JOBIMB, 2025, Vol 13, No 2, 10-19
https://doi.org/10.54987/jobimb.v13i2.1130

HIBISCUS PUBLISHER

JOURNAL OF BIOCHEMISTRY, MICROBIOLOGY AND BIOTECHNOLOGY

Website: http://journal.hibiscuspublisher.com/index.php/JOBIMB/index

JOBIMB VOL 13 NO 2 2025
AI and Biochemistry

Health Benefits of Peroxisome Proliferator-Activated Receptors (PPARs): A Narrative Review

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History

Received: 20th June 2025
Received in revised form: 21st July 2025
Accepted: 15th Aug 2025

Keywords

Peroxisome proliferator-activated receptors
Nuclear receptors
Transcriptional regulation
PPAR-dependent suppression
Therapy
Metabolism

SDG Keywords

SDG 3 Good Health and Well-being
SDG 9 Industry, Innovation and Infrastructure
SDG 4 Quality Education

Abstract

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors that play a crucial role in several physiological processes, including the metabolism of carbohydrates, proteins, and lipids, as well as regulating cellular differentiation, development, and tumorigenesis. Recent research has increasingly focused on the role of PPARs in maintaining physiological homeostasis and their potential as therapeutic targets. These receptors regulate gene expression involved in lipid and glucose metabolism, inflammation, and cellular differentiation. This narrative review aims to assess the current understanding of the health benefits of PPARs, their mechanisms of action, clinical applications, and challenges. The review includes findings from various clinical and experimental studies, along with insights from previous reviews. An exhaustive bibliographic survey was conducted which utilized search engines, such as Pubmed, Scopus, Web of Science, Science direct, Medline, Google Scholar, and ResearchGate. The search strategy involved the use of some key terms including, PPAR, nuclear receptors, transcriptional regulation, PPAR-dependent suppression. PPARs have been shown to exert significant pharmacological effects, especially in the treatment of metabolic disorders, such as diabetes and obesity. They have the ability to modulate cell differentiation, development and inflammation. While there are challenges in optimizing their efficiency, clinical trial studies suggest that PPARs will offer a promising glimpse into the future of personalized and targeted therapies. This narrative review highlights the benefits of PPARs in managing metabolic disorders, cardiovascular diseases, inflammation and even cancer. Further clinical studies are necessary to understand the adverse effects of these receptors and how they can be optimized to maintain their efficiency.

INTRODUCTION

In recent years, the spotlight has increasingly focused on the intricate world of molecular biology, with particular emphasis on the pivotal roles of nuclear receptors in maintaining physiological homeostasis and their potential as therapeutic targets [1]. Among these, peroxisome proliferator-activated receptors (PPARs) have emerged as a focus of intense research due to their profound impact on metabolic processes, including lipid metabolism, glucose homeostasis, and energy balance [2]. Peroxisome proliferator-activated receptors (PPARs) are a group of nuclear receptor proteins that play a crucial role in regulating gene expression involved in lipid and glucose metabolism, inflammation, and cellular differentiation [3]. The

rising burden of chronic diseases, particularly in children and the elderly, highlights the urgent need for therapies that ensure patient compliance while minimizing side effects. Conditions such as cancer, obesity, diabetes, and cardiovascular diseases have become increasingly prevalent. Improved treatment options now allow individuals to live with these diseases for extended periods, leading to complex management issues due to the co-existence of multiple conditions. Research indicates that the co-occurrence of diabetes and cancer is becoming more common, potentially due to shared risk factors or diabetes acting as a predisposing factor for various cancers, including colorectal, pancreatic, breast, liver, gastric, and endometrial malignancies [4].

Obesity and type-2 diabetes are recognized as important risk factors for various types of cancer, including breast, colorectal, and pancreatic cancer. The mechanisms underlying this link include metabolic dysregulation, chronic inflammation and hormonal changes, all of which are influenced by PPAR activity. For example, PPAR-γ mediates adipokine production, which can influence the proliferation and survival of cancer cells [5]. In addition, the inflammatory pathways modulated by PPARs can contribute to a tumor-promoting microenvironment which provides a further link between these metabolic disturbances and cancer risk [6].

Recent findings suggest that obesity is associated with reduced PPAR expression [7]. Furthermore, PPAR ligands have been associated with improvements in glycemic control and cancer management [8]. Thus, PPARs appear to represent a common target for managing chronic diseases such as obesity, cancers, and diabetes, and hypertension. This narrative essay aims to assess the current understanding of the health benefits of PPARs, their mechanisms of action, clinical applications, potential risks, and limitations. By shedding light on these, the study aims to contribute to the ongoing efforts to optimize PPAR-based treatments and address the clinical concerns that limit their broader clinical applications.

REVIEW METHODOLOGY

This review aimed to identify the current state of PPARs' known therapeutic activities, their mechanisms, clinical applications, and setbacks. Findings from various clinical and experimental research as well as previous reviews were included in the review. Web search engines such as PubMed, Scopus, Web of Science, ScienceDirect, MEDLINE, Google Scholar, and ResearchGate were primarily used to search for relevant published articles. We used key terms, including PPAR, nuclear receptors, transcriptional regulation, and PPAR-dependent suppression, to search for relevant published papers. The reference sections of articles were also reviewed for relevant titles of interest, which were subsequently searched for on search engines. The scope of this review is limited to PPARs.

Types of PPAR receptors, sources, number of chromosomes, functions and ligands

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors and transcription factors that play a key role in regulating energy balance both in the liver and throughout the body. In addition to their established functions in lipid and glucose metabolism, growing evidence suggests that PPARs also influence other biological processes, including the regulation of cell differentiation, blood circulation and inflammatory responses [9]. There are three main types of PPARs, each having its specific function and activated by different ligands. The three main types are:

PPAR alpha (PPARα)

PPARα is a member of the nuclear receptor subfamily that operates as a ligand-activated transcription factor [10]. It oversees lipid and glucose metabolism, cell proliferation, differentiation, inflammation, vascular biology, and cancer processes [10]. In metabolically active tissues such as the liver, heart, and brown adipose tissue, PPARα is highly expressed [11]. It is vital for preserving metabolic adaptability by adjusting the utilization and storage of fuels, especially fatty acids and lipids, in response to nutritional conditions [12]. PPARα performs its function by regulating processes such as fatty acid transport, esterification, and oxidation [11]. It controls the expression of several genes involved in different lipid metabolism pathways. These pathways include microsomal, peroxisomal, and mitochondrial fatty acid oxidation (FAO), in addition to fatty acid binding and activation, fatty acid elongation and desaturation, triglyceride (TG) synthesis and breakdown, lipid droplet formation, lipoprotein metabolism, gluconeogenesis, bile acid metabolism, and many other metabolic pathways and genes [13].

Studies of the various functions of PPARα revealed that PPARα, orchestrates various metabolic processes crucial for health. Primarily, it governs lipid metabolism by enhancing fatty acid uptake, utilization, and breakdown through gene regulation [14]. This includes boosting enzymes such as Carnitine Palmitoyltransferase 1 (CPT1) for lipid transport into mitochondria, while promoting liver gluconeogenesis and glycogen synthesis [10]. During fasting, PPARα activates ketogenesis, a vital response to energy depletion. Additionally, it curtails inflammation by inhibiting LDL uptake, foam cell formation, and proinflammatory cytokines. In aging, PPARα influences repair processes, reducing age-related lesions in vital organs [9,12].

The natural agonists of PPARα are omega-3 fatty acids and their derivatives, as summarized in **Table 1**. They are natural ligands that bind to and activate PPARα. According to Grabacka *et al.* [15], although the rat and mouse brain's natural 7(S)-Hydroxydocosahexaenoic Acid (7(S)-HDHA) was identified as a high-affinity ligand for PPARα, its 7(S) enantiomer binds to PPARα with ten times the affinity of the (R) enantiomer, which may cause dendritic activation. Fibrates like clofibrate, gemfibrozil, ciprofibrate, bezafibrate, and fenofibrate are examples of synthetic PPARα agonists. These medications are intended for the treatment of dyslipidemia, a condition marked by elevated triglycerides and low cholesterol [16].

PPAR-targeting drugs

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors that play a crucial role in regulating glucose and lipid metabolism, making them attractive targets for the treatment of metabolic disorders, such as type 2 diabetes and dyslipidemia [17]. PPAR targeting drugs, including thiazolidinediones (TZDs) and fibrates, have been developed to modulate PPAR activity and improve metabolic outcomes. PPARγ agonists, such as TZDs, have been shown to improve insulin sensitivity, reduce glucose levels, and delay the progression of type 2 diabetes [18]. PPARα agonists, such as fibrates, have been effective in reducing triglyceride levels and increasing high-density lipoprotein (HDL) cholesterol [19]. These benefits make PPAR-targeting drugs a valuable treatment option for patients with metabolic disorders. Also known as

PPARδ or PPARβ (PPARβ/δ), on the other hand is expressed in almost all tissues in the body and is the least studied of the PPARs, even though it is thought to be responsible for regulating cholesterol transport and high-density lipoprotein metabolism [20]. It is associated with the oxidation of fatty acids, which enhance lipid profiles and decreases adiposity, thereby preventing the development of obesity. PPARβ/δ controls the amount of fat consumed by animals. A Study reported that, on a high-fat diet, mice lacking PPARβ/δ showed decreased energy uncoupling and were more likely to become obese, whereas in genetically modified mice, PPARβ/δ activation resulted in resistance to obesity induced by either a genetic or a high-fat diet [11]. In the hyperglycemic condition of diabetes mellitus, cardiac muscle also exhibits decreased PPARβ/δ expression. On the other hand, overexpression of this receptor in heart cells improves glucose metabolism and reduces lipid buildup when a high-fat diet is present. As a result, the heart is protected from the damaging effects of ischemia-reperfusion, suggesting that activating this receptor could be helpful in treating diabetic cardiomyopathy [9,11].

The primary function of PPARβ/δ is to modulate gene transcription activity [21]. It has also been found to have a significant impact on various physiological and pathophysiological processes, such as mast cell immunity, bone formation, skin and brain development, wound healing, and tumorigenesis [21]. The mechanisms by which PPARβ/δ influences lipid metabolism have been less extensively studied than those of other PPARs. However, it is well established that PPARβ/δ promotes lipid catabolism in various tissues and acts as a mediator of fatty acid oxidation and fat burning [12]. The effects of PPARβ/δ on macrophages and innate and adaptive immune cells are not well understood. Nevertheless, additional research revealed that proinflammatory gene expression is down-regulated in peritoneal macrophages from PPARβ-deficient mice [12,22]. PPARβ/δ is highly expressed in hepatocytes, liver-resident macrophages (Kupffer cells), and hepatic stellate cells. Its role is crucial in the alternative activation of Kupffer cells, which, in turn, supports the proper functioning of hepatocytes and helps prevent systemic insulin resistance. Conversely, myeloid-specific PPARδ-deficient mice displayed liver inflammation, metabolic disorders, and insulin resistance [22].

Although ligand-binding specificity can vary between isotypes, both PPARα and PPARβ/δ can bind saturated and unsaturated fatty acids. However, PPARα generally exhibits a higher affinity for these molecules than PPARβ/δ [9]. Studies on potential synthetic therapeutic drugs such as GW501516 and NNC61-5920 have been conducted; however, the species specificity of natural PPARβ/δ agonists has not yet been established. Following treatment with NNC61-5920, mice fed a high-fat diet showed improved insulin sensitivity. This significant outcome, meanwhile, was not seen in a similar rat model. When GW501516 was administered to type-2 diabetic rodents, obese primates, and sedentary human volunteers, parameters such as insulin sensitivity, triglyceride levels, LDL-cholesterol levels, Apoa1 levels, and HDL-cholesterol levels improved, demonstrating the benefits of PPARβ/δ in humans [23]. However, due to the development of cancer in mice, the clinical development of this agent has been halted [9].

The carcinogenic risk of PPARβ/δ a concern for therapeutic development

Peroxisome proliferator-activated receptor beta/delta (PPARβ/δ) is a nuclear receptor that plays a crucial role in regulating various biological processes, including glucose and lipid metabolism. However, the development of PPARβ/δ agonists as therapeutic agents has been halted due to concerns over their carcinogenic risk [24]. Studies have shown that PPARβ/δ activation can promote cancer development and progression in specific tissues. For example, PPARβ/δ has been shown to enhance colon carcinogenesis by promoting cell proliferation and inhibiting apoptosis [25]. Additionally, PPARβ/δ activation has been linked to increased expression of genes involved in cell cycle progression and angiogenesis, which can contribute to tumor growth and metastasis [26].

The mechanisms underlying the carcinogenic risk of PPARβ/δ are complex and multifaceted. PPARβ/δ can regulate various signaling pathways, including those involved in cell proliferation, differentiation, and survival. Additionally, PPARβ/δ can interact with other transcription factors and coactivators to modulate gene expression and promote cancer development [27]. GW501516 has potential benefits, but Grabacka *et al.* [15] raised controversy due to potential carcinogenic effects; some studies have suggested that PPARβ/δ activation may promote tumor growth and progression in certain contexts, and it lacks specificity. GW501516 may have off-target effects, leading to unintended consequences, and there is limited research on its long-term safety and efficacy.

Carcinogenic risk of PPARβ/δ

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The PPAR-gamma (PPARγ)

This is a ligand-activated transcription factor in the form of a nuclear receptor belonging to the subfamily 1, group C, member 3. The spleen, large intestine, and white and brown adipose tissue all contain PPARγ. It is, however, most highly expressed in adipocytes, where it is essential for controlling lipid production, energy balance, and adipogenesis [11]. PPARγ is located on chromosome 3 and has three isoforms which include PPARγ1, PPARγ2 and PPARγ3 [12]. PPARγ2 is the longest isoform and is only present in the liver and fat tissues, while PPARγ1 is expressed throughout the body. Completing the trio is PPARγ3, which is predominantly expressed in the colon and adipose tissue. It's interesting to note that whereas PPARγ2 has an extra 30 amino acids at its N-terminus in mice and 28 in humans and monkeys, proteins produced from γ1 and γ3 mRNAs are identical [9,28].

All PPARγ isoforms contribute significantly to adipocyte differentiation and glucose metabolism; however, their expression patterns vary. PPARγ1 is widely expressed across all cell types, whereas PPARγ2 is mainly found in adipose tissue and exhibits stronger transcriptional activation [28]. Increased PPARγ expression can redirect fatty acids from the liver to adipose tissue, reducing liver lipotoxicity and improving steatosis [9]. Nevertheless, PPARγ seems to promote fat accumulation in hepatocytes, affecting genes involved in hepatic fatty acid uptake and re-esterification [22].

PPARγ is involved in various diseases, including obesity, diabetes, atherosclerosis, and cancer, due to its ability to reduce insulin resistance, alter adipocyte differentiation, and inhibit vascular endothelial growth factor-induced angiogenesis [14,28]. Additionally, PPARγ decreases the inflammatory response in numerous cardiovascular cells, notably endothelial cells, stimulates the paraoxonase 1 (PON1) gene, promotes PON1 synthesis and release by the liver, and regulates the advanced glycation end product (AGE)-receptor interaction [14]. Besides polyunsaturated fatty acids (PUFA), phytanic acid is also a natural PPARγ agonist found in the human diet that exhibits almost the same activity as omega-3 polyunsaturated fatty acids [12]. It enhances uptake of glucose and glucose sensitivity even with low capacity to induce adipocyte differentiation [28].

Studies of the PPARγ agonists in the treatment of neuroinflammatory diseases suggest that pioglitazone, a thiazolidinedione (TZD), exhibited inhibitory activity by reducing IκB phosphorylation, thus preventing the release and nuclear translocation of NF-κB, leading to a decrease in the expression of proinflammatory genes [29]. TZD is a PPARγ agonist that is also used to make individuals with metabolic syndrome and type 2 diabetes more sensitive to insulin [12]. Although PPARγ agonists offer significant anti-diabetic potential, their clinical uses often come with detrimental side effects. To address this, studies have explored the simultaneous targeting of PPARα and PPARγ using dual agonists [12]. It was found that dual agonists not only enhance lipid parameters and mitigate cardiovascular complications via PPARα but also exert insulin-sensitizing effects via PPARγ [30]. **Table 1** summarizes the various receptor types, their sources, chromosome numbers, functions, and ligands.

Table 1. Types of PPAR, sources and functions.

Types	Sources	Chrom-osome	Function	Ligands	Ref
PPARα	Kidney, liver, heart, skeletal muscle, brown adipose tissues and intestine	22	Fatty acid oxidation, fatty acid esterification, fatty acid transport, browning of brown adipose tissue, and energy dissipation	Palmitoleic acid, palmitic acid, Arachidonic acid, linoleic acid, Eicosatetraenoic acid, Leukotriene B4 and pristanic acid	[11,12, 14]
PPARβ/σ	Ubiquitous	6	Glucose homeostasis and Fatty acid oxidation	Carbaprostacyanin and retinoic acid	[12,14, 29]
PPARϒ	Liver, white adipose tissue, skeletal muscles, intestine, immune cells	3	Thermogenesis, glucose homeostasis, energy storage, adipogenesis, lipid synthesis and fatty acid transport	Arachidonic acid, linoleic acid, Prostaglandin J2, Eicosatetraenoic acid, 9-hydroxyoctadecadienoic acid, 13-hydroxyoctadecadienoic acid	[12,14, 29]

Pharmacodynamics of PPAR

Pharmacodynamics of peroxisome proliferator-activated receptors (PPARs) studies how these receptors interact with various ligands, such as natural fatty acids and synthetic medications, to regulate gene expression and affect physiological processes [14]. Peroxisome proliferator-activated receptors (PPARs) control the transcriptional regulation of genes involved in various biological responses [31], including energy metabolism and homeostasis, inflammation regulation, and cellular development and differentiation [12]. The pharmacodynamics of PPAR include:

Ligand binding of PPARs

PPARs are activated by binding specific ligands, such as natural fatty acids or synthetic agonists. When bound to a ligand, PPARs change shape and join with the retinoid X receptor (RXR) to move into the cell nucleus [32]. PPARs have a complex structure with terminal ligand-binding domains (five domains) that form heterodimers with nuclear retinoid X receptor (RXR) [31,33]. The structure includes: A/B, C, D, E, and F. The N-terminal region is the A/B domain, which includes activation function domain 1 (AF-1). This domain exhibits relatively low transcriptional activity and possesses ligand-independent transactivation function, allowing it to regulate PPARα activation through phosphorylation and interaction with other regions. Following the A/B region is the DNA-binding region (C domain) [21]. The human PPAR protein's C domain, spanning amino acids 101–166, contains two zinc-finger domains, crucial for DNA recognition and dimer formation. Acting as a hinge, the D domain connects the DNA-binding region to the ligand-binding region (E region) and binds the repressor functional domain on corepressor proteins. In the E/F region (amino acids 280–468), AF-2, comprising alpha helices and a beta-pleated sheet, interacts with ligands, forming hydrogen bonds and a charging clip structure that enhances binding to the coactivator's LXXLL site [21].

Transcriptional regulation of PPARs

Activated PPARs bind to retinoid X receptors (RXRs) and bind to specific DNA sequences known as peroxisome proliferator response elements (PPREs) in the promoter regions of target genes. This leads to the activation or suppression of genes related to lipid metabolism, inflammation, and insulin sensitivity. Peroxisome proliferator-activated receptors (PPARs) are nuclear receptor proteins that are regulated by multiple mechanisms [34]. These genes consist of exons and introns and are regulated by separate promoters [35]. When PPARs bind ligands such as fatty acids or synthetic agonists, they undergo conformational changes to form heterodimers with retinoid X receptors [32]. These heterodimers then bind to PPREs in the promoters of target genes [35]. Corepressors change chromatin to inhibit PPAR transcriptional activity, while coactivators like PPARγ coactivator-1 alpha (PGC-1α) enhance it [36]. Post-translational changes, like phosphorylation, significantly affect PPAR function. PPAR-mediated transcriptional regulation interacts with multiple signalling pathways, impacting metabolic balance and inflammation [31]. PPAR expression and function vary depending on the tissue, with PPARα being the main regulator of lipid metabolism in the liver and PPARγ controlling adipocyte development and lipid storage in adipose tissue [11].

Effects on gene expression

PPARs regulate genes involved in lipid metabolism (such as fatty acid oxidation and lipogenesis), glucose metabolism (such as gluconeogenesis and insulin sensitivity), inflammation (such as cytokine production and immune response), and cell proliferation (such as cell cycle regulation) [37]. They regulate genes involved in fatty acid oxidation, which is crucial for energy production, as well as lipogenesis, which is essential for the synthesis and storage of fat [38]. This well-regulated control mechanism promotes optimal energy utilization, particularly during fasting or increased energy demand in tissues such as the liver and muscles [39]. PPARs regulate genes involved in gluconeogenesis, the creation of glucose from non-carbohydrate sources [10]. They also improve insulin sensitivity, making it

easier for cells to take in glucose and maintain appropriate blood glucose levels [21]. Moreover, PPARs have anti-inflammatory properties by regulating genes involved in cytokine production and the immune response, thereby reducing the intensity of inflammatory processes observed in disorders such as metabolic syndrome and atherosclerosis [40]. Moreover, PPARs influence cell proliferation by coordinating the activity of genes that regulate cell cycle progression and apoptosis, thereby affecting cell growth, differentiation, and survival [36].

Pharmacokinetics of PPAR

Absorption

The uptake of PPAR agonists, whether taken orally, intravenously, or applied topically, is influenced by their physicochemical properties, including lipophilicity, molecular weight, and solubility [41]. When taken by mouth, these compounds come into contact with the gastrointestinal tract, where their absorption is influenced by factors such as their solubility in fat, size, and solubility in water [42]. Compounds that dissolve well in fat have better ability to pass through the intestinal wall [43,44]. Administering a substance intravenously bypasses the gastrointestinal tract, allowing rapid and complete absorption directly into the bloodstream [31]. The substance's ability to dissolve in fats remains important. Topical administration refers to the application of PPAR agonists directly onto the skin [45]. The ability of these agonists to penetrate through the outermost layer of the skin, called the stratum corneum, is determined by their lipophilicity, molecular weight, and solubility [46]. Smaller, more lipophilic molecules can penetrate deeper into the skin. Having a thorough understanding of these physicochemical features is crucial to optimizing formulation and delivery techniques for PPAR agonists, thereby maximizing their therapeutic effectiveness [47].

Distribution

When a drug designed to target PPARs enters the bloodstream, it disperses throughout the body to reach the specific tissues where PPARs are active [48]. This distribution process is influenced by several factors, including the drug's lipophilicity (affinity for fat) [13], its tendency to bind to proteins [49], and the blood flow to different tissues [41]. Additionally, drug distribution can be affected by its degree of binding to proteins in the bloodstream, potentially limiting its access to tissue [7]. Moreover, the rate of blood flow to particular organs, known as tissue perfusion, can also impact drug distribution, with tissues experiencing higher blood flow potentially receiving higher drug concentrations [50]. For a drug targeting PPARs to produce pharmacological effects, it must be distributed to tissues expressing PPARs, facilitating interaction with these receptors and influencing metabolic processes such as glucose and lipid metabolism [51].

Metabolism

PPAR-targeting medications are typically subject to hepatic metabolism, primarily via cytochrome P450 enzymes and other metabolic pathways [49]. This metabolic process can impact the drug's effectiveness, duration of action, and susceptibility to interactions with other drugs [51, 52].

The metabolism of PPARs involves their activation, regulation, and degradation. Activation occurs when specific ligands, including fatty acids or synthetic drugs, bind to the receptor, inducing a conformational change that allows it to form a heterodimer with RXR [7]. This complex then binds to DNA sequences known as PPAR response elements, leading to the transcription of genes related to lipid metabolism, glucose regulation, and inflammation [53]. Regulatory mechanisms include interactions with coactivators and corepressors, as well as post-translational modifications such as phosphorylation and acetylation [54]. Degradation of PPARs is mediated by the ubiquitin-proteasome system, ensuring tight regulation to maintain metabolic balance and prevent excessive activation [33].

Excretion

The elimination of drugs that target PPARs involves primarily being removed from the body through either the kidneys or liver [55]. Renal excretion removes drugs and their metabolites via urine, while hepatic excretion involves secreting them into bile for elimination via feces [56]. Various factors, such as the drug's size, polarity, and water solubility, affect whether it is filtered by the kidneys, secreted by the kidneys, or transported into bile by liver cells [57]. Knowing these excretion pathways is important for understanding how long the drug stays in the body and the risk of accumulation, which helps adjust doses and reduce the risk of harmful effects [52].

Clinical trials

The dawn of the 21st century has witnessed remarkable advances in the field of molecular medicine, with PPARs standing at the forefront of therapeutic innovation [58]. As lipid-sensing transcription factors, PPARs play a critical role in regulating metabolic pathways, thus holding promise for the management of complex diseases such as diabetes, obesity, cardiovascular diseases, and even certain forms of cancer [59]. The quest to understand the outcome of the clinical trial of PPARs as a key player in lipid metabolism, glucose homeostasis and inflammation as well as management/benefit in disease management has resulted in the understanding of PPARs to have further subdivided into three forms [60]; PPARs-alpha, PPARs-gamma and PPARs-delta/beta, each with distinctive tissue functions, and implications for therapeutic interventions [61]. This has further dissected the outcomes of the therapeutic applications of PPAR agonists and their implications for human health, and has also evaluated the efficacy, safety, and health benefits of PPAR agonists [58].

The significant findings from clinical trials of PPARs across various disease management areas include, for instance, PPAR-alpha agonists, traditionally used in the treatment of dyslipidemia, which have shown promise in reducing cardiovascular risk factors [62]. PPARs-gamma agonists, primarily recognized for their role in improving insulin sensitivity, have been effective in managing type 2 diabetes and have shown potential benefits in inflammatory conditions and certain cancers [63]. PPAR-delta agonists have demonstrated the ability to enhance lipid profiles and physical endurance, indicating their potential to address metabolic syndrome and obesity [64].

The clinical trials outcome underscores the therapeutic versatility of PPARs, though they also reveal the complexity of their effects, including adverse reactions and the challenge of predicting individual responses [25]. This has delved into the molecular mechanisms of PPAR action, the interplay between different PPAR subtypes, and the potential for combination therapies to enhance health outcomes [65]. The journey from bench to bedside for PPARs illustrates the potential of molecular medicine in transforming the landscape of disease management. While challenges remain in optimizing their efficacy and safety profiles, the clinical trials of PPARs offer a promising glimpse into the future of personalized and targeted therapies.

PPAR-Dependent suppression of inflammatory responses

A wide variety of stimuli can initiate inflammatory responses, although under normal conditions, these responses are short-lived. Under diseased conditions like obesity-related cancer and diabetes, prolonged inflammatory responses have been shown to cause more harm than good. Ultimately, the release of inflammatory mediators such as interleukin (IL)-2, tumor necrosis factor alpha (TNFα), IL-1β, IL-6, and IL-12, and the further activation of inflammatory transcription factors such as pStat3, pErk, pP38, and pNF-κB during chronic inflammation, lead to long-term damage. Moreover, the latter transcription factors are highly oncogenic and drive carcinogenesis. Specifically, activation of the Stat3, NF-κB, and Erk pathways has been linked to the development of inflammation-induced lung, liver, and colon cancer [66], which can be attenuated by PPARγ activation, while cancers of the lymphoid system and spleen have been documented due to PPARγ inactivation [48].

Inflammation has been implicated in both cancer and type 2 diabetes. In fact, therapies that mitigate inflammation have been shown to be beneficial in managing both conditions [67]. PPARγ mediates anti-inflammatory effects *via* numerous mechanisms, including transrepression (cross-talk between PPARγ and transcriptional factors leading to inhibition) of proinflammatory responses mediated by IL-2, TNFα, IL-1β, and IL-12 [68,69]. Such transrepression can also be mediated by PPARγ binding to coactivator complexes, such as steroid receptor coactivator 1 and cAMP response element-binding protein/p300, which then inhibit NF-κB-dependent proinflammatory gene expression [70]. Moreover, PPARγ can suppress proinflammatory gene expression by preventing the removal of corepressors from the promoters of NF-κB and other proinflammatory transcription factors [71]. Furthermore, PPARγ-mediated inhibition of MAPK and inducible nitric oxide synthase has been reported to suppress MAPK-dependent proinflammatory responses and ROS production [72]. PPARγ-dependent attenuation of inflammatory mediators such as IL-2, TNFα, IL-1β, IL-6, and IL-12, and inhibition of inflammatory transcription factors such as pStat3, pErk, pP38, and pNF-κB, can also prevent inflammation-induced tissue damage.

Overall, these PPARγ-dependent effects could attenuate the release of inflammatory cytokines from immune cells and retard the recruitment of immune cells towards cancer sites [73]. Moreover, excessive expression of proinflammatory cytokines is a hallmark of chronic inflammation, which is negatively correlated with PPARγ activity and positively correlated with not only spontaneous tumor formation [74], but also the development of type 2 diabetes [67]. Thus, PPARγ-dependent attenuation of inflammatory responses can have huge implications for both obesity-related cancers and diabetes, by preventing progression of these diseases and their complications.

Role of PPARS in atherosclerosis

Atherosclerosis is a chronic inflammatory disease that affects the arteries, leading to the formation of fatty plaques that can eventually rupture and cause heart attacks and strokes. PPARs have been implicated in the pathogenesis of atherosclerosis due to their roles in regulating lipid metabolism, inflammation, and oxidative stress [75]. The agonists of PPAR-alpha have been shown to increase the expression of genes involved in fatty acid oxidation, which can reduce the levels of circulating triglycerides and improve lipid profiles; they also have anti-inflammatory effects and can reduce the expression of adhesion molecules and chemokines that promote the recruitment of immune cells to the arterial wall [76]. PPAR-gamma is expressed in adipose tissue, where it plays a key role in regulating adipocyte differentiation and insulin sensitivity; its agonists, such as TZDs, have been shown to improve insulin sensitivity, reduce inflammation, and promote macrophage differentiation into an anti-inflammatory M2 phenotype [77]. However, the use of TZDs has been associated with an increased risk of cardiovascular events, such as heart failure and myocardial infarction, due to their potential effects on fluid retention and adipogenesis. PPAR-delta is expressed in many tissues, including adipose tissue, skeletal muscle, and the vascular wall. PPAR-delta agonists have been shown to improve lipid metabolism, reduce inflammation, and promote mitochondrial biogenesis and oxidative metabolism in skeletal muscle; they also reduce atherosclerosis in animal models by promoting reverse cholesterol transport and reducing foam cell formation [78].

Role of thiazolidinediones ln neurodegenerative disorders (TZDs)

Thiazolidinediones (TZDs) are a class of medications that have been traditionally used to treat type 2 diabetes. However, recent studies have shown that TZDs may also have a role in the treatment of neurodegenerative disorders [15]. TZDs work by activating peroxisome proliferator-activated receptor gamma (PPARγ), which has been shown to have neuroprotective effects [79]. TZDs exert their neuroprotective effects through several mechanisms, including, anti-inflammatory effects: TZDs have been shown to reduce inflammation in the brain, which is a key component of neurodegenerative disorders [80]. Antioxidant effects: TZDs have antioxidant properties that can help reduce oxidative stress and neuronal damage [81]. Improved insulin sensitivity: TZDs improve insulin sensitivity, which can help to reduce the risk of neurodegenerative disorders [14].TZDs have been shown to have potential benefits in several neurodegenerative disorders, including Alzheimer's disease: TZDs have been shown to improve cognitive function and reduce amyloid-β levels in animal models of Alzheimer's disease [15]. Parkinson's disease: TZDs have been shown to have neuroprotective effects in animal models of Parkinson's disease [79].

PPAR regulates lipid metabolism

PPARs also play a role in regulating lipoprotein metabolism, particularly the metabolism of High-Density Lipoprotein (HDL) and Low-Density Lipoprotein (LDL) [82]. PPAR-alpha is the primary subtype of PPAR that regulates HDL metabolism; it is expressed mainly in the liver, where it promotes the transcription of genes involved in HDL metabolism, such as apolipoprotein A-I and apolipoprotein A-II. PPAR-alpha activation increases the expression of genes involved in HDL biogenesis and reverse cholesterol transport, which help remove excess cholesterol from peripheral tissues and transport it back to the liver for excretion [83]. In addition to PPAR-alpha, PPAR-gamma also plays a role in regulating HDL metabolism; it activation leads to increased expression of apolipoprotein A-I and ATP-binding cassette transporter A1 (ABCA1), which are involved in HDL biogenesis and reverse cholesterol transport [84]. PPAR-alpha and PPAR-gamma also play a role in regulating LDL metabolism; PPAR-alpha activation leads to increased expression of genes involved in LDL metabolism, such as the LDL receptor and proprotein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 is a protein that promotes the degradation of LDL receptors, leading to increased LDL levels in the blood. PPAR-gamma activation, on the other hand, leads to decreased PCSK9 expression and increased LDL receptor expression, helping lower LDL levels in the blood [84].

PPARs regulates blood pressure

PPARs play a role in the regulation of blood pressure and the development of high blood pressure [85]. PPAR-alpha activation can lower blood pressure and its agonists also decrease vascular resistance and increase blood flow by increasing the production of nitric oxide, a potent vasodilator, in blood vessel [86]. PPAR-gamma activation has also been shown to have beneficial effects on blood pressure regulation, and its agonists can improve endothelial function, reduce inflammation, and enhance insulin sensitivity, all of which can contribute to the prevention and treatment of hypertension [86].

Therapeutic limitations and knowledge gaps related to PPARs

Investigating how PPARs interact with circadian rhythms, differ between sexes, and vary across species could yield valuable insights just as the argument that a variant transcript of human PPARα lacks full exon 6 due to alternative splicing, generating a truncated PPARα-tr protein lacking ligand binding domain that cannot binds to PPRE, but is capable of autonomously regulating proliferative and proinflammatory genes [49]. These insights are crucial for understanding the challenges and areas where further research is needed. It will be discussed under two categories: clinical limitations and knowledge needs. Here are some key points: Berthier *et al.* [9] discussed some potential explanations for the discordance between animal and human evidence, such as the potency and selectivity of PPAR ligands and sex-related variability in PPAR physiology. Fibrates, commonly used to treat dyslipidemia, activate PPARα.

PPARγ Agonists: Thiazolidinediones (TZDs) are insulin sensitizers used in type 2 diabetes mellitus (T2DM). Berthier *et al.* [9]: the work didn't delve deeply into neglected aspects, such as 1. Tissular Zonation: How PPARs are distributed across different liver tissue zones. 2 Cellular Heterogeneity: Variability in PPAR expression and function among different liver cell types. 3. Circadian Rhythms: How PPAR activity varies over the course of a day 4. Sexual Dimorphism: Differences in PPAR regulation between males and females 5. Species-Specific Features: Unique aspects of PPAR regulation in different species. The researchers could explore these areas further to understand the precise mechanisms underlying PPAR regulation in liver physiology [9].

PPARβ/δ: PPARδ alone is ubiquitously expressed and a target for management by the different components of metabolic syndrome. Clinical trials on selected PPARδ agonists have assessed both metabolic and vascular outcomes and no severe side effects have been reported to date, except for GW1516, which induced cancer in several organs in rodents. Any differential mechanisms of PPARδ action across tissues should be explored to develop new PPARδ agonists with improved efficacy and safety. In addition to modulating lipid and glucose metabolism, PPAR agonists play significant roles in several diseases, including primary biliary cholangitis, gout, Alzheimer's disease (AD), and lung cancer [87]. The functions of PPARβ/δ overlap with those of PPARα in peripheral tissues, whereas in the liver, they are more closely related to processes regulated by PPARγ. The role of this nuclear factor in the modulation of liver proliferation, confirming the low expression of PPARβ/δ in human HCC and the reduced expression of target genes such as Cpt-1 and TGFβ1. They also verified that the PPARβ/δ agonist GW501516 reduces the proliferative potential of Hepa1-6 hepatoma cells. On metabolism reprogramming in sorafenib-resistant HCC, identifying PPARβ/δ as a key regulator of glutamine metabolism and reductive carboxylation; consequently, inhibition of PPARβ/δ activity reversed metabolic reprogramming in HCC cells and sensitized them to sorafenib, suggesting PPARβ/δ as a potential therapeutic target [49]. The development has thus far been halted in late-phase clinical trials due to reported side effects, including increased cardiovascular risk (muraglitazar), carcinogenicity (ragaglitazar and MK-767), liver toxicity (imiglitazar), and renal injury (tesaglitazar) [87]. The inducible vascular-specific overexpression of PPARβ/δ promoted cancer angiogenesis, growth, and spontaneous metastases formation in vivo. Its relevance to human pathophysiology was confirmed by high expression of PPARβ/δ in the tumor vasculature in human tumor samples. It therefore has a highly controversial function in cancer [86].

Cancer, fetal origins of adult diseases, neurodegenerative diseases, mitochondrial function and PPARs

While PPARs are implicated in cancer progression, recent studies suggest that PPARs play a role in neuroinflammation and neurodegenerative disorders like Alzheimer's and Parkinson's disease. More recent information was garnered to understand their precise roles in Alzheimer's diseases and inflammations but detail research is still missing on the agonist's roles in different cancer types. Fetal Origins of Adult Diseases: PPARs may influence the fetal origins of adult diseases. Foley *et al.* [87] described the nuclear receptor peroxisome proliferator-activated receptor gamma (PPARG) as the master regulator of adipogenesis [88].

Human adipose-derived stem cells (hASC) isolated from adipose tissue express endogenous isoforms of PPARG, manipulating the classic hormonal cocktail that stimulates adipogenesis, and represent a biologically relevant cell-type for evaluating activity of PPARG ligands, unlike the previously common cell model employed for investigating chemical perturbation of adipogenesis, like the mouse 3T3-L1 cell line (more recently Xenopus, Zebrafish) that could not mimic exactly the understanding of PPARG signaling and phenotypic outcomes in the intact human. This model more closely resembles the true in vivo biological process, with 29% of the prioritized chemicals identified as having moderate-to-strong activity in human adipogenesis. Providing the first integrated screening approach of prioritized ToxCast chemicals in a human stem cell model of adipogenesis, and providing insight into the capacity of PPARG activating chemicals to modulate early life programming of adipose tissue.

Foley *et al.* [87] screened 49 PPARG candidate chemicals in the primary adipogenesis assay, 26 of which exhibited some differentiation activity [88]. Of those 26, 14 were considered moderate or strong hits based on hit frequency. Only 5 chemicals (lactofen, fentin hydroxide, diclofop-methyl, MEHP, and fludioxonil) demonstrated activity in every assay endpoint measured. The organotin, fentin hydroxide (aka triphenyltin hydroxide), was the most potent, with a median AC50 of 4.90 nM. This predicted activity is consistent with other chemicals in its class, including the reference compound tributylin chloride. These organotins are direct ligands for PPARG and RXRA, and stimulate 3T3-L1 adipogenesis and associated gene expression [88]. Several other studies have reported mechanistic functions for tributyltin in promoting adipogenesis, lipid accumulation, and epigenetic modification, lending further support for organotins as PPARG activators with bioactivity in human adipogenesis [80]. Wang *et al.* [24] shed light on the intricate interplay between the microbiota, lncRNA Snhg9, and lipid metabolism, opening up new avenues for understanding and potentially managing metabolic disorders. Liu *et al.* [14] attributed degenerative metabolic disorder (Alzheimer's disease)

to brain insulin resistance and deficits brought about by PPARG agonist targeting insulin sensitizers like pioglitazone, Wang *et al.* [24] stipulated that Snhg9 RNA regulates PPARγ activity by dissociating SIRT1 from CCAR2, providing insight into how a lncRNA regulates intestinal lipid metabolism, aside playing an indispensable role in metabolism, PPARG also closely correlates with inflammation. The cross-talk between metabolic syndromes and inflammation could explain how PPARG affects Alzheimer's disease. Therefore, targeting PPARG and appropriately increasing its expression may serve as a therapeutic target, with great potential to break the positive feedback loop of insulin resistance and hyperinflammation. They concluded that PPARG and others mediate the initiation of chronic inflammation and metabolic disorders that increase the risk of developing Alzheimer's disease among the population.

PPARs are linked to mitochondrial function. Peroxisomes and mitochondria jointly perform various metabolic roles, including O2 and lipid metabolism; these organelles are indispensable in a healthy liver for the breakdown of long-chain, very-long-chain, and branched-chain fatty acids through α- and β-oxidation. Subsequently, they prevent the accumulation of fatty acids (FAs) in the liver. The activation of PPARα and PPARβ/δ primarily facilitates energy combustion, whereas PPARγ activation contributes to energy storage [49]. PPARs remain promising therapeutic areas of application and investigation, it has some drawbacks including weight gain and cardiovascular risks and commendable progresses such as unraveling the intricate molecular connections between psoriasis and Alzheimer's Disease, and wide range of disease conditions and chemical, molecular signaling and modeling holds promise for improving therapeutic approaches and expanding clinical options for most conditions has been made, further studies are needed to bridge the gaps between basic science discoveries and effective clinical interventions for neurogenerative diseases, the gaps related to human relevance, biological context, and clinical implications is crucial for advancing our understanding of obesity development. Validating the role of Snhg9 in human lipid metabolism and immune relay in clinical trials and safety are still limited. The precise mechanisms of interactions between PPARγ and PGC1a, NRFS, UCP2, and PON2, and the signaling roles in therapeutic applications are still not satisfactorily established. The diagnostic value of STFs, including PPARG, from the DEG also needs rigorous large-cohort studies to ascertain their roles in biosynthesis and metabolic processes. These will be breakthrough steps toward understanding and realizing their mechanisms in various diseases, which could reveal novel therapeutic avenues.

CONCLUSION

Peroxisome proliferator-activated receptors (PPARs) are a family of transcription factors that regulate various physiological processes, including lipid and glucose metabolism, inflammation, cellular differentiation, and tumorigenesis. They have diverse functions, making them promising therapeutic targets for various diseases such as diabetes, obesity, and dyslipidemia. Studies have shown that they have the potential to treat cardiovascular diseases, certain cancers, neurodegenerative conditions, and immune-mediated disorders. However, despite their pharmacological effects, their use is associated with notable adverse effects, especially at higher doses. Extended use or high dosage is associated with adverse effects, including liver toxicity, weight gain, fluid retention, and risks of certain cancers. While PPARs remain a promising target for innovative treatments, their safe clinical use requires a more comprehensive understanding and cautious optimization in therapeutic protocols. Understanding their intricate balance between the beneficial effects and adverse outcomes is important for PPR-targeted therapies. Additionally, further research is necessary to develop strategies that enhance their safety while maintaining the desired therapeutic efficacy.

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