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Review Article

The signaling pathway of PPAR-γ and its protective role in various diseases

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Abstract

The peroxisome proliferator-activated receptor gamma (PPARγ) signaling pathway is one of the most important physiological pathways in the body, which is known for its beneficial role in regulating metabolism and modulating disease processes. This ligand-activated nuclear receptor significantly influences glucose and lipid metabolism, and is involved in various cellular functions, including anti-inflammatory, antioxidant, and anti-apoptotic responses. PPARγ activity can be regulated through multiple post-translational modifications such as acetylation, glycosylation, and phosphorylation, which underscores its complexity and therapeutic potential. In this review, we examined numerous studies investigating the role of the PPAR-γ signaling pathway in a wide range of diseases. Particular emphasis was placed on its involvement in the cardiovascular system, central nervous system (CNS), digestive system, respiratory as well as urinary systems, and allergic diseases. Accumulating evidence has shown that activation of this pathway can modulate inflammatory and oxidative responses, enhance insulin sensitivity, and provide neuroprotective and organ-protective effects. To conduct this review, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ), and Embase, using keywords such as "PPAR-γ," "Signaling Pathway," "Anti-inflammatory," "Antioxidant," and "Diseases." These searches revealed consistent findings supporting the therapeutic potential of PPARγ activation in diverse pathological conditions. The evidence suggests that targeting the PPARγ pathway may offer novel strategies for preventing and treating a variety of metabolic, inflammatory and degenerative diseases.

Keywords: PPAR-γ signaling pathway, Anti-inflammatory mechanisms, Antioxidant mechanisms, Disease.

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Peroxisome proliferator-activated receptor gamma (PPARγ) was discovered and characterized by researchers several decades ago in response to the management of liver cells by peroxisome proliferators (1). This type of receptor, which is the ligand-activated nuclear receptor, can affect the body's activities and metabolism, including glucose and lipid metabolism (2). Researchers have indicated that PPAR-γ can be effective on various body activities, including fatty acid oxidation activity, blood glucose homeostasis activity, regulation of the immune system activity, and the structure as well as function of the heart and body cells (3). As one of the most important receptors, PPAR-γ regulates the growth and differentiation and metabolism of cells. Moreover, it can be central to the improvement of the structural function of insulin and fat through its synthetic ligand, including the glitazone family (4). The PPARγ receptor has two different isoforms, i.e. PPARγ1 isoform (P1I) and PPARγ2 (P2I) isoform. PPARγ2 contains extra amino acids in the N-terminus (5). P1I is expressed in various parts of the body such as heart muscles, and the liver or fat tissues, which can be referred to endothelial cells (5-8).

P1I is expressed in various parts of the body such as heart muscles, and the liver or fat tissues, which can be referred to endothelial cells. However, P2I is usually expressed in fat cells and is necessary, particularly for adipogenesis (5-8). PPAR receptors can form a heterodimer with retinoid X receptors (RXRs). It has been found that the synergistic effects between these two ligands can increase the transcription level to its highest level (9). Investigations have shown that the combined structure of peroxisome proliferator-activated receptor and retinoid X receptor can play a role as a regulator for the absorption and metabolism of proteins and fats (10). Furthermore, it has been indicated that PPARγ is widely present in renal proximal tubules and urinary collecting ducts in renal nephrons. (11). Various studies have shown that PPAR-γ induction can cause the activity of antioxidant enzymes such as Cu, ZnSOD. Drugs that stimulate or inhibit the activity of PPARγ are widely used to treat various diseases**.** Among the most important drugs that stimulate PPARγ activity, we can mention the big family of thiazolidinediones, including rosiglitazone and pioglitazone that are among the most important medications in this class of drugs (12). Various studies and surveys have indicated that PPARγ can be regulated in different ways, including acetylation, glycosylation, phosphorylation, etc., which can indicate the significance of PPARγ in its effects on homeostasis and body metabolism**.** Post-translational modifications that regulate PPARγ have been fully characterized and described (13). In line with the regulation of PPARγ, some drugs, including telmisartan, which is an ACEI drug, can increase glucose absorption by regulating PPARγ and increasing its phosphorylation, as well as raising insulin sensitivity in adipose tissue (14). It has been shown that galangin significantly contributes to the reduction of inflammation and inhibition of the NFκB pathway in microglia cells through the PPAR-γ pathway, which indicates that PPAR-γ has anti-inflammatory effects (15). In general, drugs that stimulate PPARγ have strong anti-inflammatory and antioxidant effects and can be used therapeutically in the treatment of various diseases. The PPAR-γ receptor can have anti-fibrotic and anti-proliferative effects too. Investigations carried out on diseases have shown that fibroblast is the most important factor in the fibrotic process, and it is possible to block the fibrotic responses dependent on TGF-β through the PPAR-γ receptor (16-19). Various other studies have also shown that PPAR-γ can have anti-fibrotic effects (20, 21). Moreover, the use of this pathway has been introduced as a therapeutic strategy for fibrosis (22). A study has well indicated that the most significant factors in the antifibrotic effects of PPAR-γ can be the inhibition of the secretion of inflammatory factors, the reduction of T cell responses, the induction of cell death, and the reduction of T cell survival (23). Furthermore, it has been indicated that PPARγ activation can have remarkable anti-proliferative effects by inhibiting the cell cycle. These effects can be associated with therapeutic impacts in various diseases. However, the regulation of specific genes or activation of immune-related signaling pathways can also be other activities of PPARγ in inhibiting the process of cell proliferation (24-27).In this review, various effects of inflammation reduction and the antioxidant effects of PPARγ have been examined. Moreover, its therapeutic effects in heart diseases, the central nervous system, digestion, allergies, etc., have been investigated (figure 1).

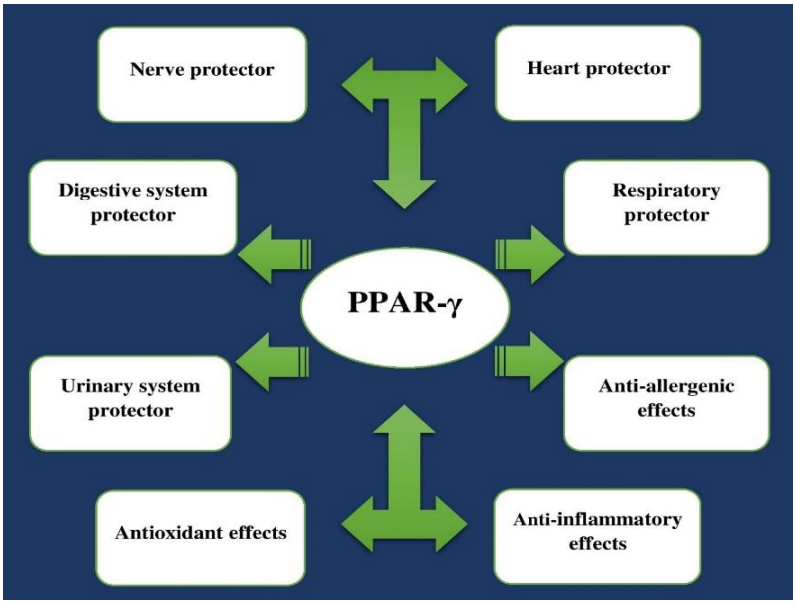

Figure 1.PPAR-γ and therapeutic objectives

Study design

This study was conducted as a systematic review, following a structured process that included topic selection, comprehensive database search (PubMed, Web of Science, EBSCO, Scopus, Google Scholar, DOAJ, and Embase), keyword identification (PPAR-γ, signaling pathway, anti-inflammatory, antioxidant, and diseases), screening of 193 retrieved articles for relevance, selection of 127 eligible studies, data extraction, synthesis of findings, and final manuscript preparation (figure 2).

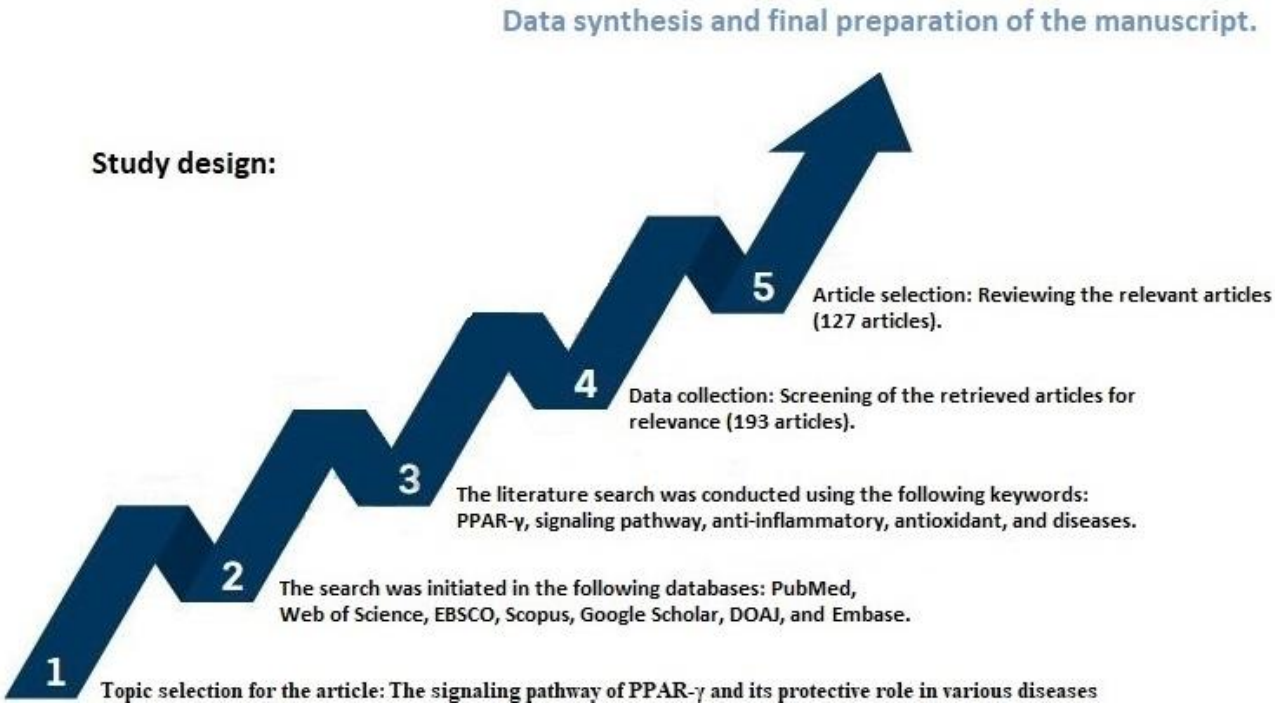

Figure 2. A visual summary of the study design, depicting the steps from topic selection to the final preparation of the manuscript.

PPAR-γ and therapeutic objectives

PPAR-γ and the cardiovascular system

PPARs can adequately regulate high blood pressure, which is a major health problem. Researchers have indicated in clinical studies that PPARγ agonists can lower blood pressure, and this effect has been reported in patients with type 2 diabetes who use these drugs to lower blood glucose (28, 29). Studies in animal models have shown that PPARγ agonists, including the thiazidoline family, depending on the drug dose, can cause a disruption in one of the components of the renin-angiotensin system in smooth muscle cells, and thus contribute to the decrease in blood pressure (30). Other investigations in laboratory studies have indicated that PPARγ agonists can have inhibitory effects on the production and/or secretion of aldosterone (31). Different studies have shown various effects of pioglitazone on the characteristics of heart valve calcification. On the one hand, it was found in a study that this drug could reduce aortic calcification. On the other hand, another study did not approve its effect. However, it has been determined that changes in gene expression structure can have an effective role in the protective, anti-inflammatory, and antioxidant effects of pioglitazone (32). It was found in some animal studies that the stimulation of PPARγ receptor could be effective against complications caused by ischemic heart diseases (33-36). However, in mice with overexpression of PPAR γ, researchers faced many cases of cardiovascular diseases as well as metabolic disorders. (37). Investigations have shown that PPAR ligands could improve cardiac damaging processes by reducing inflammatory processes (38). It has been indicated that in animals that suffered cardiac ischemia, the JNK pathway was activated and eventually apoptosis was induced. Moreover, drugs that stimulate PPARγ receptor could play their roles by inhibiting the JNK pathway and ultimately suppressing the apoptosis caused by ischemia (39). Another study showed that pioglitazone could treat cardiac hypertrophy in animals (40). Drugs affecting PPAR ligands can be highly efficient in the myocarditis by affecting the activity of macrophage inflammatory protein-

1 alpha and ultimately inhibiting it (38). Furthermore, it has been found that PPARγ can inhibit the expression of inflammatory cytokines such as TNF-α and NF-κB in the cardiac surface (41, 42).

PPAR-γ and CNS system and its neuroprotective role

Studies have shown that PPAR-ɣ can significantly contribute to the regulation of the body's metabolism and modulation of pathogenic processes in response to the agonist, ultimately regulating its gene (43). It has been found that PPARγ is expressed in different areas of the central nervous system, including microglia and astrocytes, and by influencing them, it can play different roles (44). Type 1 isoform of PPARγ is expressed in neurons and glia (45), and it is known that PPARγ is probably expressed in microglial cells depending on the state of inflammation (46). It has been proven in several studies that the expression of PPAR-γ increases after different lesions in the CNS (47-49). However, it was rejected by Paterniti *et al*., who even reported that PPARγ protein levels decreased after spinal cord trauma (50). Different studies have shown that inflammation and oxidative stress are among the most important causes of disorders of the nervous system (51). It has been indicated that the PPARγ signaling pathway, with its anti-inflammatory and antioxidant effects, can have neuroprotective effects by inhibiting apoptosis or increasing endothelial growth factor activity (44). It has also been determined that PPAR-γ activation in the central nervous system can lead to positive energy balance in laboratory animals via thiazolidines (52). Studies have shown that PPAR-γ can be central to the activation of macrophages of the central nervous system and cause their growth as well as differentiation by acting on microglia cells (53).

In an experimental study on animal models, it was found that PPAR-γ could reduce the symptoms of autoimmune encephalomyelitis (54). Other studies have indicated that one of the main problems of Parkinson's induction is the release of inflammatory cytokines that can cause damage to the nervous system. However, (PPAR)-γ agonist can have a significant role in neuroprotection and prevention or improvement of Parkinson's disease by increasing the activity of anti-inflammatory and M2 factors (55). In another study, it was determined that PPAR-γ could have an anti-inflammatory process in the glia cells of the central nervous system through the CD200-CD200R1 pathway (56). In a recent study, the relationship between the activation of the PPAR-γ pathway and the amount of alcohol consumption were investigated. In this study, it was found that gabapentin was able to activate the PPAR-γ signaling pathway, thereby reducing alcohol consumption and also the level of inflammatory cytokines in the hippocampus (57). Research on the PPAR-γ signaling pathway has shown that this pathway has neuroprotective effects with anti-inflammatory activity in various diseases. (58). With regard to Parkinson's disease, it was found that stimulation of the PPAR-γ signaling pathway could inhibit motor and olfactory disorders as well as microglia reactivity. Moreover, it could inhibit the progression of Parkinson's disease due to its anti-inflammatory effects (59). In the model of permanent focal cerebral ischemia, it was indicated that pioglitazone could have protective effects in rats by stimulating the PPARγ signaling pathway and inhibiting NF-kB (60).

In another study, it was found that the PPAR-γ signaling pathway had beneficial effects in Huntington's disease, improving motor performance and preventing the loss of neurons (61). Furthermore, in another study conducted in 2013, it was revealed that the PPAR-γ signaling pathway had anti-inflammatory effects and could have neuroprotective effects in the spinal cord trauma model (62). In a study conducted on oleic acid, it was indicated that stimulation of the PPAR-γ signaling pathway by oleic acid in cerebral ischemia model could have anti-inflammatory effects and also had protective effects on nerves (63). It was also found that the activation of the T pathway could inhibit pyroptosis and provide neuroprotection (64). It was shown that chronic mild stress with synaptic dysfunction in the hippocampus and induction of inflammation could be the causes of neurological diseases, including depression. Moreover, consumption of Aseprosaponin VI by stimulating the PPAR-γ pathway contributed to the management of this disease (65). It was indicated in another study that 3-nitropropionic acid could cause motor and cognitive disorders in rats. Furthermore, subsequent investigations have revealed that telmisartan could reduce neuroinflamation and apoptosis by stimulating the PPARγ signaling pathway, and finally, it could improve motor and cognitive functions (66). The down-regulation of JAK-STAT signal transmission and also the stimulation of SOCS3 enabled the PPARγ signaling pathway to have neuroprotective effects and inhibit the expression of genes involved in nerve damage as well as the production of inflammatory cytokines (67).

PPAR-γ and the digestive system

It has been shown that various inflammation-inducing pathways, including the TLR4/NF-kB signaling pathway, can be the most important causes of gastrointestinal diseases (68, 69). Various studies on d-pinitol have indicated that stimulation of the PPAR-γ signaling pathway and having anti-inflammatory effects enable this drug to have an important role in the treatment of ulcerative colitis (70). It

has been indicated that perindopril, which is a long-acting ACE inhibitor drug, can reduce the intestinal damage caused by methotrexate use by stimulating the PPAR-γ/SIRT1 signaling pathway and also by inhibiting anti-inflammatory pathways (71). It has been shown that dextran sulfate sodium (DSS) can cause ulcerative colitis by affecting the activity of mitochondria in the colon epithelium and inhibiting their activity. Moreover, the level of mitochondrial activity increased again and the spread of dysbiotic E. coli. decreased due to the stimulation of the PPAR-γ signaling pathway (72). Different studies have confirmed that rosiglitazone can be effective in the management of ulcerative colitis (73). However, the therapeutic effect of this drug in combination with 5-ASA can be more efficient and bring about better results (74). It has been reported that the PPAR-γ signaling pathway, while activating the mitochondria in the colon epithelial cells, increases oxygen consumption, hypoxizes the surface of the colon epithelial cells, and finally causes the growth of obligate anaerobic bacteria in the intestine (75-77).

In a study conducted by Abdulhamid in 2021 on the model of liver damage caused by alcohol consumption, it was found that telmisartan could have an effective role in reducing inflammation and oxidative stress by stimulating peroxisome proliferator-activated receptors (PPAR-γ) in addition to its hepatoprotective effects (78). Moreover, it has been found that cilostazol can have protective effects in the ischemia/reperfusion model by stimulating the PPAR-γ signaling pathway, reducing cell apoptosis, having anti-inflammatory activity, and increasing antioxidant activity (79). A study on colon inflammation and the stimulation of the PPAR-γ signaling pathway expression by α-bisabolol showed that increased activity of PPAR-γ could reduce the expression of inflammatory proteins and mitogen-activated protein kinase (MAPK) and protect against intestinal inflammation (80). Furthermore, the use of thymoquinone in the experimental model of ulcerative colitis caused by DSS showed that this phytochemical compound could induce anti-inflammatory effects by stimulating the PPAR-γ signaling pathway. Moreover, it inhibited MAPK, NF-kB, COX-2 and TNF-α, and was effective in treating intestinal inflammation (81). Different studies have shown that the PPAR-γ signaling pathway can significantly contribute to the prevention of colon cancer by inhibiting the expression of Bcl-2 protein, human telomerase reverse transcriptase (hTERT), and telomerase activity (82-84).

PPAR-γ in allergic diseases

It has been shown that stimulators of the PPAR-γ signaling pathway decrease the number of neutrophils, and reduce myeloperoxidase activity as well as the expression of adhesion molecules VCAM-1 and ICAM-1 (85-87). Studies have indicated that the negative regulation of the granulocytes can be observed when using PPAR-γ stimulants, and nanomolar-picomolar concentrations of 15d-PGJ2 change the location of eosinophils and activate actin (88). Finally, the role of PPAR-γ in food allergies is known, and this signalling pathway can act as a significant regulator of mast cell degranulation in the body (89). Substance P activates cardiac mast cells through the neurokinin-1 receptor and causes the release of histamine in the body. Moreover, it is known that PPAR-γ selective stimuli can inhibit histamine release through this pathway. It has been shown that these responses of substance P, which are mediated by the receptor, and its inhibition by the activity of other receptors, including PPAR-γ, indicate the significance of this substance in the internal structure of the body (90). Moreover, the results of a study showed that the regulation of PTEN expression by the PPARγ signalling pathway was highly significant in protecting the pathogenesis of the asthma phenotype (91).

Interestingly, natural PPARγ agonists that are found in foods cause protective effects against inflammatory and allergic diseases and can have anti-inflammatory as well as anti-allergic effects on the body (92). The PPAR-γ signalling pathway can be central to the inhibition of inflammatory and proinflammatory genes as well as the activity of inflammatory and allergenic cells (93). It has also been indicated that lactobacillus gasseri can inhibit the activity of allergenic and inflammatory pathways in the airways by activating the PPAR-γ signalling pathway (94). Furthermore, it has been determined that with regard to the management of local dermatitis with the PPAR-γ signalling pathway agonists, apart from inhibiting the activity of allergenic and inflammatory pathways, therapeutic effects can be observed (95). It was indicated in a study that agonists of the PPAR-γ signalling pathway, while inhibiting the IgE production, can hinder allergic immune responses by inhibiting inflammatory cytokines (96). Anti-inflammatory and antiallergenic activities of the PPAR-γ signalling pathway agonists can determine a new application and role for them in the management of allergic diseases (95).

PPAR-γ and the respiratory system

Many studies have been conducted on the anti-inflammatory and anti-allergic effects of the PPARγ signalling pathway in the respiratory tract. Investigations have shown that the expression of PPARγ in epithelial cells of the respiratory system increases when exposed to allergens in allergic animals (97). This signalling pathway reduces or inhibits the production of mucin caused by

smoking or exposure to cigarette smoke (97). Moreover, it reduces/ inhibits mucus secretion and collagen deposition in the respiratory tract (98). During the time of allergic inflammation in the respiratory system, the PPARγ signalling pathway can have a significant role in the handling of asthma by regulating the activity of type-2 innate lymphoid cells (99). During influenza A virus infection, the PPAR-γ pathway can reduce inflammatory responses and, on the other hand, promote tissue repair by promoting growth factors (100). It has also been found that smiglaside A induces anti-inflammatory effects by stimulating the AMPK-PPARγ signalling pathway and promoting alveolar macrophages to the M2 phenotype (101). Furthermore, it has been indicated that the PPARγ signalling pathway stimulated by curcumin effectively inhibits cell viability and inflammation caused by cigarette smoke and ultimately improves lung function by inhibiting NF-kB (102). Rosiglitazone, as a PPARγ agonist, can have remarkable protective effects during lung inflammation and reduce inflammation through this signalling pathway and also by increasing HO-1 expression (103).

The expression of the PPARγ signalling pathway is necessary for the activity and function of lung macrophages and can effectively inhibit the expression of iNOS, matrix metalloproteinas-9, and macrophage receptor-1 (104). Stimulation of the PPARγ signalling pathway by telmisartan showed that it could have protective effects, reduce the activity of inflammatory pathways as well as oxidative stress, and improve the complications caused by pneumonia via inhibiting the NF-kB inflammatory pathway (105). Fibroblast growth factor 21 (FGF21) reduces the activity of inflammatory cytokines and the excessive proliferation of smooth muscle cells of the pulmonary artery by increasing the expression of PPARγ. Thus, FGF21can reduce pulmonary blood pressure caused by hypoxia (106). It has been indicated that ginsenoside Rb1 can improve pulmonary barrier impairments by activating the PPARγ signalling pathway and inhibiting the expression of phospho-NF-κB p65 and inflammatory cytokines (107). Moreover, stimulation of the PPAR γ signalling pathway by Resolvin D1 reduces inflammation and inflammatory cytokines in ventilator-induced lung injury (108). Inhibiting the expression or activation of toll-like receptor 2 (TLR2)/nod-like receptor with pyrin domain containing 3 (NLRP3) inflammatory corpuscles by stimulating the PPARγ signalling pathway is another known mechanism for reducing inflammation in the respiratory tract (109).

PPAR-γ and the urinary system

The PPARγ signaling pathway is central to the normal activity of the kidneys, and has a homeostatic function, including the regulation of ions (110, 111). Investigations have shown that PPAR-γ agonists can have both nephroprotective and anti-inflammatory effects (112, 113). It has been shown that animals lacking the PPARγ gene suffer from severe kidney problems and fibrosis (114). In rats with acute kidney injury, consumption of oleic acid activated the MAPKs/PPAR-γ signaling pathway and reduced the activity of inflammatory cytokines as well as oxidative factors. Moreover, consumption of oleic acid improved the kidney function indicators (115, 116). In a study conducted in 2021, researchers showed that stimulation of the PPAR-γ signaling pathway by Bixin could reduce inflammation and oxidative stress and also improve fibrosis induced by carbon tetrachloride in mice (117). It has been indicated that there are mutual relationships between the PPAR-γ signaling pathway with various receptors in the renal vessels that improve the functional and protective status of the kidneys by stimulating this signaling pathway (118). In a recent study, it was found that the PPAR-γ signaling pathway could have protective and therapeutic effects in rhabdomyolysis-induced acute kidney injury in animal models (119). It has also been determined that stimulation of the PPAR-γ signaling pathway in patients with calcium oxalate (CaOx) nephrolithiasis results in the reduction of apoptosis and inflammatory responses (120). Among the side effects of diabetic nephropathy, we can refer to the increase in the levels of inflammatory cytokines and oxidative stress, and the increase in the expression of connective tissue growth factor (CTGF) and fibronectin (FN) (121-123). It was shown in a study conducted in 2022 that ombuin could improve kidney function in patients with diabetes by stimulating the PPAR γ signaling pathway (124). In another research, it was indicated that during the induction of acute hypoxic kidney damage, the PPARγ signaling pathway could play a significant role in protecting the kidneys by significantly increasing SOD on the one hand and decreasing renal endothelin on the other hand (125). Furthermore, it has been shown that the PPARγ pathway is central to the reduction of inflammation and its index in hyperuricemic nephropathy, and also it can have an important role as a protector (126, 127). The key therapeutic objectives of PPAR-γ have been summarized in figure 3 and table 1.

Table 1. The Signalling pathway of PPAR-Γ and its protective role in various diseases

Disease	Protective roles
Cardiovascular System	PPARs can regulate hypertension and lower blood pressure, particularly through its agonists that cause a disruption in one of the renin-angiotensin systems in smooth muscle cells. Moreover, PPARγ agonists can have inhibitory effects on the production and/or secretion of aldosterone. Noticeably, stimulation of the PPARγ receptor could be effective against complications caused by ischemic heart diseases. Furthermore, PPAR ligands could improve cardiac damaging processes by reducing inflammatory processes.
CNS System and the Neuroprotective Role	PPAR-γ, which is expressed in different areas of the central nervous system, has a significant role in the regulation of the body's metabolism and modulation of pathogenic processes. PPARγ is probably expressed in microglial cells depending on the state of inflammation, and the expression of PPAR-γ increases after different lesions in the CNS. Moreover, the PPARγ signaling pathway can have neuroprotective effects by inhibiting apoptosis or increasing endothelial growth factor activity. PPAR-γ activation in the central nervous system can lead to positive energy balance in laboratory animals via thiazolidines.
Digestive System	Stimulation of the PPAR-γ signaling pathway and having anti-inflammatory effects enable d-pinitol to have an important role in the management of ulcerative colitis. Perindopril can reduce the intestinal damage caused by methotrexate use by stimulating the PPAR-γ/SIRT1 signaling pathway and also by inhibiting anti-inflammatory pathways. Dextran sulfate sodium (DSS) can cause ulcerative colitis by affecting the activity of mitochondria in the colon epithelium and inhibiting their activity. The PPAR-γ signaling pathway, while activating the mitochondria in the colon epithelial cells, increases oxygen consumption, hypoxizes the surface of the colon epithelial cells, and finally causes the growth of obligate anaerobic bacteria in the intestine.
Allergic Diseases	Stimulators of the PPAR-γ signaling pathway decrease the number of neutrophils and reduce myeloperoxidase activity as well as the expression of adhesion molecules VCAM-1 and ICAM-1. The negative regulation of the granulocytes can be observed when using PPAR-γ stimulants, and nanomolar-picomolar concentrations of 15d-PGJ2 change the location of eosinophils and activate actin. Finally, the role of PPAR-γ in food allergies is known, and this signalling pathway can act as a significant regulator of mast cell degranulation in the body.
Respiratory System	The expression of PPARγ in epithelial cells of the respiratory system increases when exposed to allergens in animals that are allergic. This signaling pathway reduces or inhibits the production of mucin caused by smoking or exposure to cigarette smoke. Moreover, it reduces/inhibits mucus secretion and collagen deposition in the respiratory tract. The PPARγ signaling pathway can have a significant role in the handling of asthma by regulating the activity of type-2 innate lymphoid cells. During influenza A virus infection, the PPAR-γ pathway can reduce inflammatory responses and promote tissue repair by promoting growth factors.
Urinary System	The PPARγ signaling pathway is central to the normal activity of the kidneys and has a homeostatic function, including the regulation of ions. Investigations have shown that PPAR-γ agonists can have both nephroprotective and anti-inflammatory effects. Animals lacking the PPARγ gene suffer from severe kidney problems and fibrosis. In rats with acute kidney injury, consumption of oleic acid activated the MAPKs/PPAR-γ signaling pathway, reduced the activity of inflammatory cytokines as well as oxidative factors, and improved the kidney function indicators.

Abbreviations: PPAR: Peroxisome Proliferator-Activated Receptor, CNS: the Central Nervous System, SIRT1: Sirtuin 1, VCAM-1: vascular cell adhesion molecule 1, ICAM-1: intercellular adhesion molecule 1, 15d-PGJ2: 15-Deoxy-Δ-12,14-prostaglandin J2, MAPKs: Mitogen-activated protein kinases

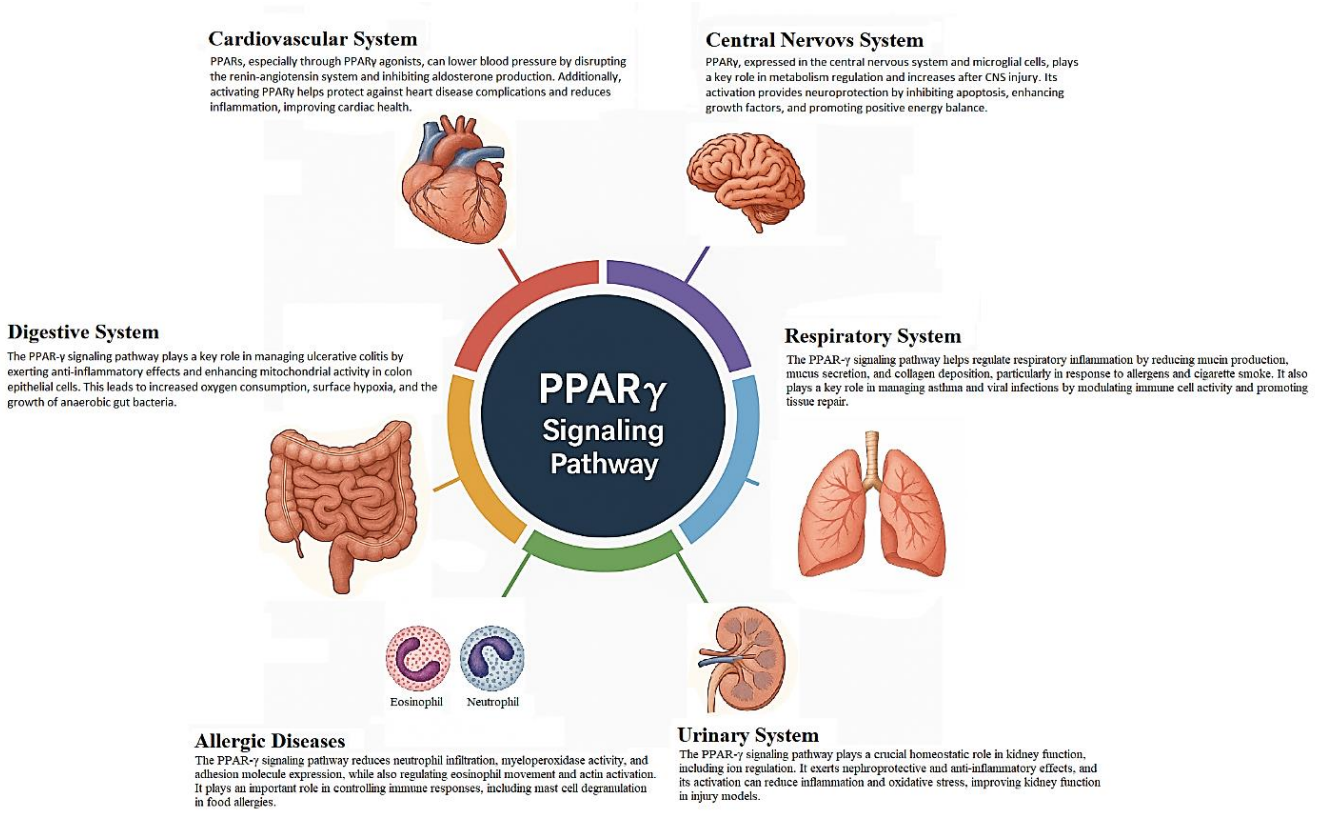

Figure 3. Visual summary of PPAR-γ-mediated signaling pathways and associated therapeutic effects in inflammation, metabolic disorders, and other diseases

Today, specific treatments are available to patients suffering from various diseases. However, the purpose of this review was to raise the awareness of researchers concerning the role of signalling pathways in the body. Knowing the role of inflammation pathways and their pathogenesis in diseases as well as investigating the signalling pathways can broaden the horizon of scientific research. The PPAR-γ signaling pathway is one of the signaling pathways that contribute to the improvement of the body's performance. With its anti-inflammatory and anti-apoptotic effects, this signaling pathway can have protective and therapeutic effects with regard to various diseases due to its anti-inflammatory and anti-apoptotic properties. Moreover, it can have a role in the improvement of physiological functions in the body.

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Investigation: AH, Resources: AH, PAB, Data Curation: KS, Writing—Original Draft Preparation: AH, Writing—Review and Editing
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