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## Biosynthesis of bioactive diterpenoids in the medicinal plant *Vitex agnus-castus*

By: [Heskes, AM](#) (Heskes, Allison M.)<sup>[1,2,3]</sup>; [Sundram, TCM](#) (Sundram, Tamil C. M.)<sup>[1,4]</sup>; [Boughton, BA](#) (Boughton, Berin A.)<sup>[5]</sup>; [Jensen, NB](#) (Jensen, Niels B.)<sup>[6]</sup>; [Hansen, NL](#) (Hansen, Nikolaj L.)<sup>[1,2,3]</sup>; [Crococoll, C](#) (Crococoll, Christoph)<sup>[7]</sup>; [Cozzi, F](#) (Cozzi, Federico)<sup>[1]</sup>; [Rasmussen, S](#) (Rasmussen, Simon)<sup>[8]</sup>; [Hamberger, B](#) (Hamberger, Britta)<sup>[1,2,3]</sup>; [Hamberger, B](#) (Hamberger, Bjorn)<sup>[1,2,3]</sup> ...More

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### Abstract

*Vitex agnus-castus* L. (Lamiaceae) is a medicinal plant historically used throughout the Mediterranean region to treat menstrual cycle disorders, and is still used today as a clinically effective treatment for premenstrual syndrome. The pharmaceutical activity of the plant extract is linked to its ability to lower prolactin levels. This feature has been attributed to the presence of dopaminergic diterpenoids that can bind to dopamine receptors in the pituitary gland. Phytochemical analyses of *V. agnus-castus* show that it contains an enormous array of structurally related diterpenoids and, as such, holds potential as a rich source of new dopaminergic drugs. The present work investigated the localisation and biosynthesis of diterpenoids in *V. agnus-castus*. With the assistance of matrix-assisted laser desorption ionisation-mass spectrometry imaging (MALDI-MSI), diterpenoids were localised to trichomes on the surface of fruit and leaves. Analysis of a trichome-specific transcriptome database, coupled with expression studies, identified seven candidate genes involved in diterpenoid biosynthesis: three class II diterpene synthases (diTPSs); three class I diTPSs; and a cytochrome P450 (CYP). Combinatorial assays of the diTPSs resulted in the formation of a range of different diterpenes that can account for several of the backbones of bioactive diterpenoids observed in *V. agnus-castus*. The identified CYP, VacCYP76BK1, was found to catalyse 16-hydroxylation of the diol-diterpene, peregrinol, to labd-13Z-ene-9,15,16-triol when expressed in *Saccharomyces cerevisiae*. Notably, this product is a potential intermediate in the biosynthetic pathway towards bioactive furan- and lactone-containing diterpenoids that are present in this species.

### Keywords

**Author Keywords:** bioactive diterpenoid; *Vitex agnus-castus*; terpene synthase; cytochrome P450; MALDI-MS imaging; Lamiaceae

**KeyWords Plus:** IN-VITRO; PHARMACOLOGICAL-ACTIVITIES; PREMENSTRUAL-SYNDROME; DIPHOSPHATE SYNTHASE; MARRUBIUM VULGARE; FRUITS; TRIFOLIA; IDENTIFICATION; YEAST; ROTUNDIFOLIA

### Author Information

**Reprint Address:** Heskes, AM (reprint author)

Univ Copenhagen, Dept Plant & Environm Sci, Plant Biochem Lab, Thorvaldsensvej 40, DK-1871 Frederiksberg C, Denmark.

**Reprint Address:** Heskes, AM (reprint author)

Univ Copenhagen, Dept Plant & Environm Sci, Ctr Synthet Biol BioSYNergy, Thorvaldsensvej 40, DK-1871 Frederiksberg C, Denmark.

**Reprint Address:** Heskes, AM (reprint author)

Univ Copenhagen, Dept Plant & Environm Sci, VILLUM Ctr Plant Plast, Thorvaldsensvej 40, DK-1871 Frederiksberg C, Denmark.

### Addresses:

[ 1 ] Univ Copenhagen, Dept Plant & Environm Sci, Plant Biochem Lab, Thorvaldsensvej 40, DK-1871 Frederiksberg C, Denmark

[ 2 ] Univ Copenhagen, Dept Plant & Environm Sci, Ctr Synthet Biol BioSYNergy, Thorvaldsensvej 40, DK-1871 Frederiksberg C, Denmark

[ 3 ] Univ Copenhagen, Dept Plant & Environm Sci, VILLUM Ctr Plant Plast, Thorvaldsensvej 40, DK-1871 Frederiksberg

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- [ 6 ] Evolva AS, Lerso Pk Alle 42-44, DK-2100 Copenhagen O, Denmark
- + [ 7 ] Univ Copenhagen, Dept Plant & Environm Sci, DynaMo Ctr, Thorvaldsensvej 40, DK-1871 Frederiksberg C, Denmark
- + [ 8 ] Tech Univ Denmark, Dept Bio & Hlth Informat, DK-2800 Lyngby, Denmark
- + [ 9 ] Univ Copenhagen, Fac Hlth & Med Sci, Dept Drug Design & Pharmacol, DK-2100 Copenhagen, Denmark

E-mail Addresses: [amh@plen.ku.dk](mailto:amh@plen.ku.dk)

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