International Journal of Food and Nutritional Science

OMMEGA Publishers
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Editorial

OPEN ACCESS

Flavonoids as Ligands for Peroxisome Proliferator-Activated Receptor γ

Ayman M. Mahmoud

Department of Zoology, Physiology Division,Faculty of Science, Beni-Suef University, Egypt

Corresponding Author: Mahmoud, A.M. Department of Zoology, Physiology Division, Faculty of Science, Beni-Suef University, Beni-Suef, Egypt. Tel: +201144168280; E-mail: ayman.mahmoud@science.bsu.edu.eg

Received Date: Aug 27, 2015 **Accepted Date: Aug 27, 2015** **Published Date: Aug 29,2015**

Citation: Mahmoud, A.M. Flavonoids as Ligands for Peroxisome Proliferator-Activated Receptor γ. (2015) Int J Food Nutr Sci 2(2): 98-99.

Flavonoids are non-nutritive dietary substances that are widely distributed in fruits and vegetables regularly consumed by humans[1]. They are assorted by their chemical structure into 6 subgroups as follows: flavonols, flavandiols, flavones, anthocyanins, proanthocyanidins and chalcones[2]. There are more than 6000 identified flavonoids and the number is certain to increase by further research conducted on them[3]. The chemical structure of flavonoids is based upon a 15-carbon skeleton which consists of two benzene rings (A and B) and a heterocyclic pyrane ring (C)[4], as shown in Figure 1. Flavonoids have attracted considerable interest because of their versatile health benefits including anti-inflammatory, antioxidant, antidiabetic,cardioprotective, hepatoprotective and anti-hyperammonemic activities[5-7].

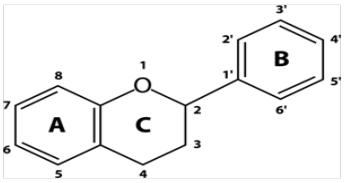

Figure 1: Basic flavonoid structure.

Peroxisome proliferator-activated receptor gamma (PPARγ) is a ligand-activated transcription factor that belongs to the nuclear receptors superfamily. PPARγ plays a central role in glucose and lipid homeostasis, adipocyte differentiation, inflammation[8], regenerative mechanisms and cell differentiation/proliferation[9]. Upon ligand binding, PPARγ heterodimerizes with the retinoid X receptor (RXR) in the nucleus. The PPAR-RXR complex binds to peroxisome proliferator response elements (PPREs), found in the promoters of the respective target genes, and thereby control their expression[10] (Figure2). Over the past two decades, extensive research exploring the physiological and therapeutic significance of PPARγ activation has been conducted. PPARγ is induced during the differentiation of preadipocytes and is expressed also in antigen-presenting cells such as dendritic cells and macrophages[8]. In these cells, PPARγ regulate genes related to lipid metabolism, immunity and inflammation[11]. In addition, PPARγ activation has been reported to inhibit cancer cell growth in vitro and in animal models. Therefore, PPARγ might represent a target of paramount importance for new cancer therapies[12,13].

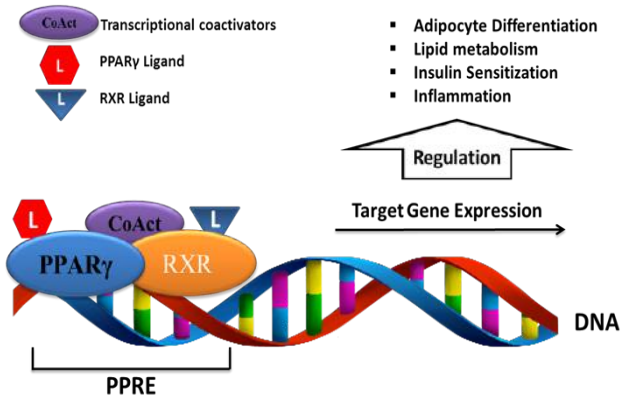

Figure 2: PPARγ activation pathway and transcriptional regulation of target genes.

The endogenous PPARγ ligands including fatty acids and prostanoids[14] are weak agonists compared to the synthetic thiazolidinedione (TZD) agonists[15]. Hepatotoxicity, edema and cardiovascular risk related to the use of TZDs lead to their withdrawal from the market[16]. Currently, there are great research efforts to develop selective PPARγ modulators (SPPARMs) but with lower toxicity[17]. Therefore, developing natural agonists that could bind and activate PPARγ has become an absolute necessity. This might provide safe PPARγ agonists that promote health benefits without adverse effects. Flavonoids may represent a source for the discovery of novel PPARγ agonists. In this context, the study of Mueller and Jungbauer [18] reported that some main metabolites of flavonoid constituents from *Trifolium*

pratense (red clover) bind to PPARγ with an affinity up to 100-fold higher than their precursors. A selection of flavonoids well characterized as PPARγ ligands is presented in Figure3. Flavonoids with EC_{50} or IC_{50} higher than 50 μM are not included.

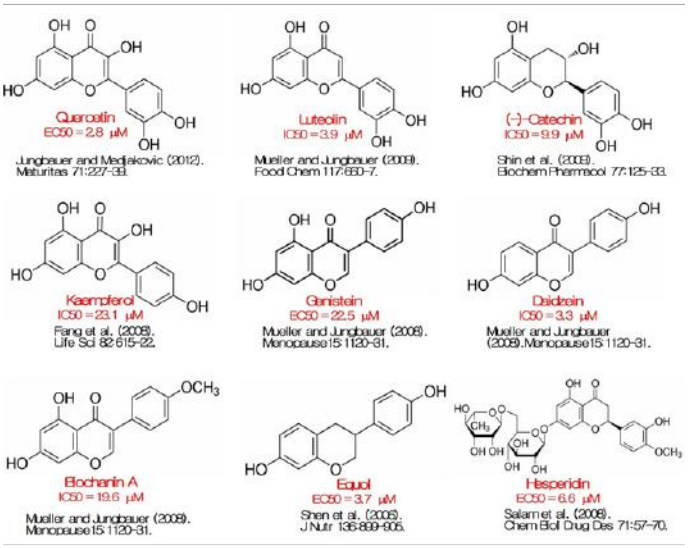

Figure 3: Flavonoids activating PPARγ.

Overall, a range of PPARγ activating flavonoids were recently characterized that bear a good potential to be further investigated for therapeutic effectiveness as well as to be explored as potential dietary supplements to counteract different diseases. Many flavonoid compounds are so far not thoroughly investigated as PPARγ activators. The identification of their ability to activate PPARγ might provide further interesting agonists in the future.

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Online ISSN: 2377-0619
Journal Title: International Journal of Food and Nutritional Science
Journal Short Name: Int J Food Nutr Sci

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