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Review

Naturally Occurring Compounds Targeting Peroxisome Proliferator Receptors: Potential Molecular Mechanisms and Future Perspectives for Promoting Human Health

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Abstract: Background: Peroxisome-proliferator-activated receptors (PPARs) constitute nuclear transcription factors controlling gene expression associated with cell growth and proliferation, diverse proteins, lipids, and glucose metabolism, being related to several other pathophysiological states such as metabolic disorders, atherogenesis, carcinogenesis, etc. The present survey aims to analyze the natural compounds that can act as agonists for the PPAR-α, PPAR-β/δ, and PPAR-γ system targeting, highlighting how the amazing biochemical diversity of natural compounds can yield new insights into this "hotspot" of the scientific field. Methods: A narrative review was performed by searching the recent international literature for the last two decades in the most authoritative scientific databases, like PubMed, Scopus, Web of Science, and Embase, using appropriate keywords. Results: Several natural compounds and/or their synthetic derivatives can act as ligands of PPARs, stimulating their transcriptional activity and enabling their use as preventive and/or therapeutic agents for several disease states, such as inflammation, oxidative stress, metabolic disturbances, atherogenesis, and carcinogenesis. Although synthetic compounds are increasingly used as drugs to manage health problems, serious side effects have been observed, while their natural analogues exhibit only few minor side effects. Conclusions: Further clinical studies on natural compounds such as ligands of PPARs and the evaluation of the related molecular mechanisms are needed to implement an effective strategy concerning the pharmaco-technology, food chemistry, and nutrition to introduce them as part of clinical and dietary practice.

Keywords: PPAR ligands; natural compounds; synthetic compounds; inflammation; lipids; glucose

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1. Introduction

Peroxisome-proliferator-activated receptors (PPARs) constitute the nuclear transcription factors controlling the gene expression related to cellular growth and proliferation, metabolism of proteins, lipids, glucose, atherogenesis, and carcinogenesis [1,2]. PPARs are activated via many environmental factors, from xenobiotics to edible plants, herbs, nuts, and fruits, and they have also been identified amongst the most prominent binding loci between genes and the environment [2–4]. Especially, a plethora of synthetic PPAR agonists have been shown to exert opposing treatment impacts as well as many side effects in atherosclerosis treatment, whereas naturally occurring compounds exhibit structure variety with low side effects and a good safety profile [5,6]. Novel evidence is currently

supporting that aromatic plants and medicinal herbs as well as their natural compounds exhibit attractive therapeutic effects against atherosclerosis disease progression through attenuating hyperlipidemia and inflammation via PPAR modulation [5,6]. Prominently, the excretion and separation of natural compounds generally cause meaningfully lower environmental pollution compared to that produced by synthesizing chemical compounds with drug-like properties, some of which may be selected as drug candidates for their subsequent testing in phase III clinical trials. Moreover, natural compounds exhibit more appropriate drug-like properties compared to synthesized compounds, presenting better physicochemical and bioavailability properties and a better possibility for high chemical affinity and target selectivity [7,8]. In the case of PPARs, the binding domain of their agonists and antagonists is highly related to their ligands' lipophilicity and molecular mass [7]. Thus, there is a strong demand to take into consideration the drug-like properties of PPAR ligands based on appropriate drug design strategies using pre-screening testing and processing [9,10].

Three different types of isoforms of PPARs have been found in mammals. They are expressed by different genes and are highly variable in structure and sequence. They are currently well-known as PPAR-α, -β/δ, and -γ. PPAR-γ has mostly been explored, presenting a greater possibility to be introduced as a potential therapeutic target in clinical practice [11,12]. Every PPAR isoform has a distinctive expression profile in several tissues and distinct actions concerning energy metabolism modulation. PPAR-α expression is mainly high in hepatic and brown adipose tissue, heart, kidney, intestinal mucosa, and muscle and can greatly regulate the genes related to lipoproteins and lipid metabolism [13]. PPAR-β/δ is highly expressed in skin, brain, and fat tissue and at lower amounts in hepatic tissue. It is also [14,15]. It has been highlighted as an essential determinant of lipid metabolism and energy modulation, mainly in adipocytes, skeletal muscle cells, and cardiomyocytes [16]. PPAR-γ has two isotypes: PPAR-γ1, which is in abundance in adipocyte, colon, and hematopoiesis cells, as well as PPAR-γ2, which is restricted to adipose tissue in the absence of disease or disorder [17,18]. PPAR-γ2 has been recognized as the main modulator of adipocyte differentiation and promotes energy loading by organizing fatty acid delivery and lipogenesis [17,18].

PPARs can mainly be triggered by fatty acids derived from the diet and their metabolites. When activated, these receptors can act as lipometabolic sensors, which can also significantly alter metabolic processes [19]. Their impact in metabolic processes takes place by a gene transcription procedure, which is identical for all PPARs [19]. PPAR stimulation requires exogenous (dietary) and endogenous binding compounds or PPAR ligands that can penetrate the cytoplasm and nuclear membranes to access the PPARs [20]. Throughout the above procedure, small soluble proteins such as fatty acid binding proteins (FABPs) might be implicated in enhancing cellular and nuclear transport. PPARs are also heterodimerized by the retinoic X α receptor (RXR-a) [21]. When there is no PPAR ligand, the PPAR-RXR heterodimer binds to compressor protein complexes, which can subsequently negatively regulate gene expression [22].

PPARs include specific N-terminal activation sites, central greatly conserved DNA-binding sites, and C-terminal ligand-binding domains (LBDs). The agonist/antagonist binding regions of PPAR isotypes show almost seventy percent sequence identity, allowing them to bind to natural fatty acids that transfer into a locus in the LBD and thereby activate them [23]. In general, hydrophobic and hydrogen-bonding interactions may contribute to stabilizing the binding of a potential ligand to PPARs [24,25]. Thus, as mentioned above, concerning the chemical space covered by PPAR ligands, there is high demand regarding the LBD in terms of both lipophilicity and molecular mass [7,10].

PPARs modulate genes' expression pertaining to many cell procedures, such as glucose metabolism, mitochondrial genesis, insulin action, cell proliferation, fat oxidation, inflammation, cell differentiation, and consequently cell survival [26]. PPAR expression has also been reported in the cardiovascular and immune systems, and especially in the innermost layer (tunica intima) and the middle layer (tunica media) of the vascular cells as

well as in the lymphocytes, dendritic cells, and macrophages, respectively. PPARs can also suppress the synthesis of cytokines (e.g., interleukin-9 and IL-6) and pro-inflammatory intermediates [27]. Throughout the activation of the ligands, PPARs are capable of inhibiting pro-inflammatory genes' expression to exert anti-inflammatory properties by intervening in the binding of transcription molecules, such as nuclear factor kappa B (NF-kB) to DNA [27,28].

Moreover, several PPAR agonists can induce endothelial nitric oxide synthase (NOS) activation by various pathways, which ameliorates vascular endothelial disorder through enhancing the endothelial bioavailability of nitric oxide (NO) and providing oxidative stress prevention [5,29,30]. PPARs have exhibited a broad bioactivity range by behaving as regulators or mediators in multiple metabolic pathways [29–31]. Therefore, they could become a target of pharmacological technology for the treatment of metabolic disorders and non-communicable diseases as well as cancer [29–31]. Although synthetic PPAR agonists such as thiazolidinediones and fibrates have been aspects of dyslipidemia and/or hyperglycemia treatment, serious side effects like bone fractures, myopathy, and increasing body weight as well as fluid retention contribute to natural compounds attracting the interest of medicine research and technology [29–31].

Notably, although PPARs have several similar actions, they also exert different effects, which are ascribed to their different expression locations in diverse tissues, sensitivities to ligands, and modulation of target genes [32]. More to the point, the PPAR LBD contains 12 α-helices, which establish the typical three-layer antiparallel α-helical sandwich with a small four-stranded sheet. The above structure outlines a bulky Y-shape hydrophobic region, with a ligand-binding cavity that is broader regarding PPARs compared to the other receptors [33,34]. The above feature could enhance the capability of PPARs to bind diverse synthetic and naturally occurring molecules that possess increased lipophilicity and an acidic moiety [11,34,35]. The PPAR-β/δ LBD is considerably smaller compared to those of PPAR-α and PPAR-γ, which are both similar concerning their shape and size. The above distinction could explain the fact that PPAR-β/δ agonists/antagonists are currently scarce compared to the other two isotypes, demonstrating that these structural features of PPAR-β/δ LBD influence its ligand-binding specificity. On the other hand, the PPAR-α LBD is characterized by higher lipophilicity, which may explain the fact that certain strong PPAR-γ ligands cannot bind to PPAR-α, also justifying the fact that PPAR-α is capable of binding to saturated fatty acids that possess higher lipophilicity. Importantly, PPARs have different ligand isotype selectivity from each other, which seems to be ascribed to single amino acid variations in their LBDs [11,34,35].

Fatty acids and their analogs constitute the most frequent in vivo PPAR ligands [36], while the main drugs used to treat metabolic syndrome are their synthetic ligands [37]. PPAR-α ligands such as fibrates and PPAR-γ ligands like thiazolidinediones are currently utilized for the therapy and management of hypertriglyceridemia and diabetes mellitus type 2, respectively [38,39]. PPAR-β/δ activation can enhance the functions of mitochondria and energy metabolism; however, PPAR-δ-related drugs remain extremely scarce [38,39]. PPAR-α/γ dual agonists have also been considered for the treatment of diabetic dyslipidemia. However, dual PPAR-α/c agonists such as naveglitazar, tesaglitazar, aleglitazar, ragaglitazar, muraglitazar, and tesaglitazar have demonstrated severe side effects, and their development was discontinued at diverse steps of the drug design procedure [40]. In recent years, novel compounds such as saroglitazar have been shown in early-stage and preclinical studies to be dual PPAR-α/γ agonists with significantly improved therapeutic activity and decreased side-effect profiles [41]. In addition, pan-PPAR ligands, which refer to single compounds that simultaneously activate all the PPAR subtypes (α, γ, and δ) may very well provide the rationale for a new category of compounds that can target all three PPAR receptors, leading to generally better outcomes than single-receptor or dual-combined (α/γ) ligands [42,43].

The present review aims to analyze and scrutinize the natural compounds that behave as agonists for the PPARs system, aiming to demonstrate whether the remarkable biochem-

ical diversity of the natural compounds can yield new insights into this "hotspot" of the scientific field.

2. Methods

A thorough and careful search of the recent international scientific literature for the last two decades in the most authoritative scientific databases, e.g., PubMed, Scopus, Web of Science, Embase, and Google Scholar, was conducted using appropriate keywords like PPAR-α, -β/δ, and -γ, agonists, non-communicable diseases, food ingredients, and natural or bioactive compounds. Exclusion criteria were gray literature, including surveys that were not written in the English language. The results were screened for their validity and the most appropriate of them were selected and are presented below. The retrieved surveys were additionally assessed for relevant surveys reported in their manuscript. The research strategy is quoted in Figure 1.

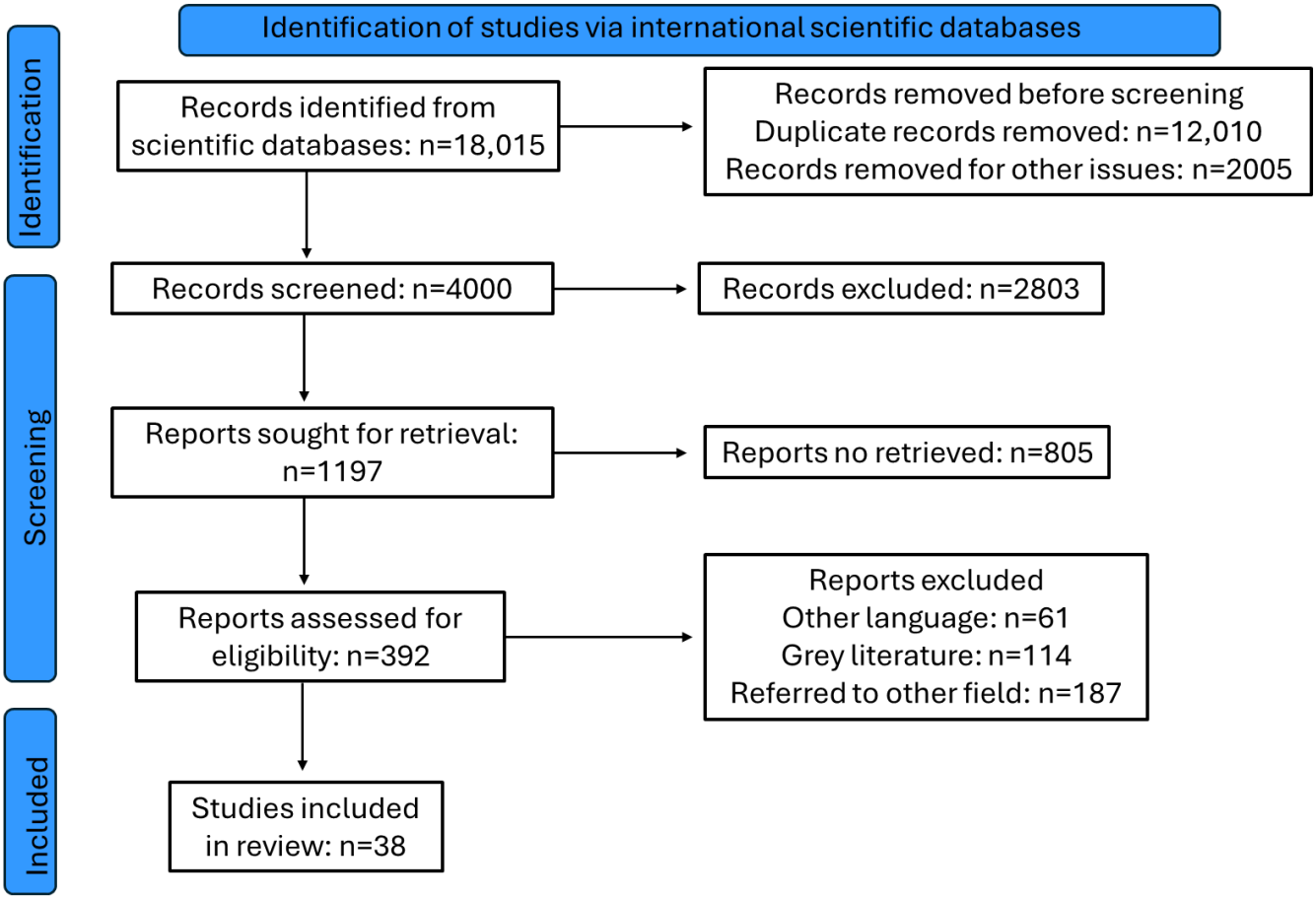


Figure 1. Flow chart diagram of study enrollment.

3. Results

In the last two decades, numerous natural bioactive molecules were shown to stimulate either a unique subtype or even more subtypes of PPARs, which have been implicated in the molecular mechanisms of diverse pathophysiological states as described in Table 1.

Hippeastrum stapfianum (Kraenzl.), *R.S.Oliveira* and *Dutilh* (Amaryllidaceae) constitutes an endemical plant species that thrives in the Brazilian savannah, which can exert diverse biological and pharmacological properties [44]. A recent study evaluated the potential effects of *H. stapfianum* leaf ethanol derivatives on the activity of the acetylcholinesterase enzyme and their effects on both PPAR-α and -γ [44]. It was observed that the *H. stapfianum* ethanol extracts stimulated PPAR-α and -γ, suppressed the acetylcholinesterase enzyme, and possessed antioxidant properties in vitro. The most prominent natural compounds

found were 7-demethoxy-9-O-methylhostasine and lycorine [44]. According to this preliminary evidence, *H. stapfianum* could be considered as a drug candidate for Alzheimer's disease by activating PPAR-α and -γ, inhibiting acetylcholinesterase, and attenuating antioxidant activity [44].

The ability of *Morus nigra* L. to exert anti-inflammation properties in lipopolysaccharide (LPS)-stimulated murine macrophage cells was also examined [45]. The inflammatory inhibitory effect was evaluated by the measurement of reactive oxygen species (ROSs), nitric oxide (NO), and tumor necrosis factor-α (TNF-α) production in RAW 264.7 cells along with the treatment with LPS from *Escherichia coli*. This study showed that the extracts from the leaves of Morus nigra can stimulate the activation of both PPAR-α and -γ [45]. The above finding appears to be due to the synergistic influence of their natural constituents as their main molecules, rutin and isoquercitrin, could not stimulate PPAR-α and -γ distinctly. Collectively, the *Morus nigra* L. extracts demonstrated sufficient anti-inflammation properties by attenuating the ROS, NO, and TNF-α release in LPS-exposed stimulated RAW 264.7 cells [45].

The triterpenoid saponin asperosaponin VI, one of the active compounds of the traditional Chinese medicine *Radix dipsaci*, has been shown to be effective in osteoporosis treatment, demonstrating anti-inflammatory activity [46]. It can also penetrate to the central nervous system (CNS), overcoming the blood–brain barrier, providing protection to the neurons, and improving several symptoms induced by neurological diseases [46]. In this aspect, Jiang et al. evaluated the potential beneficial impact of asperosaponin VI on mice treated for chronic mild stress (CMS), highlighting the fundamental molecular mechanism of its action [46]. In fact, the CMS in the mice induced a pro-inflammation state in the microglia, which caused decreased crosstalk between the microglia and neurons, an inflammatory state, and synapsis dysregulation in the hippocampus, resulting in depression-like behaviors. Based on the above evidence, asperosaponin VI could improve the negative impacts of CMS by triggering microglia to present PPAR-γ-supported neuroprotection [46].

Methoxygenol is a molecule found in certain edible raw materials like *Myristica fragrans* Houtt and Brazilian red propolis. The methoxygenol included in the above raw materials is broadly utilized for the treatment of liver and gastrointestinal disorders. However, there are no data on the preventive effects against fibrotic liver damage [47]. In this context, de Souza Basso et al. investigated the potential properties of methoxyeugenol on hepatic stellate cell phenotype regulation in both human and murine cells [47]. The research team also investigated how methoxyeugenol could exert a preventive and protective effect on hepatocyte damage in vivo and studied its favorable potential regarding the prevention of hepatic fibrosis [47]. Methoxyeugenol was shown to lower hepatic stellate cell activation through PPAR-γ stimulation. The activation of liver stellate cells eventually led to a quiescence phenotype characterized by the accumulation of fat droplets, loss of contractile function, and a reduced proliferation rate and fibroblast mRNA marker expression [47]. Methoxyeugenol also inhibited oxidative-stress-induced damage to liver cells. Furthermore, in mice with chronic hepatopathy, methoxyeugenol reduced the hepatic inflammatory status, hepatic fibrosis, mRNA expression of fibrotic genes, and NF-kB inflammatory responses [47].

Thymoquinone is a phytochemical compound and a PPAR-γ agonist that has been investigated for its potential benefits in inflammatory bowel disease management [48]. More specifically, thymoquinone (2-isopropyl-5-methyl-1,4-benzoquinone) is the main biomolecule found in the volatile oil of the seeds of *Nigella sativa* L. (family Ranunculaceae). It is widely used in the Mediterranean and Middle Eastern regions for its beneficial effects on human health [48,49]. A recent study showed that a treatment with thymoquinone considerably decreased the disorder progression index, the myeloperoxidase action, and defended the microscopic structure of the colon in inflammatory bowel disease [50]. In addition, thymoquinone reduced the expression of pro-inflammatory cytokines and mediators. Thymoquinone also increased the colonic epithelial PPAR-γ expression and suppressed the phosphorylation of NF-κB proteins and the mitogen-activated protein kinase (MAPK)

pathway [50]. Furthermore, in HT-29 cells treated with tumor necrosis factor-α (TNF-α), thymoquinone significantly attenuated the expression of the pro-inflammatory chemokines and specifically chemokine (C-X-C pattern) ligand 1 (CXCL-1), interleukin-8 (IL-8), and cyclooxygenase-2 (COX-2) mRNA. Thymoquinone similarly enhanced the HT-29 PPAR-γ mRNA and protein levels as well as its promoter activity Taken together, the results support the evidence that thymoquinone can suppress the MAPK and NF-κB pathways in vivo and in vitro in colon inflammatory states and can exert potent anti-inflammatory activity by the upregulation of PPAR-γ expression [50].

Gamma-oryzanol (γ-OZ), the primary bioactive molecule found in the germ and bran of rice, constitutes a substance with activity against inflammation and oxidation. A recent study evaluated whether γ-Oz could modulate the cytokine chain reaction by activating PPAR-gamma in lipid tissues [51]. For this purpose, three different groups of male Wistar rats received either an ad libitum control diet (C, n = 6), an enhanced sugar and enhanced fat diet (HSF, n = 6), or an enhanced sugar, enhanced fat diet and γ-Oz (HSF + γ-Oz, n = 6) for a period of thirty weeks [51]. The HSF group was shown to have problems in the functioning of the adipose tissue, which was characterized by notable lower cytokine levels, other indicators of inflammation, and redox; the treatment with γ-Oz inhibited the fatty tissue dysfunction and enhanced the overexpression of PPAR-γ. Considering the above findings, γOz could be suggested as an adjuvant therapeutic option to suppress the cytokine cascade in obese COVID-19 patients [51].

Curcumin is a chemical of plant origin, mainly in the root of *Curcuma longa* (turmeric), presenting a plethora of beneficial health actions, exerting activities against inflammation and neurological dysfunctions. A recently published study assessed the potential impact of curcumin on the differentiation of ancestral oligodendrocytes, particularly in inflammatory conditions [52]. The above study showed that curcumin could stimulate the differentiation of oligodendrocyte progenitors, counteracting their maturation arrest induced by TNF-α. The above effects were ascribed to a mechanism implicating PPAR-γ [52].

In addition, curcumin was found to affect phosphate group transfer to kinase 1/2 (ERK1/2), regulating the transition of ancestral oligodendrocytes to immature oligodendrocytes through a partly dependent PPAR pathway [52]. Curcumin was shown to enhance the amounts of PPAR-γ co-activator co-factor-1α, PGC1-α, and cytochrome c oxidase core protein COX1, while oligodendrocyte progenitors were found in the TNF-α environment via a PPAR-γ-regulated pathway [52]. These data are consistent with the proven PPAR-γ capability to induce mitochondria structure integrity and activities that are essential for the evolutionary maturation of oligodendrocytes. This study supported evidence for the potential beneficial effects of curcumin in demyelinating diseases, which could be ascribed to its neuroprotective activities and its actions against inflammation [52].

Colson et al. investigated whether the bioactive compound carnosic acid from Rosmarinus, which is used in folk medicine, may have a controlling role in the formation and functions of brown adipocytes [53]. In human pluripotent adipose-derived stem cells (hMADS) transformed to white or brown adipose tissue cells, the transcription and translation of critical regulatory genes were identified [53]. Carnosic acid was found to suppress white adipocyte browning and downregulate thermogenic factor gene expression. In particular, the effects of carnosic acid could be fully reversed, while transaction activation assays showed that carnosic acid exhibits PPAR-α/γ antagonistic activity [53].

Wogonin is a major flavonoid found in *Scutellaria radicans*. It has been considered to exert a crucial impact in terms of modulating both the inflammatory and oxidation pathological states. Research by Zhuang et al. identified novel pathways by which wogonin may enhance phagocytosis in rodent models of cerebral hemorrhage, thereby enhancing the hematoma resolution and neurological recovery after a cerebral hemorrhage [54]. The above effects could be attributed to upregulated expression of MerTK, Axl, LAMP2, and CD3 in peri-hematoma microglial and BV2 cells. In this context, the wogonin treatment of a mouse model of intracerebral hemorrhage induced microglial phagocytosis in vitro [54]. In addition, by suppressing the pro-inflammatory cytokines and pro-oxidant enzymes'

production like TNF-α, IL-1β, and inducible nitric oxide synthase (iNOS) after intracerebral hemorrhage, wogonin significantly reduced the inflammatory and oxidative stress responses [54]. Remarkably, the wogonin actions were reversed by GW9662, a PPAR-γ inhibitor. Thus, this study provides strong evidence that wogonin may improve hematoma clearance and neurobehavioral regaining with the aid of PPAR-γ [54].

Butain, a flavonoid analog, naturally found in *Faba bean*, has demonstrated glucose-regulating properties in diabetic patients. An in silico analysis further confirmed that butain may exert a significant impact in glycemic control by regulating PPAR-γ activity. On the basis of this evidence, the antidiabetic properties of butain were explored in models of diabetes induced in rats. However, butein as a hydrophobic compound has poor bioavailability [55]. Therefore, a butein formulation using the biopolymer chitosan was prepared to evaluate its synergistic glucose-lowering effects. Both butein and a butein–chitosan combination were effective in the regulation of the glucose concentration in blood of rats, whereas there were no observed side effects [55]. In addition, a possible mechanism of butein's antidiabetic effect was revealed by gene expression analysis, which was associated with PPAR-γ suppression. On the other hand, the formulation of butein–chitosan did not show the predicted synergistic glucose-lowering activity [55].

Chlorogenic acid is a naturally occurring compound isolated from *Cecropia obtusifolia* that can exert many beneficial health effects, like anticarcinogenic, neuroprotective, antioxidant, anti-inflammatory, hypoglycemic, and hypolipidemic properties. In this context, a survey explored whether chlorogenic acid can act as an insulin secretory agent by increasing the concentration of intracellular calcium ([Ca2+]i in RINm5F cells and as an insulin sensitizer and lipid-lowering factor by triggering PPAR-γ and PPAR-α expression, respectively, in the 3T3-L1 adipocyte cells [56]. RINm5F cells exposed to a concentration of 200 μM chlorogenic acid were characterized by a nine-times enhancement in [Ca2+]i in comparison with the controls and four-times in comparison with the positive controls. An enhancement in insulin release was also found analogously to that of the positive controls. Chlorogenic acid also considerably enhanced the PPAR-γ and GLUT4 mRNA expression as well as PPAR-α and fatty acid translocase protein (FATP) [56].

Furthermore, a chemoinformatic analysis supported the evidence that chlorogenic acid may have appropriate physicochemical characteristics to be regarded as a lead bioactive for the design of novel drug candidates with analogous activities. Collectively, these findings suggest that chlorogenic acid has multiple modes of activity for developing potential efficient therapies for metabolic diseases like diabetes [56]. The hypocholesterolemic and hepatoprotective effects of chlorogenic acid intake were also explored by assessing the plasma lipid profile (total cholesterol, triglycerides, HDL, and LDL) in rats provided a normal diet, a cholesterol-rich diet, or a cholesterol-rich diet including a chlorogenic acid supplement [57]. The chlorogenic acid significantly changed the hypercholesterolemic diet-induced elevations in plasma total cholesterol and LDL, whereas it decreased the HDL with dose-dependent improvements in the atherogenic index and cardiovascular risk factors [57]. The lipid deposition in the liver was considerably reduced in hypercholesterolemic animals exposed to chlorogenic acid. The hypocholesterolemic activity of the chlorogenic acid was ascribed to enhanced hepatic fatty acid catabolism via upregulation of PPAR-α mRNA expression [57].

A study by Xie et al. explored dehydroabietic acid, a natural molecule contained in pine wood and rosin, assessing whether it could stimulate PPAR-γ and PPAR-α to reduce insulin resistance and liver steatosis in high-fat diet (HFD)-fed mice [58]. Dehydroabietic acid was found to bind to PPAR-γ and PPAR-α LBDs by stable hydrogen bonds. Dehydroabietic acid has also been shown to promote 3T3-L1 differentiation by activating PPAR-γ and stimulating oxygen uptake in mitochondria in HL7702 cells through PPAR-α motivation [58]. In HFD-fed mice, dehydroabietic acid administration reduced glucose intolerance and insulin resistance and lowered liver steatosis, biomarkers of hepatic damage (alanine aminotransferase—ALT; aspartate aminotransferase—AST), and lipid accumulation [58]. Moreover, dehydroabietic acid induced PPAR-γ and PPAR-α mRNA signaling factors

participating in insulin sensitivity and fat metabolism, in vitro and in vivo, and downregulated the mRNA expression of the modulators involved in inflammation [58]. Therefore, dehydroabietic acid may be a dual PPAR-α/γ and PPAR-γ partial agonist. It is also able to alleviate insulin resistance and liver steatosis caused by HFD intake in mice [58].

Pelargonidin constitutes a naturally occurring molecule that is commonly found in fruits. It exerts diverse beneficial properties against oxidation, atherosclerosis, inflammation, hyperglycemia, and diabetes disease states. A study by Guo et al. assessed the possible effects of pelargonidin against obesity via the suppression of adipogenesis in 3T3-L1 cells [59]. More to the point, pelargonidin was particularly found to decrease 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase) LPL, glucose transporter 4 (GLUT4), and adipocyte fatty acid binding protein (A-FABP) expression [59]. Notably, the luciferase reporter assay showed that pelargonidin reduced PPAR-γ transcription action. The above evidence supported that pelargonidin may exert anti-adipogenic activity in 3T3-L1 cells via PPAR-γ suppression. Taken together, the above evidence supported that, through the downregulation of the PPAR-γ signaling pathway, pelargonidin may exhibit anti-adipogenesis activities in 3T3-L1 cells [59].

Moreover, a study investigated if magnolol, a naturally occurring neolignane molecule, may act against Alzheimer's disease stimulated through beta-amyloid (Aβ), also exploring the potential mechanisms of its action [60]. Indeed, it has been shown that magnolol reduced Aβ accumulation, toxicity, and Aβ-induced memory loss in transgenic *C. elegans* in a dose-dependent manner [60]. Notably, the above actions were negated by GW9662, a well-known PPAR-γ antagonist. Thus, magnolol appears to mitigate Aβ-stimulated Alzheimer's disease, and its potential mechanisms may be related to reducing inflammation and promoting PPAR-γ-dependent phagocytosis and Aβ degradation [60].

Another study explored whether *Malva parviflora* hydroalcoholic leaf extracts (MpHEs) may act as an anti-inflammatory agent on Alzheimer's disease progression in lean and obese transgenic 5XFAD mice [61]. MpHE was found to effectively reduce astrogliosis, the accumulation of insoluble Aβ peptides in the hippocampus, and spatial learning deficits in both animal groups. These effects have been associated with the accumulation of microglial cells that were close to Aβ plaques in the cerebral cortex and hippocampus, and with a reduction in several inflammation-related biomarkers [61]. MpHEs, including oleanolic acid and scopoletin, also preserved the phagocytic capacity of microglia through a PPAR-γ/CD36-related manner. In light of the above data, *M. parviflora* appears to inhibit neuronal inflammation by attenuating the pro-inflammatory M1 phenotype of microglia and enhancing microglial phagocytosis [61]. Hence, *M. parviflora* could be considered as an alternative agent for preventing mental loss related to metabolism dysfunction, and Alzheimer's disease development [61].

Recently, renal fibrosis has been found to be attenuated by asiatic acid, a triterpenoid molecule isolated by the *Centella asiatica* [50]. In this context, the unilateral ureteral occlusion (UUO) model was applied for exploring the mechanisms implicated in the antifibrotic effect of asiatic acid. UUO surgery was performed on Sprague-Dawley rats and mice [62]. Before surgery, the rats were treated with asiatic acid for one week, while the mice were treated with asiatic acid for three days [62]. The UUO group showed a noteworthy extent of kidney damage, interstitial fibrosis, oxidative stress, and stimulation of the transforming growth factor-β (TGF-β)/Smad and Wnt/β-catenin signals in the kidney. The pathological changes described above were significantly alleviated through the pre-treatment with asiatic acid. In addition, a co-treatment with GW9662 negated the protective beneficial effects of asiatic acid, highlighting a PPAR-γ dependent action [62]. Although the asiatic acid pre-treatment did not considerably affect the PPAR-γ expression in the kidney, it significantly increased the plasma levels of 15-deoxy-Δ12,14-prostaglandin J2 (15d-PGJ2), an endogenous PPAR-γ agonist [62]. In addition, the pre-treatment with asiatic acid increased the expression levels of active nuclear-localized sterol regulatory element-binding protein-1 (nSREBP-1); however, fatostatin, a suppressor of SREBP-1, reduced the levels of nSREBP-1 and 15d-PGJ2.

The findings provided novel insights concerning the antifibrosis actions of asiatic acid, possibly involving PPAR-γ [62].

Chromium histidinate and biotin are frequently utilized to promote health in athletes and to manage the blood sugar levels in diabetic patients. In this regard, a survey investigated the impacts of eight weeks of systematic exercise in rats combined with chromium histidinate and biotin intake on glucose, lipid, and transaminase concentrations, and PPAR-γ, insulin receptor substrate-1 (IRS-1), and NF-κB protein expression [63]. Regular exercise has been shown to significantly reduce glucose, total cholesterol, and triglyceride (TG) levels. It also increases HDL lipoprotein levels [63]. In comparison with the exercise group, the co-treatment with dietary chromium histidinate and biotin presented significant decreases in the glucose and TG concentration and an upregulation in HDL. Moreover, chromium histidinate/biotin was found to improve the amounts of IRS-1, PPAR-γ, and NF-κB protein expression in the hepatic tissue and the muscle of inactive rodents and rodents following exercise regularly [63].

Hesperetin is a natural flavanone molecule found in the rind of *Citrusaurantium* L. (Rutaceae). Some surveys have shown that hesperetin may have diverse beneficial health properties, including anti-inflammatory, anti-tumor, antioxidant, and neuroprotective activities. In this context, hesperetin derivative-14 (HD-14) is a derived form of hesperetin with reduced lipophilicity and high bioavailability. In this regard, a survey showed that HD-14 (2 μM) substantially diminished the inflammatory process in LPS-treated RAW264.7 cells [64]. In addition, HD-14 showed liver-protecting and anti-inflammation activities in C57BL/6J mice with acute hepatic damage [65]. Interestingly, PPAR-γ knockdown with small interfering RNA showed pro-inflammation actions in LPS-exposed RAW264.7 cells, whereas PPAR-γ overexpression was related to anti-inflammation properties by reducing the expression of TNF-α, IL-6, and IL-1β [64]. Collectively, the above findings demonstrate that HD-14 reduces inflammation, at least partially, by activating PPAR-γ expression [64]. Further research supported the evidence that HD-14 significantly suppressed the expression of phospho-Janus kinase 1 (p-JAK1) and phosphor signal transducer and activator of transcription 1 (p-STAT1), which may be involved in the development of the inflammation process, through the upregulation of PPAR-γ. Therefore, HD-14 might be considered as a possible anti-inflammatory agent against acute hepatic injury [64].

Resveratrol is a natural polyphenolic compound that may exert multiple beneficial effects against cardiovascular disease, including the suppression of platelet adhesion and aggregation, decreased myocardium ischemia reperfusion damage, and neointimal hyperplasia inhibition of damaged vascular tissues [65]. In this regard, one trial evaluated the action of resveratrol on oxidative stress and endothelium progenitor cellular senescence, and its potential properties on the vascular preventive ability of endothelial progenitor cells [65]. There has been evidence that endothelial progenitor cells can promote the endothelial repair of a damaged artery [65]. Resveratrol reduced the endothelial progenitor cell oxidation response and inhibited endothelium progenitor cellular senescence through the PPAR-γ/heme oxygenase-1 signal handling path [65].

Furthermore, the Huangkui capsule (HKC), an extract of *Abelmoschus manihot*, has been shown to be clinically effective in the amelioration of renal inflammation and glomerular impairment in chronic nephropathy [66]. In this context, the function of HKC as a dual PPAR-α/γ ligand was assessed in a survey investigating its antidiabetic effects on renal impairment in male Sprague-Dawley rats [66]. For this purpose, rats with diabetes-related nephropathy received HKC for 12 weeks at three different dosages: a high dosage (300 mg/kg/d), a medium dosage (175 mg/kg/d), and a low dosage (75 mg/kg/d). It was found that HKC diminished the ER/c-Jun NH2-terminal kinase action in the hepatic and renal tissues of diabetic nephropathy rats and then ameliorated kidney damage by activating PPAR-α/γ [66]. These findings provide strong evidence that HKC may have potential as an antidiabetic nephropathy factor for the therapy of diabetic nephropathy in humans through the activation of PPAR-α/γ [66].

Hyperin is a flavonoid substance that is found in a variety of plants, such as *Ericaceae*, *Guttifera*, and *Celastraceae*. Huang et al. showed that it is characterized by several pharmacological properties such as antioxidant, anti-cancer, anti-coagulant, and anti-inflammatory activities [67]. In a comprehensive study, hyperin substantially diminished the inflammatory levels in C57BL/6J mice with acute hepatic damage and lowered the TNF-α and IL-6 expression in LPS-exposed RAW264.7 cells [67]. Likewise, this study revealed that hyperin significantly stimulated PPAR-γ expression in vivo and in vitro. Interestingly, a specific blocker of PPAR-γ T0070907 and PPAR-γ small interfering (si)-RNA-facilitated silencing in RAW264.7 cells were utilized in comparison to the hyperin treatment group to assess the contribution of hyperin in improving LPS-induced inflammation [67]. Notably, in the LPS-exposed RAW264.7 cells, PPAR-γ overexpression after hyperin administration had an opposite effect on the TNF-α and IL-6 levels. In addition, P-ERK1/2 and P-P38 MAPK were significantly suppressed by hyperin [67]. Taken together, all the above results supported that hyperin could be considered a useful PPAR-γ modulator, decreasing ERK1/2 and p38 MAPK throughout the inflammatory process [67].

Schubert et al. examined the effect of natural molecules on adipophilin [perilipin 2, (PLIN2)] levels, a recognized target of PPAR-γ [68]. In a recent study, PPAR-γ antagonist 2-chloro-5-nitro-N-phenylbenzamide (GW9662) was used to verify whether natural compounds can control PLIN2 expression through PPAR-γ [68]. Surprisingly, the PLIN2 expression was upregulated at a concentration-dependent level by GW9662 rather than opposing the upregulation of PLIN2 expression in THP-1 macrophages [68]. In many human and mice macrophage cell models, this unexpected upregulation was also found to occur [56]. GW9662 increased lipogenesis and increased the TG levels in line with the upregulation of PLIN2 protein. Finally, PPARβ/δ was identified as a substantial agent of the above important GW9662 actions [68].

Phytol, a diterpene alcohol that is included in the chlorophyll molecule, is implicated in the energy assembly from light. As approximately all photosynthetic organisms utilize chlorophylls, phytol is widely found in nature among diverse vegetables [69]. Phytanic acid was shown to stimulate PPAR-γ and RXR, promoting cellular differentiation in both white and brown adipose tissue [70]. Additionally, phytanic acid can stimulate PPAR-α, affecting lipid metabolism in certain cell categories [71]. Phytanic acid can additionally be delivered from the transformation of dietary phytol in the human body [72]. Moreover, a phytol-enriched diet was found to elevate the plasma and liver amounts of phytanic acid and stimulate the mRNA levels of the PPAR-α target genes implicated in peroxisomes and mitochondria β-oxidation and fatty acid metabolism [73].

Another study examined whether *hydroxysafflower* may exert protective effects against liver fibrosis [74]. More specifically, it was found that *hydroxysafflower yellow A* decreased carbon tetrachloride (CCl4)- and HFD-regulated hepatic fibrosis and decreased the serum biochemical indicator, decreased TIMP-1 and TGF-β1 expression, and increased PPAR-γ and matrix metallopeptidase-2 (MMP-2) expression [74]. The above outcomes were substantially decreased by the PPAR-γ antagonist GW9662 by preventing p38 MAPK phosphorylation [74]. These data highlight that both PPAR-γ and p38 MAPK signaling may exert critical preventive impacts against hepatic fibrogenesis and demonstrate a new potential role for *hydroxysafflor yellow A* in the suppression of CCl4- and HFD-associated liver fibrosis [74].

Various terpenoids can activate PPAR-γ from 50 to 100 μM [63]. In this regard, isoprenols like geraniol, farnesol, and geranylgeraniol were shown to exert a possible effect to stimulate PPAR-γ in 3T3-L1 adipocytes and HepG2 hepatocytes [75]. In the above assays, geranylgeraniol, farnesol, and geranylgeraniol were 2.2, 4.1, and 3.7 times, respectively, greater than the vehicle controls. Farnesol and geranylgeraniol were also dose-dependent PPAR-α activators in the PPAR-α ligand assay system. In fact, they showed increases equal to 10 and 8.6 times compared to the vehicle controls, respectively [75]. These activities were as strong and nearly equal to 10 μM fenofibrates, which were used as positive controls for

PPAR-α. In this context, it seems that these farnesols and the geranylgeraniol isoprenols exert their effects through a dual stimulation of both PPAR-γ and PPAR-α [76].

Two new oleanane-type triterpene saponins, tarasaponin IV and elatoside L, and four well-recognized ones, namely stipuleanoside R, kalopanax-saponin F, kalopanax-saponin F-methylester, and elatoside D, were extracted from *elatoside L* and *kalopanax saponin F* and found to suppress at a dose-dependent manner TNF-α-stimulated NF-κB activation compared to the positive control, sulfasalazine [77]. Both elatoside L and kalopanax saponin inhibited the expression of iNOS and COX-2 mRNA produced by TNF-α. In addition, kalopanax saponin F, kalopanax saponin F methyl ester, and elatoside D drastically enhanced the PPAR-γ expression. No other PPAR subtype was activated by the above compounds [77].

Two novel meroterpene analogues, chrysogenester and 5-farnesyl-2-methyl-1-O-methylhydroquinone, have recently been isolated by jellyfish fungus *Penicillium chrysogenum* J08NF-4 [78]. Four well-known farnesyl meroterpenes were also isolated [78]. The dock analysis of the chrysogen ester showed that it could bind to PPAR-γ in a similar manner to amorfrutin B, a naturally occurring PPAR-γ ligand [78]. Chrysogenester induced the activation of PPAR-γ in mice Ac2F hepatic cells and enhanced the PPAR-γ protein amounts in mice RAW 264.7 macrophages. To investigate the potential anti-inflammatory properties of chrysogenester and the mechanisms involved, an in vitro study was also carried out [78]. In RAW 264.7 macrophages, chrysogenester suppressed the NF-κB p65 subunit phosphorylation and reduced the levels of several pro-inflammation-related molecules such as iNOS, NO, COX-2, TNF-α, IL-1β, and IL-6 [78]. Thus, chrysogenes may suppress the inflammatory response through the stimulation of PPAR-γ and the subsequent inhibition of the NF-κB signaling pathway, thereby reducing the levels of the above pro-inflammation-related agents [78].

Auraptene is found in several citrus fruits and has been found to have anti-inflammatory and anticarcinogenic properties [79]. In adipocytes cultures, auraptene increased the antiatherogenic, antidiabetic, and anti-inflammatory cytokine, adiponectin, and decreased the pro-inflammatory cytokine, monocyte chemoattractant protein-1 (MCP-1) [80]. The findings were negated by the treatment with GW9662, indicating that auraptene may exert the above beneficial effects by activating PPAR-γ [80]. It is likely that auraptene may control the mRNA expression of both PPAR-γ and PPAR-α target genes. These activities may contribute to the effects of citrus fruits on cardiovascular disease [80].

Furthermore, a natural pigment widely utilized in various processed foodstuffs is annatto, which is extracted from the outer layer of *Bixa orellana* seeds [81]. Both bixin and norbixin, which belong to the carotenoid phytochemical class, are principal ingredients of annatto that can exert antioxidant and anticarcinogenic activities [82]. The annatto extracts and norbixin exerted hypoglycemic properties in non-obese dogs and mice, respectively [83,84]. Moreover, it was shown that bixin and norbixin triggered PPAR-γ and bixin stimulated PPAR-γ target genes in 3T3-L1 adipocytes, resulting in enhanced adipose tissue cellular differentiation and insulin-induced glucose treatment [85]. Therefore, PPAR-γ activation may be responsible for the hypoglycemic effects of annatto and norbixin.

Certain polychlorinated compounds called chlorophellins A–C were extracted from the fungus *Phellinus ribis* [86], together with the recognized compound drosophilin A, in an attempt to find naturally occurring compounds that can activate PPAR-γ. Nuclear magnetic resonance (NMR) and mass spectrometry were applied to assign their chemical structures. Chlorophellin C was the strongest PPAR-γ agonist. It exerted rather similar PPAR-γ agonistic activity to that of rosiglitazone, a common pharmacological agent applied for the treatment of diabetes [86].

Abscisic acid is a naturally occurring phytohormone and a promising PPAR-γ ligand that can substantially improve insulin sensitivity in db/db mice [87]. Indeed, Guri et al. applied a loss-of-function methodology to explore if abscisic acid could ameliorate insulin resistance in a PPAR-γ-dependent manner on immunological cells. In db/db mice, ab-scisic acid significantly reduced the infiltration of CCR2(+) F4/80(hi) into white adipose tissue

and inhibited the expression of MCP-1 in both white adipose tissue and plasma [87]. The PPAR-γ deficiency in immunological cells, such as macrophages, reduced the abscisic acid properties to suppress white adipose tissue F4/80(hi) ATM infiltration, inhibit MCP-1 expression, and attenuate glucose tolerance [87].

Several studies have shown that oleoylethanolamide, a natural fatty acid ethanolamide, stimulates satiety and suppresses weight increase in rats and mice by activating PPAR-α [88–90]. PPAR-α mRNA and its downstream genes were examined in another study. FAT/CD36, a fatty acid binding protein (L-FABP) in liver, and uncoupling protein-2 (UCP-2) were measured to investigate the possible molecular mechanisms that might reduce lipid buildup in Zucker rats exposed to oleoylethanolamide [91]. Indeed, a two-week administration of a reasonably reduced dosage of oleoylethanolamide (5 mg/kg, single dose daily, i.p.) substantially enhanced the levels of the 3 PPAR-α target genes in the hepatic tissue of obese Zucker rats: *FAT/CD36*, *UCP-2*, and *L-FABP* [91].

Moreover, the protective role of ferulic acid and fish oil regarding gentamicin-induced nephrotoxicity in rats has been investigated in a recent study [92]. The pre- and co-administration of ferulic acid or fish oil attenuated the nephrotoxic impact of gentamicin, as reflected by the significant reductions in the serum blood urea nitrogen (BUN), creatinine, urinary albumin, and N-acetyl-beta-D-glucosaminidase (NAG) actions [92]. Both interventions significantly elevated the renal catalase (CAT) activity and PPAR-γ gene expression. Resolvin E1 was significantly raised in the fish oil group but not in the ferulic acid group [80]. Ferulic acid and fish oil were shown to have anti-inflammation and renal-protective properties that were ascribed to their capability to activate PPAR-γ. Given that ferulic acid and fish oil are naturally occurring agents, they could be considered as less dangerous alternatives when exposed to nephrotoxins [92].

Conocarpus lancifolius (Combretaceae), a Saudi Arabian medicinal plant, was found to have potent antidiabetic activity, and its fruit extract has been shown to have cytotoxic effects against MRC-5 cancer cells, as well as notable antimicrobial action [93]. In this regard, a study assessed the anti-inflammation, cytotoxicity, PPAR, and antioxidant properties of *C. lancifolius* plant extracts and their pure isolated components [93]. A novel trimethoxyellagic acid derivative and two molecules, kaempferol-3-O-rutinoside and beta-sitosterolglucoside 3, were extracted from *Conocarpus lancifolius*. Kaempferol 3-O-rhutinoside was found to activate both PPAR-α and PPAR-γ with a 2.6-times increase in the PPAR-α activity and a 2.2-times increase in the PPAR-γ activity [93]. This was the initial study that isolated and screened the potential pharmacological properties of the extracts and pure compounds from *C. lancifolius* fruits, which were associated with PPAR-α and PPAR-γ activity [93].

A 4D label-free quantitative proteomics and network pharmacological survey assessed the molecular action of a *Fructus alpiniae zerumbet* essential oil on the vascular endothelium cellular senescence in diabetes [94]. In this study, mice with diabetes receiving a high fat and high glucose diet in combination with an intraperitoneal infusion of a low dosage of streptozotocin (STZ, 30 mg/kg) and an oral administration of *Fructus alpiniae zerumbet* essential oil were used [94]. A model of human aortic endothelium cellular senescence treated with high palmitic acid and high glucose concentrations in vitro was also used. Treatment with *Fructus alpiniae zerumbet* essential oil improved the aberrant lipids' metabolic process, the pathological tissue impairment to the vessels, as well as the ageing of the vascular endothelium in diabetic mice [94]. The proteomics and network pharmacological analysis confirmed the different proteins' expressions and the potential drug targets, which were related to the PPAR-γ signaling pathway. In addition, the molecular dock analysis showed that certain small molecules derived by *Fructus alpiniae zerumbet* essential oil had an enhanced PPAR-γ affinity [94]. Thus, the *Fructus alpiniae zerumbet* essential oil improved the vascular endothelium cellular senescence in diabetic mice by activating the PPAR-γ signaling, highlighting the possible advantageous pharmacological properties of *Fructus alpiniae zerumbet* essential oil and providing a rationale for its clinical implementation in diabetic endothelium cellular senescence [94].

The objective of another study was to explore a novel naturally occurring PPAR-γ ligand with fewer side effects compared to rosiglitazone in db/db mouse animals [95]. A PPAR-γ ligand, 18:0 lysophosphatidylcholine, was identified using an in-house natural products' database with a virtual screening methodology. Further, 18:0 Lysophosphatidylcholine showed similar hypoglycemic efficacy to rosiglitazone via PPAR-γ activation. It had significantly lower side effects compared to rosiglitazone [95]. Notably, 18:0 lysophosphatidylcholine reduced liver injury and cardiotoxicity in db/db mouse animals. A decrease in fatty acid biosynthesis, facilitated by the stimulation of the phosphorylation of adenosine 5′-monophosphate (AMP)-activated protein kinase-alpha (AMPKα) and acetyl-CoA carboxylase (ACC), and an enhancement in the expression of UCP1 and PPAR-γ coactivator-1 alpha (PGC1-α), may be the potential mechanisms by which this naturally occurring molecule can attenuate the symptoms of metabolic syndrome [96].

A recombinant mouse PPAR-α, including a myc epitope, a histidine repeat, and a kinase region, applying a solid-phase binding methodology, was utilized in an attempt to find endogenous ligands of nuclear receptors triggered by PPARs [97]. A first group of compounds included (poly)unsaturated fatty acids. A second group had a general positive charge, including long-chain amines, sphingoid bases, and lysoglycosphingolipids [85]. In contrast, PPAR-α was not capable of binding to either N-acylated sphingoid bases or to sphingenine phosphorylated at the primary hydroxy group [97]. Therefore, given the role of PPAR-α and sphingolipids in various cellular processes, the binding of PPAR-α to sphingoid bases could be promising [97].

Predominant neuropathic pain constitutes a frequent unbearable symptom in multiple sclerosis. The analgesics were characterized by several adverse effects that frequently restrict the ability to achieve desired therapeutic doses. A case report study described a woman aged 61 years old and diagnosed with multiple sclerosis who suffered from persistent central neuropathic pain [98]. Acupuncture was merely partially and temporarily effective in the reduction in pain. However, a naturally occurring compound, namely palmitoylethanolamide, a glial modulator, and a PPAR-α agonist led to higher decreases in pain reduction and elevated the interval between acupuncture sessions by the administration of the natural compound [98]. A multimodal stepwise approach was found, while both acupuncture and palmitoylethanolamide affected the non-neuronal cells like stimulated glial cells, which was considered to be crucial for the progression and preservation of neuropathic pain [98].

Table 1. Naturally occurring compounds that exert potential beneficial health effects through PPARs activation.

Natural Source	Natural Compounds	Effects on PPARs	Main Results	Medical Condition Treatment	Reference
Hippeastrum stapfianum (Kraenzl.) *R.S.Oliveira and Dutilh* (Amaryllidaceae)	Lycorine, 7-demethoxy-9-O-methylhostasine, and rutin.	PPAR-α and PPAR-γ activation	Suppression of acetylcholinesterase, and antioxidant activity, in vitro.	Potential drug candidates for Alzheimer's disease.	[44]
Morus nigra L.	Flavonoids: rutin and isoquercitrin together	PPAR-α and PPAR-γ activation	Anti-inflammatory effects: regulation of ROS, NO, and TNF-α in LPS-stimulated RAW 264.7 murine cells	Inflammation.	[45]
Radix Dipsaci	Asperosaponin VI	PPAR-γ activation	Anti-inflammatory properties in mice.	Osteoporosis MCS improvement through brain barrier entry.	[46]
Myristica fragrans Houtt and Brazilian red propolis	Methoxyeugenol	PPAR-γ activation	Increase in hepatic stellate cell activation Increase in lipid droplets. Loss of contractility in mice and human cells. Decrease in proliferation rate and fibroblast marker mRNA expression. Prevention of oxidative stress damage. Reduction in inflammation, hepatic fibrosis, mRNA expression of fibrotic genes, and NF-kB in mice.	Hepatocellular disorders Liver fibrosis.	[47]
Nigella sativa L (Black cumin) volatile oil	Thymoquinone (2-isopropyl-5-methyl-1,4-benzoquinone)	PPAR-γ activation	Attenuation of myeloperoxidase activity. Protection of colon microscopic architecture in inflammatory bowel disease. Lowers the expression of pro-inflammatory cytokines and mediators at mRNA and protein levels. Phosphorylation reduction in the activated MAPK, NF-κB proteins, and colon epithelial PPAR-γ expression enhancement. Diminished CXCL-1 IL-8, cyclooxygenase-2 (COX-2), mRNA expression in HT-29 cells exposed to TNF-α. Increases in HT-29 PPAR-γ mRNA and protein expression in vivo and in vitro.	Inflammatory Bowel Disease.	[50]

Table 1. *Cont.*

Natural Source	Natural Compounds	Effects on PPARs	Main Results	Medical Condition Treatment	Reference
Rice bran and *germ*	Gamma-oryzanol	PPAR-γ activation	Inflammation and cytokine reduction. PPAR-γ overexpression, fat tissue regulation.	Obesity management and novel treatment of obese patients with COVID-19 infection.	[51]
Curcuma longa	Curcumin	PPAR-γ activation	Stimulation of the differentiation of oligodendrocyte progenitors, counteracting their maturation arrest induced by TNF-α through PPAR-γ pathway. Phosphorylation of the protein kinase ERK1/2 Regulation of the conversion of oligodendrocyte progenitors to immature oligodendrocytes. Increases in co-factor PGC1-α and the cytochrome c oxidase core protein COX-1 levels independently from TNF-α presence.	Treatment of demyelinating diseases.	[52]
Rosemary (*Rosmarinus officinalis*)	Carnosic acid	PPARα/γ antagonistic action	Inhibition of the browning process of white adipocytes and decreased expression of thermogenic key markers, suggesting that carnosic acid is able to induce whitening in thermogenic adipocytes.	Carnosic acid may be a potent therapeutic agent of overweight/obesity and associated diseases.	[53]
Scutellaria radix	Wogoxin	PPAR-γ activation	Anti-inflammatory and antioxidant effects by lowering the expression of TNF-α, IL-1β, and inducible nitric oxide synthase (iNOS) after intracerebral hemorrhage. Increases in Axl, MerTK, CD36, and LAMP2 expression in perihematomal microglia and BV2 cells. Antagonist: PPAR-γ inhibitor GW9662.	Hematoma clearance and neurobehavioral regaining by targeting PPAR-γ.	[54]
Fava bean	Butein	PPAR-γ activation	Natural butein-downregulated PPAR-γ. Butein chitosan formula: no effect.	Antidiabetic properties.	[55]

Table 1. *Cont.*

Natural Source	Natural Compounds	Effects on PPARs	Main Results	Medical Condition Treatment	Reference
Cecropia obtusifolia	Chlorogenic acid	PPAR-α and PPAR- γ activation	Insulin-releasing agent by increasing intracellular calcium concentrations ([Ca2+]i) in RINm5F cells. Insulin- and lipid-lowering regulator. Induction of PPAR-γ and -α expression in 3T3-L1 adipose tissue cells. Increasing mRNA expression of PPAR-γ and GLUT4, PPAR-α, and FATP. Upmodulation of PPAR-α mRNA in the liver.	Anti-carcinogenic, neuroprotective, antioxidant, anti-inflammatory, hypoglycemic, and hypolipidemic properties. Lipid consolidation.	[56] [57]
Pinewood, rosin	Dehydroabietic acid	PPAR-α and PPAR-γ activation	PPAR-γ and -α activation Partial PPAR-γ agonist.	Amelioration of IR and liver steatosis in high-fat-diet (HFD)-fed mice	[58]
Fruits	Pelargonidin	PPAR-γ activation	Decreased expression of HMGCR, LPL, Glut4, and A-FABP Reduction in PPAR-γ activation.	Adipogenesis inhibition in mice 3T3-L1 cells.	[59]
Magnolol	Neolignane	PPAR-γ activation	Reduced Aβ deposition, toxicity, and Aβ-induced memory impairment in transgenic *C. elegans*. Action inverted by GW9662, a selective PPAR-γ antagonist.	Mitigation of beta-amyloid-induced Alzheimer's disease.	[60]
Malva palvifloa	M. parviflora leaf hydroalcoholic extractcontaining oleanolic acid and scopoletin	PPAR-γ activation	Preservation of the phagocytic capacity of microglia through a PPAR-γ/CD36-dependent manner. Blunting the pro-inflammatory M1 phenotype of microglia and enhancing microglia phagocytosis.	Prevention of cognitive impairment associated with a metabolic disorder. Prophylactic agent for the progression of Alzheimer's disease.	[61]
Centella asiatica	Asiatic acid	PPAR-γ activation	Released promotion of endogenous PPAR-γ ligand 15d-PGJ2.	Prevention of renal fibrosis.	[62]
Organic complex of chromium and vitamin biotin	Chromium histidinate and biotin	PPAR-γ activation	Enhancement of glucose and lipid metabolism. Increases in IRS-1, PPAR-γ, and NF-κB protein expression in the liver of trained rats.	Health promotion.	[63]

Table 1. *Cont.*

Natural Source	Natural Compounds	Effects on PPARs	Main Results	Medical Condition Treatment	Reference
Citrusaurantium L.	Hesperetin, hesperetin derivative-14	PPAR-γ activation	HD-14 increased PPAR-γ expression in vitro and in vivo. PPAR-γ overexpression led to the reduction in the expression of TNF-α, IL-6, and IL-1β. PPAR-γ knockdown with small interfering RNA exerted pro-inflammatory impacts in LPS-exposed RAW264.7 cells.	Anti-inflammation agent against acute injured liver	[64]
Natural polyphenolic compound in fruits (e.g., Grapes)	Resveratrol	PPAR-γ activation	Resveratol seemed to be implicated in PPAR-γ/heme oxygenase-1 signaling pathway.	Cardiovascular Diseases: Lowered oxidative reaction of endothelial progenitor cells and suppressed endothelial progenitor cells senescence	[65]
Abelmoschus manihot	Huangkui	PPAR-α/γ activation	Huangkui improved nephropathy in diabetic rats by activating PPAR-α/γ.	Kindey Disease; Diabetic nephropathy	[66]
Ericaceae, *Guttifera*, and *Celastraceae*	Hyperin	PPAR-γ activation	Hyperin remarkably stimulated PPAR-γ expression in vivo and in vitro. Regulation of inflammation in C57BL/6J mice with acute liver injury and reduction in TNF-α and IL-6 expression in LPS-induced RAW264.7 cells. Hyperin suppressed P-ERK1/2 and P-P38 MAPK expression. PPAR-γ downregulated ERK1/2 and p38 MAPK throughout inflammation progression.	Anti-inflammatory effects	[67]
Phytol	Phytanic acid	PPAR-γ activation PPAR-α activation	PPAR-γ and RXR stimulation. Activation of cellular differentiation in both white and brown adipose tissue. Stimulation of PPAR-α to regulate lipid metabolism.	Enhancing fatty acid metabolism	[70,71,73]

Table 1. *Cont.*

Natural Source	Natural Compounds	Effects on PPARs	Main Results	Medical Condition Treatment	Reference
Hydroxysafflor yellow A	Safflomin A	PPAR-γ activation	CCl4 reduction, high-fat-diet-mediated liver fibrosis. Downregulation of the expression of TIMP-1 and TGF-β1. Upregulated the expression of PPAR-γ and MMP-2. PPAR-γ antagonist GW9662 by suppressing p38 MAPK phosphorylation adverted the above effects.	Liver fibrosis prevention	[74]
Isoprenols	Geraniol, farnesol, and geranylgeraniol	PPAR-γ activation PPAR-α activation	Activators of PPAR-γ, such as ligands in 3T3-L1 adipose tissue cells and HepG2 liver cells. Farnesol and geranylgeraniol stimulated PPAR-α by a dose-dependent manner.	Dislipedemia regulation, metabolic disorders	[75,76]
Elatoside L and *kalopanax-saponin F*	Oleanane-type triterpene saponins, tarasaponin IV, elatoside L, and stipuleanoside R, kalopanax-saponin F, kalopanax-saponin, F methylester, and elatoside	PPAR-γ activation	Suppression of NF-κB activated via TNFα, dose-dependently, compared to sulfasalazine. Elatoside L and kalopanax-saponin stimulated iNOS and COX-2 mRNA expression. Kalopanax-saponin F, kalopanax-saponin F methylester, and elatoside D enhanced PPAR-γ transactivation.	Anti-inflammation activity	[77]
Gellyfish	Jellyfish-derived fungus Penicillium chrysogenum J08NF-4	PPAR-γ activation	Chrysogenester induced PPAR-γ activation of mice Ac2F hepatic cells and enhanced its protein amounts in mice RAW 264.7 macrophages. In RAW 264.7 macrophages, chrysogenester suppressed NF-κB p65 phosphorylation and reduced pro-inflammatory mediators iNOS, NO, COX-2, TNF-α, IL-1β, and IL-6 expression in vitro.	Chrysogenester may suppress inflammation progression through activating PPAR-γ and downregulating NF-κB signaling pathway	[78]

Table 1. *Cont.*

Natural Source	Natural Compounds	Effects on PPARs	Main Results	Medical Condition Treatment	Reference
Citrus fruits	Auraptene	PPAR-γ activation	Auraptene may regulate the mRNA expression of PPAR-α and -γ target genes as a dual agonist. In cultured adipocytes, auraptene upregulated adiponectin and downregulated MCP-1. The presence of GW9662 negated the above actions.	Cardiovascular disease protection	[80]
Bixa orellana	Annato: bixin and norbixin	PPAR-γ activation	Bixin- and norbixin-stimulated PPAR-γ and bixin-stimulated PPAR-γ targeted genes in 3T3-L1 adipocytes and promoted adipocyte differentiation and insulin-induced glucose uptake.	Hypoglycemic effects	[82]
Fungus phellinus ribis	Chlorophellin A–C	PPAR-γ activation	Chlorophellin-C behaved as PPARγ agonist comparable to rosiglitazone.	Diabetes therapy	[86]
Natural phytohormone	Abscisic acid	PPAR-γ activation	PPAR-γ agonist enhanced insulin sensitivity. PPAR-γ deficiency in immune cells, diminished the capability of abscisic acid to inhibit the infiltration of F4/80(hi) ATMs into white adipose tissue, to inhibit MCP-1 expression, and to enhance glucose tolerance.	Augmentation of insulin sensitivity	[87]
Fatty-acid ethanolamide	Oleoylethanolamide	PPAR-α activation	Enhanced the expression of three PPAR-α target genes in the hepatic tissue of obese rats: FAT/CD36, L-FABP, and UCP-2.	Reduction in lipid accumulation. Satiety promotion.	[91]
Fish Plant tissues: coffee, broccoli, spinach grain bran, citrus fruits	Fish oil: ω-3 polyunsaturated fatty acids eicosapentaenoic acid (EPA, 20:5) Ferulic acid	PPAR-γ activation	Increased renal catalase activity and PPAR-γ gene expression.	Proved anti-inflammatory and renal-protective effects. Nephrotoxicity treatment	[92]
Conocarpus lancifolius (Combretaceae)	Rimethoxyellagic acid kaempferol 3-O-rutinoside and β-sitosterol glucoside	PPAR-α and PPAR-γ activation	Kaempferol 3-O-rutinoside: stimulation of PPAR-α and -γ with 2.6-fold increase in PPAR-α activity and 2.2-fold increase in PPAR-γ at 25 μ/mL.	MRC-5 cancer cell line cytotoxicity induction, and prominent antiprotozoal and antibacterial activities	[93]

Table 1. *Cont.*

Natural Source	Natural Compounds	Effects on PPARs	Main Results	Medical Condition Treatment	Reference
Fructus alpiniae zerumbet	Essential oil (EOFAZ)	PPAR-γ activation	Increased PPAE-γ activity: The small-molecule compounds in EOFAZ exhibited an increased affinity for PPAR-γ.	Improved abnormal lipid metabolism, vascular histopathological damage, and vascular endothelial aging in mice with diabetes	[94]
In-house natural product library	18:0 lysophosphatidylcholine	PPAR-γ activation	18:0 lysophosphatidylcholine showed a similar hypoglycemic impact to rosiglitazone by activating PPAR-γ and caused significantly fewer adverse side effects compared to rosiglitazone. Decrease in fatty acid biosynthesis facilitated by stimulation of the phosphorylation of adenosine 5′-monophosphate, AMPKα, and ACC, Increased the expression of UCP1 and PPAR-γ coactivator-1 alpha (PGC1-α).	Metabolic syndrome treatment	[95]
Bacteria	Medium-chain fatty acids	PPAR-γ activation	MCFAs by binding to PPAR-γ antagonized TZD-dependent adipogenesis in vitro. Exhibited suppression of PPAR-γ phosphorylation by cyclin-dependent kinase 5-linked reversing of adipose tissue insulin resistance.	Clinical treatment of diabetes	[96]
	Palmitoylethanolamide	PPAR-α activation	Palmitoylethanolamide acted as PPAR-α agonist.	Neuropathic pain treatment	[97]

ROS: reactive oxygen species; NO: nitric oxide; TNF-α: tumor necrosis factor-α; LPS: lipopolysaccharide; MCS: multiple chemical sensitivity; MAPK: mitogen-activated protein kinase; NF-kB: nuclear factor kappa B; CXCL-1: chemokine (C-X-C motif) ligand 1; IL-8: intereukin-8; COX-2: cyclooxygenase-2; ERK1/2: extracellular-signal-regulated kinase 1/2; PGC1-α: peroxisome-proliferator-activated receptor-γ coactivator-1α; hMAD: human multipotent adipose-derived stem; iNOS: inducible nitric oxide synthase; TIMP-1: tissue inhibitor of metalloproteinase-1; TGF-β1: transforming growth factor-β1; MMP-2: matrix metallopeptidase-2; MCP-1: monocyte chemoattractant protein-1; FAT/CD36: fatty acid translocase/cluster of differentiation 36; FABP: fatty-acid-binding proteins; EOFAZ: essential oil from fructus *alpiniae* zerumbet; ACC: acetyl-CoA carboxylase; AMPKα: AMP-activated protein kinase-alpha; UCP1: uncoupled protein 1; MCHF: medium-chain fatty acids; TZD: thiazolidinediones; IR: insulin resistance.

4. Discussion

PPARs exert an important impact regarding the control of cell metabolism, growth and proliferation, and are also implicated in several pathophysiological conditions. The recent literature has demonstrated that natural compounds and/or their synthetic derivatives can behave as ligands of PPARs, stimulating their transcriptional activity and enabling their use as therapeutic agents for diverse non-communicable diseases and cancer. Natural compounds seem to have more appropriate drug-like properties, exhibiting minor side effects compared to their synthetic bioactive derivatives.

The 38 natural compounds examined in the present review, all with lipophilic chemical profiles, including saponins, flavonoids, polyphenols, triterpenes, and polyunsaturated and saturated acids, act as potential PPAR ligands, mainly as activators or modulators of PPAR-γ. Rimethoxyelagic acid, kaempferol 3-O-rutinoside, β-sitosterol glycoside and geraniol, farnesol, geranylgeraniol Huangkui, and dehydroabietic acid showed dual binding properties by binding to and stimulating both PPAR-α and PPAR-γ. Remarkably, these double PPAR-α/γ agonists manifested properties associated with lipid metabolism, insulin resistance, cytotoxicity against cancer cells, liver steatosis, nephropathy, and treatment of neurodegenerative pathological states.

On the other hand, synthetic dual PPARα/γ agonists are used for the drug synthesis targeting management of the previously mentioned health issues. Nevertheless, their clinical use has been determined to be unsafe because of side effects like edema, hyperplasia, cardiac and kidney disorders, and increased body weight (e.g., glitazone and ragaglitazar) [99]. Indicatively, naveglitazar, a γ-dominant PPAR-α/γ dual agonist, was assessed for its anti-anti-cancer properties in F344 rats in a two-year follow-up survey [100]. This study showed that naveglitazar resulted in hypertrophic and proliferative outcomes on the urothelium; however, no alterations in the urinary parameters were found [100]. Accordingly, muraglitazar, another PPAR-α/γ ligand, promoted, in a dose-dependent manner, urinary bladder cancer in male Harlan Sprague-Dawley rats at concentrations of 5, 30, or 50 mg/kg/day for almost two years [101].

Regarding PPAR-γ agonists, the research is more extended. PPAR-γ modulates gene expression associated with glucose and fat metabolism. Glitazones are synthetic PPAR-γ agonists, exhibiting hypoglycemic and anti-lipid actions. While they are a part of diabetes management, they have also demonstrated serious side effects, such as myocardial infarction (rosiglitazone) [92]. On the contrary, natural PPAR-γ ligands show the same action as synthetic analogues. Notably, triggering of PPAR-γ by naturally occurring agonists like PUFAs (docosahexaenoic acid and eicosapentaenoic acid) increased the renal catalase activity and PPAR-γ gene expression, providing anti-inflammatory properties and increasing insulin sensitivity [97]. Notably, lysophosphatidylcholine decreases free fatty acid synthesis and thus can manage metabolic syndrome, avoiding implications [95].

Neuropathetic pain is generally faced through non-steroidal anti-inflammatory drugs (NSAID), exhibiting side effects like hypertension and gastrointestinal bleeding [102,103]. Palmitoylethanolamide, a natural N-acyl-ethanolamine (NAE) fatty acid amide and a PPAR-α ligand, has been implemented for decreasing neuropathetic inflammation and joint pain, anxiety, and sleep disorders without causing any serious side effects [102,104].

In contrast, studies on PPAR-β/δ activation remain extremely limited. Although PPAR-β/δ is found in all the tissues of the human body, activating lipid oxidation and causing a thermogenic effect [105], when overexpressed, it raises health concerns because of possible carcinogenesis effects [106]. Concerning PPAR-β/δ, novel ligands, either naturally occurring or synthetic, have not been explored so far as the activation of this receptor subtype lacks the advantage of specificity compared to PPAR-γ and PPAR-α and therefore a targeted and selective activation that may exert potential beneficial health effects.

Even if there is extensive research on naturally occurring PPAR-γ activators, PPAR-α and especially PPAR-β/δ activation remain less studied. Moreover, most of the current evidence has been derived mainly by in vitro assays, whereas in vivo animal studies remain scarce. Moreover, most of the in vivo animal studies included a small number

of animals of different species. Notably, there is not any human clinical study so far concerning the naturally occurring activators of PPARs. In any case, a well-balanced healthy diet that includes naturally occurring activators of PPARs, and especially PPAR-γ, might prove to be more effective for preventing and/or co-treating several pathophysiological states, such as metabolic disorders, cardiovascular diseases, cancer, and other human diseases. Indicatively, a dietary pattern such as the Mediterranean Diet that includes an increased frequency of fruit and vegetable intake as well as PUFAs, polyphenols, flavonoids, triterpenoids, and other natural bioactive molecules with strong antioxidative and anti-inflammatory activities may be considered in terms of a conglomeration of PPAR activators.

5. Conclusions

This study reviews natural compounds acting as PPAR agonists, supporting health issues and elucidating the potential of the development of new drugs or functional supplements. As far as we know, this is the first review on naturally occurring compounds targeting PPARs, which are not widely studied. Natural PPAR ligands demonstrate a multidimensional central role not only in fat and carbohydrate metabolism but also in the regulation of the central and peripheral nervous systems, inflammation, oxidative stress, and the treatment of metabolic syndrome. Although synthetic compounds are used as drugs to manage health problems, serious side effects have been observed, while the same is not the case for their natural analogues. Further clinical studies on natural compounds such as the ligands of PPARs as well as a better elucidation of the molecular mechanisms of PPARs are needed to implement a strategy in the fields of pharmacological technology and food chemistry to make them part of clinical practice and daily dietary practice, respectively.

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