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Health-Related Studies of Cardarine (GW501516) from 2015-2025

GW501516, also called Cardarine, is a synthetic ligand for peroxisome proliferator-activated receptor-β/δ (PPARδ). Because it enhances fatty-acid oxidation and endurance, it has been misused in sports. Health-related research over the past decade examines its potential anti-inflammatory, metabolic, cardiovascular and neuroprotective effects while also addressing concerns regarding tumorigenesis and other adverse outcomes. This report summarises clinical, animal and in-vitro studies published from 2015-2025, focusing on health-related outcomes.

Overview of Study Types and Models

1. **Animal and in-vitro models dominate:** Most research involves rodent disease models (obesity, liver failure, kidney injury, neurodegeneration) or cell cultures (hepatocytes, fibroblasts, smooth muscle, neurons). Only a few human data exist, usually as ex-vivo primary cell experiments or observational measures.
2. **PPARδ-dependence is common:** Many experiments use PPARδ knock-down/knock-out models or antagonists to show that observed effects depend on PPARδ activation, reinforcing that GW501516 acts via this receptor.
3. **Short-term dosing:** Studies generally use short-term administration (days to weeks), so long-term safety remains unclear.

Metabolic and Anti-Inflammatory Effects

Autophagy-Mediated Reduction of Hepatic Steatosis

- A 2019 study used primary mouse hepatocytes and obese db/db mice to test whether GW501516 promotes autophagy. In hepatocytes, GW501516 increased autophagy markers (LC3-II, Atg5, Beclin-1) and decreased p62 in a time- and dose-dependent manner [1].
- Obese mice treated with GW501516 for four weeks exhibited reduced hepatic fat deposition, lower serum triglycerides and liver enzymes, and increased fatty-acid oxidation. Co-administration of the autophagy inhibitor chloroquine abolished these benefits, demonstrating that autophagy is crucial for GW501516-mediated hepatic fat clearance [2].
- The authors concluded that PPARδ activation stimulates autophagy-lysosomal pathways to enhance lipid metabolism, improving fatty liver disease [3].

Modulation of Inflammatory Response and Fibrosis

- **Kidney inflammation (2015)** – In mice fed a high-fructose diet, GW501516 activated PPARδ target genes (PDK4 and CPT-1) and significantly reduced renal inflammatory markers (IL-1β, IL-6, MCP-1, Cd68). Importantly, this anti-inflammatory effect occurred independently of changes in the renin-angiotensin system [4].

- **Bronchial fibrosis (2023)** – Human bronchial fibroblasts from asthmatics were treated with GW501516 alone or with the PPARδ antagonist GSK0660. The agonist suppressed TGF-β-induced fibroblast-to-myofibroblast transition and reduced myofibroblast markers (α-smooth muscle actin, collagen I, tenascin C). These effects did not reduce cell viability and were seen even when the antagonist was present, suggesting involvement of non-canonical pathways [5] [6]. The study suggests potential for antifibrotic therapy in asthma.

- **Acute liver injury (2024)** – A mouse model of lipopolysaccharide/D-galactosamine-induced acute liver failure showed that GW501516 reduced mortality, decreased serum cytokines (IL-1β, IL-6, TNF-α) and nitric oxide production, and inhibited phosphorylation of p38 and JNK signaling. The protective effect was PPARδ-dependent [7].

- **Corneal wound healing and inflammation (2020)** – Topical GW501516 instillation after alkali injury in rats suppressed neutrophil and macrophage infiltration and reduced mRNA levels of inflammatory cytokines (IL-6, IL-1β, TNF-α, NF-κB). However, it promoted M2 macrophage infiltration and neovascularization; early transparency improved but later bleeding and vascularization increased [8] [9].

Effects on Metabolism and Endurance

- **Muscle glucose sparing (2017)** – A seminal study using mice showed that GW501516 treatment induced a metabolic shift. It increased fatty-acid oxidation genes (Pdk4 and Cpt1a/b), reduced respiratory exchange ratio, lowered lactate production, and preserved systemic glucose during endurance exercise [10]. Mice treated with GW501516 ran ~1.5 h longer than controls; these effects were absent in muscle-specific PPARδ knockout mice [11] [12].

- **Branched-chain amino acid metabolism (2023)** – In C2C12 myotubes, GW501516 increased PGC-1α, mitochondrial content and function, and decreased extracellular branched-chain amino acids without changing expression of catabolic enzymes, suggesting enhanced uptake/metabolism [13].

- These metabolic effects indicate potential benefits for metabolic syndrome or endurance training, but long-term outcomes remain unknown.

Cardiovascular Effects

Atherosclerosis and Plaque Stability

- A 2023 study on ApoE-deficient mice fed a high-cholesterol diet demonstrated that GW501516 reduced features of plaque vulnerability. It inhibited smooth muscle cell (SMC) phenotypic switching by suppressing endoplasmic reticulum (ER) stress and the NLRP3 inflammasome, downregulated matrix metalloproteinase-2, and improved plaque stability [14]. The study noted that patients with acute coronary syndrome had lower plasma PPARδ levels than those with stable angina, suggesting PPARδ activation might protect against plaque rupture [15].

Renal and Vascular Protection

- The high-fructose study mentioned earlier reported reduced renal inflammation; although not directly cardiovascular, decreased kidney inflammation is relevant for cardiovascular health [4].

- Early research outside the 10-year window suggested protection against pulmonary arterial smooth muscle cell proliferation and cardiac fibrosis, but these are not summarised here.

Neuroprotection and Neuroinflammation

- **Parkinson's disease models (2019-2022)** – In an MPTP mouse model of Parkinson's disease, intracerebroventricular administration of GW501516 improved motor deficits, reduced dopaminergic neuron loss, decreased pro-inflammatory cytokine production, and inhibited activation of the NLRP3 inflammasome. It also attenuated astrocyte activation without affecting microglial reaction [16].

- A follow-up in vitro study using SH-SY5Y neuroblastoma cells exposed to 6-hydroxydopamine showed that GW501516 mitigated neurotoxicity by suppressing intracellular iron accumulation, reactive oxygen species and lipid peroxidation; these protective effects were abolished by PPARδ knock-down [17]. The introduction noted that GW501516 reduced inflammatory processes and dopamine depletion in the MPTP model [18].

- These findings suggest GW501516 may protect neurons by modulating iron homeostasis and inhibiting inflammasome-mediated neuroinflammation, though clinical translation remains speculative.

Ocular Studies

- **Corneal antifibrosis (2014)** – Although slightly older than the 10-year window, a rat study showed that subconjunctival GW501516 temporarily slowed reepithelialization but later reduced keratocyte activation, myofibroblast transdifferentiation and extracellular matrix synthesis, diminishing corneal haze [19].

- **Neovascularization (2020)** – As discussed earlier, GW501516 decreased inflammation but promoted vascularization in injured corneas, indicating a trade-off between anti-inflammatory benefits and risk of abnormal vessel growth [8] [9].

Potential Safety Concerns and Detrimental Effects

Promotion of Tumorigenesis

- **Colitis-associated colorectal cancer (2018)** – In AOM/DSS-treated mice, chronic GW501516 administration enhanced colitis-associated colorectal cancer. It increased expression of pro-inflammatory genes (COX-2, IL-6, IL-8, MCP-1) and glucose transporters (Glut1, SLC1A5), leading to enhanced tumor growth and proliferation [20]. The study suggested that PPARδ activation might promote colon cancer in an inflammatory context.

- **Nasopharyngeal carcinoma (NPC) cell line (2018)** – In contrast, GW501516 inhibited proliferation of undifferentiated NPC cells (C666-1), induced G2/M arrest and apoptosis via caspase activation and BAX induction, and suppressed tumor growth in xenograft mice. The mechanism involved down-regulation of integrin-linked kinase and activation of AMPKα [21]. This shows that PPARδ activation may have cell-type-specific anti-tumor effects.

- **Immune escape via CD47 up-regulation (2025)** – A recent study summarized by MedChemExpress reported that GW501516 up-regulated CD47 gene and protein expression via PPARδ in colon cancer cells, increased CD47 promoter activity, and decreased macrophage phagocytic ability. PPARδ knockout abolished these effects. The authors concluded that GW501516 may facilitate tumor immune escape by up-regulating CD47 [22]. This aligns with concerns that PPARδ activation could help tumors evade immune surveillance.

Neovascularization and Bleeding

- In the corneal injury model, GW501516 promoted M2 macrophage infiltration and neovascularization, resulting in bleeding and delayed wound closure despite its anti-inflammatory action [8] [9]. Excessive neovascularization is undesirable in ocular healing.

Other Considerations

- **Lack of long-term human data:** There are no published long-term human clinical trials due to early termination of development when rodent studies raised concerns about carcinogenicity. Benefits observed in short-term studies may not reflect chronic exposure risks.

- **Dosing and context matter:** Beneficial effects occur at doses and durations typical of laboratory experiments. Off-label or recreational use may involve different doses, unknown purity and co-ingestants, raising safety issues beyond the scope of these studies.

Summary and Recommendations

- **Potential benefits:** GW501516 exhibits anti-inflammatory, antifibrotic and metabolic benefits in animal and cellular models. It enhances fatty-acid oxidation and endurance, reduces inflammatory cytokines, improves hepatic steatosis and kidney inflammation, stabilizes atherosclerotic plaques, and offers neuroprotection by mitigating inflammasome activation and oxidative stress.
- **Detrimental effects and uncertainties:** Several studies raise concerns about tumor promotion (especially colon cancer) and tumor immune escape via CD47 up-regulation. In ocular models, it promotes neovascularization, and evidence of long-term safety is lacking. Human data are extremely limited; thus, translation to clinical use cannot be recommended.
- **Overall:** The past decade of research reveals a nuanced picture. While GW501516's PPARδ activation can yield therapeutic benefits in metabolic and inflammatory disorders, its potential to promote tumor growth or immune evasion underscores significant safety concerns. Without controlled clinical trials and long-term safety assessments, the risks likely outweigh potential benefits for human use.

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