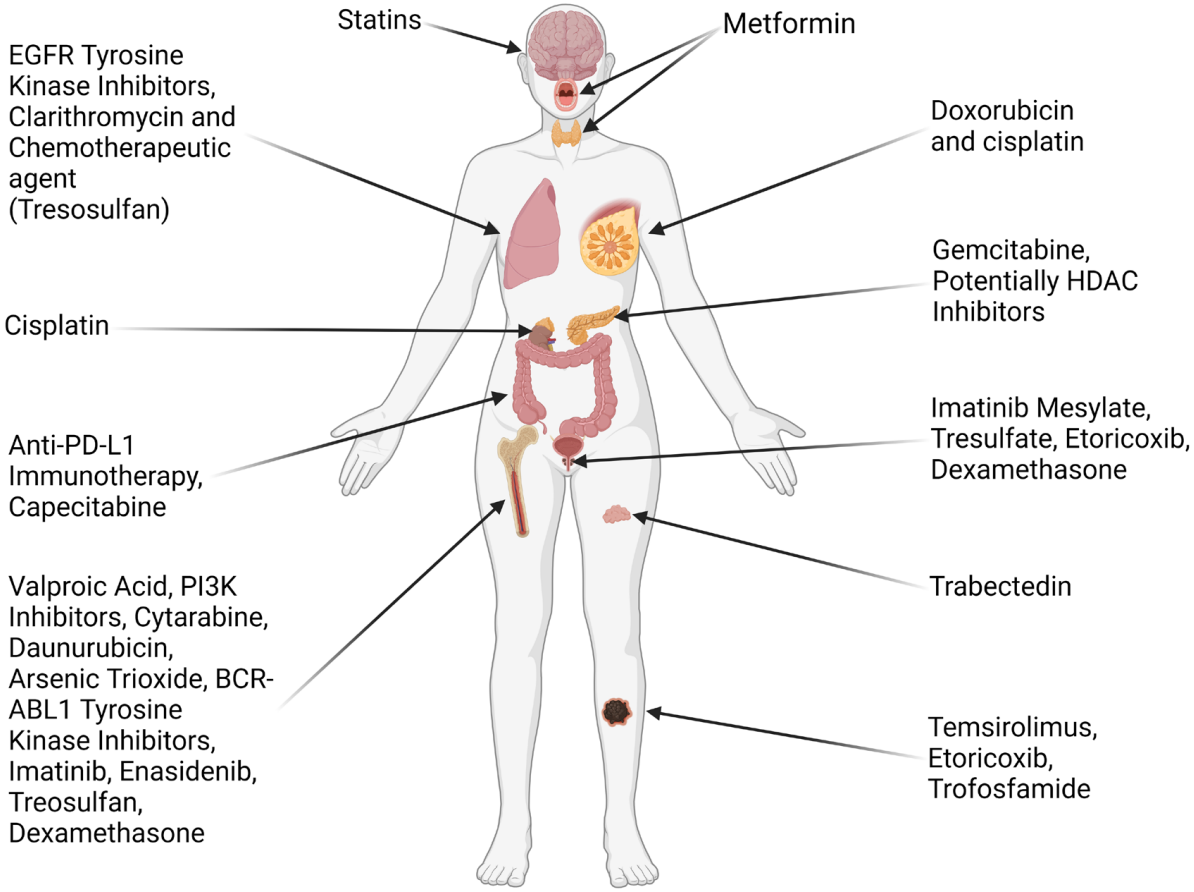

Figure 4. Pioglitazone combination therapies for the treatment of breast cancer, lung cancer, renal cancer, hepatocellular carcinoma, colorectal cancer, thyroid cancer, glioma, pancreatic cancer, and hematological malignancies (created using https://biorender.com, URL accessed on 25 January 2025).

3.7. Immunotherapy

PPAR-γ immunomodulatory effects have long been known, and there have been multiple studies seeking to assess the significance of said effects in cancer. A study conducted on mice hosting solid Ehrlich carcinoma cells by El-Sisi et al. (2014) concluded that pioglitazone administration led to a statistically significant reduction in tumor size and TNF-α amount, increase in peripheral neutrophil and splenic T- lymphocyte populations, and increase in splenic T-lymphocyte activity, CD4+/CD8+ ratio and immunoglobin G (IgG) levels, indicating elevated immune response. Similar results, although to a varying extent and except peripheral neutrophil counts, were also obtained from co-administration with doxorubicin [126]. Immunomodulation is a property that can be exploited in the context

of immunotherapy. An example of it is the use of PPAR-γ agonists to reprogram T cells; however, there were no specific reports on pioglitazone [127,128].

3.8. Clinical Evidence

To evaluate the antineoplastic potential of pioglitazone, it is important to review the latest clinical trials (Supplementary Table S1—from clinicaltrials.gov platform) [129–155]. Moghareabed et al. investigated the combined use of pioglitazone with chemotherapy for metastatic breast cancer treatment. Despite the study's statistical power being significantly restricted due to the small sample size of just 60 female participants, it was concluded that combining pioglitazone with chemotherapy was more effective than using taxol alone. This combination resulted in better radiologic responses, disease stability, and halted progression, ultimately providing a greater overall clinical benefit [156]. In contrast, the study by Agulló-Ortuño et al. showed no clear superiority of one combination over the other, when participants received carboplatin (AUC = 2) and paclitaxel (80 mg/m^2) weekly in combination with either hydroxyurea (1000 mg and 1500 mg) or pioglitazone (30, 45 and 60 mg) daily. However, treatment with hydroxyurea demonstrated slightly more favorable indications based on the measurement of uncoupling protein-2 gene expression and rate of cells with double-strand breaks [157].

Besides therapeutic use, pioglitazone can also play a role in the diagnosis of cancer. Han et al. have studied the effect of pioglitazone on 18F-2-fluoro-2-deoxy-D-glucose (18F-FDG) uptake by neoplastic lesions. In the study group of 43 patients (13F/30M, Median Age 64.0), the participants were scanned 1h after intravenous administration of 18F-FDG (5.5 MBq/kg). The same procedure was repeated the next day, 2 h after the oral administration of pioglitazone (15 or 30 mg). Results indicated a dose-independent betterment in all assessed aspects of positron emission tomography (PET) imaging in the group that responded to the administration of pioglitazone, with discrimination between the effect on malignant and inflammatory lesions. However, it must be highlighted that, like the rest of the trials discussed, this one also suffers from a small sample size, dampening the statistical significance of the results [158].

Despite the substantial number of clinical trials, evidence regarding the use of pioglitazone for cancer prevention and treatment remains insufficient. This can be attributed to the low number of participants and lack of reports, which limit the statistical value of the reported results. Thus, a large number of clinical trials is required to properly assess the antineoplastic potential of pioglitazone. More specifically, there is a need to further investigate combination therapies and adverse events. For this purpose, multiple parameters should be taken into consideration, such as population, duration of treatment, and follow-up appointments. Regarding population, its size and diversity need to be increased, especially in phase II and III trials, for future studies to possess enough power to be considered for applications in standardized cancer care.

4. Discussion

Concerns have been raised regarding the elevated risk of bladder cancer, which has been reported since 2012. This can be attributed to overexpression of PPARγ, which is present in the urinary bladder and several other tissues. This adverse event is prevalent, especially in cases of prolonged pioglitazone administration, indicating a time-dependent and dose-dependent pharmacological profile. However, analysis does not suggest a strong dose-dependence relationship, since bladder cancer risk can be attributed to comorbidities and administration of antidiabetic drugs, such as metformin. Existing studies suggest a slightly, but significantly, elevated risk of bladder cancer associated with pioglitazone administration in a time- and dose-dependent manner [41]. This suggestion is confirmed

by the cohort study conducted by Mamtani et al. (2012), who initiated TZD or SU treatment in 18,459 and 41,396 T2DM patients, respectively. Out of the 59,855 patients, 33,730 were males and 26,125 were females. Regarding bladder cancer incidence, 60 cases were reported in the TZD group and 137 cases were reported in the SU group. No difference was found between the two groups. Interestingly, in the TZD group long-term treatment ($\geq$5 years) was associated with an increased risk of bladder cancer, but not among those with shorter duration of exposure to TZDs. This observation was not limited only to pioglitazone, but may apply to other TZDs [159].

Another cohort study which gathered data from the French national health insurance information system, indicates the time- and dose-dependent pharmacological profile of pioglitazone. The study included 155,535 T2DM patients, out of whom 83,755 were males and 71,780 were females. The risk was increased by 75% for cumulative doses $\geq$28,000 mg over the span of $\geq$24 months. Analysis by sex revealed a significant association between pioglitazone and bladder cancer for males, but not for females [160]. This was contradicted by the meta-analysis of Tang et al. (2018), who found no gender difference, though they did indicate a higher bladder cancer risk for Europeans versus US or Asian populations, which could be attributed to dissimilar genetic backgrounds or socioeconomic factors [161]. Lastly, it is important to acknowledge that T2DM patients have an increased risk of bladder cancer at baseline. Other confounding factors, such as cigarette smoking, exposure to arylamines, and schistosomal infection, should be taken into consideration. Thus, it is plausible that the TZDs may exacerbate a pre-existing high-risk state of T2DM patients [162].

Due to the structure of these studies, there is no conclusive data regarding the risk–benefit ratio of pioglitazone. To date, there is no study that proves the direct cause–effect relationship between pioglitazone and bladder cancer [41].

Similar concerns have been raised regarding the association of metformin with risk of bladder cancer. While metformin does not decrease bladder cancer risk, it improves clinical parameters such as recurrence-free survival (RFS), progression-free survival (PFS), and cancer-specific survival (CSS) [121]. Although no effect was reported between overall survival (OS) and bladder cancer, studies show a positive outlook [122]. Another meta-analysis conducted in bladder cancer patients showed neither a protective nor a harmful effect of metformin exposure [123]. Few reports indicate decreased bladder cancer risk in metformin users versus never-users. However, the link between metformin and bladder cancer risk is not clear due to co-administration of other drugs and small proportion of metformin users versus never-users [124]. Overall, meta-analyses show no association of metformin with bladder cancer risk. Considering that these studies are limited to T2DM or bladder cancer patients, a consensus cannot be drawn regarding the risk of bladder cancer in the general population.

5. Conclusions

Based on the aforementioned, it is safe to assume that pioglitazone, as well as other TZDs, possess antineoplastic agents properties. PPARγ receptors, being implicated in multiple pathways, lead to diverse results in tumors. Although in vitro studies have been carried out with positive results, the adverse events presented indicate that additional studies are required in order to fully assess the risk to benefit ratio in an evidence-based manner. While in vitro studies have been carried out with positive results, cohort studies indicate a time- and dose-dependent relationship between pioglitazone administration and bladder cancer risk. Higher risk is observed in T2DM patients undergoing treatment for more than 2 years and at higher cumulative doses. Considering that overall risk remains relatively low, pioglitazone administration is recommended with caution for individuals at higher risk.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/app15041925/s1, Table S1: Molecular mechanisms of pioglitazone.

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