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Diterpenes and other metabolites from sage (Salvia officinalis L.) and their effect on the human peroxisome proliferator-activated receptor (PPAR) γ

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Introduction

Sage (Salvia officinalis, Lamiaceae) has been used both as a culinary herb and as a medicinal plant for centuries. Preparations of the aerial parts of sage have been used as a traditional remedy against diabetes, and the glucose-lowering effects have been proven in animal studies. It has been suggested that diterpenes are responsible for the anti-diabetic effects of sage but the bioactive compounds and their mechanism of action are still unknown.

PPARγ is a master regulator of adipocyte differentiation and hence, is highly involved in the regulation of insulin sensitivity. Extracts of sage and diterpenes from sage have been reported to activate PPARγ [1,2]. The aim of this study was to find further PPARγ activators among the sage metabolites.

Phytochemical analysis

Sage was cultivated and harvested at Department of Horticulture, University of Aarhus. 5 kg of frozen aerial parts were subjected to a 2-step sequential extraction procedure using n-hexane and CH3Cl. The CH3Cl extract was initially separated by silica gel flash column chromatography using n-hexane–EtOAc gradients, and for final purification of sage metabolites reverse phase semi-preparative HPLC with CH3CN–water gradients were used.

The phytochemical analysis of sage resulted in the isolation of the diterpenes carnosol (1), 20-deoxocarnosol (2), carnosic acid (3), 20-hydroxyferruginol (4), 20-deoxocarnosic acid (6), 12-O-methylcarnosic acid (8), manool (11), and a new abietane diterpene being the epirosmanol ester of 12-O-methylcarnosic acid (10). In addition, viridiflorol (7), oleandric acid (9), and α-linolenic acid were also isolated. All compounds were identified by 1D- and 2D-NMR and HR-ESI mass spectrometry.

Activation of PPARγ

Extracts of sage activate PPARγ and increase insulin-stimulated glucose uptake in adipocytes [1]. In this study, we tested the isolated sage metabolites for their ability to activate PPARγ. α-Linolenic acid is a known PPARγ agonist. 12-O-Methylcarnosic acid (5) was also found to significantly activate PPARγ in a transactivation bioassay (using mouse embryonic fibroblasts) giving a 7-fold activation at 10 µM relative to the vehicle (DMSO) (Fig. 1) [3]. Rosiglitazone was used as a positive control.

Carnosol (1) and carnosic acid (3) have previously been reported to activate PPARγ [2]. In our study they were only weak activators. Oleandric acid, which is an agonist of PPARα [4] was also shown to be a weak activator of PPARγ.

Conclusions

- One new compound isolated from sage: the epirosmanol ester of 12-O-methylcarnosic acid (10).
- 20-hydroxyferruginol (4) isolated from sage for the first time.
- 12-O-methylcarnosic acid (5) was found to significantly activate PPARγ.
- Anti-diabetic activity of sage might be mediated through activation of PPARγ.

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