

## REVIEW ARTICLE

PPAR- $\gamma$  Signaling in Metabolic Homeostasis

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## Abstract

**BACKGROUND:** Peroxisome proliferator-activated receptor (PPAR)- $\gamma$ , or also known as nuclear receptor subfamily 1 group C member 3 (NR1C3), is a PPAR which serves as master regulator of adipocytes differentiation, and plays an important role in lipid metabolism or adipogenesis. Recent study showed that PPAR- $\gamma$  is expressed in most tissue and also has critical impact in many metabolic homeostasis disorders.

**CONTENT:** Dysregulation of PPAR- $\gamma$  is correlated to the development of obesity, type 2 diabetes, atherosclerosis, cardiovascular disease, acute kidney injury, autoimmune disease, gastrointestinal disease and Alzheimer's disease. Abundant number of new emerging compounds, with *in vitro* and *in vivo* effectiveness as natural and synthetic agonists of PPARs, are investigated, developed and used as

the treatment of metabolic disorders of glucose and/or lipid and other diseases.

**SUMMARY:** Based on all studies explanation, targeting PPAR- $\gamma$  is proven to be a good therapeutic method for reducing negative effect of several metabolic homeostasis disorder. Now, many natural and synthetic agonists of PPARs are used as the treatment of metabolic disorders of glucose and/or lipid or another metabolic homeostasis disorder. Such agonists have different properties and specificities for individual PPARs receptors, different absorption and distribution, and distinctive gene expression profiles, which ultimately lead to different clinical outcomes.

**KEYWORDS:** PPAR- $\gamma$ , dysregulation, agonist, adipogenesis, metabolic disorder, homeostasis

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## Introduction

Peroxisome proliferator-activated receptor (PPAR) is member of the nuclear receptor superfamily of ligand-inducible transcription factors. In mammals, there are three PPARs: PPAR- $\alpha$  (also called nuclear receptor subfamily 1 group C (NR1C)1), PPAR- $\beta/\delta$  (NR1C2) and PPAR- $\gamma$  (NR1C3). By binding to PPAR-responsive regulatory elements as obligate heterodimers with retinoid X receptor (RXR), the PPARs control expression of networks of genes involved in adipogenesis, lipid metabolism, inflammation and maintenance of metabolic homeostasis.(1)

Potential molecular targets that implicated in many disease processes are PPARs that nuclear receptor proteins involved in a wide variety of regulatory functions, making them important targets in the management of metabolic conditions. Dysregulation of PPAR- $\gamma$  is known to be correlated with the development of obesity, type 2 diabetes, atherosclerosis and other diseases condition.(2) Nuclear receptor PPAR- $\gamma$ , one factor effecting obesity, insulin resistance and cardiovascular disease (CVD), is required for adipose tissue formation but is also a target of insulin-sensitizing drugs for treating diabetes.(3)

PPAR- $\gamma$  is a member of the nuclear receptor family that includes 48 human transcription factors. The activity

of those transcription factors is regulated by the direct binding of steroid and thyroid hormones, vitamins, lipid metabolites, and xenobiotics. Binding of PPAR- $\gamma$  to specific DNA sequences requires heterodimerization with a second member of the nuclear receptor family, RXR. Binding of agonist ligands to PPAR- $\gamma$  triggers a conformation change which attracts transcriptional co-activators, including members of steroid receptor co-activator (SRC) family. In the absence of ligand, PPAR- $\gamma$  has the potential to actively silence genes to which it is bound by recruiting transcriptional co-repressor complexes containing nuclear receptor co-repressor (N-CoR) or silencing mediator of retinoid and thyroid receptors. The transcriptional co-activators and co-repressors exist in multiprotein complexes including histone-modifying enzymes, such as histone acetyltransferases and histone deacetylases, respectively. By altering chromatin structure, activity of these histone-modifying enzymes affecting the gene transcription.(3)

### PPAR- $\gamma$ Signaling

Even though all three isotypes of PPARs have been shown to modulate lipid metabolism, each isotype has their specific functions.(4) PPAR activity depends on many pathways, that is the reason why these transcriptional factors are found at the crossroads of major regulatory networks. Specifically, PPAR- $\gamma$  is found in adipose tissues and is activated by fatty acid (FA) or their derivatives, which plays a role in insulin sensitivity, adipogenesis and placental function. It activates transcription in concert with co-activators including SRC1, and has also been implicated in some number of neoplastic processes, including colorectal cancer. PPAR- $\gamma$  is the molecular target of thiazolidinedione (TZD) class of anti-diabetic drugs, which include rosiglitazone and pioglitazone.(4,5) TZD is a potent insulin sensitizer that acts through the nuclear receptor PPAR- $\gamma$  and are highly effective oral medications for type 2 diabetes.(1)

Activation of PPAR- $\gamma$  in Tamm-horsfall protein (THP)-1 cells by either 15-deoxy- $\Delta$ 12,14-prostaglandin J2 (15d-PGJ2) or TZD stimulates changes in surface marker expression characteristic of monocytic differentiation, including induction of class B scavenger receptor cluster of differentiation (CD)36. As a result of CD36 induction, PPAR- $\gamma$ -activated THP-1 cells have an increased capacity to take up oxidized low-density lipoproteins (OxLDL).(5)

The expression of PPAR- $\gamma$  is widespread and is found at moderate levels in most tissues, with high levels of the protein are found in placenta and large intestine.(4) The

activity PPAR- $\gamma$  is also regulated by phosphorylation events.

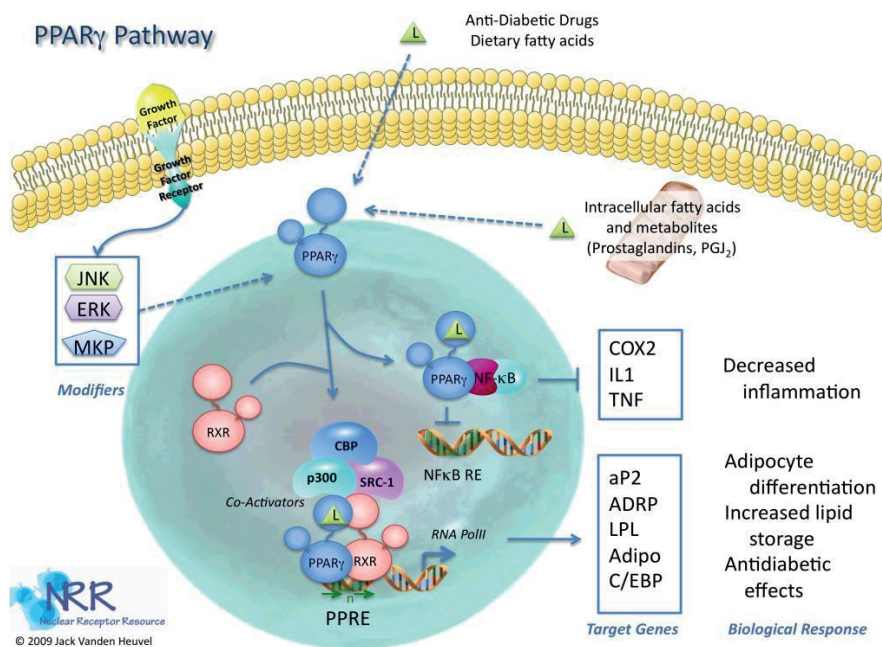
Specifically, the recruitment of adaptor molecules, including SRC homology 2 containing protein (SHC) and the growth factor receptor-bound protein-2 (GRB2)-SOS complex by several growth factor receptors, which leads the phosphorylation of Ras and Raf1 molecules. This in turn activates the mitogen-activated protein kinases (MAPK) of the extracellular signal-regulated kinase (ERK) type that occurs by sequential activation of transforming growth factor (TGF)- $\beta$  activated kinase-1 (TAK1) and MAPK/ERK kinases (MEK). The activities of PPAR- $\gamma$  are inhibited by these kinases.(6,7) Activation of p38 TAK1/MAPK cascade is followed by up-regulation of PPAR- $\gamma$ .(8) The detail of PPAR- $\gamma$  signaling pathway can be seen in Figure 1.

Some research also show that the activity of PPAR- $\gamma$  is stimulated by V-akt murine thymoma viral oncogene homolog 1 regulatory pathway, where phosphatidylinositol 3-kinase (PI3K) is activated by H-ras that catalyzes the conversion of phosphatidylinositol 4,5-biphosphate to Phosphatidylinositol 3,4,5-triphosphate which then activates Akt.(6,9)

### PPAR- $\gamma$ in Obesity and Diabetes

Obesity happens because of over-nutrition, and slowly it has led to the increased incidence of plentiful chronic diseases, such as type 2 diabetes and CVD. In chronic disease such as obesity and diabetes mesenteric adipose tissue (MAT) hypertrophy is regulated by the activation of PPAR family of nuclear receptors, mainly alpha and gamma form.(10) PPAR- $\gamma$ , is highly expressed in adipocytes, skeletal muscle, liver, and kidney, and has been shown to regulate the expression of genes that mediates adipocyte differentiation, lipid accumulation by adipocytes by modulating numerous genes regulating adipogenesis, lipid uptake and lipid metabolism, energy metabolism, insulin action, and PPAR- $\gamma$  activation improves insulin sensitivity and glucose, adiponectin, and FA uptake.(11-13)

As in obesity and diabetes, PPAR- $\gamma$  has an insulin-sensitizing effect by increasing glucose uptake and reduces hunger, postprandial blood glucose and the concentration of free FA (FFA).(14) The mechanism involved in adipogenesis process, when the differentiation of pre-adipocytes into mature insulin sensitive adipocytes which produces adiponectin, is stimulated by the members of two families of transcription factors, they are the CCAAT/enhancer binding proteins (C/EBPs) and PPARs.(15)



**Figure 1. PPAR- $\gamma$  signaling pathway.**(7) (Adapted with permission from Nuclear Receptor Resource). PGJ<sub>2</sub>: prostaglandin J<sub>2</sub>; JNK: c-Jun N-terminal kinases; MKP: mitogen-activated protein kinase phosphatase; COX: cyclooxygenase; IL: interleukin; TNF: tumor necrosis factor; aP2: adipocyte protein 2; ADRP: adipose differentiation-related protein; LPL: lipoprotein lipase.

PPAR- $\gamma$  is also involved in the physiological function to insulin resistance, with activation either stimulates (+) or represses (-) key metabolic pathways in adipose, muscle, and liver tissue and in macrophages, and promotes the flux of FFAs from muscle and liver to adipose tissue. Besides having its metabolic effects, PPAR- $\gamma$  activation also increases macrophage-mediated cholesterol efflux via upregulation of ABC transporter protein-A1 (ABCA1), as showed in Figure 2.(16)

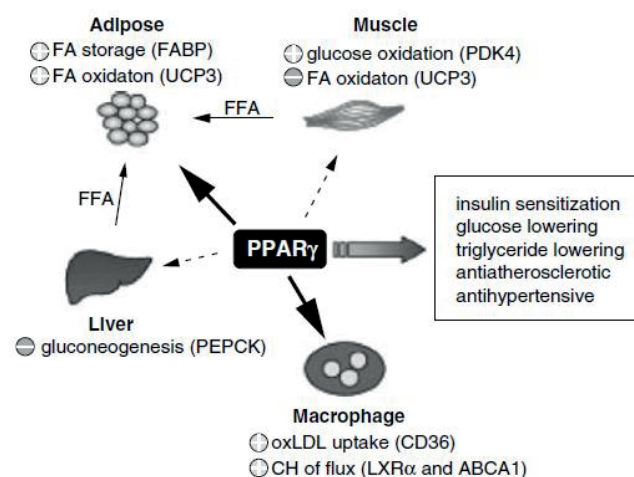
## PPAR- $\gamma$ in Heart and Cardiovascular

Being the leading cause of morbidity and mortality and contributing for more than one-third of global morbidity, CVD has become the most vital global health threat.(17,18) Heart disease, vascular disease, atherosclerosis, stroke and hypertension are classified as CVD. CVD is a life course disease that begins with the evolution of risk factors.(18) The most important independent risk factor for CVD is dyslipidemia, followed by hypertension, obesity, sedentary lifestyle, diabetes and chronic inflammation. These factors are directly regulated by diet, metabolism and physical activity.

The PPAR family including PPAR- $\gamma$  of nuclear receptor transcription factors is an important regulator of cardiac metabolism and has been targeted for pharmacologic therapies designed to modulate metabolism. PPAR- $\gamma$  which is adipose-enriched controls the expression of genes involved in FA storage and adipogenesis. The

exact mechanism by which PPAR- $\gamma$  regulates myocardial metabolism is unclear. The PPAR- $\gamma$  control myocardial metabolism by transcriptionally regulating genes encoding enzymes involved in FA and glucose utilization. The expression and activity of the PPAR- $\gamma$  and their coactivator protein such as PGC-1 $\alpha$  is dynamically regulated in several cardiomyopathic and metabolic diseases.(19-21)

Discovery of PPARs as an important regulator of metabolic pathways has brought us a significant insight of the mechanisms which regulates these processes. PPARs act as nutritional sensors that regulate a variety of homeostatic functions including metabolism, inflammation



**Figure 2. Physiological effect of PPAR- $\gamma$ .**(16) (Adapted with permission from Nature). FABP: FA-binding protein; UCP3: uncoupling protein 3; PDK4: pyruvate dehydrogenase kinase 4; PEPCK: phosphoenolpyruvate carboxykinase; CD36: cluster of differentiation 36; LXR- $\alpha$ : Liver X receptor  $\alpha$ .

and development.(19-22) PPAR- $\alpha$  is the main metabolic regulator for catabolism whereas PPAR- $\gamma$  regulates anabolism or storage. PPAR is expressed in cardiovascular system as endothelial cells, vascular smooth muscle cells and monocytes/macrophages. It has been shown that they play an important role in the modulation of inflammatory, fibrotic and hypertrophic responses.(17,20,21,23)

Action of PPAR- $\gamma$  agonists is not only of metabolism in insulin-responsive tissues, yet more directly in the inflammatory, cardiac and vascular cells associated with CVD such as coronary heart disease, atherosclerosis, and stroke.(17,22) PPAR- $\gamma$  expressed in macrophages, endothelial cells, and smooth muscle cells in normal vasculature, and atherosclerotic lesions. Although there were concerns that PPAR- $\gamma$  agonists could be pro-atherogenic, as they may promote the macrophages uptake of lipids and accelerate the foam cell formation, this compounds is known for their ability to reduce atherosclerosis in human patients and animal models. These anti-atherogenic effects can be independent of their beneficial effects on metabolism.(22) In addition to effects of PPAR- $\gamma$  in the arterial wall that might influence the occurrence atherothrombotic events, experimental evidence suggest that PPAR- $\gamma$  activation may mitigate ischemia reperfusion injury (IRI) if such events occur.(20,21,23,24)

Different cell types are reported to have different mechanisms for PPAR- $\gamma$  to inhibit inflammation.(21) PPAR- $\gamma$  agonists have been shown to block the proliferation and increase the apoptosis of vascular smooth muscle cells, suggesting more beneficial of PPAR- $\gamma$  activation in vasculature.(19,21) The beneficial effects are largely attributable to anti-inflammation activity of PPAR- $\gamma$  and its role in modulating lipid homeostasis in macrophages. Vascular inflammation has been increasingly acknowledged as an important factor in the pathogenesis of atherosclerosis.(25) The importance of macrophage PPAR- $\gamma$  in CVD has begun to be appreciated ever since foam cells in atherosclerotic lesions were found to have a high level of PPAR- $\gamma$  expression.(19-21,23).

PPAR- $\gamma$  activation decreases inflammatory cytokines (e.g., tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-6, and IL-1 $\beta$ ) produced by macrophages.(22,25) By inducing the expression of Liver X receptor (LXR)- $\alpha$  and ATP-binding cassette A1, PPAR- $\gamma$  activation promotes cholesterol efflux from macrophages resulting in inhibition of foam cell formation. Consistently, macrophage-specific PPAR- $\gamma$  knockout mice have reduced basal cholesterol efflux, most likely because of the decreased expression of lipoprotein lipase (LPL), scavenger receptor CD36, LXR- $\alpha$ , and ATP-

binding cassette G1. More profound effects on macrophages by PPAR- $\gamma$  are also possible since it has been recently shown that PPAR- $\gamma$  controls alternative activation of macrophages and can thereby improve insulin resistance. It is likely that this effect on differentiation of macrophages is also important in effects of CVD.(23)

### PPAR- $\gamma$ in Acute Kidney Injury

The decline of kidney capacity to excrete nitrogenous wastes and maintain body fluid and electrolyte balance characterizes acute kidney injury (AKI).(26) Until now, AKI is associated with high mortality rates and remains as a significant and serious problem for the most common reason of nephrology consultation in the hospitalized patient.(27)

The Acute Kidney Injury Network defined AKI more specifically as an abrupt reduction in kidney function which is associated with increased serum creatinine level, either  $>0.3$  mg/dL or 50% in 48 hours. The lack of oxygen to tissues because of reduced blood supply is known as ischemia.(26) Ischemia is one of the primary causes of AKI, alongside hypoxia and nephrotoxicity.(27) Meanwhile, reperfusion is associated with rapid resumption of oxygenated blood to tissues. IRI is one of the constant reasons for renal dysfunction and is observed in clinical situations, such as kidney transplantation, partial nephrectomy, renal artery angioplasty, aortic aneurysm, and ureteral obstruction.(26)

One factor that has an essential role in maintaining calcium hemostasis is vitamin D. Vitamin D deficiency is mostly observed in patients suffering from renal dysfunction, and it is considered as an independent risk factor for AKI in the moment.(26) Previous studies showed that adults with vitamin D deficiency have higher urinary protein excretion compare to those without. Low serum vitamin D can increase urinary protein excretion, either directly by interrupting the integrity of the glomerular basement membrane filtration, or indirectly by suppressing renin transcription and altering the hemodynamic balance.(28)

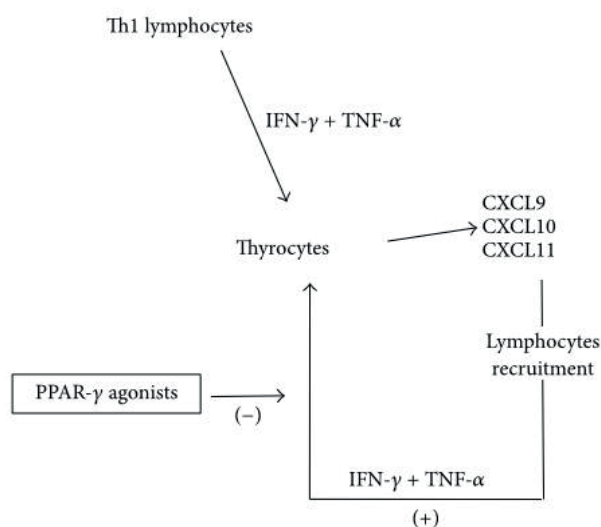
PPAR- $\gamma$  is found in lower expression levels in urinary bladder, intestine, kidney, and spleen. In kidney, it is primarily expressed in the distal medullary collecting ducts, with fewer expression in the glomeruli and renal microvasculature.(29) The PPAR- $\gamma$  agonists such as rosiglitazone and ciglitazone are documented to lessen renal IRI by attenuating neutrophil infiltration, the expression of intercellular adhesion molecule (ICAM) and oxidative stress in renal tissues.(26) Thus it showed that PPAR- $\gamma$  agonists have protective effects against IRI.(29) Both vitamin D

receptor and PPAR- $\gamma$  are ligand-activated nuclear receptors. Recently, some few *in vitro* studies suggested that crosstalk between these two nuclear receptors with involvement of PPAR- $\gamma$  in vitamin demediates biological responses. These days, some studies are designed to investigate the activation of PPAR- $\gamma$  as potential mechanism in vitamin demediated protection against IRI-induced AKI.(26)

### PPAR- $\gamma$ in Autoimmune Disease

Latest studies suggest that PPAR- $\gamma$  has important roles in T-cell survival, activation, and differentiation into Th1 or Th17 cells, implying their therapeutic potential as drug targets for treating autoimmune diseases or graft rejection.(30) Autoimmune thyroid diseases (AITD) is the most common autoimmune disorders and includes Hashimoto's thyroiditis (HT) and Graves' disease (GD), whose clinical features are hypothyroidism and thyrotoxicosis, respectively. AITD generally has low severity but can affect the quality of life significantly. It is also considered as a cause of considerable medical costs.

PPAR- $\gamma$  expression has been shown in thyroid tissue from patients with thyroiditis or GD.(31,32). In patients with AITD, HT and GD, PPAR- $\gamma$  is strongly expressed in their thyroid tissue. Meanwhile, in patients with gonorrhoea, it is expressed in the orbital tissue. Furthermore, there are enough experimental studies that show the importance of the C-X-C chemokine receptor (CXCR)3 and cognate chemokines (chemokine C-X-C motif ligand (CXCL)9, CXCL10, and CXCL11) in the Th1 immune response and in inflammatory diseases, such as AITD. *In vitro* studies have shown that



**Figure 3. Autoimmunity Cascade regulate by PPAR- $\gamma$  agonists.** (33) (Adapted with permission from Hindawi).

PPAR- $\gamma$  agonists strongly inhibit the expression and release of CXCR3 chemokines in some cells, such as thyrocytes, orbital fibroblasts, preadipocytes, and myoblasts.(33)

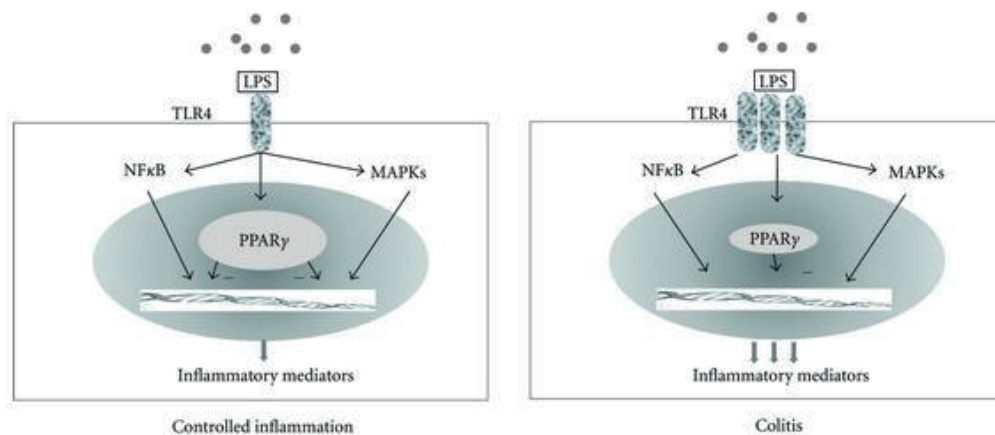
Several cell types, for example thyrocytes, which are under the influence of cytokines (such as interferon (IFN)- $\gamma$  and TNF- $\alpha$ ), can modulate the autoimmune response through the production of CXCL9, CXCL10, and CXCL11. These chemokines can cause migration into different tissues of Th1 lymphocytes, which in turn secrete more IFN- $\gamma$  and TNF- $\alpha$ , further stimulating chemokine production by the target cells, thus perpetuating the autoimmune cascade. PPAR- $\gamma$  agonists play an inhibitory role in this process (Figure 3).(33)

### PPAR- $\gamma$ in Gastrointestinal Disease

Inflammatory disease is a disease that includes wide variety of pathologic conditions that affect many organs and tissues, including inflammatory bowel disease (IBD).(34) IBD, Crohn's disease (CD), and ulcerative colitis (UC) are common causes of gastrointestinal illness characterized by chronic and relapsing intestinal inflammation.(35) PPAR- $\gamma$  emerged as an important regulator of bowel cell proliferation/differentiation (34), and PPAR- $\gamma$  highly expressed in gastrointestinal epithelium from duodenum to rectum (35,36), but get lesser in macrophages and lymphocytes (35) that PPAR- $\gamma$  is induced during differentiation of colonic epithelial cells.

In the colon, PPAR- $\gamma$  expression are not uniform throughout the colon, with significantly higher expression was observed in the proximal colon epithelium its expression is closely linked to intestinal-microbial interaction.(35,36) This impaired expression was found in both inflamed and non-inflamed areas and limited to epithelial cells. This finding offers that this modified expression is not secondary to the inflammatory process.(35)

A hypothetical model of influence of PPAR- $\gamma$  expression in UC (Figure 4). Induction of PPAR- $\gamma$  expression in epithelial cells by bacterial lipopolysaccharide (LPS)-activated toll-like receptor (TLR) 4, in turn leads to break or inhibits nuclear factor kappa B (NF- $\kappa$ B) activity and MAPK pathways to produce inflammatory mediators.(35,37) The reduced expression of PPAR- $\gamma$  together with TLR4 up-regulation might enhance the inflammatory mediator production so that resulting in mucosal damage. PPAR- $\gamma$  receptors are widely and highly expressed in the colon, being a key regulator factor of bacteria-induced mucosal inflammation. Besides that, they



**Figure 4. Influence of PPAR- $\gamma$  expression in UC.**(35) (Adapted with permission from Hindawi).

are also directly involved in the mechanism of action of mesalazine, which is largely used and effective in UC.(35)

### PPAR- $\gamma$ in Alzheimer's disease

PPAR- $\gamma$  is expressed in the brain at the low levels under physiological conditions. However, in some pathological situations, including cerebral ischemia and Alzheimer's disease, PPAR- $\gamma$  expression has been shown to be elevated. More recently, a detailed study of gene expression has reported that messenger RNA (mRNA) levels of PPAR- $\gamma$ , but not of other PPAR isoforms, were elevated in the brains of patients with Alzheimer's disease. These findings suggested that PPAR- $\gamma$  might play a role in regulating pathophysiological features of Alzheimer's disease, and has established the basis for modulation of PPAR- $\gamma$  activity in the treatment of the disease.(35,38,39)

Alzheimer's disease is characterized by the extracellular deposition of  $\beta$ -amyloid fibrils within the brain and the subsequent association and phenotypic activation of microglial cells associated with the amyloid plaque. The activated microglia mount a complex local proinflammatory response with the secretion of a diverse range of inflammatory products. Nonsteroidal anti-inflammatory drugs (NSAIDs) are efficacious in reducing the incidence and risk of Alzheimer's disease and significantly delaying disease progression. Number of epidemiological studies demonstrated that NSAID treatment reduces Alzheimer's disease risk by as much as 80% and it was suggested that these effects arise from the ability of these drugs to stimulate PPAR- $\gamma$  and to inhibit inflammatory responses in the Alzheimer's disease brain.(38,40,41)

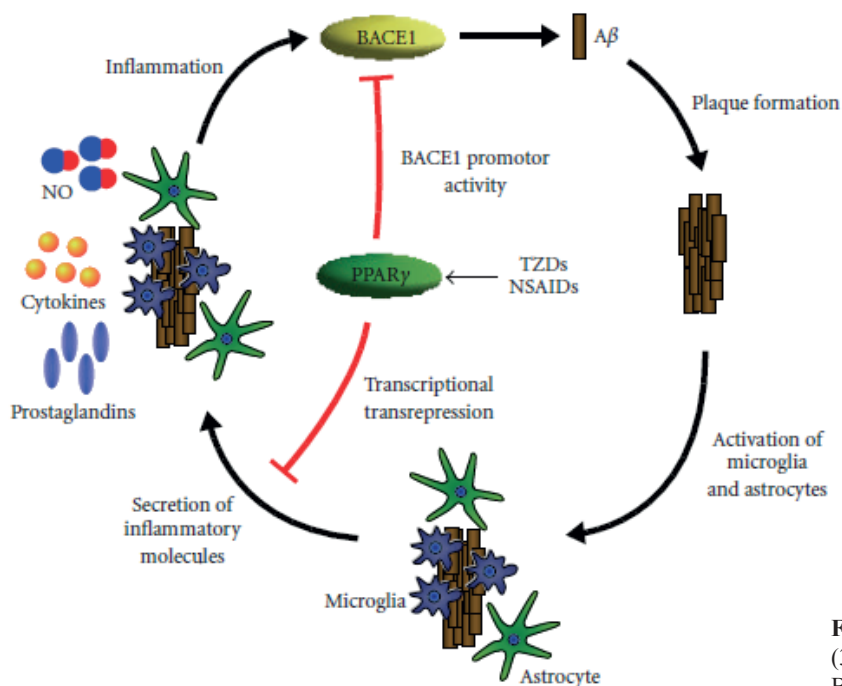
PPAR- $\gamma$  exhibits a wide range of activities to positively influence the pathology of Alzheimer's disease.

Beside the ameliorating effect of PPAR- $\gamma$  agonists in the inflammatory status of the Alzheimer's disease brain by repressing the secretion of proinflammatory molecules and the enhancement of mitochondrial function, a direct involvement in the processing of the  $A\beta$  peptide has been shown in Figure 5.(38)

### PPAR- $\gamma$ as Main Regulator of Adipogenesis

PPAR- $\gamma$  is highly expressed in white and brown adipose tissues. It is considered a main regulator of adipogenesis. Ectopic expression of PPAR- $\gamma$  in non-adipogenic embryonic fibroblast stimulates the adipocytes gene transcription program and drives adipogenesis. PPAR- $\gamma$  is essential for adipogenesis, and there is no single factor has been identified that can drive adipogenesis without PPAR- $\gamma$ . PPAR- $\gamma$  not only play critical role for adipogenesis, but also for the maintenance of the fully differentiated adipocytes. (42) Mutation of the PPAR- $\gamma$  gene has been implicated in lipodystrophy and other metabolic diseases as well, such as hypertension and insulin resistance.(43) However, as well as the other gene, PPAR- $\gamma$  is also regulated by numbers of transcription factors. Some numbers of transcription factors have been reported to positively or negatively regulate adipogenesis and PPAR- $\gamma$  expression. But, whether these factors directly regulate PPAR- $\gamma$  expression is often unclear.(42)

There are several positive regulators of PPAR- $\gamma$ , but some of them have been shown to bind the gene locus and/or activate the PPAR- $\gamma$  promoter in reporter assay. It is indicating that these factors regulate PPAR- $\gamma$  expression directly. One of transcription factors that positively regulate PPAR- $\gamma$  expression is C/EBPs including  $\alpha$ ,  $\beta$ , and  $\delta$  that



**Figure 5. Effects of PPAR $\gamma$  on A $\beta$  metabolism.** (38) (Adapted with permission from Hindawi). BACE1: beta-secretase 1.

are crucial for adipogenesis because of it play a role as a pioneer for adipogenesis. It recruits histone H3 lysine 4 (H3K4) mono- and di-methyltransferase myeloid/lymphoid or mixed-lineage leukemia 4 (MLL4) to establish a subset of active adipogenic enhancers including the PPAR- $\gamma$  gene locus. In the early of adipogenesis, C/EBPs are induced immediately by adipogenic chemical such as isobutylmethyl-xanthine and dexamethasone.(42)

Recent study showed that PPAR- $\gamma$  and C/EBP- $\alpha$  positively regulate each other's expression and cooperate to promote adipogenesis. PPAR- $\gamma$  is essential for C/EBP- $\alpha$ -stimulated adipogenesis in fibroblast and conversely C/EBP- $\alpha$  knock-out fibroblast show severe defects in PPAR- $\gamma$ -stimulated adipogenesis in the absence of synthetic PPAR- $\gamma$  ligands. PPAR- $\gamma$  directly activates endogenous C/EBP- $\alpha$  gene transcription. Once induced, C/EBP- $\alpha$  binds to the PPAR- $\gamma$  gene locus and further induces and maintains its expression in mature adipocytes through a positive feedback loop.(44)

One of transcription factors that play a role as negative regulator of PPAR- $\gamma$  expression is GATAs. GATA-2 and GATA-3 are highly expressed in the preadipocyte fraction of the white adipose tissue. Constitutive expression of GATA-2 or GATA-3 inhibits 3T3-F442A differentiation and PPAR- $\gamma$  expression through inhibit the activity of 0.6-kb PPAR- $\gamma$  promoter. GATA-2 and GATA-3 also found to inhibit the transcriptional activities of C/EBP- $\alpha$  and C/EBP- $\beta$  through physical interactions but it still unclear whether GATA-2/3 directly repress PPAR- $\gamma$  expression in preadipocytes.(45)

Genetic variation of PPAR- $\gamma$  is also proposed as the other factor that influences activity and development of type 2 diabetes mellitus through altering insulin signaling pathway. The Pro12Ala polymorphism leads to a diminished stimulation of PPAR- $\gamma$  subsequent lowered levels of differentiated adipose tissue accumulation which is altered insulin sensitivity. In contrast, several studies have proven that there is no consistent association between Pro12Ala polymorphism to metabolic disorder particularly type 2 diabetes mellitus did not show a direct influence of that polymorphism in the development of diabetes mellitus.(11)

Based on all of explanations above, PPAR- $\gamma$  is the master regulator of adipocytes differentiation that plays an important role in lipid metabolism. Differentiated adipocyte is a key of insulin sensitizing effect. PPAR- $\gamma$  controls the expression of numerous factors secreted from adipose tissue that influence insulin sensitivity (*e.g.*, adiponectin and leptin) and upregulates the glucose transporter type 4 (GLUT4) expression that involved in glucose homeostasis.(46) Not only play a role in metabolic homeostasis, PPAR- $\gamma$  also involved in several diseases that induced by inflammation. PPAR- $\gamma$  is also expressed in various immune system cell types, particularly in antigen presenting cells, such as dendritic cells and macrophages.(47) Inflammation also plays a role in cardiovascular event as a cascade of obesity and diabetes. Activating PPAR- $\gamma$  is proven to be a good therapeutic method for reducing negative effect of obesity and would give a best outcome while consuming high level of fat from diet.(48)

Many natural agonists of PPARs such as unsaturated FAs, Prostaglandin J2 (PGJ2), and Carbaprostacycline and synthetic agonist of PPARs such as Fenofibrate, Rosiglitazone, and Farglitazar, are used in treatment of glucose and lipid disorders and other diseases.(48) PPARs perform different activities, largely via endogenous ligands produced in the metabolic pathways of FAs; and they are called lipid sensors. PPARs agonists have different properties and specificities for individual PPARs receptors, different absorption and distribution, and distinctive gene expression profiles, which ultimately lead to different clinical outcomes.(49,50) The synthesis of new drug generation, PPAR- $\alpha/\gamma$  dual agonists connecting positive influences on both lipid and glucose metabolism, has been developed lately as a response to treatment challenge of the coexisting type 2 diabetes mellitus with dyslipidemia. These double agonists not only have anti-diabetic activity but also reduce atherosclerosis development. They also shown anti-inflammatory, improve endothelial function, decrease plasma free fatty acids and lower blood pressure.(51)

TZD has well known to be an effective agonist for PPAR- $\gamma$  for years. However, the adverse effects of TZD which led restricted clinical application are suggested to be a result of full PPAR- $\gamma$  activation, contrasting the weak agonistic effect of endogenous PPAR- $\gamma$  ligands such as FAs and prostanoids. Long term-activation of PPAR- $\gamma$  TZD is known to be a risk factor by attenuating endothelial dysfunction.(52) Great research efforts have recently been undergone to explore the potential of selective PPAR- $\gamma$  modulators (SPPARMs), compounds that improve glucose homeostasis but elicit reduced side effects due to partial PPAR- $\gamma$  agonism based on selective receptor-cofactor interactions and target gene regulation. An example for a recently identified SPPARM is N-acetylfarnesylcysteine. New emerging compounds with *in vitro* and *in vivo* effectiveness as both a full and partial agonist are depending on the investigated PPAR- $\gamma$  target gene.(46)

Natural products are important source for the discovery and development of new drugs. Natural products possess high chemical pattern diversity and are optimized to give different biological functions, proposing them a high drug-likeness and making them a complete source for identification of new drug. It was not surprising if there are many significant research efforts to explore the PPAR- $\gamma$  activating potential of a wide range of natural products originating from medicinal plants.(53) PPAR- $\gamma$ -ligands used to often identified in plants that are common food sources, including the tea plant, soybeans, palm oil, ginger, and grapes. The presence of PPAR- $\gamma$  ligands in food products

warrants an exploration whether this nuclear receptor may be effectively activated by the intake of nutraceuticals, by consumption of functional foods or by dietary supplements.(54) Although most of the agonists identified in food sources are weak PPAR- $\gamma$  agonists, the effects of their metabolites deserve further research to better estimate their preventive potential and give more safe medicine with an effective outcome.

## Conclusion

PPAR- $\gamma$  is most highly expressed in adipose tissue where it is essential for adipogenesis. The expression of PPAR- $\gamma$  is widespread and is found at moderate levels in most tissues, with high levels. Several studies show that many functions and critical role of PPAR- $\gamma$  in metabolic homeostasis, and also involved in several diseases that induced by inflammation. PPAR- $\gamma$  dysregulation is linked to the development of obesity, type 2 diabetes, atherosclerosis, CVD, AKI, neuroinflammation disease, autoimmune disease, gastrointestinal disease and Alzheimer's disease. In studies of several diseases above, the mechanism of how PPAR- $\gamma$  works is often stated clearly. Many studies based on meta-analysis are used to describe the correlation between level of PPAR- $\gamma$  expression with increased symptom of disease or any metabolic marker. Many of them suggest that genetic variations of PPAR- $\gamma$  are proposed as the factor that influences activity and development of several metabolic disorders. Based on all studies explanation, targeting PPAR- $\gamma$  is proven to be a good therapeutic method for reducing negative effect of several metabolic homeostasis disorder. Now, many natural and synthetic agonists of PPARs are used in the treatment of glucose and lipid disorders or another metabolic homeostasis disorder which have different properties and specificities for individual PPARs receptors, different absorption and distribution, and distinctive gene expression profiles, which ultimately lead to different clinical outcomes.

## References

1. Ahmadian M, Suh J, Hah N, Liddle C, Atkins A, Downes M, *et al.* PPAR $\gamma$  signaling and metabolism: the good, the bad and the future. *Nat Med.* 2013; 99: 557-66.
2. Janani C, Ranjitha KB. PPAR gamma gene -- a review. *Diabetes Metab Syndr.* 2015; 9: 46-50.
3. Lehrke M, Lazar M. The many faces of PPAR $\gamma$ . *Cell.* 2005; 123: 993-9.

4. SABiosciences [Internet]. PPAR Pathway [cited April 20, 2016]. Available from: [http://www.sabiosciences.com/pathway.hp?sn=PPAR\\_Pathway](http://www.sabiosciences.com/pathway.hp?sn=PPAR_Pathway).
5. Chawla A, Barak Y, Nagy L, Liao D, Tontonoz P, Evans RM. PPAR- $\gamma$  dependent and independent effects on macrophage-gene expression in lipid metabolism and inflammation. *Nat Med.* 2001; 7: 48-52.
6. Kelly DP. The pleiotropic nature of the vascular PPAR gene regulatory pathway. *Circ Res.* 2001; 89: 935-7.
7. Nuclear Receptor Resource [Internet]. PPAR $\gamma$  Pathway [cited April 20, 2016]. Available from: [http://nrresource.org/drawings/ppargamma\\_pathway.html](http://nrresource.org/drawings/ppargamma_pathway.html).
8. Hata K, Nishimura R, Ikeda F, Yamashita K, Matsubara T, Nokubi T, *et al.* Differential roles of Smad1 and p38 kinase in regulation of peroxisome proliferator-activating receptor gamma during bone morphogenetic protein 2-induced adipogenesis. *Mol Biol Cell.* 2003; 14: 545-55.
9. Zhang J, Fu M, Zhu X, Xiao Y, Mou Y, Zheng H, *et al.* Peroxisome proliferator-activated receptor delta is up-regulated during vascular lesion formation and promotes post-confluent cell proliferation in vascular smooth muscle cells. *J Biol Chem.* 2002; 277: 11505-12.
10. Ortuño Sahagún D, Márquez-Aguirre AL, Quintero-Fabián S, López-Roa RI, Rojas-Mayorquín AE. Modulation of PPAR gamma by nutraceuticals of complementary treatment for obesity related disorders and inflammatory diseases. *PPAR Res.* 2012; 2012: 318613. doi: 10.1155/2012/318613.
11. González JPM, Borrrella CC, Mayoral R, Gudino LC, Hoghtower CM, Sarmiento RG. PPAR gamma pro12Ala polymorphism and type 2 diabetes: a study in a spanish cohort. *J Genet Stud.* 2014; 2: 1. doi: 10.7243/2054-1112-2-1.
12. Berger J. Role of PPAR $\gamma$ , transcriptional cofactors, and adiponectin in the regulation of nutrient metabolism, adipogenesis and insulin action: view from the chair. *Int J Obes Relat Metab Disord.* 2005; 29: S3-4.
13. Choi S, Kim E, Jung J, Marciano D, Jo A, Koo J, *et al.* PPAR $\gamma$  antagonist gleevec improves insulin sensitivity and promotes the browning of white adipose tissue. *Diabetes.* 2016; 65: 829-39.
14. Akyurek N, Aycan Z, Cetinkaya S, Akyurek O, Yilmaz Agladioglu S, Ertan U. Peroxisome proliferator activated receptor (PPAR)-gamma concentrations in childhood obesity. *Scand J Clin Lab Invest.* 2013; 73: 355-60.
15. Farmer S. Regulation of PPAR $\gamma$  activity during adipogenesis. *Int J Obes Relat Metab Disord.* 2005; 29: S13-6.
16. Larsen T, Toubro S, Astrup A. PPAR $\gamma$  agonists in the treatment of type II diabetes: is increased fatness commensurate with long-term efficacy?. *Int J Obes Relat Metab Disord.* 2003; 27: 147-61.
17. Das SK, Chakrabarti R. Role of PPAR in cardiovascular diseases. *Recent Pat Cardiovasc Drug Discov.* 2006; 1: 193-209.
18. Meiliana A, Wijaya A. Novel Biomarkers in Cardiovascular Disease: A Review. *Indones Biomed J.* 2010; 2: 66-91.
19. Huang JV, Greyson CR, Schwartz GG. PPAR- $\gamma$  as a therapeutic target in cardiovascular disease: evidence and uncertainty. *J Lipid Res.* 2012; 53: 1738-54.
20. Calkin AC, Thomas MC. PPAR Agonists and Cardiovascular Disease in Diabetes. *PPAR Res.* 2008; 2008: 1-12.
21. Finck B. The PPAR regulatory system in cardiac physiology and disease. *Cardiovasc Res.* 2007; 73: 269-77.
22. Duan SZ, Ivashchenko CY, Usher MG, Mortensen RM. PPAR- $\gamma$  in the cardiovascular system. *PPAR Res.* 2008; 2008: 745804. doi: 10.1155/2008/745804.
23. Rojas J, Salazar J, Martínez MS, Palmar J, Bautista J, Chávez-Castillo M, *et al.* Macrophage heterogeneity and plasticity: impact of macrophage biomarkers on atherosclerosis. *Scientifica.* 2015; 2015: 851252. doi: 10.1155/2015/851252.
24. Faraci FM. Protecting against vascular disease in brain. *Am J Physiol Heart Circ Physiol.* 2011; 300: H1566-82.
25. Ding X, Wang R, Liu L, Yu Q, Wang Z, Ma Z, *et al.* Interaction between peroxisome proliferator-activated receptor gamma and smoking on cardiovascular disease. *Physiol Behav.* 2016; 153: 28-32.
26. Kapil A, Singh J, Kaur T, Singh B, Singh A. Involvement of peroxisome proliferator-activated receptor gamma in vitamin D-mediated protection against acute kidney injury in rats. *J Surg Res.* 2013; 185: 774-83.
27. Basile DP, Anderson MD, Sutton TA. Pathophysiology of acute kidney injury. *Compr Physiol.* 2012; 2: 1303-53.
28. de Bragança AC, Volpini RA, Canale D, Gonçalves JG, Shimizu MHM, Sanches TR, *et al.* Vitamin D deficiency aggravates ischemic acute kidney injury in rats. *Physiol Rep.* 2015; 3: e12331. doi: 10.14814/phy2.12331.
29. Cheng CF, Chen HH, Lin H. Role of PPAR- $\alpha$  and its agonist in renal diseases. *PPAR Res.* 2010; 2010: 345098. doi: 10.1155/2010/345098.
30. Choi J, Bothwell A. The nuclear receptor PPARs as important regulators of T-cell functions and autoimmune diseases. *Mol Cells.* 2012; 33: 217-22.
31. Kasai K, Banba N, Hishinuma A, Matsuura M, Kakishita H, Matsumura M, *et al.* 15-Deoxy- $\Delta$ 12,14-prostaglandin J2 facilitates thyroglobulin production by cultured human thyrocytes. *Am J Physiol Cell Physiol.* 2000; 279: C1859-69.
32. Mimura L, Villares S, Monteiro M, Guazzelli I, Bloise W. Peroxisome proliferator-activated receptor- $\gamma$  gene expression in orbital adipose/connective tissues is increased during the active stage of graves' ophthalmopathy. *Thyroid.* 2003; 13: 845-50.
33. Ferrari S, Fallahi P, Vita R, Antonelli A, Benvenga S. Peroxisome proliferator-activated receptor- $\gamma$  in thyroid autoimmunity. *PPAR Res.* 2015; 2015: 1-8.
34. Martin H. Role of PPAR-gamma in inflammation. Prospects for therapeutic intervention by food components. *Mutat Res.* 2010; 690: 57-63.
35. Annese V, Rogai F, Settesoldi A, Bagnoli S. PPAR $\gamma$  in inflammatory bowel disease. *PPAR Res.* 2012; 2012: 1-9.
36. Necela B, Thompson E. Pathophysiological Roles of PPAR $\gamma$  in Gastrointestinal Epithelial Cells. *PPAR Research.* 2008; 2008: 1-8.
37. Sartor R. Mechanisms of disease: pathogenesis of Crohn's disease and ulcerative colitis. *Nat Clin Pract Gastroenterol Hepatol.* 2006; 3: 390-407.
38. Kummer MP, Heneka MT. PPARs in Alzheimer's disease. *PPAR Res.* 2008; 2008: 1-8.
39. Jiang Q, Heneka MT, Landreth GE. The role of peroxisome proliferator-activated receptor- $\gamma$  PPAR $\gamma$  in Alzheimer's disease. *CNS Drugs.* 2008; 22: 1-14.
40. Combs CK, Johnson DE, Karlo JC, Cannady SB, Landreth GE. Inflammatory mechanisms in Alzheimer's disease: inhibition of  $\beta$ -amyloid-stimulated proinflammatory responses and neurotoxicity by PPAR- $\gamma$  agonists. *J Neurosci.* 2000; 20: 558-67.
41. Heneka MT, Reyes-Irisarri E, Hüll M, Kummer MP. Impact and therapeutic potential of PPARs in alzheimers disease. *Curr Neuropharmacol.* 2011; 9: 643-50.
42. Lee JE, Ge K. Transcriptional and epigenetic regulation of PPAR $\gamma$  expression during adipogenesis. *Cell Biosci.* 2014; 4: 29. doi: 10.1186/2045-3701-4-29.
43. Monajemi H, Zhang L, Li G, Jenning EH, Cao H, Maas M, *et al.* Familial partial lipodystrophy phenotype resulting from a

- single-base mutation in deoxyribonucleic acid-binding domain of peroxisome proliferator-activated receptor gamma. *J Clin Endocrinol Metab.* 2007; 92: 1606-12.
44. Wu Z, Bucher NL, Farmer SR. Induction of peroxisome proliferator-activated receptor gamma during the conversion of 3T3 fibroblasts into adipocytes is mediated by C/EBPbeta, C/EBPdelta, and glucocorticoids. *Mol Cell Biol.* 1996; 16: 4128-36.
  45. Tong Q, Tsai J, Tan G, Dalgin G, Hotamisligil GS. Interaction between GATA and the C/EBP family of transcription factors is critical in GATA-mediated suppression of adipocyte differentiation. *Mol Cell Biol.* 2005; 25: 706-15.
  46. Wang L, Waltenberger B, Pferschy-Wenzig E-M, Blunder M, Liu X, Malainer C, *et al.* Natural product agonists of peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ): a review. *Biochem Pharmacol.* 2014; 91: 73-89.
  47. Szeles L, Torocsik D, Nagy L. PPARgamma in immunity and inflammation: cell types and diseases. *Biochim Biophys Acta.* 2007; 1771: 1014-30.
  48. Grygiel-Górniak B. Peroxisome proliferator-activated receptors and their ligands: nutritional and clinical implications – a review. *Nutr J.* 2014; 13: 17. doi: 10.1186/1475-2891-13-17.
  49. Heikkinen S, Auwerx J, Argmann CA. PPAR $\gamma$  in human and mouse physiology. *Biochim Biophys Acta.* 2007; 1771: 999-1013.
  50. Margeli A, Kouraklis G, Theocharis S. Peroxisome proliferator activated receptor-gamma (PPAR-gamma) ligands and angiogenesis. *Angiogenesis.* 2003; 6: 165-9.
  51. Lo Verme J, Fu J, Astarita G, La Rana G, Russo R, Calignano A, *et al.* The nuclear receptor peroxisome proliferator-activated receptor-alpha mediates the anti-inflammatory actions of palmitoylethanolamide. *Mol Pharmacol.* 2005; 67: 15-9.
  52. Caballero A, Saouaf R, Lim SC, Hamdy O, Abou-Elenin K, O'Connor C, *et al.* The effects of troglitazone, an insulin-sensitizing agent, on the endothelial function in early and late type 2 diabetes: a placebo-controlled randomized clinical trial. *Metabolism.* 2003; 52: 173-80.
  53. Weidner C, de Groot JC, Prasad A, Freiwald A, Quedenau C, Kliem M, *et al.* Amorphutins are potent antidiabetic dietary natural products. *Proc Natl Acad Sci USA.* 2012; 109: 7257-62.
  54. Doshi LS, Brahma MK, Bahirat UA, Dixit AV, Nemmani KV. Discovery and development of selective PPAR $\gamma$  modulators as safe and effective antidiabetic agents. *Expert Opin Investig Drugs.* 2010; 19: 489-512.