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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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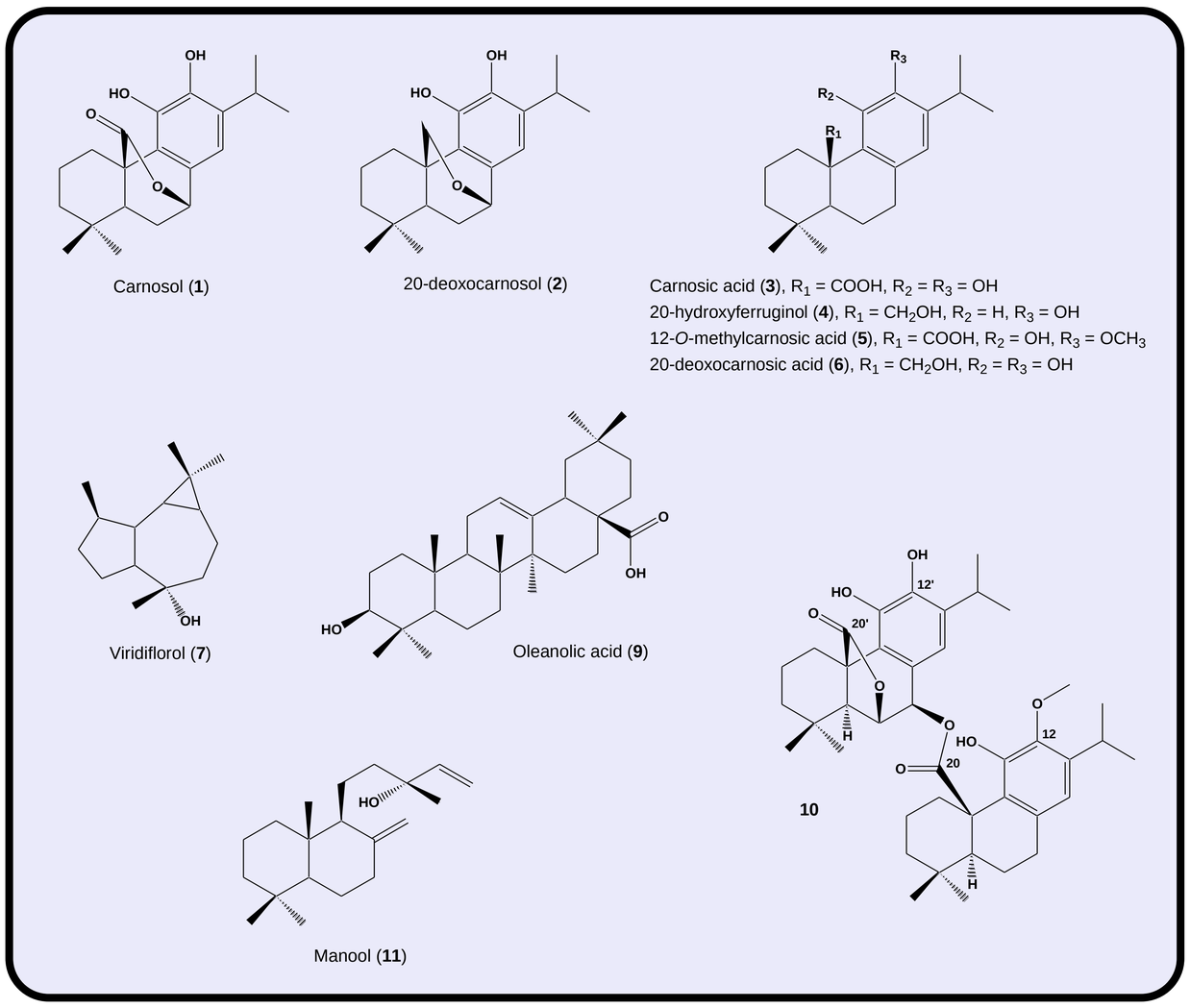
Introduction

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 CH_2Cl_2. The CH_2Cl_2 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 CH_3CN–water gradients were used.

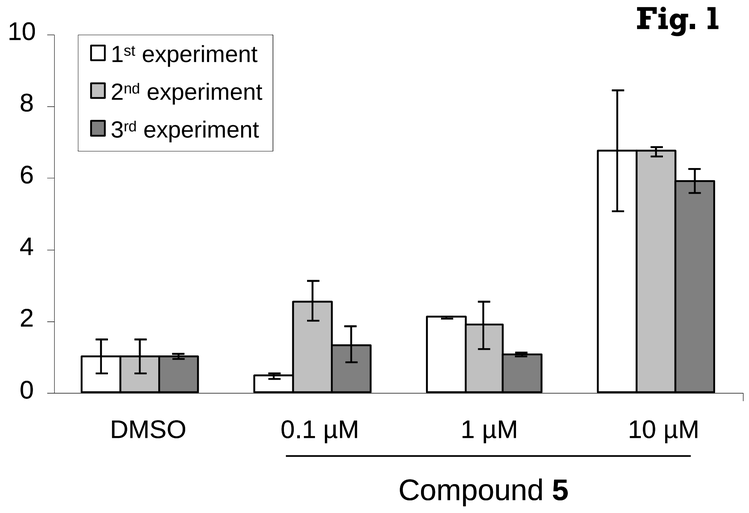
The phytochemical analysis of sage resulted in the isolation of the diterpenes carnosol (**1**), 20-deoxocarnosol (**2**), carnosic acid (**3**), 20-hydroxyferruginol (**4**), 20-deoxocarnosic acid (**6**), 12-*O*-methylcarnosic acid (**5**), manool (**11**), and a new abietane diterpene being the epirosmanol ester of 12-*O*-methylcarnosic acid (**10**). In addition, viridiflorol (**7**), oleanolic 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. Oleanolic acid, which is an agonist of PPARα [4] was also shown to be a weak activator of PPARγ.

Fig. 1



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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References: [1] Christensen et al. (2009) *Phytother. Res.*, in press; [2] Rau et al. (2006) *Planta Med.* **72**, 881-887; [3] Jørgensen et al. (2009), in preparation; [4] Liu, J. (1995) *J. Etnopharmacol.* **49**, 57-68.