Chapter

Food-Based PPARγ Ligands

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Abstract

Foods and herbs have long been used medicinally and the interest in natural product therapies have returned in the recent decades. PPARγ is a transcription factor that regulates expression of a variety of metabolic genes. The discovery of full activators of PPARγ have been useful in the treatment of diabetes but are not without side effects. The discovery of food based PPARγ ligands have allowed the exploration of natural treatment of a variety of diseases with potentially fewer side effects due to the ligand based activation rather than full activation. Here we present background on the PPARγ transcription factors and summarize several compounds and the food sources that have demonstrated therapeutic potential for disease states including diabetes, cancer, and cardiovascular disease.

Keywords: PPARγ, peroxisome proliferator-activated receptor gamma, nutraceuticals, cinnamon, diabetes, inflammation

1. Introduction

Peroxisome proliferator-activated receptor gamma (PPARγ) is a transcription factor that is activated by ligand binding as well as via ligand-independent activation. PPARγ plays an active role in regulation of glucose and lipid metabolism but more recently has been examined for its role in numerous disease states including: diabetes, cardiovascular disease, cancer, inflammation, angiogenesis and metastasis [1–6]. Some research also suggests it provides potential for anti-aging activity [7]. Prior to the discovery of the thiazolidinedione (TZD) drugs used for treatment of diabetes, the general consensus was that PPARγ was subject only to ligand-independent activation [8]. It was the discovery of these drugs that suggested that PPARγ was also sensitive to ligand-dependent activation [8–11]. The goal of the first generation TZDs was to target insulin sensitivity and although the drugs were successful with this they were not without toxicity concerns. The focus more recently has looked to natural methods to accomplish therapeutic level results and PPARγ provides a viable target with multiple mechanisms available for activation and a variety of functional food sources for PPARγ ligands.

PPARγ is a member of the nuclear receptors gene subfamily and is found on chromosome 3. Other members of the gene family include PPARα and PPARβ/δ. In addition due to alternative splicing, there are multiple isoforms of PPARγ, known as PPARγ1 and PPARγ2 [12, 13]. PPARγ1 is expressed at high levels in white and brown adipose tissue, however, lower levels of expression of PPARγ1 are found in all tissues as well as the immune cells. PPARγ2 is expressed only in white and brown adipose

tissue [14]. Although disease states are sometimes related to changes in expression of these isoforms and inefficient signaling associated with the pathway, some research has demonstrated that specific variants have been linked to early onset type 2 diabetes. Nearly half of these patients had a variant in PPARγ2 resulting in an amino acid substitution of tyrosine to cysteine in the activation function domain 1 (AF1). Of note is also that of these patients, 83% also had diabetic kidney disease [15]. Another study demonstrated that loss of function mutation of arginine 288 to histidine in the ligand-binding domain (LBD) resulted in significant conformational changes in the protein that lead to blunting of the activation via prostaglandins [16].

Mouse studies have shown that knockout of PPARγ2 results in insulin resistance [13]. In contrast, it was demonstrated that activation of PPARγ in mouse adipocytes improves insulin sensitivity [17]. Together these studies support the effects of PPARγ activity on insulin resistance and type 2 diabetes in addition to its known role in adipocyte differentiation [12, 18]. PPARγ also controls the expression of the skeletal muscle and adipose glucose transporter (GLUT4), and adipose tissue based hormones adiponectin, resistin and leptin [19–21]. It is clear from these studies that modulation of PPARγ activity plays a significant role in patient wellness considering the effects of activation on glucose homeostasis, lipid metabolism and adipocyte differentiation. These effects strongly suggest that activation of PPARγ in a controlled fashion provide strong potential for improvement of patient quality of life. Nutraceuticals offer this type of low level controlled activation that may benefit the patient even beyond the potential for the synthetic drugs targeting PPARγ activation.

The structure of PPARγ contains multiple protein domains of importance as shown in **Figure 1**. The individual domains are separated based on function and can themselves be modified in most cases. The activation function domain 1 (AF1) is on the N-terminus and is subject to phosphorylation, and small ubiquitin like modifiers (SUMOylation). In general SUMOylation leads to suppression of transcriptional activity while ubiquitination increase transcriptional activity. Phosphorylation can increase or decrease transcriptional activity depending on the site of phosphorylation and the enzyme catalyzing the phosphorylation event. In general deacetylation by Sirt-1, the histone deacetylase leads to dissociation of the nuclear receptor corepressor (NCoR) and increased transcriptional activity [22]. The next domain is the DNA binding domain (DBD) responsible for interacting with the DNA in conjunction with the retinoid c receptor (RXR). RXR houses a binding site for 9-cis-retinoic acid, which when bound allows RXR to complex with the PPARγ complex and interaction with DNA [23]. The HD domain is a regulatory domain named due to the histidine

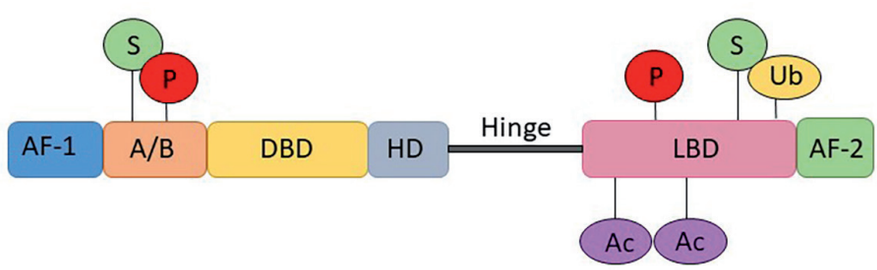

Figure 1.
The structure of PPARγ. AF-1 is the activated function 1 domain. A/B houses a SUMOylation (S) and phosphorylation (P) site. DBD is the DNA binding domain. HD is the conserved protein domain with histidine and aspartate that interacts with the coactivator PGC-1α. The ligand binding domain (LBD) is attached via a hinge region and houses a SUMOylation, phosphorylation, ubiquitination (Ub) and two acetylation (Ac) sites. AF-2 is the activated function.

(H)-aspartate (D) amino acids conserved in the region. The HD domain interacts with either the coactivator, peroxisome proliferator-activated receptor gamma coactivator (PGC-1α) or the corepressors NCoR and silencing mediator of retinoid and thyroid hormone receptors (SMRT) [24]. On the C-terminal end is the ligand binding domain (LBD) that when ligand bound by an activator, stimulates transcription. When no ligand is bound, and the corepressor is bound, transcription is limited. The LBD is also subject to phosphorylation, ubiquitination, SUMOylation and acetylation. Each of these affect the likelihood of ligand activation. Of interest are the histone deacetylase enzyme (HDAC) which deacetylate the ligand binding domain. Inhibition of this HDAC, limits deacetylation of the LBD and leads towards PPARγ activation via the ligand independent pathway [25].

The PPARγ pathway involves several overlapping cellular functions. Activation of PPARγ, either ligand-independent or ligand dependent, leads to change in the immune system, metabolic organs including skeletal muscle and adipose tissue [26–28]. For example in the immune system macrophages and regular T cells, activation of PPARγ in general will decrease inflammation. Inflammation is decreased in the heart and brain but lipid storage is increased in the heart as well as growth. In white adipose tissue lipid metabolism and glucose homeostasis is improved with activation. Of particular interest is the fact that activation of PPARγ increases remodeling and browning of white adipose tissue, a benefit that will likely lead to better ability for patients to manage weight (ref). It is clear that there are strong benefits to PPARγ activation, but potential side effects such as lipid storage in the heart, sodium and fluid retention and increased desire for food can also result in unwanted effects [22].

It is important to consider how PPARγ activation can be achieved while minimizing the potentially harmful side effects. A benefit also exists to activate PPARγ in a ligand dependent fashion versus the ligand independent activation. Endogenous ligands to PPARγ are typically fairly weak agonists while the TZDs are strong agonists [8, 29]. The first generation TZD troglitazone was pulled from the market in the US approximately 3 years after first becoming available because it resulted in severe or fatal hepatotoxicity in numerous cases [30–34]. Other TZDs were taken off the European market and restricted in the US markets due to potentially dangerous side effects including myocardial infarction, heart failure, hepatic failure [35–38]. It is still currently believed that these side effects resulted in part to the full PPARγ activation rather than the moderate activation offered by the weaker ligand agonists [29]. Gene expression, especially expression of genes involved in metabolic process that are sensitive to endogenous ligands as well, should be tightly controlled with an effective regulatory method that allows frequent adjustment of expression levels in response to the environment. Altering expression of genes fully by fully activating PPARγ poses several concerns, especially since there is so much overlap within the PPARγ activation pathway. Thus, an increased emphasis on natural and less specific activators is warranted. Natural ligands are particularly useful in this situation because the full and permanent activation is not desired. Given the range of disease state linked to PPARγ signaling, exploring the potential natural food based ligands is an essential tool in moving patient wellness forward.

2. Food sources and therapeutic potential

Several herbs and foods have been used medicinally for centuries, although mechanism of action was not known and in some cases remains unclear. Many of the

compounds found in common herbs and foods have been discovered to be ligands of the nuclear receptors such as PPARγ. A variety of studies presented summarize the compound identified to harbor therapeutic potential as a PPARγ ligand resulting in partial activation of the transcription factor and expression of a variety of metabolic and growth genes. Many of these compounds are found in overlapping herbs or spices. For example, cinnamon contains numerous compounds that are demonstrated ligands including: 2-hydroxychalcone, cinnamaldehyde, catechin, eugenol, ethylcinnamate, epicatechin, and cinnaminc acid. As expected, cinnamon has been used medicinally to treat digestive disorders and metabolic problems for decades.

Given the large number of compounds that function as PPARγ ligands, detailed discussion of each is warranted, but an overall summary is also important. **Table 1** identifies several of the compounds of interest, their food sources and conveniently lists references that pertain to the studies. Apigenin acts as a partial agonist for PPARγ, inducing an effect of agonism in the absence of a full agonist, and antagonism in the presence of a full agonist. This is due to the low binding affinity that apigenin has for PPARγ itself [6, 39]. However, even with this low binding affinity, it has shown to still produce beneficial effects through this pathway. Due to its interactions with PPARγ, apigenin has anti-inflammatory effects, and has been used for treatment of colitis, or inflammation of the intestines. However, beyond its interactions with PPARγ, apigenin has also been shown to decrease food-intake, and help with weight loss [39]. Apigenin has a lot of potential clinical use and application, and can be found in marjoram, sage, thyme, holy basil, parsley, and alfalfa [6, 39].

2-Hydroxychalcone is another example of a partial agonist for PPARγ. Similar to apigenin, this partial agonism of PPARγ leads to anti-inflammatory effects induced by 2-Hydroxychalcone. Although the pathways for these effects are not yet understood in the case of 2-Hydroxychalcone, it is an example of a PPARγ ligand that has shown anti-inflammatory effects [4, 6, 39]. As for food sources of 2-Hydroxychalcone, it is primarily found in cinnamon [6, 39].

PPARγ agonists	**Food Sources**	**References**
Apigenin	Marjoram, sage, thyme, holy basil, parsley, alfalfa	[6, 39]
2-Hydroxychalcone	Cinnamon	[6, 39]
Luteolin	Marjoram, sage, rosemary, tarragon, thyme, parsley, alfalfa	[6, 39]
Rosmarinic Acid	Marjoram, sage, rosemary, lavender, thyme, oregano	[6, 39]
Cinnamaldehyde, Cinnamic Acid	Cinnamon, clove	[6, 39]
Resveratrol	Bilberries (European blueberries), peanuts, grapes, wine	[5, 6, 32]
Quercetin	Dill, bay leaves, oregano, pomegranate fruit, apples, tarragon, parsley, chive, lovage	[6, 39]
Catechin	Apples, marjoram, sage, rosemary, cinnamon, pomegranate fruit, cacao, green tea, grapes, apricots, cherries	[4, 6, 40, 41]
Eugenol	Cinnamon, clove	[6, 39]
Epicatechin	Cacao, tea, cinnamon, thyme, apples, grapes	[6, 42, 43]

Table 1.
Select compounds that function as PPARγ agonists and the food sources.

Luteolin acts as a partial agonist for PPARγ, thus affecting PPARγ-dependent gene expression and causing agonism, or an increase in gene expression in the absence of a full agonist, and causing antagonism, or a decrease in gene expression in the presence of a full agonist. However, luteolin uniquely acts as a full agonist for the gene expression of insulin dependent glucose transporters (GLUT-4) in the 3 T3-L1 mouse cell model [4]. Currently it is unclear if this effect is also seen in humans, however it is a potential target for future research. Luteolin also has an effect on inflammation through its effect on proinflammatory cytokines such as interleukin-8 (IL-8) [4]. Although the clinical implications are still unclear for luteolin, recent studies have started to uncover some of the potential beneficial effects it may have. In an in vitro study in human intestinal cells, luteolin has shown to prevent the damage caused by chemotherapeutic treatment. As for the sources of luteolin, luteolin has been shown to be present in marjoram, sage, rosemary, tarragon, thyme, parsley, and alfalfa [6, 39].

Similar to luteolin, rosmarinic acid also acts as a partial agonist for PPARγ, allowing for weak agonism in the absence of a full agonist, and antagonism in the presence of a full agonist [6]. Rosmarinic acid has shown to have anti-inflammatory activity in cell culture assays, however its clinical applications should still be further explored and elaborated on. Rosmarinic acid does however have a poor bioavailability, so its application in humans may be limited regardless of its ability to bind to PPARγ [39]. It still has shown activity as a PPARγ ligand though, so it may be worth further investigation. As far as where rosmarinic acid can be found, it is seen in marjoram, oregano, rosemary, sage, thyme, and lavender [6, 39].

Cinnamic acid and cinnamaldehyde work very similarly. Cinnamaldehyde acts as a partial agonist for PPARγ, allowing for weak agonism in the absence of a full agonist, and antagonism in the presence of a full agonist. Cinnamic acid functions in a similar way, but with a much higher binding affinity for PPARγ [6, 44]. They have both shown a plethora of beneficial effects related to its effect on PPARγ. These include, but are not limited to reducing amyloid-β plaques in Alzheimer's disease, anti-inflammatory effects, as well as improving glucose and lipid levels as well as insulin sensitivity in Diabetes [39, 44, 45]. Although not all of these effects have been shown in humans yet, some have, and there is great potential for clinical application of cinnamaldehyde. As far as the sources of cinnamaldehyde and cinnamic acid, they can both be found in cinnamon as well as clove [6, 39].

Similar to luteolin, resveratrol also acts as a partial agonist for PPARγ-dependent gene expression, which leads to slight agonism in the absence of a full agonist, and antagonism in the presence of a full agonist. Resveratrol affects both glucose and lipid metabolism, and can also have an effect on inflammation in animal models. Resveratrol has also been shown to improve insulin sensitivity in human patients, which is a contributing factor for Type 2 Diabetes, and can help in control of that disease state beyond metabolism of foods consumed. These mechanisms indicate Resveratrol as potentially beneficial in patients with Type 2 Diabetes, as it can help with glucose metabolism, insulin action, and the storage of fat, potentially lowering their risk of cardiovascular events associated with fats [4]. As for the sources of resveratrol, resveratrol has been shown to be present in foods such as bilberries (European blueberries), grapes, wines, and peanuts [5, 6].

Quercetin acts as a partial agonist for PPARγ-dependent gene expression, causing agonism, or an increase in gene expression in the absence of a full agonist, and causing antagonism, or a decrease in gene expression in the presence of a full agonist [4, 6]. Quercetin has also been shown in a mouse fibroblast cell model (3 T3-L1), that it promotes glucose uptake through insulin-dependent glucose transporters (GLUT-4),

however does not affect the production of lipid stores through adipogenesis [4]. Additionally quercetin has shown anti-inflammatory effects in vivo, and is very similar in this regard to resveratrol [4, 39, 46, 47]. Quercetin is also fairly abundant in food sources, and can be found in dill, bay leaves, oregano, pomegranate fruit, apples, tarragon, parsley, chive, and lovage [6, 39].

Catechin too binds to PPARγ, however unlike the previous compounds mentioned, catechin acts as a full agonist for PPARγ-dependent gene expression, and as such does not provide antagonism [4]. This being said, the effects of catechin are expected to differ from the other compounds mentioned previously. One of these differences seen is that the negative enantiomer of catechin promotes the differentiation of mesenchymal stem cells into adipocytes, or fat cells [40]. Alternatively, the positive enantiomer of catechin has anti-inflammatory properties, similar to those previously mentioned [41]. Altogether, both enantiomers of catechin appear to have beneficial effects in terms of health, and both appear to affect the PPARγ pathways. Additionally, the sources of catechin are plentiful, as it can be found in apples, marjoram, sage, rosemary, cinnamon, pomegranate fruit, cacao, green tea, grapes, apricots, and cherries [4, 6, 40, 41].

Although the activities of eugenol through PPARγ are not yet well-defined, it is known to bind to PPARγ with a greater affinity than that of catechin, which acts as a full agonist [4, 6]. Eugenol is also a compound that has been demonstrated to increase insulin sensitivity, and has seen use in essential oils for that purpose [39]. Eugenol has also shown anti-inflammatory effects, like all of the other compounds discussed in this chapter [39]. As for where eugenol is found though, it is seen mostly in clove and cinnamon [6, 39].

Ethyl cinnamate is very similar to cinnamic acid and cinnamaldehyde. It too works similarly in terms of agonism, but has a binding affinity more similar to that of cinnamic acid as opposed to cinnamaldehyde [6]. Additionally, as a PPARγ agonist, it shows the same anti-inflammatory effects that all of the other compounds previously mentioned exhibit [39]. In terms of food sources for ethyl cinnamate though, it is seen in mainly cinnamon and clove [6, 39].

Epicatechin is very similar to the compound discussed earlier, catechin. They both have great binding affinities for PPARγ, and have very similar effects [6]. Like catechin, epicatechin has anti-inflammatory properties. However unlike catechin, epicatechin has also been shown to inhibit PPARγ signaling as well as adipogenesis, or the development of fat stores. Altogether, epicatechin has many positive effects, whether related to its actions on PPARγ, or it's other bioactivities, and has great promise for medicinal application [42, 43]. In terms of sources of epicatechin, it can be found most prominently in cacao, but also in tea, cinnamon, thyme, apples, grapes, and many other fruits and vegetables [6, 42, 43].

3. Conclusion

As presented there are several natural sources of PPARγ ligands found in spices and food that are commonly consumed. The degree of activation varies on whether the ligand acts as a full agonist or simply as a partial agonist. Molecules that demonstrate a low binding affinity, less than 100 μM, include apigenin, 2-hydoxylchalcone, luteolin, rosmarinic acid, cinnamaldehyde and cinnamic acid, resveratrol and quercetin. Those with moderate binding affinities of 100 to 500 μM, are catechin and eugenol. Those with higher binding affinities include ethylcinnamate and

epicatechin. It is important to note that many of these compounds have also been shown to interact in other signaling pathways in the body that could lead to an altered therapeutic response. Together these provide a variety of sources to treat diseases related to PPARγ activity such as inflammation, diabetes, and heart disease.

Conflict of interest

The authors declare no conflict of interest.

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