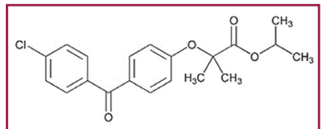
Nutraceuticals molecular targets

Nutraceuticals molecular targets (III)

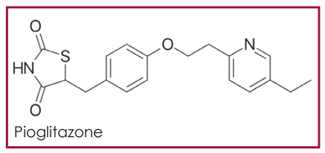
Targeting protein receptors with polyphenols as new anti-obesity therapies

In the previous column we proposed the use of a global scientific approach to elucidate the beneficial effects of plant polyphenols and other dietary compounds on human health (1). This approach included: i) the identification of the metabolites derived from food components that are responsible for the health effects and the associated metabolic markers; ii) the elucidation of their protein targets and concomitant metabolic pathways; iii) *in silico* techniques to screen for millions of compounds against the known molecular targets and finding for new candidates; iv) appropriate cellular and animal models to verify the mechanism of action and toxicity; v) human trials to demonstrate the beneficial effects associated to specific compounds. The transition of this global strategy occurs from the scientific field to the industry, and therefore the consumer, will take a few years. In the meantime, we will review some proteins or metabolic processes that have been recently proposed as putative targets in the alleviation of metabolic syndrome and obesity-related pathologies such as type 2 diabetes mellitus (T2DM).

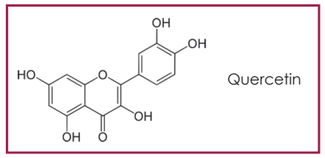
The search for drugs with hypolipidemic effects started in the mid-1950s with the development of compounds with chloro bi-phenyl moiety, the fibrates. Despite their potent lipid lowering activity, some of these drugs have exhibited worrying side effects, such as hepatomegaly and a risk of myopathy. Currently, these drugs are still widely prescribed both in USA and Europe (2). Looking at their chemical structure that bear a bi-phenyl moiety, one might think that plant polyphenols would be also candidates to reach similar molecular targets than those interacting with fibrates. In an attempt to synthesize more potent fibrate hypolipidemic drugs, Japanese researchers discovered, in the early 1980s, a group of compounds with a biphenyl ether moiety that showed hypolipidemic and hypoglycemic effects in diabetic mice model (3). The combination of the phenyl ether moiety with the thiazolidinedione structure led to the discovery of glitazones. Again, phenyl moieties, such as those found in multiple plant polyphenols, seems to be a structural coincidence. Ciglitazone was the first developed glitazone in 1982, followed by troglitazone, which was discovered by Sankyo Co in 1988 (4).



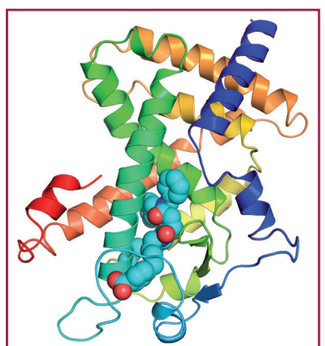
Fenofibrate



Pioglitazone



Quercetin


Peroxisome-proliferator-activated receptor (PPARγ)

Glitazones or thiazolidinediones (TDZs) are agonists (ligands or activators) of the peroxisome-proliferator-activated receptor γ (PPARγ), a nuclear receptor that is a key player in various biological processes related to glucose and lipid homeostasis. In 1994, the role of PPARγ as a major adipogenic transcription factor was discovered and one year later, PPARγ was suggested to mediate the antidiabetic action of TDZs (5, 6). PPARγ has since become one of the most important pharmacological targets for the development of new drugs focused to ameliorate T2DM. PPARγ is mostly expressed in adipose tissue, but it also appears in other tissues such as pancreatic beta cells and vascular endothelium. Ligand binding at PPARγ regulates transcription of several target genes that regulate fatty acid metabolism, glucose uptake, adipocyte differentiation, inflammation and intravascular lipolysis. Among the various actions of glitazones are promoting lipogenesis in adipose tissue, which results in reduced serum free fatty acid concentrations, reduced hepatic fat content and increased hepatic and peripheral insulin sensitivity (7).

Basically, activation of PPARγ improves lipid management at different tissues and increases fatty acid storage. Indeed, PPARγ promotes adipocyte differentiation; stimulates fatty acid storage in adipocytes via the activation of several genes, such as lipoprotein lipase, fatty acid transport protein, CD36, and acyl-coA synthetase; and decreases free fatty acid secretion, resulting in enhanced adipocyte insulin signaling. All these effects can explain the body weight gain induced by TZD administration, a major drawback in the use of these drugs in the treatment of T2DM. Despite the efficacy of TDZs to reduce T2DM, glitazones remain to be a controversial class of drugs. These drugs display well-documented adverse effects, such as fluid retention, body weight gain, increased risk for bone fractures an edema, and the risk of heart failure. Among the glitazones developed in the last two decades, troglitazone was withdrawn in 2000 due to hepatoxicity and the European marketing authorization of rosiglitazone was suspended in 2010 due to cardiovascular safety concerns. Currently, only pioglitazone is allowed for T2DM therapy by the European Medicines Agency.

Pioglitazone seems to be associated to a reduced risk of cardiovascular disease and stroke in patients with insulin resistance in large randomized-controlled trials (7). However, to fully prove the safety and efficacy of pioglitazone, further evidences and meta-analysis may be required. Experimental evidences reveal that potent PPARγ activators must be administrated with caution since these compounds exacerbate liver steatosis in animal models (8). Adverse events may be due to the pleiotropic character and systemic effects of PPARs, which suggest the need of tissue-selective mechanism of action.

Alternatively, some natural compounds have been suggested as biological ligands of PPARγ. The case of plant polyphenols is specially relevant since these compounds have been proposed as selective regulators of PPARγ, which may be devoid of glitazones' undesirable effects. Several PPARγ ligands have been identified in plants and other common food sources, including the tea plant, soybeans, palm oil, ginger, grapes, and wine, and a number of culinary herbs and spices (9) (eg, *Origanum vulgare*, *Rosmarinus officinalis*, *Salvia officinalis*, and *Thymus vulgaris*). The use of these compounds, which are often weak PPARγ agonists, may become an alternative for the prevention of obesity through dietary intervention. Among the natural products that have been well characterized as PPARγ ligands or PPARγ expression modulators, various phenolic compounds from plants have been identified (9), either in obese animal models or *in silico* studies (10, 11). Notable exceptions documented were catechins, phenylpropanoids and quercetin (12, 13). Therefore, the role of polyphenols as partial PPARγ agonists based on selective receptor–cofactor interactions and target gene regulation may deserve intensive research (14).

In the development of new synthetic PPARγ agonists, we must consider plant polyphenols as a potential source to discover lead compounds. These compounds may not be as potent as PPARγ agonists but may behave as fine or mild regulators of PPARγ by improving lipid management and glucose sensitivity and lacking the side effects of glitazones. These new generation "selective PPARγ modulators" must be designed to induce specific changes in PPAR conformation, resulting in the differential activation of genes activated by PPARγ, leading to a set of specific biological effects (2). Another concern may appear then, will the consumer and the industry be prepared for labelling products in such a way: "contains polyphenols with lipid lowering/glucose reduction effects through PPARγ modulation"? I believe that first legislative and regulatory panels still have much work to be done.

REFERENCES

1. Herranz-Lopez M, Olivares-Vicente M, Encinar JA, Barrajon-Catalan E, Segura-Carretero A, Joven J, Micol V: Multi-Targeted Molecular Effects of Hibiscus sabdariffa Polyphenols: An Opportunity for a Global Approach to Obesity. *Nutrients* 2017, 9.
2. Lalloyer F, Staels B: Fibrates, glitazones, and peroxisome proliferator-activated receptors. *Arterioscler Thromb Vasc Biol* 2010, 30:894-899.
3. Kawamatsu Y, Saraie T, Imamiya E, Nishikawa K, Hamuro Y: Studies on antihyperlipidemic agents. I. Synthesis and hypolipidemic activities of phenoxyphenyl alkanoic acid derivatives. *Arzneimittelforschung* 1980, 30:454-459.
4. Fujiwara T, Yoshioka S, Yoshioka T, Ushiyama I, Horikoshi H: Characterization of new oral antidiabetic agent CS-045. Studies in KK and ob/ob mice and Zucker fatty rats. *Diabetes* 1988, 37:1549-1558.
5. Tontonoz P, Hu E, Spiegelman BM: Stimulation of adipogenesis in fibroblasts by PPAR gamma 2, a lipid-activated transcription factor. *Cell* 1994, 79:1147-1156.
6. Lehmann JM, Moore LB, Smith-Oliver TA, Wilkison WO, Willson TM, Kliewer SA: An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma). *J Biol Chem* 1995, 270:12953-12956.
7. Johns E, McKay G, Fisher M: Glitazones (thiazolidinediones). *Br J Cardiol* 2017, 24:113-116.
8. Rull A, Geeraert B, Aragones G, Beltran-Debon R, Rodriguez-Gallego E, Garcia-Heredia A, Pedro-Botet J, Joven J, Holvoet P, Camps J: Rosiglitazone and Fenofibrate Exacerbate Liver Steatosis in a Mouse Model of Obesity and Hyperlipidemia. A Transcriptomic and Metabolomic Study. *J Proteome Res* 2014.
9. Wang L, Waltenberger B, Pferschy-Wenzig EM, Blunder M, Liu X, Malainer C, Blazevic T, Schwaiger S, Rollinger JM, Heiss EH, et al: Natural product agonists of peroxisome proliferator-activated receptor gamma (PPARgamma): a review. *Biochem Pharmacol* 2014, 92:73-89.
10. Encinar JA, Fernandez-Ballester G, Galiano-Ibarra V, Micol V: In silico approach for the discovery of new PPARgamma modulators among plant-derived polyphenols. *Drug Des Devel Ther* 2015, 9:5877-5895.
11. Garcia-Vallve S, Guasch L, Tomas-Hernandez S, del Bas JM, Ollendorff V, Arola L, Pujadas G, Mulero M: Peroxisome Proliferator-Activated Receptor gamma (PPARgamma) and Ligand Choreography: Newcomers Take the Stage. *J Med Chem* 2015, 58:5381-5394.
12. Dominguez-Avila JA, Gonzalez-Aguilar GA, Alvarez-Parrilla E, de la Rosa LA: Modulation of PPAR Expression and Activity in Response to Polyphenolic Compounds in High Fat Diets. *Int J Mol Sci* 2016, 17.
13. Herranz-Lopez M, Barrajon-Catalan E, Segura-Carretero A, Menendez JA, Joven J, Micol V: Lemon verbena (Lippia citriodora) polyphenols alleviate obesity-related disturbances in hypertrophic adipocytes through AMPK-dependent mechanisms. *Phytomedicine* 2015, 22:605-614.
14. Higgins LS, Depaoli AM: Selective peroxisome proliferator-activated receptor gamma (PPARgamma) modulation as a strategy for safer therapeutic PPARgamma activation. *Am J Clin Nutr* 2010, 91:267S-272S.

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