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REVIEW

The potential of natural products for targeting PPARα

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Abstract Peroxisome proliferator activated receptors (PPARs) α, -γ and -β/δ are ligand-activated transcription factors and members of the superfamily of nuclear hormone receptor. These receptors play key roles in maintaining glucose and lipid homeostasis by modulating gene expression. PPARs constitute a recognized druggable target and indeed several classes of drugs used in the treatment of metabolic disease symptoms, such as dyslipidemia (fibrates, *e.g.* fenofibrate and gemfibrozil) and diabetes (thiazolidinediones, *e.g.* rosiglitazone and pioglitazone) are ligands for the various PPAR isoforms. More precisely, antidiabetic thiazolidinediones act on PPARγ, while PPARα is the main molecular target of antidyslipidemic fibrates. Over the past few years, our understanding of the mechanism underlying the PPAR modulation of gene expression has greatly increased. This review presents a survey on terrestrial and marine natural products modulating the PPARα system with the objective of highlighting how the incredible chemodiversity of natural products can provide innovative leads for this "hot" target.

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1. Introduction

Peroxisome proliferator activated receptors (PPARs) are nuclear transcription factors that, in response to the binding of small ligands, regulate the expression of genes involved in cellular development, metabolism (lipid, carbohydrate and protein) and also tumorigenesis. PPARs are activated by many environmental factors, from xenobiotics to food compounds and they have been proposed to be one of the most important connection points between genes and environmental stimuli.

PPARs were first identified in *Xenopus* frogs as receptors that induce the proliferation of peroxisomes[1] (the organelles involved in catabolism of long fatty acids and reduction of reactive oxygen species) and they were cloned in 1990 as members of the nuclear receptor family, which includes also the classical steroid hormone receptors. At that time, they were classified as "orphan receptors" since they exhibited conserved features of the nuclear receptor family, but they were not linked to a defined family of endogenous ligands.

Among their multifaceted activities, PPARs induce or repress transcription of a large number of different genes related to the regulation of glucose, lipid, and cholesterol metabolism. Thus, natural and synthetic PPAR modulators have been identified as a promising approach to treat diabetes, dyslipidemia, obesity and hypertension[2]. Many of these ailments can be comprised under the big umbrella definition of metabolic syndrome, a disorder affecting more than a quarter of the world adult population related to imbalance of storage and energy utilization. In fact, metabolic syndrome includes a series of pathological risk factors of metabolic origin, such as insulin resistance, hyperinsulinemia, abdominal obesity, impaired glucose tolerance, type 2 diabetes, dyslipidemia (increased blood serum triglycerides), low high-density lipoprotein (HDL) and high low-density lipoprotein (LDL) cholesterol levels, elevated blood pressure, and a pro-inflammatory and prothrombic state, that could promote development of cardiovascular affections. Moreover, recent research indicates that metabolic syndrome–associated obesity induces chronic low-grade local tissue inflammation which is prodromic to other disease conditions, such as fatty liver, polycystic ovary syndrome, asthma, and some types of cancer[2].

Three isotypes of PPARs encoded by separate genes have been identified in mammals, sharing a high level of sequence and structural homology, indicated as PPARγ, -α, and -β (also called -δ), the first being the most extensively studied. Each PPAR subtype exhibits a unique tissue expression profile and has different functions in the regulation of energy metabolism. PPARα is highly expressed in muscles, liver, heart, and kidney, and mainly regulates genes involved in the metabolism of lipids and lipoproteins; PPARβ/δ is abundantly expressed throughout the body but at low levels in the liver. It has emerged as an important regulator of lipid metabolism and energy balance primarily in adipose tissue, skeletal muscle, and the heart. The PPARγ protein exists in two isoforms: PPARγ1, abundantly expressed in adipose tissue, large intestine, and hematopoietic cells, and PPARγ2, restricted to adipose tissue under physiological conditions[3].

PPARs can be activated by dietary fatty acids and their metabolites, and, upon activation, they act as lipid sensors able to markedly redirect metabolism following a gene transcription process that is identical in all three PPAR subtypes. Similarly to other nuclear receptors, the three known subtypes have N-terminal transactivation domains, central highly conserved DNA-binding domains, and C-terminal ligand-binding domains (LBD). The ligand-binding domains of the PPAR isoforms share 60%–70% sequence identity, thus enabling the three isoforms to bind naturally occurring fatty acids, which enter a pocket in the LBD activating the receptor.

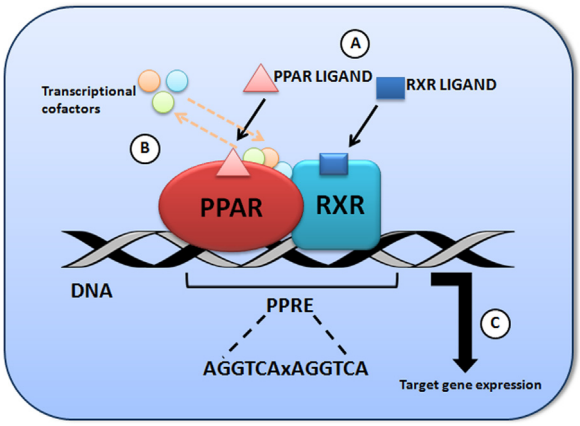

Figure 1 PPAR transcriptional activation in the cell nucleus. (A) Binding of PPAR/RXR ligands; (B) Changes in the associated transcriptional cofactors; (C) Activation of the transcriptional complex.

After ligand binding, the PPARs heterodimerize with their obligate partner, the retinoic acid-X receptor (RXR) and, as such, they bind to peroxisome proliferator response elements (PPREs), distinct regions of DNA in the promoter region of the respective target genes. The PPRE consensus sequence usually consists of a direct repeat of the hexameric sequence AGGTCA separated by one less well conserved spacer nucleotide (DR-1). PPARα was shown to bind to the 5′ motif of the PPRE, whereas RXR binds to the 3′ motif[4] (Fig. 1).

The activity of PPAR receptors is finely regulated by other intermediate compounds, collectively known as co-repressors and co-activators. In the absence of ligands, PPAR–RXR heterodimers recruit co-repressors and associated histone deacetylases and chromatin-modifying enzymes, silencing transcription by so-called active repression (ligand-independent repression). Once the ligand binds to PPAR, a conformational change in PPAR–RXR complexes causes release of repressors and their exchange with co-activators. Ligand-activated complexes recruit the basal transcriptional machinery and polymerase II, resulting in an enhanced gene expression leading to transcription of proteins. For example, carnitine palmitoyl transferase I (CPT-I), acylCoA synthase, β-ketoacyl-CoA thiolase and others, in turn regulate lipid metabolism, including uptake, synthesis, and oxidation of fatty acids, lipoprotein assembly, as well as lipid transport with the final goal of maintaining the balance of lipids and energy metabolism[4].

Screening for PPAR ligands has led to identification of a plethora of natural and synthetic agonists able to activate them. For example, PPARα are activated by fibrates, lowering triglyceride levels and raising high density lipoprotein (HDL); PPARγ is activated by glitazones, drugs that can relieve insulin resistance in diabetes. PPARβ/δ is activated by an array of long-chain fatty acids and prostaglandins and, as shown recently, by retinoic acid.

2. PPARα functions and modulators

PPARα acts as a sensor of nutritional status, particularly energy balance. This key function has been better characterized in the

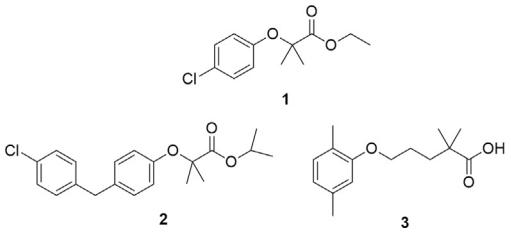

Figure 2 Representative members of the fibrate family.

liver, where it regulates key genes encoding proteins and enzymes involved mainly in lipid transport and β-oxidation of fatty acids[5]. However, the reduction in the levels of circulating or cellular lipids by PPARα activation is attributed to the stimulation of fat degradation in several others peripheral tissues expressing PPARα, including brown adipose tissue, kidney, heart, and skeletal muscle. In particular, PPARα activation stimulates the expression of lipoprotein lipase and increases its activity by stimulating apolipoproteins A–V (activator of lipoprotein lipase) and reducing apolipoprotein C-III (inhibitor of lipoprotein lipase). The effect is a reduction of triglyceride levels in chylomicrones and in very low-density lipoprotein (VLDL) particles, an increase in HDL cholesterol and a promotion of cholesterol efflux from cells to HDL, mediated by stimulation of expression of the ATP-binding cassette A1 transport protein[3]. Recently, it has been demonstrated that PPARα is also widely expressed in the digestive tract, where it exerts an anti-inflammatory effect. Since mice lacking PPARα develop an increased inflammation as compared to wild type (WT) mice, treatment with PPARα agonists has been proposed to inhibit inflammatory diseases development[6].

Intriguingly, PPARα is also expressed in the hippocampus where it is involved in synaptic plasticity and memory through regulation of the expression of cAMP-response-element binding protein (CREB), a critical transcription factor regulating the formation of memories. Consequently, mice lacking PPARα display decreased spatial learning and memory. While targeting PPARα has been widely employed as a strategy to target dyslipidemia, the treatment of cognitive dysfunction and/or dementia has not yet been exploited as a potential indication for PPARα modulating drugs, mainly due to the pharmacokinetic problems in the crossing of the blood–brain barrier.

Overall, the most important and better exploited function of PPARα is the regulation of the expression of genes involved in lipid metabolism, and is thus linked to metabolic syndrome, atherosclerosis and cardiovascular diseases. The archetypal PPARα agonists are fibrates, small molecules embedding an aryloxyacetic acid moiety. The first PPARα agonist to be used in clinical therapy to treat dyslipidemia was clofibrate (**1**) in 1965, well before the discovery of its target about 25 years later. Successively, looking for an improvement in the pharmacological profile of this molecule, some analogues were synthesized and biologically evaluated. These compounds, commonly referred to as "second generation fibrates", include fenofibrate (**2**), ciprofibrate, bezafibrate, and the dimethylphenoxypentanoic derivative gemfibrozil (**3**, Fig. 2)[7,8].

Paradoxically, the research to find synthetic exogenous ligands of PPARα has not been accompanied by comparable successes in the discovery of endogenous activators of this orphan receptor. In 2009, Chakravarthy et al.[9] proposed that the phospholipid 1-palmitoyl-2-oleoyl-*sn*-glycerol-3-phosphocholine (16/18-GPC) was the main endogenous ligand of PPARα. Later, a number of other endogenous ligands have been proposed for PPARα, including saturated or unsaturated fatty acids and eicosanoids, such as palmitic acid, oleic acid, linoleic acid, arachidonic acid, oleoylethanolamide (a naturally occurring lipid related to the endocannabinoid anandamide), palmitoylethanolamide, and leukotriene B4. Recently, Roy et al.[10] reported the discovery of three endogenous PPARα ligands that play a key role in modulating PPARα function in brain, 3-hydroxy-(2,2)-dimethyl butyrate, hexadecanamide, and 9-octadecenamide. It is very likely that, more than possessing a single high-affinity natural ligand, PPARα may be able to sense the total flux of fatty acids in metabolically active tissues. In addition, PPARα activity can be indirectly stimulated by phosphorylation. Not yet clearly identified amino acid residues contained in different domains of PPARα can be phosphorylated, thus promoting the transcriptional activity of PPARα even in the absence of ligands. PPARα can be phosphorylated by various kinases, such as mitogen-activated protein kinase (MAPK), protein-kinase C (PKC) and AMP-activated protein kinase[11].

3. Natural products modulating PPARα

Natural products have proven historically to be a prolific and essential tool for drug discovery and the field of PPAR interacting molecules makes no exception to this general rule. A significant research effort has indeed been undertaken over the last two decades to explore the potential of a wide range of natural products originating from traditionally used medicinal plants or dietary sources. This approach has great attractiveness due to the intrinsic potential of natural sources and to the encouraging possibility of modulating PPAR activation by dietary interventions or *ad hoc* food supplements.

Undoubtedly, the greatest part of these research efforts has been devoted to find PPARγ modulators, in the search for natural products able to improve metabolic parameters in diabetic animal models, with reduced side effects when compared to thiazolidinedione, full agonists of this receptor. Honokiol, amorfrutins, and amorphastilbol are nice examples of molecules possessing these positive features, also because, in some cases, their mechanism of action includes the simultaneous activation of PPARα (as in the case of amorphastibol) or the PPARγ-dimer partner retinoid X receptor (as in the case of honokiol)[8].

The activation of PPARα has been comparatively much less investigated, although a number of papers has been appearing in recent years. In this review, we have tried to collect the most significant and promising PPARα-modulating natural products. This collection of molecules does not aim to be complete or exhaustive, but more realistically at providing an overview on the most significant (in our opinion) researches. To this aim, we have found logical to organize the molecules according to their (likely) biogenetic origin and, consequently, their chemical scaffolds. In this way, some structural moieties crucial for the activities of a certain class of compounds could be more clearly evidenced.

While there is no shortage of reviews on PPARγ modulators[12–14], including natural products, to the best of our knowledge, general

reviews on natural PPARα modulators are still lacking, although some papers have reported on the activity of certain classes of natural products[15].

3.1. Terpenes

3.1.1. Monoterpenes

A PPARα modulating activity has been reported for the acyclic monoterpene linalool (**4**) and for the two isomeric aromatic monoterpenes carvacrol (**5**) and thymol (**6**)[16,17] (Fig. 3).

Linalool is contained in most herbal essential oils and teas, where it contributes to the definition of aroma and flavors. The mixture of L- and D-linalool was found to act as a direct ligand of PPARα reducing cellular lipid accumulation, inducing fatty acid oxidation and significantly reducing the concentrations of saturated fatty acids, effects which were markedly attenuated by silencing PPARα expression. The effects of 1 mmol/L linalool appeared comparable to those of 0.1 mmol/L fenofibrate[16].

Carvacrol (**5**) and thymol (**6**), monocyclic aromatic monoterpenes of thyme oil, were found to be somewhat weak agonists of PPARα and PPARγ receptors and, at the same time, to suppress the expression of COX-2. Since *p*-cymene was inactive on both these endpoints, Authors drew the reasonable conclusion that the –OH group is essential for these activities[17].

The glycosylated secoiridoid excelside B (**7**) and some related metabolites extracted from *Fraxinus excelsior* L. were found to moderately activate PPARα, thus, at least partly, explaining the activity of the plant extract[18].

3.1.2. Sesquiterpenes

trans-Caryophyllene (**8**), major component of the essential oils of many plants and traditionally used in cosmetics for its typical aroma, was found to be able to interact with the LBD of PPARα and, consequently, exert an effect in the regulation of cellular lipid metabolism. In particular, caryophyllene activity resulted in a significant reduction of intracellular triglyceride concentrations and increase of hepatic fatty acid uptake[19]. The activity of an hydrocarbon like caryophyllene, lacking any polar functional group and characterized by a small molecular weight, may appear surprising. However, the same molecule has also shown a selective and potent activity on cannabinoid CB_2 receptor[20,21], whose previously known ligands invariably showed polarized bonds, thus indicating the privileged status of this natural product.

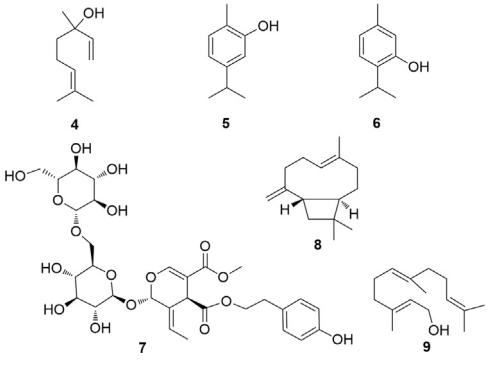

Figure 3 PPARα-modulating mono- and sesquiterpenes.

The acyclic alcohol derivative farnesol (**9**) which, as pyrophosphate, is the precursor of all the sesquiterpenoids and of squalene in the cholesterol biosynthetic pathway, was found to upregulate the expression of PPARα and the PPARα-regulated genes fatty acyl-CoA oxidase and carnitine palmitoyl transferase with a consequent lowering of serum triglyceride levels in rats[22,23].

3.1.3. Diterpenes

A series of diterpenes have been reported to be able to modulate PPARα although, almost invariably, these compounds were dual PPARα/γ activators. This is the case of dehydroabietic acid (10, Fig. 4), a major component of the oleoresin produced by several conifer species[24]. This molecule has been proposed to be useful to suppress chronic inflammation in obesity and to improve obesity-related insulin resistance. Pseudolaric acid B (**11**) and analogues have been isolated from the trunk bark of the Chinese tree *Pseudolarix kaempferi*. These diterpenes showed concentration-dependent activation of PPARα, -γ and -β isoforms. Interestingly, esterification of the free carboxy group of these compounds markedly reduced the activity, indirectly suggesting an interaction with the fatty acid binding site. However, authors suggested that pseudolaric acid B may act also by modifying the phosphorylation state of the receptor[25].

Analogously to linear monoterpenes and sesquiterpenes, also in the case of diterpenes, the branched-fatty alcohol, (*E*)-phytol (**12**), ubiquitous in vegetal cells as carbon side-chain of chlorophylls, can be metabolically transformed into phytanic acid (**13**). Phytol itself is able to upregulate the expression of PPARα-target genes in hepatocytes, while phytanic acid has been reported to activate PPARγ, the retinoid-X-receptor (RXR) and PPARα[26]. Not surprisingly, also geranylgeraniol (**14**) proved to be able to activate both PPARα and PPARγ. Thus, branched-fatty alcohols, widespread in many dietary plants, may be collectively indicated as a class of PPAR ligands[23]. This class has been investigated in detail by Hostler et al.[4], who concluded that unsaturated fatty acids show a wider specificity to PPAR isoforms compared to saturated fatty acids, as a consequence of the marked differences in the structural flexibility.

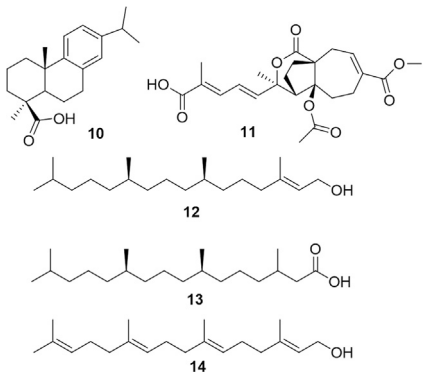

Figure 4 PPARα-modulating diterpenes.

3.1.4. Triterpenes and steroids

The pentacyclic triterpene oleanolic acid (**15**, Fig. 5) was found to stimulate PPARα activation in keratinocytes while, interestingly, the closely related ursolic acid, differing only for the methylation pattern on ring E, failed to express this activity[27]. The steroidal saponins ginsenosides, recognized as the main responsible for the pharmacological activities of ginseng, have been disclosed to inhibit the induction of PPARα-target genes by acting as competitive inhibitors of PPARα, with a consequent increased serum concentrations of total cholesterol, triglycerides, and HDL cholesterol[28]. One of the ginsenosides, namely ginsenoside Rf

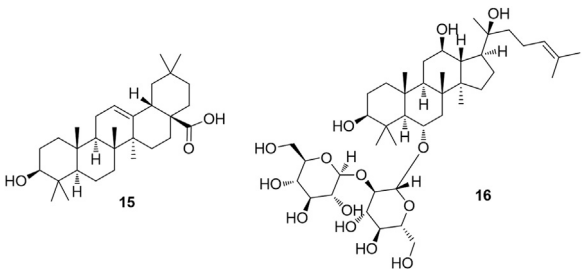

Figure 5 PPARα-modulating triterpenes.

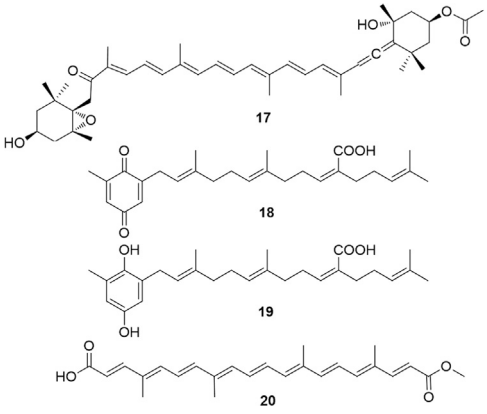

Figure 6 PPARα-modulating carotenoids.

(**16**), was identified as the most potent analogue in this activity[29]. Thus, PPARα inhibition can be identified as an important molecular mechanism mediating ginseng induced alterations in serum lipid profiles.

3.1.5. *Carotenoids*

Fucoxanthin (**17**, Fig. 6) is a marine carotenoid characterized by an allene functionality and a conjugated ketone, widely distributed in marine algae, including edible brown algae, such as gulfweed (*Sargassum fulvellum*), dashima (*Laminaria japonica*) and hijiki (*Hizikia fusiformis*). This carotenoid was found to significantly down-regulate the hepatic *Pparγ* mRNA expression level and, in contrast, up-regulate *Pparα* mRNA, thus reducing triglyceride levels in the liver[30]. Sargaquinoic acid (**18**) and sargahydroquinoic acid (**19**) from the seaweed *Sargassum yezoense* were identified as novel PPARα/γ dual agonists with little effect on PPARδ activation[31] (Fig. 6).

Bixin (**20**) is a carotenoid obtained from the pericarp of the seeds of *Bixa orellana* which was demonstrated to moderately activate PPARα, inducing the mRNA expression of PPARα-target genes involved in fatty acid oxidation in HepG2 hepatocytes. Treatment with bixin was proved to ameliorate obesity induced dysfunctions of carbohydrate metabolism (hyperglycemia and hyperinsulinemia)[32].

3.2. *Polyketides*

Since fatty acids are physiological modulators of PPAR, it is not surprising that the C_{12} branched and triunsaturated fatty acid monotriajaponide A (**21**), obtained from a Chinese specimen of the sponge *Plakortis simplex* acted as a potent agonist of both PPARγ and PPARα[33]. Cyclic polyketides as anthraquinones and prenylated phloroglucinols also showed an interesting activity in the modulation of PPARα (Fig. 7).

3.2.1. *Anthraquinones*

The *C*-glycosylated anthraquinone mangiferin (**22**), a secondary metabolite of *Salacia oblonga* root, an Ayurvedic medicine with anti-diabetic and anti-obesity properties, showed a weak effect on the transactivation of PPARγ and PPARα[34]. Interestingly, norathyriol (**23**) enhanced hepatic expression of PPARα, an effect completely suppressed by the selective PPARα antagonist MK-886. This clearly highlights the negative role played by the sugar unit of mangiferin, likely due to the increase in polarity. An enzymatic transformation of mangiferin into norathyriol has been proved both *in vitro* and *in vivo*[35].

3.2.2. *Prenylated polyketides*

Isohumulone (**24**) and isocohumulone (**25**), are among the main bitter agents, responsible for the taste imparted by hop (*Humulus lupulus* L.) to beer. These compounds, formed by isomerization of humulones during the brewing process, have been found to activate PPARα and -γ with a positive effect on dyslipidemia in diabetic animals[36]. Another study found that treatment with isohumulones reduced plasma triglyceride and free fatty acid levels[37] mediated by an up-regulation of mRNA for acyl-CoA oxidase, acyl-CoA synthetase, hydroxymethylglutaryl-CoA synthetase, lipoprotein lipase[38,39]. Although it can be argued that PPARα modulation is not the single mechanism explaining the effects of isohumulones, these molecules exert an undoubted positive effect on symptoms of metabolic syndrome.

3.3. *Phenylpropanoids*

Rosmarinic acid (**26**), the main phenylpropanoid of oregano extract showed a moderate PPARα transactivaction activity (about 20% when compared to WY14643)[40]. The rhamnose bearing phenylpropanoid verbascoside (**27**) was demonstrated to exert its positive effects on inflammatory bowel disease, at least partly, through PPARα. Indeed, the verbascoside mediated anti-inflammatory activity is weakened in *Ppar-α* knock-out mice[41] (Fig. 8).

3.3.1. *Coumarins*

During an investigation of the mechanisms underlying the effects of the widespread coumarin umbelliferone (**28**) on alcoholic fatty liver, Authors found an elevated expression of the fatty acid oxidation genes (including PPARα) with a stimulated fatty acid β-oxidation activities and beneficial effects on hepatic lipid metabolism[42]. The prenylated coumarin osthole (**29**), isolated from *Cnidium monnieri* and *Angelica pubescens*, significantly activated both PPARα and PPARγ in a dose-dependent manner, thus giving a marked increase in the expression of PPAR-target genes[43]. Osthole was also hypothesized to activate PPARα through an AMPK-dependent pathway which induces phosphorylation, and therefore activation, of PPARα[44]. The *O*-geranoylated coumarin auraptene (**30**) was demonstrated to serve as a dual agonist for PPARα and PPARγ in luciferase ligand assay[45]. A different investigation has shown that auraptene induces up-regulation of PPAR-target genes, such as acyl-CoA oxidase (ACO), carnitinepalmitoyl transferase 1 A (CPT1A) and acyl-

CoA synthetase (ACS). Authors concluded that auraptene may improve lipid abnormality through PPARα activation in the liver[46].

3.3.2. *Lignans*

Sesamin (**31**), a major lignan of sesame seeds, upregulates the PPARα-associated signaling and downregulates the liver X receptor α (LXRα)-mediated pathway, a combined effect that induces an evident improvement of hepatic steatosis and related inflammation[47]. The biosynthetically and chemically related sesamol (**32**), also present in sesame seed oil, share this effect[48].

3.3.3. *Tannins*

A recent paper from the Khan's group[49] reported the results of an investigation of the effects of fruits of *Terminalia bellerica* (Combretaceae), entering in the composition of triphala, a popular Ayurvedic formulation for treating diabetes. A series of ellagitannins, *e.g.* corilagin (**33**), and of gallotannins, *e.g.* 1,2,3,4,6-penta-*O*-galloyl-β-D-glucose (**34**) were found to enhance PPARα and PPARγ signaling.

3.4. *Polyphenols*

3.4.1. *Chalcones and stilbenes*

The cyclohexenyl chalcone panduratin A (**35**, Fig. 9), isolated from *Boesenbergia pandurata* rhizomes, was shown to be a natural AMPK stimulator, with consequent activation of PPARα/δ, the same mechanism as reported before for osthole (**29**)[50]. A certain structural similarity between the two compounds could provide an explanation for the common mechanism of action.

Resveratrol (**36**, Fig. 9) is probably one of the most intensely investigated phytochemicals and surely the best known stilbene. A plethora of pharmacological activities have been attributed to this flavonoid, present in the skin and seeds of grapes but also in many other natural sources. A series of experiments on several cells have shown that resveratrol activates the nuclear receptors PPARα and PPARγ[51]. However, the activity of this stilbene seems to be higher when the oxidative state of the cell is stronger and to decrease as the effect of oxidants decrease[52]. A recent paper by Takizawa et al.[53] evaluated in detail the chemical basis of the activation of PPARα by resveratrol. The results of experiments using the crystal structure of the PPARα LBD indicated that the 4′-hydroxyl group of resveratrol is critical for the direct activation of PPARα. In agreement with this conclusion, the activity of resveratrol is shared by its dimethylated analogue pterostilbene (**37**), which indeed maintains a free hydroxyl group at position 4′. Actually, the agonistic activity of **37** on PPARα is even higher than that of resveratrol, probably due to the beneficial lowering of polarity on ring A[54]. Vaticanol C (**38**), reported to be a complex resveratrol tetramer activates PPARα and PPARβ/δ, but not PPARγ, both *in vitro* and *in vivo*. The molecular size of vaticanol C is much larger than that of resveratrol and it is hard to believe that the two molecules could share the same binding pocket[55].

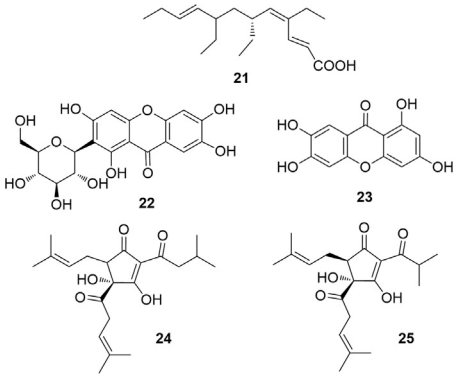

Figure 7 PPARα-modulating polyketides.

3.4.2. *Flavonoids*

The flavanones hesperetin (**39**) and naringenin (**40**) (Fig. 9) and their glycosides, present in dried, immature fruit of *Citrus aurantium*, induced expression of PPARγ in a dose-dependent manner while only naringenin was able to activate PPARα[56]. The effects of this activation translated into *in vivo* increasing in hepatic fatty acid oxidation, decreasing in hepatic cholesterol and cholesterol ester synthesis, reduction of both VLDL derived and endogenously synthesized fatty acids[57]. Interestingly, naringenin also decreases cholesterol and bile acid production modulating another nuclear receptor family (LXRα)[58].

Hispidulin (**41**), a common flavone, acts as a direct PPARα agonist and exerts hypolipidemic effect by enhancing the

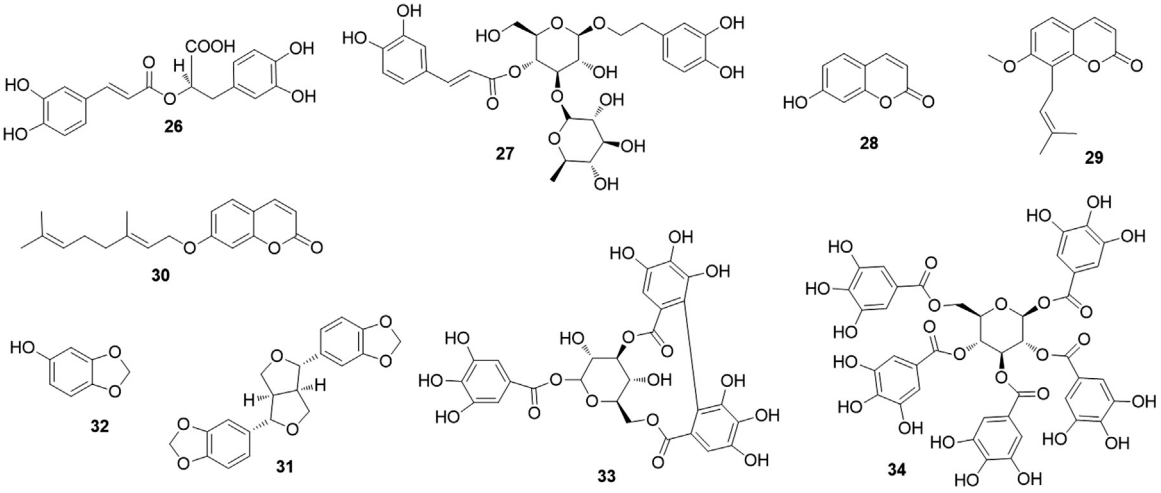

Figure 8 PPARα-modulating phenylpropanoids and tannins.

expression of fatty-acid β-oxidation genes. *In vivo* data suggested that 3-month treatment with hispidulin or fenofibrate in dyslipidaemic rat improved the lipid profile[59]. The related flavone wogonin (**42**), commonly extracted from the traditional Chinese medicine *Scutellaria baicalensis,* showed a somewhat similar pharmacological profile. In addition, it has been recently shown that PPARα activation by wogonin downregulates osteopontin a multifunctional protein involved in several physiological and pathological events, including cancer and cardiovascular diseases[60]. Another flavone, 5,7-dimethoxyflavone (**43**), also demonstrated to increase PPARα/γ activation, was proposed to prevent and treat skin photoaging, being able to prevent and contrast negative effects of oxidative stress and inflammation[61].

Icariin (**44**), a glycosylated and prenylated flavonol obtained from *Epimedium brevicornum* Maxim (a traditional Chinese herb known as Yin Yang Huo), up-regulated PPARα and PPARγ protein levels. This effect, combined to the already known inhibition of NF-κB expression, can explain the potent neuroprotective and anti-inflammatory effects attributed to this compound[62,63].

Epigallocatechin-3-gallate (**45**), the major polyphenolic constituent of green tea (*Camellia sinensis*), increases the expression of PPARα and confers susceptibility to cancer cells *via* suppression of the enzyme heme oxygenase-1[64].

3.4.3. *Isoflavonoids*

Several Authors have investigated the effects of the simple isoflavonoid genistein (**46**, Fig. 10) on the modulation of PPARα. This compound was found to protect against oleic acid-induced steatosis with a complex mechanism that includes an increase in PPARα expression[65]. Interestingly, 3′-hydroxygenistein (**47**) reached a higher activation efficiency than its precursor and, similarly, while the strictly related isoflavonoid daidzein (**48**) only slightly activated PPARα, its metabolite 6-hydroxydaidzein (**49**) exerted a much higher PPARα activity[66]. As seen before in the case of resveratrol, a comparison among isoflavonoids shows the impact of ring A functionalization on the PPARα modulating activity. However, in the case of resveratrol data available pointed to a crucial role played by the 4′-hydroxyl group for the direct activation of PPARα (see above). In the case of isoflavonoids, a methylation at that key position seems to be not only well tolerated but even to increase the activity. Thus, biochanin A (**50**), differing from genistein only by methylation of the 4′ OH group, was several-fold more potent than its precursor. Similarly, formononetin (**51**), bearing the same methylation relationship with daidzein was at least an order of magnitude more potent than its demethylated analogue[67]. Of course, it is not easy to unambiguously exclude that these effect are mainly related to an increase in the bioavailability of the molecules rather than on an improved

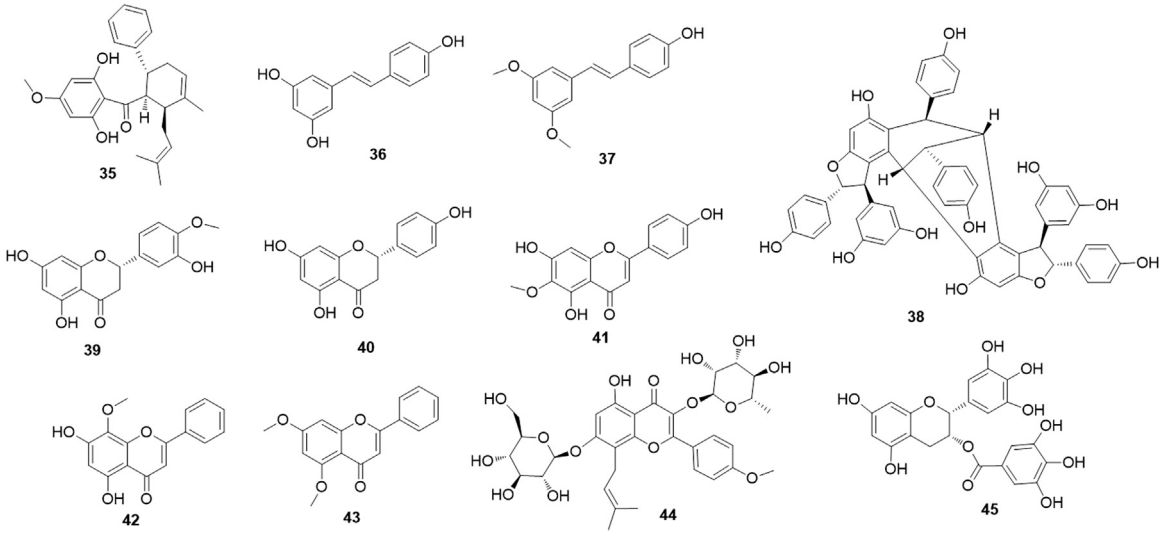

Figure 9 PPARα-modulating chalcones, stilbenes and flavonoids.

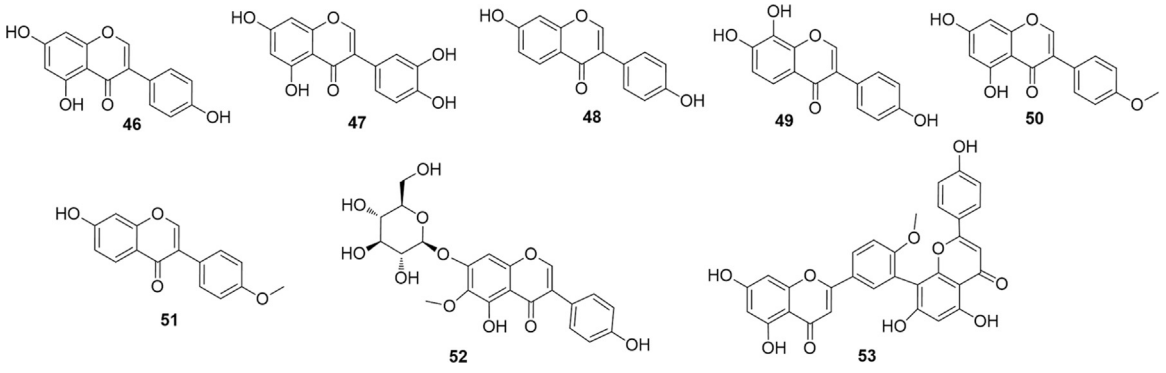

Figure 10 PPARα-modulating isoflavonoids and biflavonoids.

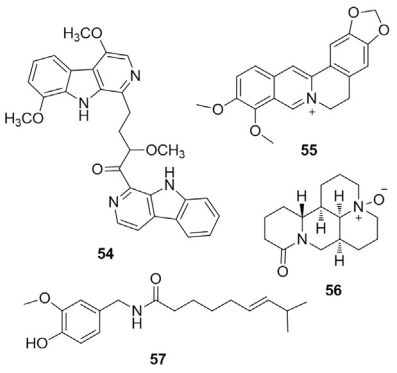

Figure 11 PPARα-modulating alkaloids.

interaction with the binding site. Different abilities to recruit co-activators or co-repressors, and/or cross-activation of other nuclear receptors cannot also be excluded.

The glycosylated isoflavonoid tectoridin (**52**) was isolated from the flowers of *Pueraria lobata* (Willd.) Ohwi. (Puerariae Flos), used in traditional Chinese medicine as a remedy for liver injury. Since impaired fatty acid catabolism in the liver can be likely caused by the blockade of PPARα function by ethanol, it can be anticipated that administration of PPARα agonists to ethanol-fed animals could prevent fatty liver by reversing PPARα dysfunction. An investigation by Xiong et al.[68] demonstrated that the effects of tectoridin are indeed mediated by a marked inhibition of the ethanol-induced decrease of PPAR expression and its target genes.

3.4.4. *Biflavonoids*

Bilobetin (**53**), a biflavonoid isolated from *Ginkgo biloba* was found to exert a positive effect on hyperlipidaemia, lipotoxicity and insulin resistance in rats. However, these effects could not be related to a direct PPARα agonism, while the involvement of proteon kinase A (PKA) is more likely. PKA activation in the liver by bilobetin appears to stimulate the phosphorylation (specifically of Thr129 and/or Ser163), nuclear translocation and activity of PPARα[69].

3.5. *Alkaloids*

The class of PPARα modulators belonging to the alkaloid biogenetic pathway is comparatively small, although some promising examples have been reported. This is the case of the recent paper describing the activity of picrasidine C (**54**, Fig. 11), a dimeric β-carboline-type alkaloid isolated from the root of *Picrasma quassioides*. This compound was identified as a selective PPARα agonist (no activity on PPARβ/δ and PPARγ was observed), comparable to the positive control WY14643, with a consequent induction of the mRNA expression of several PPARα-regulated genes. *In silico* docking calculations confirmed that picrasidine C fitted well within the PPARα LBD forming a series of crucial interactions, including hydrogen bonds with Cys276 and Thr279 [70].

The isoquinoline alkaloid berberine (**55**) has been shown to have a body weight reducing effect in diabetic rats, mediated by hypolipidemic effects, including restoration of normal total cholesterol, triglyceride, fatty acid and low density lipoprotein-cholesterol levels[71]. These effects are likely to be, at least partly, mediated by the selective activation of PPARα: berberine binds directly to the LBD of PPARα with similar affinity to fenofibrate[72]. Similar positive effects on body weight and dyslipidemia have been reported for oxymatrine (**56**) isolated from the medicinal plant *Sophora flavescens*[73]. These effects seem to be mediated by down-regulation of SREBF1 and up-regulation of PPARα mediated metabolic pathways. The pseudoalkaloid capsaicin (**57**), the spicy component of hot pepper, has been found to lower glucose, insulin and leptin levels, and to reduce the impairment of glucose tolerance in obese mice. Capsaicin is the archetypal agonist of transient receptor potential TRPV1 and the above effect can be modulated by the expression/activation of this endpoint. However, luciferase assays revealed that capsaicin is capable of binding PPARα and, indeed, *Pparα* mRNA and PPARα-target gene levels were higher in the livers of obese mice supplemented with dietary capsaicin than in those of the obese controls[74].

3.6. *Total extracts*

Several total extracts have been reported to modulate PPARα activity and exert positive impact on dyslipidemia and metabolic syndrome symptoms. A selection of them has been collected in Table 1. The effect of a complex network of compounds, as a total extract is, on a complex and largely interrelated system as PPARα is, can be evaluated and rationalized with great difficulty. However, it is undoubted that several still unexplored natural sources of potential PPARα modulators are available. Thus, the list reported in Table 1[75–112] is should encourage natural product chemists to make efforts aimed at the detailed characterization of the active principle(s) responsible for the action of these extract.

4. Conclusions

The objective of this review was to collect in a single manuscript the most promising natural products having shown activity on the modulation of PPARα and, therefore, holding a potential in the treatment of metabolic syndrome. Our collection of compounds was organized on the basis of the biogenetic origin and, consequently, of the chemical structure, regardless the detailed mechanism of PPARα modulation. Our efforts were not addresses at creating a comprehensive collection of all the natural products reported to interact in some extent with PPARα, but to show the great chemodiversity of natural products able to modulate this important nuclear receptor.

Throughout this review, we have avoided reporting quantitative data since these can largely depend on type of cell line used and different cell lines might provide different results depending on the presence of cofactors (co-activators or co-repressors) and/or metabolic processes. Thus, quantitative comparisons among the different compounds would have been in many cases inappropriate. Moreover, it is now clear that *in vitro* assays can give only a rough idea of the quantitative effects of compounds on PPARα, and a careful investigation *in vivo* is in any case necessary.

In this review we have decided to focus on PPARα modulators, but we are well aware that there is growing evidence that the ligands able to bind and activate both PPARα and PPARγ can provide therapeutical advantages over PPARα selective ligands, due to synergistic increase in lipid metabolism and insulin sensitivity. Not surprisingly, PPARα/γ dual agonistic approach has been recently intensively exploited by pharmaceutical industry

Table 1 A selection of total extracts reported to target PPARα.

Species name	Class of active metabolites	Ref.
Acacia (bark)	Polyphenols	75
Allium sativum (oil)	–	76
Anethum graveolens (seed)	–	77
Camellia sinensis (leaves)	Catechin-enriched extract	78–80
Chlorella sorokiniana	Fatty acids	81
Chrysanthemum zawadskii	–	82
Cinnamomi Cassiae (bark)	–	83, 84
Citrus limon (peel)	Polyphenols	85, 86
Clematis sp.	–	87
Crataegus pinnatifida (fruit)	–	88
Cucurbita moschata (stem parts)	–	89
Emblica officinalis	Polyphenols	90, 91
Eugenia jambolana (seeds)	Flavonoids	92
Ganoderma lucidum	–	93
Glycine max (seeds)	Isoflavones	94–98
Helicteres isora	Saponins	99
Hericium erinaceus	–	100
Litsea coreana	Flavonoids	101
Momordica charantia (fruit)	–	102, 103
Momordica grosvenori	Flavones	104
Pearsonothuria graeffei	Saponins	105
Pinellia ternata	–	106
Punica granatum (flower)	–	107
Rehmannia glutinosa	Oligosaccharides	108
Syzygium cumini	–	109
Vaccinium myrtillus	Anthocyanins	110
Vitis vinifera (seed)	Proanthocyanidins	111, 112

– Not applicable.

and compounds like muraglitazar and tesaglitazar have indeed demonstrated efficacy in glucose normalization and correction of lipid abnormalities in diabetic patients[8]. Unfortunately, further development of these compounds failed at clinical trials, due to heart failure and renal toxicities[11,12]. Thus, again natural products or herbal medicines can be a valuable alternative strategy to find drugs for metabolic syndrome with low adverse side effects. Although, generally, activation of PPARα by natural compounds is not as strong as that by synthetic compounds, such as fibrates, the administration of a partial PPAR agonist may offer some advantages and could join the desired efficacy with a lower degree of potential adverse effects. The generic "antidiabetic" or "hypolipidemic" effects of many botanicals could likely be ascribed to activation of the PPAR signaling system. A deep investigation on these effects and the discovery and characterization of their putative PPAR-activating compounds would pave the way preparation of innovative dugs, food supplements, nutraceuticals for the management of the metabolic syndrome.

It is clear that natural products have still much to say also in the field of PPARα modulation.

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