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Review Article

The Role of Peroxisome Proliferator Activated Receptor-gamma (PPARγ) in Drug-Induced Hepatotoxicity: A Narrative Review

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Abstract

Background: Drug-induced hepatotoxicity is an acute or chronic liver damage due to drugs or herbals. Its diagnosis is difficult since the presentation is similar to various hepatobiliary disorders. It is one of the major reasons for drug failures at clinical phases of drug-development and withdrawal from the market. Peroxisome proliferator-activated receptors (PPARs) are transcription factors that belong to the nuclear hormone receptor superfamily; comprising PPARα, PPARγ and PPARβ/δ. They have different distribution and expression profiles, and this leads to different clinical outcomes. This review focuses on the protective role of the PPARγ in liver damage giving special emphasis to drug-induced hepatotoxicity.

Methods: This narrative review employed a systematic search strategy to identify relevant literature on the role of PPARγ in drug-induced hepatotoxicity. We searched major academic databases such as PubMed, Elsevier, EMBASE, Web of Science, and Google Scholar databases using a combination of keywords related to PPARγ, drug-induced liver injury (DILI), and hepatotoxicity. We included original research articles, reviews, and meta-analyses published in English without time bound. The retrieved articles were critically appraised for their methodology, quality of evidence, and relevance to the topic of interest.

Result and Conclusion: Ligands acting on PPARγ showed hepatoprotective activity and this protective effect is mediated through activation of Nrf2 and enhancing PPARγ mRNA expression. Further studies are recommended to understand the molecular mechanisms of hepatoprotective agents acting on PPARγ.

Keywords: Anti-tuberculosis drugs, Cyclophosphamide, Hepatotoxicity, Paracetamol, Peroxisome proliferator-activated receptors

Introduction

Drug-Induced Hepatotoxicity

Liver is one of the most important organs of humans with several functions (1). It is essential to synthesize various body proteins and to detoxify endogenous toxic metabolic byproducts and ingested toxins by the organism. Thus, loss of total liver function might lead to death within minutes (2). It involves in various biochemical pathways including growth, nutrient supply, fight against diseases, energy provision and reproduction(3). These unique involvements in metabolism and its relationship with the gastrointestinal tract made liver a target for drug-induced toxicity. After administration, drugs are generally metabolized by liver to biologically inactive forms (metabolites) and then eliminated from the body. However, certain drugs may be metabolized into metabolites that can lead to liver damage (4). Due to this reason, drug-induced liver damage became a leading cause of failures in drug development at clinical phases of investigation, and about one-fourth of drugs are prematurely terminated or withdrawn from market (5, 6).

Drug-induced damage to hepatic and bile duct cells may also result in cholestasis. In turn, cholestasis that leads to intrahepatic accumulation of excretion products and toxic bile acids. This accumulation can lead to further hepatic injury (7, 8). Fulminant liver failure, where patients without a history of liver disease present with hepatic encephalopathy and coagulopathy preceding jaundice, is the most detrimental clinical presentation in drug-induced liver damage (9).

Two major mechanisms are involved in drug-induced hepatotoxicity. These are intrinsic and idiosyncratic hepatotoxicity (10). Intrinsic hepatotoxicity is dose-related toxicity. As exposure increases, a threshold is reached, above which individuals respond with toxicity that becomes more severe with increasing dose. This can affect all individuals at some dose and predictable using routine animal testing (11). Idiosyncratic hepatotoxicity, on the other hand, a toxicity that can be further subdivided to immunologic and metabolic toxicities. Immunologic idiosyncrasy refers to injury in the presence of clinical signs of drug hypersensitivity such as fever, rash, eosinophilia, and a prompt response to re-challenge with the drug. Conversely, metabolic idiosyncrasy refers to an injury in the absence of these clinical signs (12). The deficiency of PPARγ in hepatic stellate cells is associated with excessive fibrotic tissue formation in the liver (13).This review focuses on the potential role of PPARγ in drug-induced hepatotoxicity.

Peroxisome proliferator-activated receptors (PPARs)

Peroxisome proliferator-activated receptors (PPARs) were discovered in 1990. They are categorized as members of the nuclear hormone receptor superfamily; function as transcription factors and modulators of gene expression (14). They are involved in regulating glucose and lipid homeostasis, inflammation, proliferation and differentiation (15). Thus, such involvement results in chronic diseases related to alterations in glucose and lipid metabolism. Some of the diseases are diabetes, obesity, non-alcoholic fatty liver disease, and atherosclerosis (16).

PPARs are expressed in several tissues, including hepatocytes, adipocytes, muscles and endothelial cells. However, the affinity depends on the isoform of PPAR and different distribution and expression profiles, and this leads to different clinical outcomes (17). PPARs are ligand-activated transcription factors and comprise three subtypes: PPARα, PPARγ, and PPARβ/δ (18). When they are activated by specific ligands, all the three receptors become transcription factors that regulate the expression of distinct target genes (19). PPARα is highly expressed in brown adipose tissue, which is followed by liver, heart, kidney, and skeletal muscle. Whereas, PPARγ is expressed mainly in adipose tissue but also, in the heart, kidney, colon, spleen, intestine, skeletal muscle, liver, and macrophages at lower levels. The third one, PPARβ/δ is the least understood and it is ubiquitously expressed (20).

PPARs play a major role in the down regulation of oxidative stress, and mitochondrial and proteasomal dysfunction (21). PPAR agonists are reported to attenuate oxidative stress-mediated diseases (22). It has been shown that liver diseases mediated through oxidative stress can be ameliorated by various agents, those acting on PPARs (23-26).

Role of PPARγ in Liver

PPARs exert transcriptional activity in the liver; regulating a wide spectrum of physiological functions. Some of them are regenerative mechanisms, cholesterol and bile acid homeostasis, lipid and glucose metabolism, cell differentiation/proliferation and inflammatory responses (27). In patients diagnosed with fatty liver disease, hepatic expression of PPARγ is involved in hepatic steatosis, insulin sensitivity, and triglyceride clearance (28). It has been reported that PPARγ agonists might have various therapeutic advantages including anti-diabetic activity.

Thiazolidinediones, for instance, are currently available anti-diabetic agents acting on PPARγ. They promote insulin sensitization and improve dyslipidemia in

diabetic patients (29,30). The first approved drug from the thiazolidinedione class was troglitazone. But, it has been withdrawn from market in 2000 due to its fatal hepatotoxicity (31). This idiosyncratic hepatotoxicity is mediated through oxidative stress and it involves mitochondrial dysfunction (32,33). The other agents, rosiglitazone and pioglitazone, have only rarely have been linked to acute liver injury. This observation could indicate that hepatotoxicity is not a class effect for thiazolidinedione. Baseline and routine monitoring of alanine aminotransferase levels as well as monitoring for clinical symptoms of liver injury, are recommended (34).

Adipose PPARγ deficiency elicits secondary liver phenotypes, encompassing fatty liver, enhanced gluconeogenesis, and decreased response to insulin action on hepatic glucose production. Thus, loss of fat PPARγ may result in progressive steatosis, lipodystrophy, and insulin resistance in the liver and fat (35). PPARγ co-activator 1α plays an important role in the intermediary metabolism by co-activating key transcription factors of hepatic gluconeogenesis and glucose uptake in muscles (36). Furthermore, PPARγ may directly affect liver and pancreatic β-cells to improve glucose homeostasis (37).

PPARγ agonists decrease pro-inflammatory cytokines in macrophages. Through PPARγ activity, berberine inhibited the expression and production of tumor necrosis factor α, monocyte chemo-attractant protein 1, and interleukin-6 in acetylated low-density lipoprotein-stimulated macrophages (38). Administration of PPARγ agonists, through activation of PPARγ signaling, protects liver against fibrosis and inflammation in mice and rats (39,40). There is a positive correlation between PPAR protein expression and total superoxide dismutase (SOD) activity. But, a negative correlation was found with the activation of NF-κB p65 protein expression in obstructive jaundice rats. SOD protein expression and enzyme activity will be decreased as a result of reductions in PPAR expression, which might lead to enhanced oxidative stress and lipid peroxidation in the liver (41). PPARγ has shown wide anti-inflammatory effects and plays a major role in controlling fibrogenesis and reducing oxidative stress. PPARγ ligands might be potential anti-fibrotic candidates for the management and prevention of hepatic fibrosis (42,43).

Materials and Methods

Literature Search

Authors performed a literature search in December 2023 from the PubMed, Elsevier, EMBASE, Web of Science and Google Scholar databases. The following terms (i) PPARγ/Peroxisome proliferator-activated

receptor gamma and (ii) Hepatotoxicity or Liver damage or Drug-induced liver injury or drug-induced liver disease or drug-induced liver damage were used during the search.

Inclusion and Exclusion Criteria

Studies published in peer-reviewed journals in English language, studies with full text, experimental studies providing data on PPARγ effects on drug induced hepatotoxicity were included in this study. Reviews, duplicate studies, studies without detailed research outcome were excluded.

PPARγ in Cyclophosphamide-Induced Hepatotoxicity

Cyclophosphamide (CP) is an alkylating agent used to treat various types of cancer, lupus nephritis, and nephrotic syndrome (44). Even though CP has a broad spectrum of applications, there are deleterious effects shown in humans and experimental animals (45, 46). Since kidney and liver are the two important organs for CP metabolism and excretion, nephrotoxicity and hepatotoxicity are considered as main side effects of this drug on the abovementioned organs (47). These and other toxicities limited the clinical use of CP (48).

CP is a prodrug that needs metabolic activation by hepatic microsomal CYP_{450} mixed function oxidase system. This activation gives phosphoramide mustard and acrolein. During these processes, induction of oxidative stress has been noticed (49). CP is presumed to enable the production of free radicals and inhibit endogenous antioxidant activities, including SOD, glutathione (GSH) and catalase (CAT) (50).

Reactive oxygen species (ROS) lead to lipid peroxidation of the cell membrane and results in loss of cell membrane integrity. Treatment with PPARγ-agonists showed hepatoprotective activity through an increment of the PPARγ mRNA expression (51). For instance, Umbelliferone, a coumarin derivative, administration showed hepatoprotective effects through activation of nuclear factor erythroid 2-related factor 2 (Nrf2) and PPARγ, and subsequent suppression of inflammation and oxidative stress in CP-induced hepatotoxicity **(Figure 1)** (52). Nrf2 is a transcription factor, which is known to induce various antioxidant and cytoprotective genes (53). The following table is a summary of the evidence showing the role of PPARγ in CP-induced hepatotoxicity (Table 1).

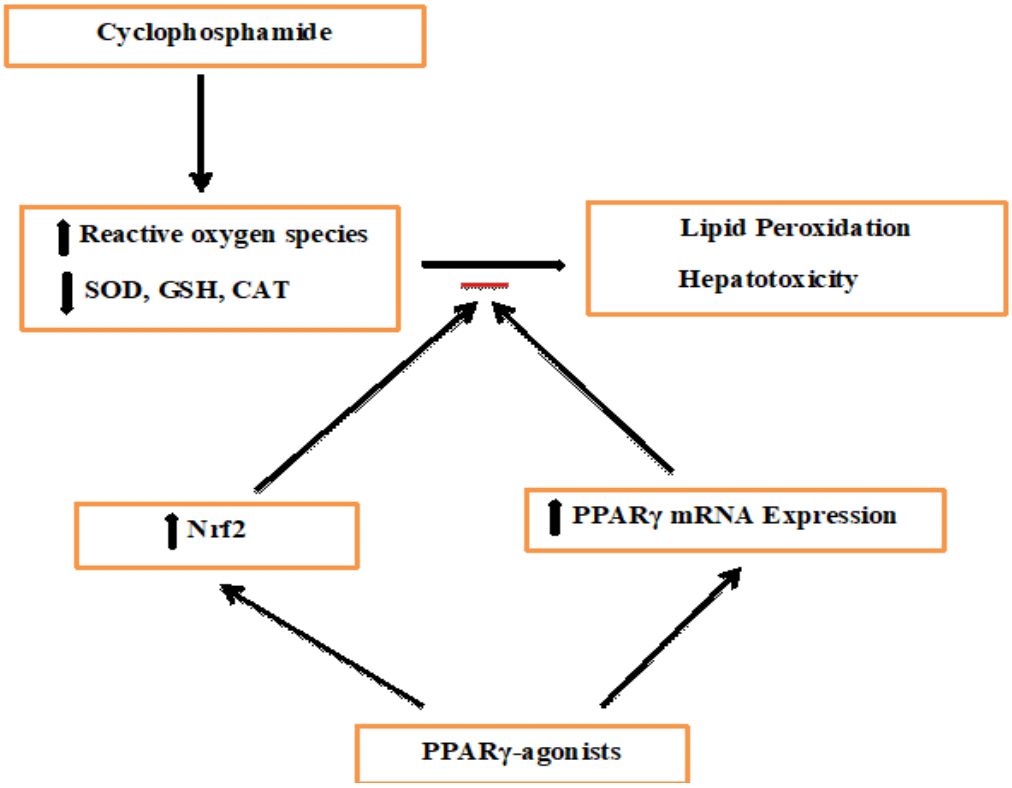

Figure 1: Major Hepatoprotective Mechanisms of PPARγ-agonists, CAT (catalase), GSH, (glutathione), Nrf2 (nuclear factor erythroid 2-related factor 2), (SOD (superoxide dismutase).

Table 1: The Relationship and Protective Role of PPARγ agonists in the Cyclophosphamide-Induced Hepatotoxicity

Ligand	Method and Intervention	Major Outcome	References
Fenofibrate (FEN) (PPARα agonist) and pioglitazone (PIO) (PPARγ agonist)	• Rats were administered with FEN and PIO (150 and 10 mg/kg/day, respectively) for 4 weeks orally in a different group, then five days before the end of the experiment, both groups were administered cyclophosphamide (CP) (150 mg/kg, i.p.).	• Pretreatment with PIO, but not FEN, before CP challenge improved hepatic function and liver histology, and significantly reversed oxidative and inflammatory parameters. • Activation of PPARγ, but not PPARα, showed protection against CP-induced hepatotoxicity, through activation of antioxidant and anti-inflammatory mechanisms. • To conclude, PPARγ activation might have hepatoprotective effects, as evidenced by PIO.	(54)
Umbelliferone (UMB), a coumarin derivative.	• Rats were administered with UMB (50 and 100 mg/kg, orally) two weeks prior to CP injection. Five days after CP (150 mg/kg, i.p) administration, the rats were sacrificed and samples were collected for analyses. • PPARγ mRNA abundance was determined by quantitative reverse transcription-polymerase chain reaction (qRT-PCR).	• Supplementation of UMB attenuated CP-induced inflammation and oxidative stress, as evidenced by restoration of the antioxidant defense activity and expression, and suppression of the pro-inflammatory cytokines. • CP-induced alterations in liver histology were reduced by UMB. • CP-induced rats showed significant down-regulation of Nrf2, HO-1 and PPARγ, an effect that was markedly reversed by UMB. • UMB pretreatment prevented down-regulation of PPARγ mRNA and resulted in marked up-regulation of liver PPARγ protein expression. • The hepatoprotective activity of UMB might depend on co-activation of PPARγ and Nrf2, and subsequent suppression of oxidative stress and inflammation.	(52)
Hesperidin (HES), a flavonoid, is isolated from the orange *Citrus aurantium*.	• The rats were administered with a single dose of CP (200 mg/kg, i.p), followed by treatment with HES (25 and 50 mg/kg, orally) for 11 consecutive days. At the end of the experiment, blood samples and liver tissue were collected. • Quantitative polymerase chain reaction (qPCR) was used to determine liver PPARγ-mRNA expression level.	• CP resulted in reduced glutathione content, and the activities of the antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase, were reduced. CP administration induced downregulation of PPARγ and upregulation of NF-κB and iNOS mRNA expression. • Administration of HES rejuvenated the altered markers in a dose-dependent manner. • To conclude, this protective effect might be mediated through up-regulation of hepatic PPARγ expression and abrogation of inflammation and oxidative stress.	(51)

18β-Glycyrrhetinic acid (18β-GA)	• Rats were administered 18β-GA (25 and 50 mg/kg, orally) for 2 weeks prior to CP (150 mg/kg, i.p) injection. Five days after CP administration, rats were sacrificed and samples were collected. • Gene expression analysis was performed using quantitative reverse transcription polymerase chain reaction.	• Administration of 18β-GA prevented CP-induced oxidative stress and inflammation as evidenced by restoration of the antioxidant defenses and through diminishing the pro-inflammatory cytokines, lipid peroxidation, and NO production. • 18β-GA (50 mg/kg) administration produced significant up-regulation of both Nrf2 and PPARγ in the liver of CP-administered rats and effective than 25 mg/kg. • 18β-GA protected liver against CP-induced hepatotoxicity through activation of Nrf2 and PPARγ.	(55)
Gamma-glutamylcysteine ethyl ester (GCEE), a precursor of glutathione	•Rats were administered with GCEE (100 mg/kg) for 15 days and CP (150 mg/kg) on day 16. At day 21, rats were sacrificed and various samples were collected. •Quantitative RT-PCR was used to study gene expression	• GCEE administration suppressed lipid peroxidation and nitric oxide production and restored glutathione, and enzymatic antioxidants in the liver, which were associated with downregulation of COX-2, iNOS, and NF-κB. • GCEE up-regulated PPARγ and imparted its hepatoprotective effect through activating PPARγ, preventing GSH depletion, and attenuating oxidative stress, inflammation, and apoptosis.	(56)

Key: Cyclophosphamide (CP), nuclear factor erythroid 2-related factor 2 (Nrf2), heme oxygenase (HO-1), nuclear factor-kappa B (NF-κB), inducible nitric oxide synthase (iNOS),

Role of PPARγ in Other Drug-Induced Hepatotoxicities

Paracetamol (PCM) is an analgesic and antipyretic drug that is safe at its therapeutic doses. However, it is associated with acute liver damage during acute overdose (57). PCM-induced hepatotoxicity is one of the most common causes of liver failure (58). PPARγ may function to protect mitochondria from ROS, resulting from PCM overdose (59).

In a recent study, both curcumin and silymarin showed anti-apoptotic and anti-inflammatory effects on liver tissues by decreasing Bax and increasing Bcl2 mRNA expression in PCM-induced hepatotoxicity in adult male albino rats. PPARγ mRNA expression has been reported to significantly increase with curcumin treatment. The possible hepatoprotective mechanism could be via activating PPARγ, which is involved in the inhibition of sterol regulatory element binding protein 2 (SREBP-2) and low-density lipoprotein receptor (LDLR) gene expression. These proteins could reinstate lipid storage capacity of hepatic stellate cells and protect against liver steatosis and fibrosis (57).

Some anti-tuberculosis drugs are associated with hepatotoxicity, including isoniazid, pyrazinamide and rifampicin (60, 61). Isoniazid is a highly effective drug in the management of tuberculosis (62). Even though the biochemical basis of isoniazid-induced hepatotoxicity remains elusive, it has been reported that isoniazid can disrupt multiple endobiotics metabolic pathways, which are all critical for hepatocellular functions (63). Hydrazine, the reactive metabolite of isoniazid, was shown to inhibit the activity of solubilized complex I in mouse hepatocytes resulting in mitochondrial oxidative stress. Thus, isoniazid-induced oxidative stress affects mitochondrial dynamics and might lead to liver damage (64).

As reported by *Mahmoud* and his colleagues, administration of berberine (25 and 50 mg/kg, orally) for 45 days showed a protective effect against isoniazid-induced oxidative stress and inflammation in rats, through up-regulating PPARγ and subsequently suppressing NF-κB, iNOS and release of the pro-inflammatory cytokines. Gene expression analysis using quantitative polymerase chain reaction in rats treated with berberine showed increased liver PPARγ mRNA expression when compared with the control groups (13).

Chronic alcohol intake has also been reported to cause alcoholic liver disease which involves three stages; steatosis (fatty liver), hepatitis, and cirrhosis. The main pathologic mechanisms for fatty liver development include an increase in plasma corticosterone, induction of zinc deficiency, hyperlipolysis

of adipose tissue and reverse triglyceride (TG) transport to liver, and induction of leptin deficiency (65). Treatment with 4-Methylcoumarin-(5,6-g)-hesperetin (4-MCH) was found to attenuate inflammatory responses in alcoholic hepatitis through PPARγ activation in mice. In addition, 4-MCH was found to suppress the release of inflammatory cytokines including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). The expression of PPARγ was also up-regulated in the 4-MCH group (66).

High intake of the western diets such red meat and processed meat, high-fat dairy products and sweet items, is associated with obesity and metabolic syndrome. This also increases the risk of type 2 diabetes mellitus and cardiovascular diseases (67). Animals fed with a western diet develop advanced nonalcoholic fatty liver disease, including nonalcoholic steatohepatitis (NASH) and hepatic fibrosis (68). Chronic dietary intake of quercetin is reported to reduce oxidative stress. Literature reports showed that Quercetin can alleviate hepatic fat accumulation in mice liver fed with western diet. This might be through increasing PPARγ expression (67).

Conclusion

The peroxisome proliferator-activated receptors are members of the nuclear receptor superfamily of ligand-dependent transcription factors. They are involved in regulating glucose and lipid homeostasis, inflammation, proliferation and differentiation. Thus, they play a major role in the down-regulation of oxidative stress, mitochondrial and proteasomal dysfunction. Even though the exact mechanism is still obscure, various agonists of PPARγ showed a promising effect in preventing drug-induced hepatotoxicity through activation of Nrf2 and enhancing PPARγ mRNA expression. Since hepatotoxicity is a major concern in drug development, further researches including pre-clinical and clinical studies should be encouraged on hepatoprotective agents acting through PPARγ.

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Consent for publication

All authors provided consent for the publication of the manuscript detailed above.

Author Contributions

All authors participated in the conception of the work, data collection, drafting the article, critical revision of the article and in the final approval of the version to be published.

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