Plant Archives Volume 20 No. 2, 2020 pp. 8805-8810 **e-ISSN:2581-6063 (online), ISSN:0972-5210**

BENEFICIAL EFFECTS OF VARIOUS PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR AGONISTS ON LIPID PROFILES AND OBESITY : A REVIEW

Shahad W. Ahmed[1]* and Nada N. AL-Shawi[2]

[1]*Department of Clinical and Laboratory Sciences, College of Pharmacy, University of Baghdad, Baghdad, Iraq.
[2] Department of Pharmacology and Toxicology, College of Pharmacy, University of Baghdad, Baghdad, Iraq.

Abstract

Peroxisome proliferator-activated receptors are family of nuclear receptors and are set of three receptor sub-types encoded by distinct genes: PPAR-α is also known also known nuclear receptor subfamily 1, group C, member 1 (NR1C1) and it is highly expressed in liver, skeletal muscle, kidney, heart and the vascular wall, PPAR-β/δ (NR1C2) and PPAR-γ (NR1C3) and it is predominantly detected in adipose tissue, intestine and macrophages.

Such family of receptors acts as lipid sensors and regulates a broad range of genes in many metabolically-active tissues; where, such receptors family can regulate lipid and lipoprotein metabolism, glucose homeostasis, weight gain associated with insulin resistance in type 2 diabetic patients, cell proliferation, fibrogenesis and differentiation.

The peroxisome proliferator-activated receptors are activated by fatty acid derivatives and pharmacological agents such as fibrates and thiazolidinediones (glitazones) which are specific for PPAR-α and PPAR-γ respectively. Furthermore, PPAR-β/δ is also called fatty acid-activated receptor; and its activation in skeletal muscle cells can increase the uptake and catabolism of fatty acids through β-oxidation.

The dual peroxisome proliferator-activated receptor agonist activate both alpha and gamma isoforms; and the pan PPAR agonist can activate all of alpha, beta/delta, and gamma isoforms. The current review illustrates the effect of various PPAR agonists on obesity.

Key words : Peroxisome proliferator-activated receptors, natural agonists, synthetic agonists, lipid profile, obesity.

Introduction

General Considerations

Peroxisome proliferator activated receptors (PPARs) are a group of nuclear receptor proteins which can act as transcription factors that play important roles in the regulation of genes that essential for cell differentiation, growth and various metabolic processes such as carbohydrates, lipids, and proteins metabolism (Michalik *et al*, 2006). Moreover, PPARs also known as insulin and lipid sensors (Grygiel-Gorniak,2014).

Such receptors subtypes are ligand-activated transcription factors consisting of an N-terminal DNA binding domain and a C-terminal Ligand Binding Domain (LBD) (Lagana *et al*, 2016). Furthermore, the family of PPARs consists of three isoforms: PPAR-α (NR1C1), PPAR-β/δ (NR1C2) and PPAR-γ (NR1C3); where, PPAR-α is highly present in the metabolically-active tissues; moreover, the PPAR-γ, which has three forms: PPARγ1, PPARγ2 and PPARγ3 are primarily expressed in white and brown adipose tissue; and the third isoform (PPARβ/δ) is practically-found in all tissues (Xu *et al*.2018). All the three PPARs forms have natural agonists, such as variety of polyunsaturated long-chain fatty acids and arachidonic acid derivatives; in addition, each form of PPAR can be activated by synthetic agonists (Fan *et al*, 2018).

Peroxisome proliferator activated receptors (PPARs) types:

Peroxisome proliferator activated receptor-

Author for correspondence : E-mail: shahad_wisam2020@yahoo.com

alpha (PPAR-α)

Peroxisome proliferator activated receptor-alpha (PPAR-α) is widely expressed in tissues with elevated fatty acid (FAs) catabolism level; where, such receptor form can regulate genes that control FA uptake; and it can play a major role in the oxidation of FAs in the liver; moreover, PPAR-α is highly-expressed in tissues that oxidize FAs at a rapid rate; while, such receptor form is expressed in low levels in small and large intestine, adrenal gland, and skeletal muscle (Braissant *et al*,1995) Furthermore, the activation of PPAR-α can reduce the quantities of available FAs for synthesis of triglyceride and very low density lipoprotein (VLDL) in liver; in addition, its activation can promote FA oxidation in fasting (Sander *et al*,1999).

The physiological role of PPAR-α receptor form is to detect the overall flux of dietary FAs; where, it can raise the apo-lipoproteins production such as apo-AV, apo-CIII, resulting in reduced of triglycerides (TGs) level in circulation; and the activation of PPAR-α can decrease the levels of TGs in the liver and the circulation; furthermore, some of the PPAR-α agonists can mildly-increase high density lipoprotein-cholesterol (HDL-C) level in humans (Ide *et al*,2003); for example, fenofibrate increased HDL-C levels by 10% to 25%, to a degree directly dependent of baseline TG and HDL-C levels (Michel *et al*,2008).

The PPAR-α binds to number of ligands, for example, arachidonic acid (AA) metabolites such as leukotrienes (LTs), prostaglandins (PGs), and to a class of lipid lowering drugs that primarily mediate their clinical effects by activating PPAR-α such as synthetic fibrate drugs (bezafibrate, fenofibrate, clofibrate and gemfibrozil) (Sher *et al*,1993).

Peroxisome proliferator activated receptor-gamma (PPAR-γ)

Two distinct N-terminal isoforms named as PPARγ1 and PPARγ2 have been found in mice and humans (Mukherjee *et al*,1997).

The PPAR-γ primarily exists in adipose tissue, intestine and macrophages. Two isoforms of PPAR-γ are observed in the humans and mouse: PPAR-γ1, which present in almost all tissues except muscle, and PPAR-γ2, which mainly present in adipose tissue and the intestine (Park *et al*,2017). The PPAR-γ has been involved in the pathology of many diseases like diabetes, and atherosclerosis; where, it has been shown that such form of receptor be an active regulator of target genes associated in lipid and glucose metabolism; and the PPAR-γ agonists are effective antidiabetic agents such as most insulin-sensitizing medications [(i.e., the thiazolidinediones) (glitazones)]; where, such group of drugs can activate PPAR-γ and is associated with enhanced insulin sensitivity as a way of lowering glucose serum level without increasing pancreatic insulin secretion (Willson *et al*,2000); furthermore, PPAR-γ agonists may also have beneficial effects in treatment of other disorders such as atherosclerosis, inflammation and cancer (Kim *et al*,2015); moreover, PPAR-γ agonists have been used in the treatment of hyperlipidemia (Burdick *et al*,2005) and increase HDL-C levels (Willson *et al*,2000); additionally, activation of PPAR-γ can reduce the inflammatory response of certain cells, especially endothelial cells (Hamblin *et al*,2009).

Peroxisome proliferator activated receptor-delta/beta (PPAR δ/β)

Peroxisome proliferator-activated receptor-delta [(PPAR-δ), also known as PPAR-β] is a member of the PPAR subgroup in the nuclear receptor superfamily. Although PPAR-δ is widely expressed, its level of expression in different tissues differs depending on the type of cell and the state of the disease (Xu *et al*,2013).

The essential feature of PPAR-δ is modulation of cellular energy consumption; and in muscle cells, activation of PPAR-δ by ligands can shift energy production to FAs oxidation from glycolysis as an alternative energy source, which increase muscle endurance (Fan *et al*,2017). The PPAR-δ is also called fatty acid-activated receptor (FAAR); and its activation in skeletal muscle cells can increase the uptake and catabolism of FAs through β-oxidation (Holst *et al*,2003).

In addition to its role on fatty acid oxidation, PPAR-δ is highly found in pancreatic islet beta cells and its activation can stimulate insulin secretion which in turn can lead to enhance blood glucose homeostasis through a number of mechanisms (Iglesias *et al*,2012). Researchers reported that PPAR-δ agonists may have beneficial effects in the metabolic syndrome via increasing FAs consumption in the adipose tissue and skeletal muscle and weight loss could be expected as well (Luquet *et al*,2005).

A potent ligand, GW501516, can cause a significant dose-dependent rise in HDL-C while it can reduce low density lipoprotein-cholesterol (LDL-C), triglycerides (TGs) and insulin levels in the insulin resistant middle-aged obese rhesus monkeys; furthermore, GW501516 was also reported to enhance expression of the reverse cholesterol transporter ATP-binding cassette A1 and it can induce apolipoprotein A1-specific cholesterol efflux (Oliver *et al*,2001).

Dual peroxisome proliferator-activated receptor (PPAR) agonists :

Dual PPAR Alpha/Gamma

The dual peroxisome proliferator-activated receptor alpha and gamma isoforms of the family of nuclear transcription factors are considered as medical targets for therapeutic action of drugs that treat not only the hyperglycemia of diabetes, but also the dyslipidemia (Ahmed *et al*,2007); where, such isoforms have been shown to improve obesity and diabetes symptoms. Fibrates can enhance lipid profiles; and TZDs (glitazones) can reduce blood glucose and inflammation; furthermore, it has been shown that fibrates can act synergistically with TZDs to improve obesity-induced insulin resistance (Tsuchida *et al*,2005).

Since PPARs have key roles as energy homeostasis and as regulators of inflammation; thus, much research has been directed towards developing synthetic PPAR ligands. It was realized that in the 1990s the lipid-modifying properties of the fibrates were attributable to selectively activate PPAR-α; moreover, TZDs, which are structural analogs of fibrates, were eventually shown to activate PPAR-γ; furthermore, synthetic PPAR-γ agonists have been established, and preclinical research is clarifying this receptor's role; additionally, agents that activate multiple PPAR isoforms are being developed such as dual PPARα/γ and pan-PPAR α/γ/δ agonists (Bart *et al*,2005).

Therapeutic effect of PPAR agonists :

Thiazolidinediones (TZDs) (Glitazones)

Thiazolidinediones (TZDs) (glitazones) is a class of heterocyclic compounds composed of a five-membered C3NS ring. Such family of medications is used for the treatment of diabetes mellitus type 2 that which introduced in late 1990s (Hulin *et al*,1996).

The TZDs or glitazones are family of antidiabetic drugs and the first compounds known as high affinity PPAR-γ agonists, are rosiglitazone, pioglitazone, and troglitazone (Henke *et al*,1998;Cobb *et al*,1998). Also, TZDs (glitazones) have potent anti-inflammatory, antithrombotic effects that may improve glucose tolerance and the long-term cardiovascular (CV) risk associated with atherosclerosis in type-2 diabetes patients (Staels,2005). Additionally, it has been reported that the beneficial effects of TZDs on glucose metabolism are regulated by binding to PPAR-γ, and induction of adipogenesis, which is considered as the mechanism of weight loss by TZDs (glitazones) (Spiegelman,1998).

Researchers also reported that troglitazone was shown to have a dose-response effect in improving ovulation and hirsutism that appeared to be mediated by decreased levels of hyper-insulinemia and decreased levels of free testosterone (Azziz *et al*,2001). But, it has been published that troglitazone is removed from the worldwide market due to its hepatotoxicity; while, pioglitazone and rosiglitazone are still available today; where, both medications are effective in improving insulin sensitivity, glycemic control, ovulation and menstrual regularity without hepatotoxicity seen in troglitazone (Stout *et al*,2005).

Fibrates

The class of fibrate medications has been in use since the late 1960s; where, clofibrate is the first member followed by fenofibrate, bezafibrate, gemfibrozil, and ciprofibrate over the next few decades (WHO,1980).

The fibrates are synthetic ligands bind to peroxisome proliferator–activated receptor (PPAR-α) (Berger *et al*,2002) which clinically minimize TG serum levels, and this depends on PPAR-α pathways that increased FAs uptake (by inducing FAs transport protein), increased FA β-oxidation, and increased transcription of lipoprotein lipase (LPL) and decrease transcription of apolipoprotein (CPU) C-III that block LPL activity (Watts *et al*,1999). Furthermore fibrates has been shown to decrease serum TGs and increase HDL-c through PPAR-α-mediated action and also such class has anti-inflammatory and anti-atherosclerotic effect (Marx *et al*,2001). Additionally, fenofibrate, an agonist of PPAR-α can decrease body mass independent of food intake (Rachid *et al*,2015).

Aleglitazar

Aleglitazar, a dual peroxisome proliferator-activated receptor agonist that has beneficial effects on lipid profiles (Lincoff *et al*,2014), its agonistic activity for PPAR-α can control lipid levels which in turn improve dyslipidemia; and its agonistic activity for PPAR-γ regulates glucose levels that improve insulin sensitivity in diabetes (Henry *et al*,2009). Moreover, aleglitazar can improve glycemic control and not only reduce fasting plasma glucose, fasting insulin, and the glycated hemoglobin (HbA1c) levels in monkeys, but it also can improve insulin sensitivity (Barbara *et al*,2011). In addition to its glycemic and lipid benefits, aliglitazar can minimize PPAR-related weight gain and edema in patients with type 2 diabetes (Bénardeau *et al*,2009).

Bezafibrate

Bezafibrate (marketed as Bezalip and several other names) is a fibrate drug, an agonist of PPAR-α and also have high-affinity to PPAR-γ and PPAR-β; so it is

considered as a pan-PPAR agonist (Tenenbaum *et al*,2005). It is used to treat hyperlipidemia; and it helps to reduced serum LDL-C and TGs, and increase HDL-C (Janos *et al*,2006). Moreover it has been reported that, bezafibrate is more effective in lowering body weight and blood glucose than fenofibrate in overweight-mice fed with high-fat diet (Fernandes-Santos *et al*,2009); additionally, it can increase HDL-C, decreases TGs, and enhances insulin sensitivity in diabetic patients (Tenenbaum *et al*,2006).

Bavachinin (BVC)

Bavachinin (BVC) is a flavonoid that contained within the seed of *Psoralea corylifolia* Linn. plant, which has been used in traditional Chinese medicines to avoid and treat type 2 diabetes in clinical researches; moreover, BVC has been described as a novel natural pan-PPAR agonist *in vivo* and *in vitro* in metabolic syndrome, BVC does not antagonize, but synergizes with TZDs and fibrates. This synergistic effect is induced by binding of BVC with PPAR-γ or -α (Chen *et al* ,2009).

Authors reported that the combination of PPAR-β/δ and PPAR-γ agonists has been shown to reduce insulin resistance, control glucose metabolism and improve exercise capacity; thus, BVC has glucose-lowering effects without weight gain and hepatotoxicity (Balakumar *et al*,2007).

IVA337

The IVA337 is a next-generation pan-PPAR agonist developed to produce moderate and well-balanced activation of the three PPAR isoforms (α, β/δ, and γ); and it displayed an anti-ϕıbrotic efϕıcacy superior to selective PPAR-α, PPAR-γ, or PPARβ/δ agonists; this particular agonist have a good efϕıcacy and safety proϕıle with no weight gain in pre-clinical models as well as in clinical phase 1 and 2 studies in patients with type 2 diabetes (Wettstein *et al,*2017).

Conclusion

The peroxisome proliferator-activated receptors (PPARs) are family of nuclear receptors and are set of three receptor sub-types: PPAR-α (NR1C1), PPAR-β/δ (NR1C2) and PPAR-γ (NR1C3) each encoded by distinct genes; and act as lipid sensors and can regulate a broad range of genes in many tissues such as liver, adipose tissue, and skeletal muscles. Each form of the PPARs is a therapeutic target that can be activated by natural and synthetic ligands, which may have beneficial effects on lipid profile and obesity.

References

Ahmed, I., K. Furlong, J Flood, V. P. Treat and B. J. Goldstein (2007) Dual PPAR α/γ agonists: promises and pitfalls in type 2 diabetes. *American journal of therapeutics.* **14(1)** : 49-62.

Azziz, R., D. Ehrmann, R. S. Legro, R. W. Whitcomb, R. Hanley, A. G. Fereshetian, M. O'Keefe, M. N. Ghazzi and PCOS/ Troglitazone Study Group (2001) Troglitazone improves ovulation and hirsutism in the polycystic ovary syndrome: a multicenter, double blind, placebo-controlled trial. *The Journal of clinical endocrinology and metabolism.* **86(4)** : 1626–1632.

Balakumar, P., M. Rose, S. S. Ganti, P. Krishan and M. Singh (2007) PPAR dual agonists: are they opening Pandora's Boxϕı. *Pharmacological Research.* **56(2)** : 91-98.

Bénardeau, A., J. Benz, A. Binggel, D. Blum, M. Boehringer, U. Grether and K. Püntener (2009) Aleglitazar, a new, potent, and balanced dual PPARα/γ agonist for the treatment of type II diabetes. *Bioorganic & Medicinal Chemistry Letters.* **19(9)** : 2468-2473.

Berger, J. and D. E. Moller (2002) The mechanisms of action of PPARs. *Annual review of medicine.* **53(1)** : 409-435.

Braissant. O., F. Foufelle, C. Scotto, M. Dauça and W. Wahli (1996) Differential expression of peroxisome proliferator-activated receptors (PPARs): tissue distribution of PPAR-alpha,-beta, and-gamma in the adult rat. *Endocrinology* **137(1)** : 354-366.

Chen, Q. and Y. Zhu (2009) The effects of traditional Chinese medicine compound on diabetes. *Chin J Med Guid.* **11** : 81–84.

Cobb, J. E., Blanchard S G, Boswell E G, Brown K K, Charifson P S, Cooper J P and Lake D H (1998) N-(2-Benzoylphenyl)-l-tyrosine PPARγ agonists. 3. Structure- activity relationship and optimization of the N-aryl substituent. Journal of medicinal chemistry **41(25)** : 5055-5069.

Fan, W., W. Waizenegger, C. S. Lin, V. Sorrentino, M. X. He, C. E. Wall and J. Auwerx (2017) PPARδ promotes running endurance by preserving glucose. *Cell metabolism.* **25(5)** : 1186-1193.

Farnier, M. (2008) Update on the clinical utility of fenofibrate in mixed dyslipidemias: mechanisms of action and rational prescribing. *Vascular health and risk management.* **4(5)** : 991.

Fernandes-Santos, C., R. E. Carneiro, L. de Souza Mendonca, M. B. Aguila and C. A. Mandarim-de-Lacerda (2009) Pan-PPAR agonist beneficial effects in overweight mice fed a high-fat high-sucrose diet. *Nutrition.* **25(7-8)** : 818-827.

Grygiel-Górniak, B. (2014) Peroxisome proliferator-activated receptors and their ligands: nutritional and clinical implications-a review. *Nutrition journal.* **13(1)** : 17.

Hamblin, M., L. Chang, Y. Fan, J. Zhang and Y. E. Chen (2009) PPARs and the cardiovascular system. *Antioxidants &*

redox signaling. **11(6)** : 1415-1452.

Hansen, B. C., X. T. Tigno, A. Bénardeau, M. Meyer, E. Sebokova and J. Mizrahi (2011) Effects of aleglitazar, a balanced dual peroxisome proliferator-activated receptor a/ϕι agonist on glycemic and lipid parameters in a primate model of the metabolic syndrome. *Cardiovascular Diabetology*. **10(1)** : 7.

Henke, B. R., S. G. Blanchard, M. F. Brackeen, K. K. Brown, J. E. Cobb, J. L. Collins and S. A. Kliewer (1998) N-(2-benzoylphenyl)-L-tyrosine PPARγ agonists. 1. Discovery of a novel series of potent antihyperglycemic and antihyperlipidemic agents. *Journal of medicinal chemistry*. **41(25)** : 5020-5036.

Henry, R. R., A. M. Lincoff, S. Mudaliar, M. Rabbia, C. Chognot and M. Herz (2009) Effect of the dual peroxisome proliferator-activated receptor-α/γ agonist aleglitazar on risk of cardiovascular disease in patients with type 2 diabetes (SYNCHRONY): a phase II, randomised, dose-ranging study. *The Lancet*. **374(9684)** : 126-135.

Holst, D., S. Luquet, V. Nogueira, K. Kristiansen, X. Leverve and P. A. Grimaldi (2003) Nutritional regulation and role of peroxisome proliferator-activated receptor d in fatty acid catabolism in skeletal muscle. *Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids*. **1633(1)** : 43-50.

Hong, F., P. Xu and Y. Zhai (2018) The opportunities and challenges of peroxisome proliferator-activated receptors ligands in clinical drug discovery and development. *International Journal of Molecular Sciences*. **19(8)** : 2189.

Hulin, B., P. A. McCarthy and E. M. Gibbs (1996) The glitazone family of antidiabetic agents. *Current Pharmaceutical Design*. **2(1)** : 85-102.

Ide, T., H. Shimano, T. Yoshikawa, N. Yahagi, M. Amemiya-Kudo, T. Matsuzaka and K. Ohashi (2003) Cross-talk between peroxisome proliferator-activated receptor (PPAR) α and liver X receptor (LXR) in nutritional regulation of fatty acid metabolism. II. LXRs suppress lipid degradation gene promoters through inhibition of PPAR signaling. *Molecular Endocrinology*. **17(7)** : 1255-1267.

Iglesias, J., S. Barg, D.Vallois, S. Lahiri, C. Roger, A. Yessoufou and F. Gribble (2012) PPAR β/δ affects pancreatic ß cell mass and insulin secretion in mice. *The Journal of clinical investigation*. **122(11)** : 4105-4117.

Kersten, S., J. Seydoux, J. M. Peters, F. J. Gonzalez, B. Desvergne and W. Wahli (1999) Peroxisome proliferator–activated receptor α mediates the adaptive response to fasting. *The Journal of clinical investigation*. **103(11)** : 1489-1498.

Kim, J. H., J. Song and K. W. Park (2015) The multifaceted factor peroxisome proliferator-activated receptor γ (PPARγ) in metabolism, immunity, and cancer. *Archives of pharmacal research*. **38(3)** : 302-312.

Laganà, A. S., S. G. Vitale, A. Nigro, V. Sofo, F. M. Salmeri, P. Rossetti and M. Buscema (2016) Pleiotropic actions of peroxisome proliferator-activated receptors (PPARs) in dysregulated metabolic homeostasis, inflammation and cancer: Current evidence and future perspectives. *International journal of molecular sciences*. **17(7)** : 999.

Lincoff, A. M., J. C. Tardif, G. G. Schwartz, S. J. Nicholls, L. Rydén, B. Neal and A. Weichert (2014) Effect of aleglitazar on cardiovascular outcomes after acute coronary syndrome in patients with type 2 diabetes mellitus: the AleCardio randomized clinical trial. *Jama*. **311(15)** : 1515-1525.

Luquet, S., C. Gaudel, D. Holst, J. Lopez-Soriano, C. Jehl-Pietri, Fredenrich and P. A. Grimaldi (2005) Roles of PPAR delta in lipid absorption and metabolism: a new target for the treatment of type 2 diabetes. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*. **1740(2)** : 313-317.

Marx, N., N. Mackman, U. Schönbeck, N. Yilmaz, V. Hombach, P. Libby and J. Plutzky (2001) PPARalpha activators inhibit tissue factor expression and activity in human monocytes. *Circulation*. **103(2)** : 213–219.

Michalik, L., J. Auwerx, J. P. Berger, V. K. Chatterjee, C. K. Glass, F. J. Gonzalez and C. N. Palmer (2006) International Union of Pharmacology. LXI. Peroxisome proliferator-activated receptors. *Pharmacological reviews*. **58(4)** : 726-741.

Mukherjee, R., L. Jow, G. E. Croston and J. R. Paterniti (1997) Identification, characterization, and tissue distribution of human peroxisome proliferator-activated receptor (PPAR) isoforms PPARγ2 versus PPARγ1 and activation with retinoid X receptor agonists and antagonists. *Journal of Biological Chemistry*. **272(12)** : 8071-8076.

Oliver, W. R., J. L. Shenk, M. R. Snaith, C. S. Russell, K. D. Plunket, N. L. Bodkin and H. E. Xu (2001) A selective peroxisome proliferator-activated receptor δ agonist promotes reverse cholesterol transport. *Proceedings of the national academy of sciences*. **98(9)** : 5306-5311.

Park, Y. K., L. Wang, A. Giampietro, B. Lai, J. E. Lee and K. Ge (2017) Distinct roles of transcription factors KLF4, Krox20, and peroxisome proliferator-activated receptor γ in adipogenesis. *Molecular and cellular biology*. **37(2)**.

Rachid, T. L., A. Penna-de-Carvalho, I. Bringhenti, M. B. Aguila, C. A. Mandarim-de-Lacerda and V. Souza-Mello (2015) PPAR-α agonist elicits metabolically active brown adipocytes and weight loss in diet-induced obese mice. *Cell biochemistry and function*. **33(4)** : 249-256.

Sher, T., H. F. Yi, O. W. McBride and F. J. Gonzalez (1993) cDNA cloning, chromosomal mapping, and functional characterization of the human peroxisome proliferator activated receptor. *Biochemistry*. **32(21)** : 5598-5604.

Spiegelman, B. M. (1998). PPAR-gamma: adipogenic regulator and thiazolidinedione receptor. *Diabetes*. **47(4)** : 507-514.

Staels, B. and J. C. Fruchart (2005) Therapeutic roles of peroxisome proliferator–activated receptor agonists. *Diabetes*. **54(8)** : 2460-2470.

Stout, D. L. and S. E. Fugate (2005) Thiazolidinediones for treatment of polycystic ovary syndrome. Pharmacotherapy: *The Journal of Human Pharmacology and Drug Therapy*. **25(2)** : 244-252.

Tenenbaum, A., E. Z. Fisman, V. Boyko, M. Benderly, D. Tanne, M. Haim and S. Behar (2006) Attenuation of progression of insulin resistance in patients with coronary artery disease by bezafibrate. *Archives of internal medicine*. **166(7)** : 737-741.

Tenenbaum, A., M. Motro and E. Z. Fisman (2005). Dual and pan-peroxisome proliferator-activated receptors (PPAR) co-agonism: the bezafibrate lessons. *Cardiovascular Diabetology*. **4(1)** : 14.

Tsuchida, A., T. Yamauchi, S. Takekawa, Y. Hada, Y.Ito, T. Maki and T. Kadowaki (2005) Peroxisome proliferator–activated receptor (PPAR) α activation increases adiponectin receptors and reduces obesity-related inflammation in adipose tissue: comparison of activation of PPARa, PPARφι, and their combination. *Diabetes*. **54(12)** : 3358-3370.

W.H.O. cooperative trial on primary prevention of ischaemic heart disease using clofibrate to lower serum cholesterol: mortality follow-up. Report of the Committee of Principal Investigators (1980). *Lancet* (London, England). **2(8191)** : 379–385.

Watts, G. F. and S. B. Dimmitt (1999) Fibrates, dyslipoproteinaemia and cardiovascular disease. *Current opinion in lipidology*. **10(6)** : 561-574.

Wettstein, G., J. M. Luccarini, L. Poekes, P. Faye, F. Kupkowski, V. Adarbes and A. Philippot (2017) The new-generation pan-peroxisome proliferator-activated receptor agonist IVA337 protects the liver from metabolic disorders and fibrosis. *Hepatology communications*. **1(6)** : 524-537.

Willson, T. M., P. J. Brown, D. D. Sternbach and B. R. Henke (2000) The PPARs: from orphan receptors to drug discovery. *Journal of medicinal chemistry*. **43(4)** : 527-550.

Xu, M., X. Zuo and I. Shureiqi (2013) Targeting peroxisome proliferator-activated receptor-β/δ in colon cancer: how to aimφι. *Biochemical pharmacology*. **85(5)** : 607-611.

Xu, P., Y. Zhai and J. Wang (2018) The role of PPAR and its cross-talk with car and lxr in obesity and atherosclerosis. *International journal of molecular sciences*. **19(4)** : 1260.