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Publication date:
2009

Document version
Final published version

Citation for published version (APA):

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Human peroxisome proliferator-activated receptor (PPAR) γ agonists identified in selected plant extracts by bioassay-guided fractionation

Kathrine B. Christensen⁵,⁶, Rasmus K. Petersen⁵, Karsten Kristiansen⁴, and Lars P. Christensen⁶

−Department of Food Science, University of Aarhus, DK-8500 Aarhus, Denmark,
−Institute of Chemical Engineering, Biotechnology & Environmental Technology, University of Southern Denmark, DK-5230 Odense M.
−Department of Biology, University of Copenhagen, DK-2200 Copenhagen

⁎E-mail: kbc@kmb.sdu.dk

Introduction

Abdominal obesity is associated with a set of risk factors known as the metabolic syndrome. Type 2 diabetes (T2D) is one of these and is caused by a combination of insulin resistance and β-cell failure. Lifestyle modifications are rarely sufficient for the treatment of T2D, thus thiazolidinedione (TZD) drugs are often prescribed. TZDs are agonists of PPARγ, a key regulator of adipogenesis. Activation of PPARγ causes re-distribution of fat in the body, which leads to increased insulin sensitivity. Severe side-effects are associated with the use of TZDs e.g. weight gain and edemas. These side-effects occur because TZDs are full PPARγ agonists. However, it has been suggested that partial PPARγ agonists do not have severe side-effects.

Plants have been used in the traditional treatment of diabetes but the mechanism of action of the bioactive compounds is rarely known. In this study, we focused on the identification of natural products from medicinal plants able to activate PPARγ. In a screening for partial PPARγ agonists we identified several plant species (60% hit rate) able to activate PPARγ and increase insulin-stimulated glucose uptake in adipocytes without having an adipogenic potential. Many of these were also activators of PPARα and δ [1].

Purple coneflower (Echinacea purpurea)

The n-hexane extract of the flowers of purple coneflower was one of the most promising extracts with respect to activation of PPARγ. Bioassay-guided fractionation led to the isolation and identification of α-linolenic acid, linoleic acid, palmitoleic acid, dodeca-2E,4Z,10Z-trien-8-ynoic acid isobutyramide, dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutyramide, dodeca-2E,4E-dienoic acid isobutyramide, and the new hexadeca-2E,9Z,12Z,14E-tetraenoic acid isobutyramide (1).

A luciferase-based PPARγ transactivation assay using mouse embryonic fibroblasts was used for initial assessment of bioactivity. All three fatty acids are well-known PPARγ agonists and were also found to be active in our test-system. The alkamides also activated PPARγ, of which compound 1 was the most effective of these (Fig. 1) [2].

Compound 1 had no adipogenic potential and was able to positively affect insulin-stimulated glucose uptake in a manner similar to that of Rosiglitazone, which was used as positive control (Fig. 2) [2].

Elderflowers (Sambucus nigra)

Extracts of elderflowers were promising with respect to effect on insulin-stimulated glucose uptake. Bioassay-guided fractionation led to the isolation of three compounds able to activate PPARγ: α-linolenic acid, linoleic acid, and naringenin.

Buckwheat (Fagopyrum tataricum)

Buckwheat seeds have been reported to have anti-diabetic effects. In our screening, aerial parts, and not the seeds, were able to activate PPARγ and increase insulin-stimulated glucose uptake with no adipogenic potential. Buckwheat contains flavonoids and phenolic acids with quercetin-3-O-rutinoside, quercetin-3-O-glucoside, kaempferol-3-O-rhamnoside, and 5-O-caffeylquinic acid were not able to activate PPARγ.

Conclusions

- High hit-rate among plants for identification of PPAR modulators.
- PPAR modulators from plants are in general fatty acids together with specific metabolites such as:
  - Alkamides (preferably ≥ C₁₆)
  - Flavonoid aglycones
- In general, flavonoid glycosides and phenolic acids do not activate PPARs.
- Potential synergistic effects exist between some of the identified PPAR modulators as overall bioactivity could not be explained completely by individual activities.

This work was funded by the EU Interreg IIIA project “Plants for Diabetes” and was a cooperation between University of Southern Denmark, University of Aarhus, Christian-Albrechts-Universität zu Kiel, and Development Centre Aarslev.