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

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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 PPAR γ, a key regulator of adipogenesis. Activation of PPAR γ 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 PPAR γ agonists. However, it has been suggested that partial PPAR γ 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 PPAR γ. In a screening for partial PPAR γ agonists we identified several plant species (60% hit rate) able to activate PPAR γ and increase insulin-stimulated glucose uptake in adipocytes without having an adipogenic potential. Many of these were also activators of PPAR α 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 PPAR γ. 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 isobutylamide, dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamide, dodeca-2E,4E-diienoic acid isobutylamide, and the new hexadeca-2E,9Z,12Z,14E-tetraenoic acid isobutylamide (1).

A luciferase-based PPAR γ transactivation assay using mouse embryonic fibroblasts was used for initial assessment of bioactivity. All three fatty acids are well-known PPAR γ agonists and were also found to be active in our test-system. The alkamides also activated PPAR γ, 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 PPAR γ: α-linolenic acid, linoleic acid, and naringenin. Naringenin activated PPAR γ in a dose-dependent manner (Fig. 3). Naringenin structurally resembles phytoestrogens (e.g. genistein), which are PPAR γ agonists. Major elderflower metabolites such as quercetin-3-O-rutinoside, quercetin-3-O-glucoside, kaempferol-3-O-rhamnoside, and 5-O-cafeoylquinic acid were not able to activate PPAR γ.

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 PPAR γ and increase insulin-stimulated glucose uptake with no adipogenic potential. Buckwheat contains flavonoids and phenolic acids with quercetin-3-O-rutinoside as the major component [3]. Bioassay-guided fractionation led to the conclusion that α-linolenic and linoleic acid are primarily responsible for the PPAR effect of buckwheat.

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.

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