Journal of Stress Physiology & Biochemistry, Vol. 19, No. 4, 2023, pp. 163-177 ISSN 1997-0838

REVIEW

PPAR gamma Agonists – Plant Compounds

Anil Kumar Moola [1], Shobana G. [2] and C. Janani [3]*

[1] *Department of Biotechnology, Aditya Degree College, Lakshmi Narayana Nagar, Kakinada, Andhra Pradesh, India - 533 003*

[2] *Department of Biochemistry, Srimad Andavan Arts and Science College, Tiruchirappalli,. Tamil Nadu, India - 622 005*

[3] *Department of Biotechnology, Srimad Andavan Arts and Science College, Tiruchirappalli,. Tamil Nadu, India – 622 005*

*E-Mail: ***janabio.net@gmail.com***

Received August 17, 2023

The nuclear receptor peroxisome proliferator activated receptor-gamma (PPARg) controls adipocyte differentiation, as well as lipid metabolism and insulin sensitivity. As a result, PPARg is a promising candidate gene for a variety of human diseases, such as obesity and type 2 diabetes. Hyperglycemia associated with the metabolic syndrome and type 2 diabetes is treated with agonists of the nuclear receptor PPARg. The PPARg agonists of the thiazolidinedione type, despite being effective in normalizing blood glucose levels, have serious side effects, making the discovery of novel ligands extremely important . Natural products have historically proven to be a promising source of structures for drug development, and recent research has focused on the PPARg-activating potential of a wide range of natural products derived from traditionally used medicinal plants or dietary sources. This review highlights recent studies that have advanced our understanding of this receptor's role in metabolism, with a focus on the effects of compounds in the plant

Key words: PPAR gamma, type 2 diabetes, natural products

Diabetes is a chronic disease that affects a large number of people around the world. It happens when the pancreas doesn't produce enough insulin or when the body can't use the insulin it does produce effectively. Many metabolic changes (obesity, lipid profile, and hypertension) are involved in the etiology of the disease, all of which have a variable impact on the disease's progression. Having the ability to genetically influence diabetes will greatly aid in the proper production of therapeutics and, eventually, the prevention of disease complications, progression, and development. The most common type of diabetes, Type 2 Diabetes Mellitus (T2D), is a complex metabolic disorder that affects 90 percent of diabetic patients worldwide.

Diabetes is a metabolic disease that has grown in importance in modern society as a result of the serious long-term health complications it causes. Type 2 diabetes mellitus (T2DM) has become a global epidemic in the twenty-first century, despite significant advancements in the understanding and management of this complex, multifactorial disease. Type 2 diabetes mellitus (T2DM) is the most common type of diabetes, accounting for over 80% of all cases (Berg *et al.*, 2002; Mlinar *et al.*, 2007; Coman *et al.*, 2012). Disturbances in glucose metabolism are major contributors to diabetes. The hormone responsible for glucose homeostasis is insulin, which is released by pancreatic -cells (Garrett and Grisham, 1999; Sesti, 2006). Insulin stimulates the uptake of glucose from the circulatory system by hepatocytes, myocytes, and adipocytes. Depending on the situation, glucose can be used as an energy source through glycolysis or stored as glycogen in muscle or liver cells. Insulin resistance is defined as the inability of cells to respond to normal levels of circulating insulin (Berg *et al.*, 2002), resulting in the onset of the disease.

Moderate wine intake has been correlated with decrease incidences of cardiovascular sicknesses, inflammation, and metabolic sicknesses which includes kind 2 diabetes, obesity, and excessive pressure in blood. We studied binding of ligands from exceptional wines to the peroxisome proliferator-activated receptor γ (PPARγ), a key component in glucose and lipid metabolism. Ellagic acid and epicatechin gallate (ECG) had been diagnosed with the aid of using fueloline chromatography and mass spectroscopy with inside the maximum lively wine division. They had an similarity to PPARγ much resembling that of the standard pharmaceutical agent rosiglitazone (Zoechling *et al.*, 2011).

Natural compounds may be viable alternatives or complements to currently available treatments for diabetes. They may even lower the disease's risk. A positive aspect is that large amounts can be consumed in everyday diets. A large number of plants and natural biomolecules have been studied for their anti-diabetic properties in the literature. Plants, for example, have been used to prevent diabetes-related conditions since antiquity (Soumyanath, 2006). The mechanism is frequently not fully understood, but more research is being done to better understand the mechanisms of action of various plants and natural compounds. The role of medicinal plants and their active constituents for anti-diabetic agents is discussed in this study. The importance of diabetes management, reducing risks, and using anti-diabetic drugs was also stressed in this research. These extracts/compounds' detailed action mechanisms for their actions are also identified.

Antioxidant Effects in plants

A variety of phytochemicals (phenols, terpenoids, nitrogen-containing alkaloids, and sulphur-containing compounds) present in plants have been linked to anti-diabetic properties (Gothai *et al.*, 2016). Phenolic compounds have been linked to changes in inflammatory behavior (CRP, IL-6, IL-1, and TNF-), transpiration factor enzymes (NF-B, PPAR), and genes associated with T2DM (Anuradha 2013). Ginger (Zingiber officinale Roscoe) remains used as an essential cooking spice and natural remedy across the world. Gingerols, the main smelly additives of ginger, are recognised to enhance diabetes, together with the impact of enhancement towards insulin sensitivity. (Priya *et al.*, 2011)

Researchers have looked at the antioxidant and anti-diabetic effects of various plant sections (Kim *et al.*, 2011; Priya *et al.*, 2011; Unuofin, *et al.*, 2018; Unuofin and Lebelo, 2020). Such antioxidants found in the human body, such as glutathione and thioredoxin, mop up ROS

by donating reducing counterparts to free radicals in the shape of a hydrogen atom or an electron, rendering them less dangerous in the body environment. In relation to T2DM therapy, some plant-derived compounds have been ascribed the following properties: stimulate the ERK1/2 and AMPK pathways (Yang *et al.*, 2009; Ohno *et al.*, 2013; Ahad *et al.*, 2014). downregulate COX-2 gene expression, resulting in enhanced proinflammatory mediator liberation (Prabhakar, *et al.*, 2013; Guo, *et al.*, 2014) Increase glucose resistance and insulin sensitivity (Choi, *et al.*, 1991; Tsai, *et al.*, 2012); reduce inflammatory cell influx (Li *et al.*, 2009); lower serum levels of proinflammatory cytokines IL-1, IL-6, and TNF-; inhibit NF-B pathway activation (Ahad *et al.*, 2014) and repress macrophage chemostatic protein (MCP-1) and ICAM expression (Kumar *et al.*, 2013) Figure 1 illustrates the possible antioxidant activity of plant secondary metabolites in the T2DM pathway caused by oxidative stress Via ROS/RNS, oxidative stress findings in diabetes were affected with Insulin resistance.

Antioxidants present in natural phytocompounds have received a lot of attention recently, and they're already being used therapeutically to clean up reactive organisms and avoid oxidative stress-related diabetes. Insulin tolerance, beta cell dysfunction, and insulin secretion are all caused by oxidative stress in diabetics, which can be modulated by phytocompounds with high antioxidant capacity by controlling blood sugar levels or attenuating at least one of the mechanisms linked to insulin resistance: beta cell activity, glucose (re)absorption, and incretin-related pathways (Unuofin and Lebelo 2020).

In a cell culture model of rat adipocytes the treatment of anthocyanins PPAR gamma and target adipocyte specific genes (LPL, aP2, and UCP2) were significantly up-regulated. Leptin and adiponectin as well as their mRNA levels were also increased by anthocyanins resulting from the increased phosphorylated MAPK. The mechanisms of action of anthocyanins in the amelioration of obesity can be mediated by upregulation of the thermogenic mithocondrial uncoupling protein 2 (UCP-2) and the lipolytic enzyme hormone sensitive lipase (HSL) as well as by down-regulation of the nuclear factor plasminogen activator inhibitor-1 (PAI-1) (Jayaprakasam *et al.*, 2005). Some of the previous findings have been also discovered in human adipocytes treated with anthocyanins (Tsuda *et al.*, 2006). Further studies using a diabetic mouse model KK-Ay-mice have shown similar differences after anthocyanin and cyanidin- 3-glucoside administration. Gene expression of TNF-a and MCP-1 in mesenteric WAT was decreased and GLUT-4 increased, while a novel potential target gene retinol binding protein-4 was significantly decreased by 2 g/kg anthocyanin. in diet. The anthocyanin treatment enhanced the energy expenditure related genes UCP-2 and adiponectin and downregulation of PAI-1 that is induced by IL-6 in obese subjects, which suggests that also anti-inflammatory mechanisms of anthocyanins are involved (Moskaug *et al.*, 2004; Abahusian *et al.*, 1993)

Following food intake, lipid-derived ligands such as unsaturated fatty acids bind to this nuclear receptor, which causes the expression of a large number of genes involved in metabolism. PPARs have been shown to interact with structurally unrelated natural products such as flavonoids, polyphenols (e.g., resveratrol), and organic acids such as punicic acid or abscisic acid in micromolar concentrations (Huang *et al.*, 2005; Hontecillas *et al.*, 2009; Guri *et al.*, 2007). However, due to interactions with a number of other proteins, these molecules do not appear to have clear beneficial molecular or physiological in vivo effects, making further development of these compounds difficult. The antidiabetic thiazolidinediones (TZDs), which include the commonly used medication rosiglitazone (Avandia), stimulate PPAR powerfully. These PPAR activators have recently come under fire due to negative clinical side effects (Anonymous 2010) such as weight gain and other disorders (Rosen 2010).

Nuclear Receptor (PPAR) within the broader nuclear receptor superfamily, PPAR is the third member of a subdivision that also includes PPAR and PPAR (Willson *et al.*, 2000). The name PPAR comes from the discovery that a structurally diverse array of compounds that activate PPAR, the family's first member to be cloned, also increases the size and number of peroxisomes in rodent liver (Issemann & Green, 1990). The fibrate class of lipid-lowering drugs has been shown to target PPAR, which is highly expressed in the liver, kidney, heart, and skeletal muscle. In humans, however, these agents do not promote the proliferation of peroxisomes (Bentley *et al.*,

1993; Ashby *et al.*, 1994). Although recent studies have suggested that it may be an important regulator of cholesterol trafficking in macrophages, little is known about the physiological role(s) of PPAR, which is expressed in many tissues (Braissant *et al.*, 1996).

In the decade since it was first cloned (Zhu *et al.*, 1993), however, an extensive body of literature relating to the biology of PPAR has emerged. Three mRNA isoforms are produced by different promoter usage and alternate splicing of the gene: PPAR1 and PPAR3 mRNA encode the same protein product; the PPAR2 isoform has an additional 28 amino acids at its N-terminus. PPAR1 is widely expressed, albeit at low levels, in adipose tissue, whereas PPAR2 and PPAR3 are highly expressed. Indeed, the receptor is important for fat cell differentiation, as it promotes the formation of mature lipid-laden adipocytes by inducing the expression of adipocyte-specific genes and inducing the expression of adipocyte-specific genes (Tontonoz *et al.*1995; Ntambi and Young-Cheul 2000; Janani *et al.*, 2019).

Recent studies with mice genetically engineered to lack PPAR have confirmed its critical role in the development of both white and brown adipocytes in vivo (Barak *et al.*, 1999; Kubota *et al.*, 1999; Rosen *et al.*, 1999; Janani and Ranjitha Kumari 2017), and clinical phenotypes of patients with PPAR gene mutations suggest a similar role in the regulation of human adipose tissue mass (Chatterjee, 2000; Agarwal & Garg, 2002; Hegele *et al.*, 2002).

Role in Type II Diabetes Mellitus

The thiazolidinediones (TZDs) are synthetic compounds that can normalize elevated plasma glucose levels in obese, diabetic rodents and may be efficacious therapeutic agents for the treatment of noninsulin-dependent diabetes mellitus (Christensen *et al.*, 2009)

Thiazolidinediones are insulin sensitizing drugs that target the peroxisome proliferator-activated receptor (PPAR) γ. An n-hexane extract of the flowers of Echinacea purpurea was found to activate PPARγ without stimulating adipocyte differentiation. Bioassay-guided fractionations yielded five alkamides, of which one was new, and three fatty acids that all activated PPARγ. The new alkamide hexadeca-2E,9Z,12Z,14E-tetraenoic acid isobutylamide (5) was identified by analysis of spectroscopic data and found to activate PPARγ with no concurrent stimulation of adipocyte differentiation. Compound five was further shown to increase insulin-stimulated glucose uptake. The data suggest that flowers of E. purpurea contain compounds with potential to manage insulin resistance and type 2 diabetes (Christensen *et al.*, 2009).

The use of TZDs to treat type-2 diabetes mellitus is complicated by systemic fluid retention. Guan *et al.* (2005) found that treatment of mice with amiloride, a collecting duct-specific diuretic, reversed the enhanced renal Na+ absorption, edema, and water weight gain caused by TZDs. Deletion of Pparg in mouse collecting duct blocked TZD-induced weight gain, decreased renal Na+ avidity, and increased plasma aldosterone. Treatment of cultured mouse collecting ducts with TZDs increased amiloride-sensitive Na+ absorption and Scnn1g (600761) mRNA expression through a Pparg-dependent pathway. Guan *et al.* (2005) concluded that SCNN1G is a PPARG target gene in the collecting duct and that activation of this pathway mediates fluid retention associated with TZDs.

Choi *et al.* (2010) showed that obesity induced in mice by high fat feeding activates the protein kinase CDK5 (123831) in adipose tissues. This results in phosphorylation of the nuclear receptor PPARG, a dominant regulator of adipogenesis and fat cell gene expression, at ser273. This modification of PPARG does not alter its adipogenic capacity, but leads to dysregulation of a large number of genes whose expression is altered in obesity, including a reduction in the expression of the insulin-sensitizing adipokine adiponectin (605441). The phosphorylation of PPARG by CDK5 is blocked by antidiabetic PPARG ligands such as rosiglitazone and MRL24. This inhibition works both in vitro and vivo, and is completely independent of classic receptor transcriptional agonism. Similarly, inhibition of PPARG phosphorylation in obese patients by rosiglitazone was very tightly associated with the antidiabetic effects of this drug. Choi *et al.* (2010) concluded that these results suggested that CDK5-mediated phosphorylation of PPARG may be involved in the pathogenesis of insulin resistance and presented an opportunity for development of an improved generation of antidiabetic drugs through PPARG.

Choi *et al.* (2011) described novel synthetic compounds that have a unique mode of binding to PPAR-gamma, completely lack classic transcriptional agonism, and block the Cdk5-mediated phosphorylation in cultured adipocytes and in insulin-resistant mice. Moreover, one such compound, SR1664, has potent antidiabetic activity without causing the fluid retention and weight gain that are serious side effects of many of the PPAR-gamma drugs. Also, unlike TZDs, SR1664 does not interfere with bone formation in culture. Choi *et al.* (2011) concluded that new classes of antidiabetes drugs can be developed by specifically targeting the Cdk5-mediated phosphorylation of PPAR-gamma. Dutchak *et al.* (2012) reported that FGF21 (609436) is an inducible, fed-state autocrine factor in adipose tissue that functions in a feed-forward loop to regulate the activity of PPAR-gamma. FGF21 knockout (KO) mice displayed defects in PPAR-gamma signaling including decreased body fat and attenuation of PPAR-gamma-dependent gene expression. Moreover, FGF21-KO mice were refractory to both the beneficial insulin-sensitizing effects and the detrimental weight d edema side effects of the PPAR-gamma agonist rosiglitazone. Δ9-tetrahydrocannabinol (THC), reasons acute vasorelaxation in diverse arteries. Here we display for the primary time that THC additionally reasons slowly growing vasorelaxation thru activation of peroxisome proliferator-activated receptors gamma (PPARγ). In vitro, THC (10 μM) triggered time-established vasorelaxation of rat remoted arteries. Time-established vasorelaxation to THC become just like that produced with the aid of using the PPARγ agonist rosiglitazone and become inhibited with the aid of using the PPARγ antagonist GW9662 (1 μM), however now no longer the cannabinoid CB1 receptor antagonist AM251 (1 μM). Time-established vasorelaxation to THC calls for an intact endothelium, nitric oxide, manufacturing of hydrogen peroxide, and de novo protein synthesis. This lack of characteristic in FGF21-KO mice become coincident with a marked boom withinside the sumoylation of PPAR-gamma, which reduces its transcriptional activity. Adding lower back FGF21 averted sumoylation and restored PPAR-gamma activity. Dutchak *et al.* (2012) concluded that FGF21 is a key mediator of the physiologic and pharmacologic movements of PPAR-gamma.

Jonker *et al.* (2012) diagnosed FGF1 (131220) as a important transducer withinside the manner of metabolic homeostasis via dinner party or famine in mice. Jonker *et al.* (2012) connected the law of FGF1 to the nuclear receptor PPAR-gamma. FGF1 is the prototype of the 22-member FGF own circle of relatives of proteins and has been implicated in a number of physiologic processes, consisting of development, wound healing, and cardiovascular changes. Surprisingly, FGF1 knockout mice displayed no extensive phenotype beneathneath wellknown laboratory conditions. Jonker *et al.* (2012) confirmed that FGF1 changed into incredibly prompted in adipose tissue in reaction to a high-fats weight-reduction plan and that mice missing FGF1 advanced an competitive diabetic phenotype coupled to aberrant adipose enlargement whilst challenged with a high-fats weight-reduction plan. Further evaluation of adipose depots in FGF1-poor mice discovered a couple of histopathologies withinside the vasculature network, an accentuated inflammatory reaction, aberrant adipocyte length distribution, and ectopic expression of pancreatic lipases. On withdrawal of the high-fats weight-reduction plan, this infected adipose tissue did not well resolve, ensuing in significant fats necrosis. In phrases of mechanisms, Jonker *et al.* (2012) confirmed that adipose induction of FGF1 withinside the fed kingdom is regulated via way of means of PPAR-gamma appearing via an evolutionarily conserved promoter-proximal PPAR reaction element (PPRE) withinside the FGF1 gene. The discovery of a phenotype for the FGF1 knockout mouse mounted the PPAR-gamma-FGF1 axis as important for retaining metabolic homeostasis and insulin sensitization.

These fundamental insights have culminated with TZDs being recently approved for use in the management of type 2 diabetes. Troglitazone, the first TZD in widespread clinical use, was withdrawn following concerns regarding its hepatotoxicity (Watkins & Whitcomb, 1998); subsequent studies have suggested, however, that this potentially fatal idiosyncratic adverse event is unlikely to be a class effect, but rather reflects the generation of a specific metabolite unique to troglitazone (Willson *et al.*, 2000).

Although originally synthesized as derivatives of clofibrate, unexpectedly the TZDs were found to exhibit

insulin-sensitizing actions in rodent models of T2DM as far back as the early 1980s, a finding that was later confirmed in man (1999). It is only relatively recently, however, that the molecular basis for this action has been elucidated. In the mid-1990s Kliewer and colleagues reported that TZDs function as selective high-affinity ligands for PPARγ (Lehmann *et al.*, 1995). Furthermore, the rank order of their potencies for receptor activation *in vitro* correlates closely with their glucose lowering activity *in vivo* (Berger *et al.*, 1996; Willson *et al.*, 1996). Taken together, these data strongly suggested PPARγ to be the molecular target for the antidiabetic actions of the TZDs. The therapeutic efficacy of the currently available TZDs is, however, limited, and several side-effects have been reported (Schoonjans & Auwerx, 2000). Accordingly, selective non-TZD PPARγ ligands (e.g. tyrosine agonists) have been developed and shown to exert potent antidiabetic effects in preclinical studies and early clinical trials (Fiedorek *et al.*, 2000; Willson *et al.*, 2000), whilst compounds that activate RXR (the heterodimeric partner for PPARγ) also improve insulin sensitivity *in vivo* (Mukherjee *et al.*, 1997), findings which support the contention that this receptor is indeed a key regulator of insulin action. Moreover, a unique chemically distinct PPARγ ligand, FMOC-L-leucine (F-L-Leu) has been reported to promote differential cofactor recruitment leading to a modified pattern of target gene activation, which promotes insulin sensitization, yet with less adipogenic activity than other PPARγ ligands (Rocchi *et al.*, 2001), a finding which has obvious attractions from the therapeutic standpoint.

Therefore studies have focused on their heterozygous littermates, who appear to exhibit greater insulin sensitivity in hyperinsulinaemic euglycaemic clamp studies (Miles *et al.*, 2000) and are protected against the development of insulin resistance when subjected to high fat feeding (Kubota *et al.*, 1999), as compared with their wild-type counterparts. At first glance these findings may appear counterintuitive, i.e. how can a reduction in PPARγ activity in heterozygous null mice protect against insulin resistance when PPARγ activators such as TZDs are potent insulin sensitizers. A reduction in PPARγ activity, due to heterozygous PPARγ deficiency, decreases the triglyceride content of white adipose tissue, skeletal muscle and liver (possibly as a consequence of enhanced leptin expression and fatty acid combustion), thereby ameliorating high fat diet-induced obesity and insulin resistance. Moreover, although heterozygous PPARγ deficiency and TZD treatment exert opposing effects on total white adipose tissue mass, the former also decreases lipogenesis, whereas the latter stimulates adipocyte differentiation and apoptosis, thereby both protecting against the development of adipocyte hypertrophy and, accordingly, alleviating insulin resistance (Yamauchi *et al.*, 2001).

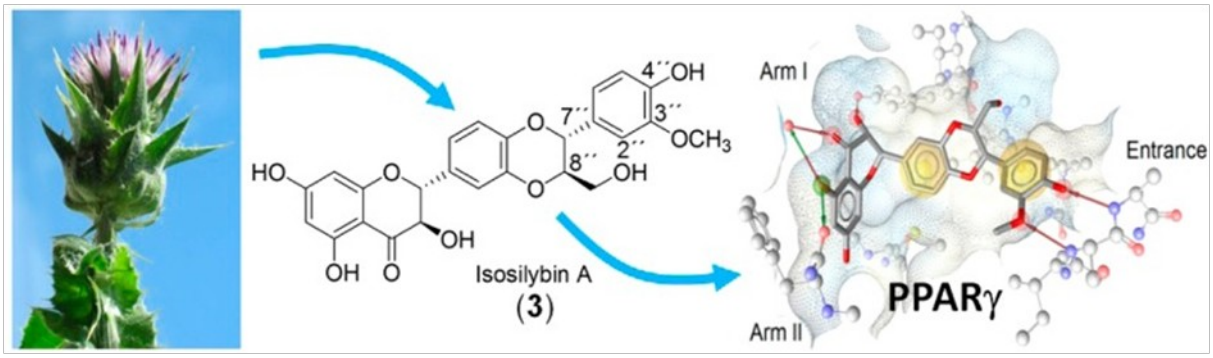
Additional proof of a key function for PPARγ in figuring out human adiposity has been furnished with the aid of using the identity of 4 unrelated German topics in whom a missense mutation at codon 115 (Pro115Gln) in PPARγ2 became observed to be related to extreme obesity (BMIs starting from 37 to forty seven kg/m2; Ristow *et al.*, 1998). With the previous expertise that phosphorylation of PPARγ2 at an adjoining serine residue (Ser114) had formerly been proven to lessen the capacity of the receptor to mediate adipocyte differentiation and lipid accumulation (Hu *et al.*, 1996; Adams *et al.*, 1997), the authors speculated that the Pro115Gln mutation would possibly impair such phosphorylation, main to a receptor with stronger transcriptional activity, adipogenic motion and consequently obesity. Indeed, overexpression of the mutant receptor in murine fibroblasts brought about multiplied differentiation of the cells into adipocytes and extra mobile accumulation of triglyceride whilst in comparison with the wild-kind receptor. Interestingly, the authors speculated that such an activating PPARγ mutation is probably anticipated to be related to much less insulin resistance than could commonly be predicted for the diploma of obesity. In help of this contention, they located that overweight topics bearing the Pro115Gln mutation had decrease fasting serum insulin concentrations than different overweight topics of their cohort. However, it ought to be mentioned that 3 in their affected people had already evolved T2DM, and a greater specific estimate of insulin resistance and beta cellular characteristic could be required to verify this hypothesis. Identification of isosilybin a from milk thistle seeds as an agonist of peroxisome proliferator-activated receptor gamma. Likewise some of the plant secondary metabolites

acts as agonist of PPARg expression were listed in Table 1.

Table. 1. PPAR gamma agonists

S.No	Name of the plant	Name of the Plant Family	Name of the compound	Mechanism of action of compound	References
1.	*Cannabis sativa*	Cannabaceae	Ajulemic acid Apigenin Chrysin Kaempferol	Agonist	Lee *et al.*, 2009 Liang *et al.*, 2001
2.	*Poria cocos* Wolf	Polyporaceae	Dehydrotrametenolic acid	Agonist	Sato *et al.*, 2002
3.	*Glycyrrhiza uralensis* Fisher	Fabaceae	Prenylflavonoid (*Glycycoumarin, glycyrin, dehydroglyasperin C and dehydroglyasperin D*	Agonist	Kuroda *et al.*, 2003
4.	*Saururus chinensis*	Saururaceae	Saurufuran	Agonist	Atanas *et al.*, 2013
5.	*Notopterygium incisum*	Apiaceae	Falcarindiol	Agonist	Hwang *et al.*, 2002
6.	Hydrangea macrophylla var. thunbergii	Hydrangeaceae	Hydrangeic acid	Agonist	Zhang *et al.*, 2009
7.	*Amorpha fruticosa* L.	Fabaceae	Amorfrutins	Agonist	Weidner *et al.*, 2012
8.	*Astragalus membranaceus*Moench	Fabaceae	Formononetin	Agonist	Shen *et al.*, 2006
9.	*Bixa orellana* L.	Bixaceae	Bixin and norbixin	Agonist	Takahashi *et al.*, 2009
10.	*Camellia sinensis* (L.) Kuntze	Theaceae	(−)-Catechin	Agonist	Shin *et al.*, 2009
11.	*Cannabis sativa*L.	Cannabaceae	Δ9-Tetrahydrocannabinol	Agonist	O'Sullivan *et al.*, 2005
12.	*Chromolaena odorata* (L.)	Asteraceae	(9*S*,13*R*)-12-Oxo-phytodienoic acid	Agonist	Dat *et al.*, 2009
13.	*Coix lacryma-jobi* var. *ma-yuen*	Poaceae	Hydroxy unsaturated fatty acids	Agonist	Yokoi *et al.*,2009
14.	*Cornus alternifolia* L.f.	Cornaceae	Kaempferol-3-*O*-*β*-glucopyranoside	Agonist	He *et al.*,2012
15.	*Commiphora mukul* (Hook. ex Stocks)	Burseraceae	Commipheric acid	Agonist	Cornick *et al.*, 2009
16.	*Cymbopogon citratus* (DC.) Stapf	Poaceae	Citral	Agonist	Katsukawa *et al.*, 2010
17.	*Echinacea purpurea* (L.) Moench	Asteraceae	Alkamides	Agonist	Christensen *et al.*, 2009
18.	*Elaeis guineensis* Jacq.	Arecaceae	Tocotrienols	Agonist	Fang *et al.*, 2010
19.	*Elephantopus scaber* L.	Asteraceae	Deoxyelephantopin	Agonist	Zou *et al.*,2008
20.	*Epimedium elatum* C. Morren & Decne.	Berberidaceae)	Acylated flavonol glycosides	Agonist	Tantry *et al.*, 2012
21.	*Euonymus alatus*(Thunb.) Siebold	Celastraceae	Kaempferol and quercetin	Agonist	Fang *et al.*, 2010
22.	*Glycine max* (L.) Merr.	Fabaceae	Genistein	Agonist	Dang *et al.*, 2003
23.	*Glycyrrhiza glabra* L.	Fabaceae	5′-Formylglabridin, (2*R*,3*R*)-3,4′,7-	Agonist	Kuroda *et al.*, 2010

			trihydroxy-3′-prenylflavane, echinatin, (3*R*)-2′,3′,7-trihydroxy-4′-methoxyisoflavan, kanzonol X, kanzonol W, shinpterocarpin, licoflavanone A, glabrol, shinflavanone, gancaonin L, glabrone		
24.	*Glycyrrhiza inflata* Batalin	Fabaceae	Licochalcone E	Agonist	Park *et al.*, 2012
25.	*Glycyrrhiza uralensis* Fisch. ex DC.	Fabaceae	Flavonoids and 3-arylcoumarins	Agonist	Kuroda *et al.*, 2003
26.	*Limnocitrus littoralis* (Miq.) Swingle	Rutaceae	Meranzin	Agonist	Do *et al.*, 2007
27.	*Magnolia officinalis* Rehder & E.H. Wilson	Magnoliaceae	Magnolol	Agonist	Choi *et al.*, 2009
28.	*Momordica charantia* L.	Cucurbitaceae	Cucurbitane-type triterpene glycoside	Agonist	Nhiem *et al.*, 2012
29.	*Notopterygium incisum* C.T. Ting ex H.T. Chang	Apiaceae	Polyacetylenes	Agonist	Atanasov *et al.*, 2013
30.	*Origanum vulgare* L.	Lamiaceae	Biochanin A	Agonist	Mueller *et al.*, 2008
31.	*Panax ginseng*C.A. Mey.	Araliaceae	Ginsenoside 20(*S*)-protopanaxatriol	Agonist	Han *et al.*, 2006
32.	*Pseudolarix amabilis* (J. Nelson) Rehder	Pinaceae	Pseudolaric acid B	Agonist	Jaradat *et al.*, 2002
33.	*Robinia pseudoacacia*var. *umbraculifer* DC.	Fabaceae	Amorphastilbol	Agonist	Kim *et al.*,2012
34.	*Pueraria thomsonii* Benth.	Fabaceae	Daidzein	Agonist	Shen *et al.*, 2006
35.	*Sambucus nigra*L.	Adoxaceae	α-Linolenic acid, linoleic acid, and naringenin	Agonist	Christensen etal .,2010
36.	*Silybum marianum* (L.) Gaertn.	Asteraceae	Isosilybin A	Agonist	Pferschy-Wenzig *et al.*, 2014
37.	*Terminalia bellerica* Roxb.	Combretaceae	Gallotannins	Agonist	Yang *et al.*, 2013
38.	*Thymus vulgaris*L.	Lamiaceae	Carvacrol	Agonist	Hotta *et al.*, 2010
39.	*Vitis vinifera* L.	Vitaceae	Ellagic acid, epicatechin gallate	Agonist	Zoechling *et al.*, 2011
40.	*Wolfiporia extensa* (Peck) Ginns	Polyporaceae	Dehydrotrametenolic acid	Agonist	Sato *et al.*, 2002
41.	*Zingiber officinale*Roscoe	Zingiberaceae	6-Shogaol	Agonist	Isa *et al.*, 2008
42.	*Pistacia lentiscus* L.	Anacardiaceae	Oleanonic acid	Agonist	Petersen *et al.*, 2011
43.	*Piper chaba*	Piperaceae	Retrofractamide A	Agonist	Mourad *et al.*, 2013
44.	*Kaempferia parviflora*	Zingiberaceae	Methoxyflavonols	Agonist	Matsuda *et al.*, 2011
45.	*Stevia rebaudiana*	Asteraceae	Austroinulin	Agonist	Metibemu *et al.*, 2017



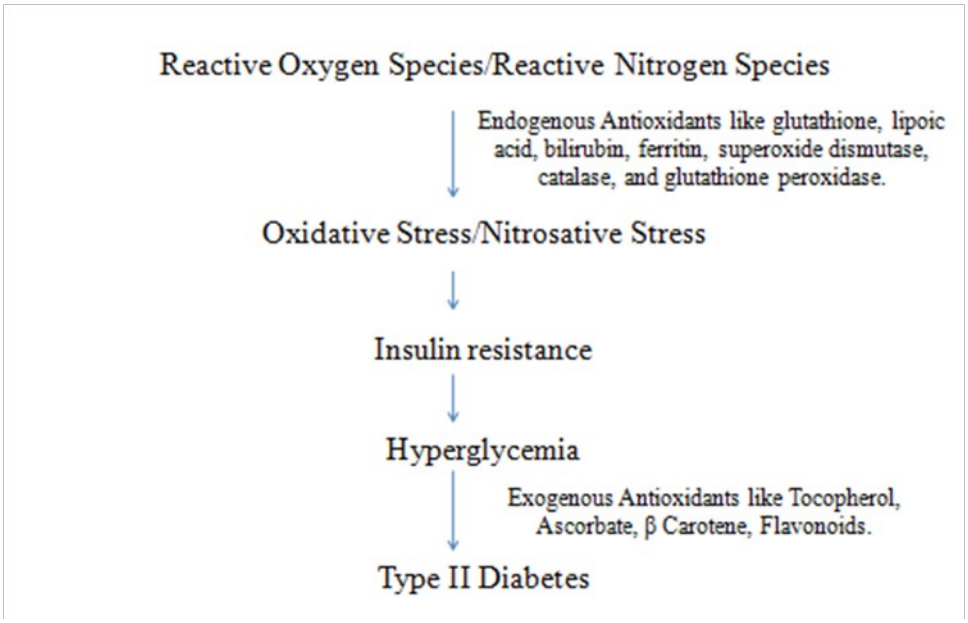


Figure. 1. Potential of antioxidants in Type II Diabetes

CONCLUSION

The study of the reviewed information of the numerous PPAR gamma will become obvious that, despite the fact that those dealers are classed collectively in keeping with their important PPAR target, they have got very unique and on occasion conflicting scientific benefit and unfavorable occasion profiles. It is speculated that that is due to their unique residences and specificities for the unique PPAR receptors (every of which goals specific genes). The maximum placing is the conflicting kind 2 diabetes. In scientific practice, PPAR-a agonists, consisting of the fibrates, enhance dyslipidaemia, even as the PPAR-γ agonists, consisting of the plant secondary metabolites will enhance insulin resistance and diabetes.

CONFLICT OF INTERESTS

The authors declare that they have no potential conflicts of interest.

REFERENCES

Abahusian MA, Wright J, Dickerson JWT and Vol EB (1993) Retinol, a-tocopherol and carotenoids in diabetes. *Eur J Clin Nutr* 53, 630–635.

Agarwal, A.K. and Garg, A. (2002) A novel heterozygous mutation in peroxisome proliferator-activated receptor-γ gene in a patient with familial partial lipodystrophy. *Journal of Clinical Endocrinological Metabolism*, 87, 408–411.

Ahad, A. Ganai, A. A. Mujeeb, M. and Siddiqui, W. A. (2014) Chrysin, an anti-inflammatory molecule, abrogates renal dysfunction in type 2 diabetic rats. *Toxicology and Applied Pharmacology*, 279, 1, 1–7,.

Ahad, A. Mujeeb, M. Ahsan, H. and Siddiqui W. A. (2014). Prophylactic effect of baicalein against renal dysfunction in type 2 diabetic rats. *Biochimie*, 106, 101–110.

Anonymous (2010) Regulators restrict Avandia in the US and suspend it in the EU. *Nat Rev Drug Discov* 9, 828–828.

Anuradha, C. V. (2013). Phytochemicals targeting genes relevant for type 2 diabetes. *Canadian Journal of Physiology and Pharmacology*, 91, 6, 397–411.

Ashby J, Brady A, Elcombe CR, Elliott BM, Ishmael J, Odum J, Tugwood JD, Kettle S, Purchase IF. (1994). Mechanistically-based human hazard assessment of peroxisome proliferator-induced hepatocarcinogenesis. *Hum Exp Toxicol* 13 Suppl 2: S1–117.

Atanasov A.G., Blunder M., Fakhrudin N., Liu X., Noha S.M., Malainer C. 2013. Polyacetylenes from *Notopterygium incisum*--new selective partial agonists of peroxisome proliferator-activated receptor-gamma. *PLoS One.* 8, e61755.

Barak Y, Nelson MC, Ong ES, Jones YZ, Ruiz-Lozano P, Chien KR, Koder A, Evans RM (1999) PPARγ is required for placental, cardiac, and adipose tissue development. *Mol Cell* 4, 585–595.

Bentley P, Calder I, Elcombe C, Grasso P, Stringer D, Wiegand HJ. (1993). Hepatic peroxisome proliferation in rodents and its significance for humans. *Food Chem Toxicol* 31, 857–907.

Berg JM, Tymoczko JL, Stryer L (2002). Biochemistry, 5th Ed. W. H. Freeman and Company, New York.

Braissant OL, Foufelle F, Scotto CH, Dauça MI, Wahli WA. (1996) Differential expression of peroxisome proliferator-activated receptors (PPARs): tissue distribution of PPAR-alpha,-beta, and-gamma in the adult rat. *Endocrinology*. 137(1), 354-66.

Chang, C. L. T. Lin, Y. Bartolome, A. P. Chen, Y. C. Chiu, S. C. and Yang, W. C. (2013) Herbal therapies for type 2 diabetes mellitus: chemistry, biology, and potential application of selected plants and compounds. Evidence-based Complementary and Alternative Medicine. 2013, 1-33.

Chatterjee, V.K.K. (2000) Resistance to thyroid hormone, and peroxisome proliferator activated receptor γ resistance. *Biochemistry Society of Transactions*, 29, 227–231.

Choi JH, Banks AS, Estall JL, Kajimura S, Boström P, Laznik D, Ruas JL, Chalmers MJ, Kamenecka TM, Blüher M, Griffin PR. (2010). Anti-diabetic drugs inhibit obesity-linked phosphorylation of PPARγ by Cdk5. *Nature*. 466(7305), 451-6.

Choi JH, Banks AS, Kamenecka TM, Busby SA, Chalmers MJ, Kumar N, Kuruvilla DS, Shin Y, He Y, Bruning JB, Marciano DP. (2011) Antidiabetic actions of a non-agonist PPARγ ligand blocking Cdk5-mediated phosphorylation. *Nature*. 477(7365), 477-81.

Choi, J. Yokozawa, T. and Oura, H. (1991). Improvement of hyperglycemia and hyperlipemia in streptozotocin-diabetic rats by a methanolic extract of Prunus davidiana stems and its main component, prunin. *Planta Medica*, 57, 3, 208– 211.

Choi S.S., Cha B.Y., Lee Y.S., Yonezawa T., Teruya T., Nagai K. (2009) Magnolol enhances adipocyte differentiation and glucose uptake in 3T3-L1 cells. *Life Sci.* 84, 908–914.

Christensen K.B., Petersen R.K., Kristiansen K., Christensen L.P. (2010) Identification of bioactive compounds from flowers of black elder (Sambucus nigra L.) that activate the human peroxisome proliferator-activated receptor (PPAR) gamma. *Phytother Res.* 24(Suppl 2), S129–S132.

Christensen K.B., Petersen R.K., Petersen S., Kristiansen K., Christensen L.P. (2009). Activation of PPARgamma by metabolites from the flowers of purple coneflower (Echinacea purpurea) *J Nat Prod.* 72, 933–937.

Christensen KB, Petersen RK, Petersen S, Kristiansen K, Christensen LP. (2009) Activation of PPARγ by metabolites from the flowers of purple coneflower (Echinacea purpurea). *Journal of natural products.* 72(5), 933-937.

Coman C, Rugina OD, Socaciu C. (2012). Plants and natural compounds with antidiabetic action. *Notulae Botanicae Horti Agrobotanici Cluj-Napoca*. 40(1), 314-325.

Cornick C.L., Strongitharm B.H., Sassano G., Rawlins C., Mayes A.E., Joseph A.N. (2009). Identification of a novel agonist of peroxisome proliferator-activated receptors alpha and gamma that may contribute to

the anti-diabetic activity of guggulipid in Lep(ob)/Lep(ob) mice. *J Nutr Biochem.* 20, 806–815.

Dang Z.C., Audinot V., Papapoulos S.E., Boutin J.A., Lowik C.W. (2003). Peroxisome proliferator-activated receptor gamma (PPARgamma) as a molecular target for the soy phytoestrogen genistein. *J Biol Chem.* 278, 962–967.

Dat N.T., Lee K., Hong Y.S., Kim Y.H., Minh C.V., Lee J.J. (2009). A peroxisome proliferator-activated receptor-gamma agonist and other constituents from Chromolaena odorata. *Planta Medica.* 75, 803–807.

Do Q.T., Lamy C., Renimel I., Sauvan N., Andre P., Himbert F. (2007). Reverse pharmacognosy: identifying biological properties for plants by means of their molecule constituents: application to meranzin. *Planta Medica.* 73, 1235–1240.

Dutchak PA, Katafuchi T, Bookout AL, Choi JH, Ruth TY, Mangelsdorf DJ, Kliewer SA. (2012). Fibroblast growth factor-21 regulates PPARγ activity and the antidiabetic actions of thiazolidinediones. *Cell*. 148(3), 556-567.

Fakhrudin N., Ladurner A., Atanasov A.G., Heiss E.H., Baumgartner L., Markt P. (2010). Computer-aided discovery, validation, and mechanistic characterization of novel neolignan activators of peroxisome proliferator-activated receptor gamma. *Mol Pharmacol.* 77, 559–566.

Fang F., Kang Z., Wong C. (2010). Vitamin E tocotrienols improve insulin sensitivity through activating peroxisome proliferator-activated receptors. *Mol Nutr Food Res.* 54,, 345–352.

Fiedorek, F.T., Wilson, G.G., Frith, L., Patel, J. & Abou-Donia, M. (2000) Monotherapy with G1262570, a tyrosine-based non-thiazolidinedione PPARγ agonist, improves metabolic control in type 2 diabetes mellitus patients. *Diabetes*, 49 (Suppl. 1), Abstract 157-OR.

Garrett RH, Grisham CM (1997). Biochemistry, 2nd Ed. Harcourt Brace College Publishers, Orlando, Florida.

Gothai, S. Ganesan, P. Park, S Y.. Fakurazi, S. Choi, D. K. and Arulselvan, P. (2016). Natural phyto-bioactive compounds for the treatment of type 2 diabetes: inflammation as a target. *Nutrients*,. 8. 8, 461.

Guan, Y. Hao, C. Cha D. R. (2005). Thiazolidinediones expand body fluid volume through PPAR*y* stimulation of ENaC-mediated renal salt absorption. *Nature Medicine*, 11, 8, 861–866.

Guo, R. Liu, B. Wang, K. S. Zhou, W. Li, and Y. Xu, (2014). Resveratrol ameliorates diabetic vascular inflammation and macrophage infiltration in db/db mice by inhibiting the NF-*κ*B pathway. *Diabetes and Vascular Disease Research*, 11, 2,. 92–102.

Guri AJ, *Hontecillas* R, Si H, Liu D, Bassaganya-Riera J (2007) Dietary abscisic acid ameliorates glucose tolerance and obesity-related inflammation in db/db mice fed high-fat diets. *Clin Nutr* 26, 107–116.

Han K.L., Jung M.H., Sohn J.H., Hwang J.K. (2006) Ginsenoside 20S-protopanaxatriol (PPT) activates peroxisome proliferator-activated receptor gamma (PPARgamma) in 3T3-L1 adipocytes. *Biol Pharmaceut Bull.* 29, 110–113.

Hegele, R.A., Henian, C., Frankowski, C., Mathews, S.T. & Leff, T. (2002) PPARG F388L, a transactivation-deficient mutant, in familial partial lipodystrophy. *Diabetes*, 51, 3586–3590.

Hontecillas R, O'Shea M, Einerhand A, Diguardo M, Bassaganya-Riera J (2009) Activation of PPAR gamma and alpha by punicic acid ameliorates glucose tolerance and suppresses obesity-related inflammation. *J Am Coll Nutr* 28, 184–195.

Hotta M., Nakata R., Katsukawa M., Hori K., Takahashi S., Inoue H. *(*2010) Carvacrol, a component of thyme oil, activates PPARalpha and gamma and suppresses COX-2 expression. *J Lipid Res.* 51, 132–139.

Huang TH, Kota BP, Razmovski V, Roufogalis BD (2005) Herbal or natural medicines as modulators of peroxisome proliferator-activated receptors and related nuclear receptors for therapy of metabolic syndrome. *Basic Clin Pharmacol* 96, 3–14.

Hwang B.Y., Lee J.H., Nam J.B., Kim H.S., Hong Y.S., Lee J.J. (2002) Two new furanoditerpenes from *Saururus chinenesis* and their effects on the activation of peroxisome proliferator-activated receptor gamma. *J Nat Prod.* 65, 616–617.

Hwang, B. Y., J. H. Lee, J. B. Nam, H. S. Kim, Y. S. Hong & J. J. Lee: (2002). Two new furanoditerpenes

from Saururus chinenesis and their effects on the activation of peroxisome proliferator-activated receptor gamma. *J. Nat. Prod.* , 65, 616– 617.

He Y.Q., Ma G.Y., Peng J.N., Ma Z.Y., Hamann M.T. (2012) Liver X receptor and peroxisome proliferator-activated receptor agonist from *Cornus alternifolia*. *Biochim Biophys Acta.* 1820, 1021–1026.

Isa Y., Miyakawa Y., Yanagisawa M., Goto T., Kang M.S., Kawada T. (2008) 6-Shogaol and 6-gingerol, the pungent of ginger, inhibit TNF-alpha mediated downregulation of adiponectin expression via different mechanisms in 3T3-L1 adipocytes. *Biochem Biophys Res Commun.* 373, 429–434.

Issemann I, Green S. (1990). Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators. *Nature*. 347(6294), 645-50.

Janani C and Kumari BR. (2015). PPAR gamma gene–a review. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*. 1;9(1), 46-50.

Janani C, and Kumari BR. (2017). Antidiabetic activity of methanolic leaves extracts of transformed soybean in 3T3-L1 preadipocytes cell line. *Int J Pharm Sci Res.* 1;8(11), 4732-4744.

Janani C, Sundararajan B, Kumari BR. (2019) Construction and transformation of peroxisome proliferator activated receptor gamma (RnPPARγ) gene using Agrobacterium tumefaciens into Glycine max L. Merr. *Gene Reports*. 16, 100427.

Jaradat M.S., Noonan D.J., Wu B., Avery M.A., Feller D.R. (2002) Pseudolaric acid analogs as a new class of peroxisome proliferator-activated receptor agonists. *Planta Medica.* 68, 667–671.

Jayaprakasam B, Vareed SK, Olson LK and Nair MG (2005) Insulin secretion by bioactive anthocyanins and anthocyanidins present in fruits. *J Agric Food Chem* 53, 28–31.

Jonker JW, Suh JM, Atkins AR, Ahmadian M, Li P, Whyte J, He M, Juguilon H, Yin YQ, Phillips CT, Ruth TY. PS21-100. (2012). A PPAR-FGF1 axis is required for adaptive adipose remodelling and metabolic homeostasis. *Nederlands Tijdschrift voor Diabetologie*. 10(3), 170-170.

Katsukawa M., Nakata R., Takizawa Y., Hori K., Takahashi S., Inoue H. (2010). Citral, a component of lemongrass oil, activates PPARalpha and gamma and suppresses COX-2 expression. *Biochim Biophys Acta.* 1801, 1214–1220.

Kim T., Lee W., Jeong K.H., Song J.H., Park S.H., Choi P. (2012) Total synthesis and dual PPARalpha/gamma agonist effects of amorphastilbol and its synthetic derivatives. *Bioorg Med Chem Lett.* 22, 4122–4126.

Kim, S. Shin, B. C. Lee, M. S. Lee, H. and Ernst, E. (2011) "Red ginseng for type 2 diabetes mellitus: a systematic review of randomized controlled trials," *Chinese Journal of Integrative Medicine*, 17. 12, 937–944.

Kubota N *et al.* (1999) PPARγ mediates high-fat diet-induced adipocyte hypertrophy and insulin resistance. *Mol Cell* 4, 597–609.

Kumar, B. Gupta, S. K. Srinivasan B. P. (2013). Hesperetin rescues retinal oxidative stress, neuroinflammation and apoptosis in diabetic rats. *Microvascular Research*, 87, 65–74.

Kuroda M., Mimaki Y., Honda S., Tanaka H., Yokota S., Mae T. (2010). Phenolics from Glycyrrhiza glabra roots and their PPAR-gamma ligand-binding activity. *Bioorg Med Chem.* 18, 962–970.

Kuroda, M., Y. Mimaki, Y. Sashida, T. Mae, H. Kishida, T. Nishiyama, M. Tsukagawa, E. Konishi, K. Takahashi, T. Kawada, K. Nakagawa M. (2003). Kitahara: Phenolics with PPAR-gamma ligand-binding activity obtained from licorice (Glycyrrhiza uralensis roots) and ameliorative effects of glycyrin on genetically diabetic KK-A(y) mice. *Bioorg. Med. Chem. Lett.* 13, 4267– 4272.

Lee, C. H., Olson P., Evans R. M. (2003). Minireview: lipid metabolism, metabolic diseases, and peroxisome proliferator activated receptors. *Endocrinology*, 144, 2201– 2207.

Li, J. J. Lee, S. H. Kim D. K. (2009). Colchicine attenuates inflammatory cell infiltration and extracellular matrix accumulation in diabetic nephropathy. *American Journal of Physiology-Renal Physiology*, 297, 1, F200–F209,.

Liang, Y. C., Tsai S. H., Tsai D. C., Lin Shiau S. Y., Lin J.

K. (2001). Suppression of inducible cyclooxygenase and nitric oxide synthase through activation of peroxisome proliferator activated receptor gamma by flavonoids in mouse macrophages. *FEBS Lett.*, 496, 12– 18.

Matsuda H, Kogami Y, Nakamura S, Sugiyama T, Ueno T, Yoshikawa M. (2011) Structural requirements of flavonoids for the adipogenesis of 3T3-L1 cells. *Bioorg. Med. Chem.*, 19, 2835–2841.

Metibemu DS, Akinloye OA, Akinbamiwa BA, *et al.* (2017) Austroinulin from Stevia rebaudiana a Potential Agonist of the Peroxisome Proliferator-activated Receptor (PPARγ): an in-silico Study. *J Syst Biol Proteome Res.,* 1(1), 10-15

Miles, P.D., Barak, Y., He, W., Evans, R.M. & Olefsky, J.M. (2000) Improved insulin-sensitivity in mice heterozygous for PPARγ deficiency. *Journal of Clinical Investigations*, 105, 287–292.

Mlinar B, Marc J, Janez A, Pfeifer M (2007). Molecular mechanisms of insulin resistance and associated diseases. *Clin Chim Acta* 375:20-35

Moskaug JO, Carlsen H, Myhrstad M & Blomhoff R (2004) Molecular imaging of the biological effects of quercetin and quercetin-rich foods. *Mech Ageing Dev* 125, 315–324.

Mourad AA, Nakamura S, Ueno T, Minami T, Yagi T, Yasue H, Komatsu R, Yoshikawa M, Taye AM, El-Moselhy MA, Khalifa MM, Matsuda H. (2013). Adipogenetic effects of retrofractamide A derivatives in 3T3-L1 cells. *Bioorg. Med. Chem. Lett.*, 23, 4813–4816.

Mueller M., Lukas B., Novak J., Simoncini T., Genazzani A.R., Jungbauer A. (2008). Oregano: a source for peroxisome proliferator-activated receptor gamma antagonists. *J Agr Food Chem.* 56, 11621–11630.

Mukherjee, R., Davies, P.J.A., Crombie, D.L., Dischoff, E.D., Cesario, R.M., Jow, L., Hamann, L.G., Mondon, C.E., Nadzan, A.M., Paterniti, J.J.R. & Heyman, R.A. (1997) Sensitization of diabetic and obese mice to insulin by retinoid X receptor agonists. *Nature*, 386, 407–410.

Nhiem N.X., Yen P.H., Ngan N.T., Quang T.H., Kiem P.V., Minh C.V. (2012). Inhibition of nuclear transcription factor-kappaB and activation of peroxisome proliferator-activated receptors in HepG2 cells by cucurbitane-type triterpene glycosides from Momordica charantia. *J Med Food.* 15, 369–377.

Ntambi JM, Young-Cheul K. (2000) Adipocyte differentiation and gene expression. *The Journal of nutrition*. 130(12), 3122S-6S.

Ohno, M. Shibata, C. Kishikawa T. (2013). The flavonoid apigenin improves glucose tolerance through inhibition of microRNA maturation in miRNA103 transgenic mice. *Scientific Reports*, 3, 1, 2013.

O'Sullivan S.E., Tarling E.J., Bennett A.J., Kendall D.A., Randall M.D. (2005). Novel time-dependent vascular actions of Delta9-tetrahydrocannabinol mediated by peroxisome proliferator-activated receptor gamma. *Biochem Biophys Res Commun.* 337, 824–831.

Park H.G., Bak E.J., Woo G.H., Kim J.M., Quan Z., Yoon H.K. (2012). Licochalcone E has an antidiabetic effect. *J Nutr Biochem.* 23, 759–767.

Petersen R.K., Christensen K.B., Assimopoulou A.N., Frette X., Papageorgiou V.P., Kristiansen K. (2011) Pharmacophore-driven identification of PPARgamma agonists from natural sources. *J Comput-Aid Mol Des.* 25, 107–116.

Pferschy-Wenzig E.M., Atanasov A.G., Malainer C., Noha S.M., Kunert O., Schuster D. (2014) Identification of isosilybin a from milk thistle seeds as an agonist of peroxisome proliferator-activated receptor gamma. *J Nat Prod.* 77, 842–847.

Prabhakar, O. (2013) Cerebroprotective effect of resveratrol through antioxidant and anti-inflammatory effects in diabetic rats. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 386, 8, 705–710.

Priya RM, Padmakumari KP, Sankarikutty B, Lijo Cherian O, Nisha VM, Raghu KG. (2011). Inhibitory potential of ginger extracts against enzymes linked to type 2 diabetes, inflammation and induced oxidative stress. International *Journal of Food Sciences and Nutrition*. 62(2), 106-110.

Rau O., Wurglics M., Paulke A., Zitzkowski J., Meindl N., Bock A. (2006) Carnosic acid and carnosol, phenolic diterpene compounds of the labiate herbs rosemary

and sage, are activators of the human peroxisome proliferator-activated receptor gamma. *Planta Medica.* 72, 881–887.

Rocchi, S., Picard, F., Vamecq, J., Gelman, L., Potier, N., Zeyer, D., Dubuquoy, L., Bac, P., Champy, M.-F., Plunket, K.D., Leesnitzer, L.M., Blanchard, S.G., Desreumaux, P., Moras, D., Renaud, J.-P. & Auwerx, J. (2001) A unique PPARγ ligand with potent insulin-sensitising yet weak adipogenic activity. *Molecular Cell*, 8, 737–747.

Rosen CJ (2010) Revisiting the rosiglitazone story–lessons learned. *N Engl J Med* 363, 803–806

Rosen ED, Sarraf P, Troy AE, Bradwin G, Moore K, Milstone DS, Spiegelman BM, Mortensen RM (1999) PPARγ is required for the differentiation of adipose tissue *in vivo* and *in vitro*. *Mol Cell* 4, 611–617.

Sato M., Tai T., Nunoura Y., Yajima Y., Kawashima S., Tanaka K. (2002) Dehydrotrametenolic acid induces preadipocyte differentiation and sensitizes animal models of noninsulin-dependent diabetes mellitus to insulin. *Biol Pharmaceut Bull.* 25, 81–86.

Sato, M., Tai T., Nunoura Y., Yajima Y., Kawashima S. & Tanaka K. (2002). Dehydrotrametenolic acid induces preadipocyte differentiation and sensitizes animal models of noninsulin- dependent diabetes mellitus to insulin. *Biol. Pharm. Bull.*, 25, 81– 86.

Schoonjans K, Auwerx J. (2000). Thiazolidinediones: an update. *The Lancet*. 355(9208), 1008-1010.

Sesti G (2006). Pathophysiology of insulin resistance. *Beat Pract Res Clin Endocrinol Metab* 20, 665-679.

Shen P., Liu M.H., Ng T.Y., Chan Y.H., Yong E.L. (2006). Differential effects of isoflavones, from Astragalus membranaceus and Pueraria thomsonii, on the activation of PPARalpha, PPARgamma, and adipocyte differentiation in vitro. *J Nutr.* 136, 899–905.

Shin D.W., Kim S.N., Lee S.M., Lee W., Song M.J., Park S.M. 2009 (-)-Catechin promotes adipocyte differentiation in human bone marrow mesenchymal stem cells through PPAR gamma transactivation. *Biochem Pharmacol.* 77, 125–133.

Soumyanath A (2006). Traditional Medicines for Modern Times - Antidiabetic Plants, Ed. CRC Press, Boca Raton, London, New York.

Takahashi N., Goto T., Taimatsu A., Egawa K., Katoh S., Kusudo T. (2009). Bixin regulates mRNA expression involved in adipogenesis and enhances insulin sensitivity in 3T3-L1 adipocytes through PPARgamma activation. *Biochem Biophys Res Commun.* 390, 1372–1376.

Tantry M.A., Dar J.A., Idris A., Akbar S., Shawl A.S. (2012). Acylated flavonol glycosides from Epimedium elatum, a plant endemic to the Western Himalayas. *Fitoterapia.* 83, 665–670.

Tontonoz P, Hu E, Spiegelman BM. (1995) Regulation of adipocyte gene expression and differentiation by peroxisome proliferator activated receptor γ. *Current opinion in genetics & development*. 5(5), 571-576.

Tsai, S.-J. Huang, C.-S. Mong, M.-C. Kam, W.-Y. Huang, H.-Y. and Yin, M.-C. (2012) Anti-inflammatory and antifibrotic effects of naringenin in diabetic mice. *Journal of Agricultural and Food Chemistry*, 60, 1, 514–521,.

Tsuda T, Ueno Y, Yoshikawa T, Kojo H & Osawa T (2006). Microarray profiling of gene expression in human adipocytes in response to anthocyanins. *Biochem Pharmacol* 71, 1184–1197.

Unuofin J. O., Otunola, GA. and Afolayan, A. J. (2018) In vitro *α*-amylase, *α*-glucosidase, lipase inhibitory and cytotoxic activities of tuber extracts of Kedrostis africana (L.) *Cogn. Heliyon*. 4, 9, e00810,.

Unuofin JO, Lebelo SL. (2020). Antioxidant effects and mechanisms of medicinal plants and their bioactive compounds for the prevention and treatment of type 2 diabetes: an updated review. *Oxidative medicine and cellular longevity.* 13; 1-36.

Watkins PB, Whitcomb RW. (1998). Hepatic dysfunction associated with troglitazone. *New England Journal of Medicine.* 338(13), 916-917.

Weidner C., de Groot J.C., Prasad A., Freiwald A., Quedenau C., Kliem M. (2012). Amorfrutins are potent antidiabetic dietary natural products. *Proc Natl Acad Sci USA.* 109, 7257–7262.

Weidner C., de Groot J.C., Prasad A., Freiwald A., Quedenau C., Kliem M. (2012). Amorfrutins are potent antidiabetic dietary natural products. *Proc Natl Acad Sci USA.* 109, 7257–7262.

Willson TM, Brown PJ, Sternbach DD, Henke BR. (2000). The PPARs: from orphan receptors to drug discovery. *Journal of medicinal chemistry*. 43(4), 527-50.

Yamauchi, T., Kamon, J., Waki, H., Murakami, K., Motojima, K., Komeda, K., Ide, T., Kubota, N., Terauchi, Y., Tobe, K., Miki, H., Tsuchida, A., Akanuma, Y., Nagai, R., Kimura, S. & Kadowaki, T. (2001) The mechanisms by which both heterozygous peroxisome proliferator-activated receptor gamma (PPARγ) deficiency and PPARγ agonist improve insulin resistance. *Journal of Biological Chemistry*, 276, 41245–41254

Yang M.H., Vasquez Y., Ali Z., Khan I.A., Khan S.I. (2013) Constituents from *Terminalia* species increase PPARalpha and PPARgamma levels and stimulate glucose uptake without enhancing adipocyte differentiation. *J Ethnopharmacol.* 149, 490–498.

Yang, L.-P. Sun, H.-l. Wu L.-M. (2009). Baicalein reduces inflammatory process in a rodent model of diabetic retinopathy. *Investigative Opthalmology & Visual Science*, 50(5), 2319.

Yokoi H., Mizukami H., Nagatsu A., Ohno T., Tanabe H., Inoue M. (2009) Peroxisome proliferator-activated receptor gamma ligands isolated from adlay seed (Coix lacryma-jobi L. var. ma-yuen STAPF.) *Biol Pharmaceut Bull.* 32, 735–740.

Zhang H, Matsuda H, Yamashita C, Nakamura S, Yoshikawa M. (2009) Hydrangeic acid from the processed leaves of Hydrangea macrophylla var. thunbergii as a new type of anti-diabetic compound.*Eur J Pharmacol*. 606(1-3), 255-61.

Zhu Y, Alvares K, Huang Q, Rao MS, Reddy JK. (1993). Cloning of a new member of the peroxisome proliferator-activated receptor gene family from mouse liver. *Journal of Biological Chemistry*. 268(36), 26817-26820.

Zoechling A, Liebner F, Jungbauer A. (2011). Red wine: a source of potent ligands for peroxisome proliferator-activated receptor γ. *Food & function.,* 2(1), 28-38.

Zoechling A., Liebner F., Jungbauer A. (2011) Red wine: a source of potent ligands for peroxisome proliferator-activated receptor gamma. *Food Funct.* 2, 28–38.

Zou G., Gao Z., Wang J., Zhang Y., Ding H., Huang J. (2008) Deoxyelephantopin inhibits cancer cell proliferation and functions as a selective partial agonist against PPARgamma. *Biochem Pharmacol.* 75, 1381–1392.