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Biosynthesis of bioactive diterpenoids in the medicinal plant Vitex agnus - castus (Article) (Open Access)

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Abstract

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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. © 2018 The Authors The Plant Journal published by John Wiley & Sons Ltd and Society for Experimental Biology.

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Author keywords

bioactive diterpenoid | cytochrome P450 | Lamiaceae | MALDI-MS imaging | terpene synthase | Vitex agnus - castus

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References (84)

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View all 84 references

1 Alam, G., Wahyuono, S., Ganjar, I.G., Hakim, L., Timmerman, H., Verpoorte, R.
Tracheospasmolytic activity of viteosin-A and vitexicarpin isolated from Vitex trifolia
(2002) *Planta Medica*, 68 (11), pp. 1047-1049. Cited 22 times.
doi: 10.1055/s-2002-35650
View at Publisher

2 Andersen-Ranberg, J., Kongstad, K.T., Nielsen, M.T.
Expanding the landscape of diterpene structural diversity through stereochemically controlled combinatorial biosynthesis
(2016) *Angewandte Chemie Int. Edn*, 128, pp. 2182-2186. Cited 4 times.

3 Anwar, L., Efdi, M., Ninomiya, M., Ibrahim, S., Putra, D.P., Tanaka, K., Koketsu, M.
Labdane diterpene lactones of Vitex pubescens and their antileukemic properties

(2017) *Medicinal Chemistry Research*, 26 (10), pp. 2357-2362.
http://www.springerlink.com/content/1054-2523
doi: 10.1007/s00044-017-1937-3

View at Publisher

4 Atmaca, M., Kumru, S., Tezcan, E.
Fluoxetine versus Vitex agnus castus extract in the treatment of premenstrual dysphoric disorder

(2003) *Human Psychopharmacology*, 18 (3), pp. 191-195. Cited 81 times.
doi: 10.1002/hup.470

View at Publisher

5 Bach, S.S., Bassard, J.-É., Andersen-Ranberg, J., Møldrup, M.E., Simonsen, H.T., Hamberger, B.
High-throughput testing of terpenoid biosynthesis candidate genes using transient expression in nicotiana benthamiana

(2014) *Methods in Molecular Biology*, 1153, pp. 245-255. Cited 16 times.
http://www.springer.com/series/7651
doi: 10.1007/978-1-4939-0606-2_18

View at Publisher

6 Bohlmann, J., Meyer-Gauen, G., Croteau, R.
Plant terpenoid synthases: Molecular biology and phylogenetic analysis

(1998) *Proceedings of the National Academy of Sciences of the United States of America*, 95 (8), pp. 4126-4133. Cited 634 times.
doi: 10.1073/pnas.95.8.4126

View at Publisher

7 Boughton, B.A., Thinagaran, D., Sarabia, D., Bacic, A., Roessner, U.
Mass spectrometry imaging for plant biology: a review (Open Access)

(2016) *Phytochemistry Reviews*, 15 (3), pp. 445-488. Cited 38 times.
doi: 10.1007/s11101-015-9440-2

View at Publisher

8 Brattström, A.
(2014) *Dopaminergic activity of Vitex diterpenoids*
28 January 2014

9 Brückner, K., Tissier, A.
High-level diterpene production by transient expression in Nicotiana benthamiana

(2013) *Plant Methods*, 9 (1), art. no. 46. Cited 25 times.
http://www.plantmethods.com/content/9/1/46
doi: 10.1186/1746-4811-9-46

View at Publisher

10 Brückner, K., Božić, D., Manzano, D., Papaefthimiou, D., Pateraki, I., Scheler, U., Ferrer, A., (...), Tissier, A.
Characterization of two genes for the biosynthesis of abietane-type diterpenes in rosemary (Rosmarinus officinalis) glandular trichomes

(2014) *Phytochemistry*, 101, pp. 52-64. Cited 33 times.
www.elsevier.com/inca/publications/store/2/7/3/index.htt
doi: 10.1016/j.phytochem.2014.01.021

View at Publisher

11 Caniard, A., Zerbe, P., Legrand, S., Cohade, A., Valot, N., Magnard, J.-L., Bohlmann, J., (...), Legendre, L.
Discovery and functional characterization of two diterpene synthases for sclareol biosynthesis in Salvia sclarea (L.) and their relevance for perfume manufacture

(2012) *BMC Plant Biology*, 12, art. no. 119. Cited 59 times.
http://www.biomedcentral.com/1471-2229/12/119
doi: 10.1186/1471-2229-12-119

View at Publisher

12 Carmichael, A.R.
Can Vitex Agnus castus be used for the treatment of mastalgia? What is the current evidence? (Open Access)

(2008) *Evidence-based Complementary and Alternative Medicine*, 5 (3), pp. 247-250. Cited 19 times.
doi: 10.1093/ecam/nem074

View at Publisher

13 Chen, F., Tholl, D., Bohlmann, J., Pichersky, E.
The family of terpene synthases in plants: A mid-size family of genes for specialized metabolism that is highly diversified throughout the kingdom

(2011) *Plant Journal*, 66 (1), pp. 212-229. Cited 335 times.
doi: 10.1111/j.1365-313X.2011.04520.x

View at Publisher

14 Chen, X., Berim, A., Dayan, F.E., Gang, D.R.
A (-)-kolavenyl diphosphate synthase catalyzes the first step of salvinorin A biosynthesis in Salvia divinorum

(2017) *Journal of Experimental Botany*, 68 (5), pp. 1109-1122. Cited 3 times.
http://jxb.oxfordjournals.org/
doi: 10.1093/jxb/erw493

View at Publisher

15 Corlay, N., Lecsö-Bornet, M., Leborgne, E., Blanchard, F., Cachet, X., Bignon, J., Roussi, F., (...), Litaudon, M.
Antibacterial Labdane Diterpenoids from Vitex vestita

(2015) *Journal of Natural Products*, 78 (6), pp. 1348-1356. Cited 10 times.
http://pubs.acs.org/journal/jnprdf
doi: 10.1021/acs.jnatprod.5b00206

View at Publisher

16 Daniele, C., Coon, J.T., Pittler, M.H., Ernst, E.
Vitex agnus castus: A systematic review of adverse events

(2005) *Drug Safety*, 28 (4), pp. 319-332. Cited 76 times.
doi: 10.2165/00002018-200528040-00004

View at Publisher

17 Edgar, R.C.
MUSCLE: Multiple sequence alignment with high accuracy and high throughput

(2004) *Nucleic Acids Research*, 32 (5), pp. 1792-1797. Cited 16336 times.
doi: 10.1093/nar/gkh340

View at Publisher

18 Eryigit, T., Çig, A., Okut, N., Yildirim, B., Ekici, K.

Evaluation of chemical composition and antimicrobial activity of Vitex agnus castus L. fruits' essential oils from West Anatolia, Turkey

(2015) *Journal of Essential Oil-Bearing Plants*, 18 (1), pp. 208-214. Cited 2 times.
http://www.tandfonline.com/loi/teop20?open=16&repitition=0#vol_16
doi: 10.1080/0972060X.2014.976665

View at Publisher

19 Guo, J., Zhou, Y.J., Hillwig, M.L., Shen, Y., Yang, L., Wang, Y., Zhang, X., (...), Huang, L.

CYP76AH1 catalyzes turnover of miltiradiene in tanshinones biosynthesis and enables heterologous production of ferruginol in yeasts

(2013) *Proceedings of the National Academy of Sciences of the United States of America*, 110 (29), pp. 12108-12113. Cited 111 times.
http://www.pnas.org/content/110/29/12108.full.pdf+html
doi: 10.1073/pnas.1218061110

View at Publisher

20 Guo, J., Ma, X., Cai, Y., Ma, Y., Zhan, Z., Zhou, Y.J., Liu, W., (...), Huang, L.

Cytochrome P450 promiscuity leads to a bifurcating biosynthetic pathway for tanshinones

(2016) *New Phytologist*, 210 (2), pp. 525-534. Cited 25 times.
http://www.wiley.com/bw/editors.asp?ref=0028-646X&site=1
doi: 10.1111/nph.13790

View at Publisher

21 Haas, B.J., Papanicolaou, A., Yassour, M., Grabherr, M., Blood, P.D., Bowden, J., Couger, M.B., (...), Regev, A.

De novo transcript sequence reconstruction from RNA-seq using the Trinity platform for reference generation and analysis

(2013) *Nature Protocols*, 8 (8), pp. 1494-1512. Cited 1474 times.
doi: 10.1038/nprot.2013.084

View at Publisher

22 Hall, B.G.

Building phylogenetic trees from molecular data with MEGA

(2013) *Molecular Biology and Evolution*, 30 (5), pp. 1229-1235. Cited 325 times.
doi: 10.1093/molbev/mst012

View at Publisher

23 Hamann, T., Møller, B.L.

Improved cloning and expression of cytochrome P450s and cytochrome P450 reductase in yeast

(2007) *Protein Expression and Purification*, 56 (1), pp. 121-127. Cited 33 times.
doi: 10.1016/j.pep.2007.06.007

View at Publisher

24 He, Z., Chen, R., Zhou, Y., Geng, L., Zhang, Z., Chen, S., Yao, Y., (...), Lin, S.

Treatment for premenstrual syndrome with Vitex agnus castus: A prospective, randomized, multi-center placebo controlled study in China

(2009) *Maturitas*, 63 (1), pp. 99-103. Cited 36 times.
doi: 10.1016/j.maturitas.2009.01.006

View at Publisher

25 Henderson, M.S., McCrindle, R.
Premarrubiin. A diterpenoid from Marrubium vulgare L.

(1969) *Journal of the Chemical Society C: Organic*, (15), pp. 2014-2015. Cited 32 times.
doi: 10.1039/j39690002014

View at Publisher

26 Hillwig, M.L., Xu, M., Toyomasu, T., Tiernan, M.S., Wei, G., Cui, G., Huang, L., (...), Peters, R.J.
Domain loss has independently occurred multiple times in plant terpene synthase evolution

(2011) *Plant Journal*, 68 (6), pp. 1051-1060. Cited 34 times.
doi: 10.1111/j.1365-313X.2011.04756.x

View at Publisher

27 Hoberg, E., Orjala, J., Meier, B., Sticher, O.
Diterpenoids from the fruits of Vitex agnus-castus

(1999) *Phytochemistry*, 52 (8), pp. 1555-1558. Cited 53 times.
doi: 10.1016/S0031-9422(99)00181-8

View at Publisher

28 Ignea, C., Trikka, F.A., Kourtzelis, I., Argiriou, A., Kanellis, A.K., Kampranis, S.C., Makris, A.M.
Positive genetic interactors of HMG2 identify a new set of genetic perturbations for improving sesquiterpene production in Saccharomyces cerevisiae

(2012) *Microbial Cell Factories*, 11, art. no. 162. Cited 21 times.
http://www.microbialcellfactories.com/content/11/1/162
doi: 10.1186/1475-2859-11-162

View at Publisher

29 Ignea, C., Ioannou, E., Georgantea, P., Loupassaki, S., Trikka, F.A., Kanellis, A.K., Makris, A.M., (...), Kampranis, S.C.
Reconstructing the chemical diversity of labdane-type diterpene biosynthesis in yeast (Open Access)

(2015) *Metabolic Engineering*, 28, pp. 91-103. Cited 22 times.
http://www.elsevier.com/inca/publications/store/6/2/2/9/1/3/index.htt
doi: 10.1016/j.ymben.2014.12.001

View at Publisher

30 Ignea, C., Athanasakoglou, A., Ioannou, E., Georgantea, P., Trikka, F.A., Loupassaki, S., Roussis, V., (...), Kampranis, S.C.
Carnosic acid biosynthesis elucidated by a synthetic biology platform

(2016) *Proceedings of the National Academy of Sciences of the United States of America*, 113 (13), pp. 3681-3686. Cited 17 times.
http://www.pnas.org/content/113/13/3681.full.pdf
doi: 10.1073/pnas.1523787113

View at Publisher

31 Jarry, H., Spengler, B., Wuttke, W., Christoffel, V.
In vitro assays for bioactivity-guided isolation of endocrine active compounds in Vitex agnus-castus

(2006) *Maturitas*, 55 (SUPPL. 1), pp. S26-S36. Cited 31 times.
doi: 10.1016/j.maturitas.2006.06.014

View at Publisher

32 Jensen, N.B., Strucko, T., Kildegaard, K.R., David, F., Maury, J., Mortensen, U.H., Forster, J., (...), Borodina, I.
EasyClone: Method for iterative chromosomal integration of multiple genes in Saccharomyces cerevisiae

(2014) *FEMS Yeast Research*, 14 (2), pp. 238-248. Cited 75 times.
http://www.wiley.com/bw/journal.asp?ref=1567-1356
doi: 10.1111/1567-1364.12118

View at Publisher

33 Jia, M., Potter, K.C., Peters, R.J.
Extreme promiscuity of a bacterial and a plant diterpene synthase enables combinatorial biosynthesis

(2016) *Metabolic Engineering*, 37, pp. 24-34. Cited 13 times.
http://www.elsevier.com/inca/publications/store/6/2/2/9/1/3/index.htt
doi: 10.1016/j.ymben.2016.04.001

View at Publisher

34 Kilicdag, E.B., Tarim, E., Bagis, T., Erkanli, S., Aslan, E., Ozsahin, K., Kuscu, E.
Fructus agni casti and bromocriptine for treatment of hyperprolactinemia and mastalgia

(2004) *International Journal of Gynecology and Obstetrics*, 85 (3), pp. 292-293. Cited 22 times.
www.elsevier.com/locate/ijgo
doi: 10.1016/j.ijgo.2004.01.001

View at Publisher

35 Kiuchi, F., Matsuo, K., Ito, M., Qui, T.K., Honda, G.
New norditerpenoids with trypanocidal activity from Vitex trifolia

(2004) *Chemical and Pharmaceutical Bulletin*, 52 (12), pp. 1492-1494. Cited 34 times.
http://cpb.pharm.or.jp/cpb/200412/c12_1492.pdf
doi: 10.1248/cpb.52.1492

View at Publisher

36 König, S.
Composition and activity of Vitex agnus-castus
(2014) *Biomacromol. Mass Spect.*, 3, pp. 291-312. Cited 2 times.

37 De Kraker, J.-W., Franssen, M.C.R., Dalm, M.C.F., De Groot, A., Bouwmeester, H.J.
Biosynthesis of germacrene a carboxylic acid in chicory roots. Demonstration of a cytochrome p450 (+)-germacrene a hydroxylase and $NADP^+$-dependent sesquiterpenoid dehydrogenase(s) involved in sesquiterpene lactone biosynthesis

(2001) *Plant Physiology*, 125 (4), pp. 1930-1940. Cited 57 times.
doi: 10.1104/pp.125.4.1930

View at Publisher

38 De Kraker, J.-W., Franssen, M.C.R., Joerink, M., De Groot, A., Bouwmeester, H.J.
Biosynthesis of costunolide, dihydrocostunolide, and leucodin. Demonstration of cytochrome P450-catalyzed formation of the lactone ring present in sesquiterpene lactones of chicory

(2002) *Plant Physiology*, 129 (1), pp. 257-268. Cited 64 times.
doi: 10.1104/pp.010957

View at Publisher

39 Kulkarni, R.R., Shurpali, K., Puranik, V.G., Sarkar, D., Joshi, S.P.
Antimycobacterial labdane diterpenes from leucas stelligera

(2013) *Journal of Natural Products*, 76 (10), pp. 1836-1841. Cited 13 times.
doi: 10.1021/np400002p

View at Publisher

40 Lange, B.M., Fischedick, J.T., Lange, M.F., Srividya, N., Šamec, D., Poirier, B.C.
Integrative approaches for the identification and localization of specialized metabolites in Tripterygium roots

(2017) *Plant Physiology*, 173 (1), pp. 456-469. Cited 6 times.
http://www.plantphysiol.org/content/173/1/456.full.pdf
doi: 10.1104/pp.15.01593

View at Publisher

41 Lee, C., Lee, J.W., Jin, Q., Lee, H.J., Lee, S.-J., Lee, D., Lee, M.K., (...), Hwang, B.Y.
Anti-inflammatory constituents from the fruits of Vitex rotundifolia

(2013) *Bioorganic and Medicinal Chemistry Letters*, 23 (21), pp. 6010-6014. Cited 17 times.
doi: 10.1016/j.bmcl.2013.08.004

View at Publisher

42 Li, J.-L., Chen, Q.-Q., Jin, Q.-P., Gao, J., Zhao, P.-J., Lu, S., Zeng, Y.
IeCPS2 is potentially involved in the biosynthesis of pharmacologically active Isodon diterpenoids rather than gibberellin

(2012) *Phytochemistry*, 76, pp. 32-39. Cited 11 times.
doi: 10.1016/j.phytochem.2011.12.021

View at Publisher

43 Lim, J.C.W., Chan, T.K., Ng, D.S., Sagineedu, S.R., Stanslas, J., Wong, W.F.
Andrographolide and its analogues: Versatile bioactive molecules for combating inflammation and cancer

(2012) *Clinical and Experimental Pharmacology and Physiology*, 39 (3), pp. 300-310. Cited 105 times.
doi: 10.1111/j.1440-1681.2011.05633.x

View at Publisher

44 Liu, Q., Majdi, M., Cankar, K., Goedbloed, M., Charnikhova, T., Verstappen, F.W.A., de Vos, R.C.H., (...), Bouwmeester, H.J.
Reconstitution of the costunolide biosynthetic pathway in yeast and Nicotiana benthamiana (Open Access)

(2011) *PLoS ONE*, 6 (8), art. no. e23255. Cited 38 times.
http://www.plosone.org/article/fetchObjectAttachment.action?uri=info%3Adoi%2F10.1371%2Fjournal.pone.0023255&representation=PDF
doi: 10.1371/journal.pone.0023255

View at Publisher

45 Luo, D., Callari, R., Hamberger, B., Wubshet, S.G., Nielsen, M.T., Andersen-Ranberg, J., Hallström, B.M., (...), Hamberger, B.
Oxidation and cyclization of casbene in the biosynthesis of Euphorbia factors from mature seeds of Euphorbia lathyris L.

(2016) *Proceedings of the National Academy of Sciences of the United States of America*, 113 (34), pp. E5082-E5089. Cited 15 times.
http://www.pnas.org/content/113/34/E5082.full.pdf
doi: 10.1073/pnas.1607504113

View at Publisher

46 Matsuda, S.P.T., Schepmann, H.G.
(2008) *Ginkgo biloba levopimaradiene synthase*
(20 May 2008)

47 Meier, B., Berger, D., Hoberg, E., Sticher, O., Schaffner, W.
Pharmacological activities of Vitex agnus-castus extracts in vitro

(2000) *Phytomedicine*, 7 (5), pp. 373-381. Cited 54 times.
doi: 10.1016/S0944-7113(00)80058-6

View at Publisher

48 Munro, T.A., Rizzacasa, M.A., Roth, B.L., Toth, B.A., Yan, F.
Studies toward the pharmacophore of salvinorin A, a potent κ opioid receptor agonist

(2005) *Journal of Medicinal Chemistry*, 48 (2), pp. 345-348. Cited 87 times.
doi: 10.1021/jm049438q

View at Publisher

49 Nakano, C., Oshima, M., Kurashima, N., Hoshino, T.
Identification of a new diterpene biosynthetic gene cluster that produces O-methylkolavelool in herpetosiphon aurantiacus

(2015) *ChemBioChem*, 16 (5), pp. 772-781. Cited 13 times.
http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1439-7633
doi: 10.1002/cbic.201402652

View at Publisher

50 Nyiligira, E., Viljoen, A.M., Van Heerden, F.R., Van Zyl, R.L., Van Vuuren, S.F., Steenkamp, P.A.
Phytochemistry and in vitro pharmacological activities of South African Vitex (Verbenaceae) species

(2008) *Journal of Ethnopharmacology*, 119 (3), pp. 680-685. Cited 30 times.
doi: 10.1016/j.jep.2008.07.004

View at Publisher

51 Omosa, L.K., Amugune, B., Ndunda, B., Milugo, T.K., Heydenreich, M., Yenesew, A., Midiwo, J.O.
Antimicrobial flavonoids and diterpenoids from Dodonaea angustifolia (Open Access)

(2014) *South African Journal of Botany*, 91, pp. 58-62. Cited 15 times.
doi: 10.1016/j.sajb.2013.11.012

View at Publisher

52 Ono, M., Yamamoto, M., Masuoka, C., Ito, Y., Yamashita, M., Nohara, T.
Diterpenes from the fruits of Vitex rotundifolia

(1999) *Journal of Natural Products*, 62 (11), pp. 1532-1537. Cited 63 times.
doi: 10.1021/np990204x

View at Publisher

53 Ono, M., Sawamura, H., Ito, Y., Mizuki, K., Nohara, T.
Diterpenoids from the fruits of Vitex trifolia

(2000) *Phytochemistry*, 55 (8), pp. 873-877. Cited 41 times.
doi: 10.1016/S0031-9422(00)00214-4

View at Publisher

54 Ono, M., Ito, Y., Nohara, T.
Four new halimane-type diterpenes, vitetrifolins D - G, from the fruit of Vitex trifolia

(2001) *Chemical and Pharmaceutical Bulletin*, 49 (9), pp. 1220-1222. Cited 43 times.
doi: 10.1248/cpb.49.1220

View at Publisher

55 Ono, M., Yanaka, T., Yamamoto, M., Ito, Y., Nohara, T.
New diterpenes and norditerpenes from the fruits of Vitex rotundifolia

(2002) *Journal of Natural Products*, 65 (4), pp. 537-541. Cited 61 times.
doi: 10.1021/np0105331

View at Publisher

56 Ono, M., Yamasaki, T., Konoshita, M., Ikeda, T., Okawa, M., Kinjo, J., Yoshimitsu, H., (...), Nohara, T.
Five new diterpenoids, viteagnusins A-E, from the fruit of Vitex agnus-castus

(2008) *Chemical and Pharmaceutical Bulletin*, 56 (11), pp. 1621-1624. Cited 26 times.
http://www.jstage.jst.go.jp/article/cpb/56/11/1621/_pdf
doi: 10.1248/cpb.56.1621

View at Publisher

57 Ono, M., Nagasawa, Y., Ikeda, T., Tsuchihashi, R., Okawa, M., Kinjo, J., Yoshimitsu, H., (...), Nohara, T.
Three new diterpenoids from the fruit of Vitex agnus-castus

(2009) *Chemical and Pharmaceutical Bulletin*, 57 (10), pp. 1132-1135. Cited 21 times.
http://www.jstage.jst.go.jp/article/cpb/57/10/1132/_pdf
doi: 10.1248/cpb.57.1132

View at Publisher

58 Ono, M., Eguchi, K., Konoshita, M., Furusawa, C., Sakamoto, J., Yasuda, S., Ikeda, T., (...), Nohara, T.
A new diterpenoid glucoside and two new diterpenoids from the fruit of Vitex agnus-castus

(2011) *Chemical and Pharmaceutical Bulletin*, 59 (3), pp. 392-396. Cited 16 times.
http://www.jstage.jst.go.jp/article/cpb/59/3/392/_pdf
doi: 10.1248/cpb.59.392

View at Publisher

59 Paddon, C.J., Westfall, P.J., Pitera, D.J., Benjamin, K., Fisher, K., McPhee, D., Leavell, M.D., (...), Newman, J.D.
High-level semi-synthetic production of the potent antimalarial artemisinin

(2013) *Nature*, 496 (7446), pp. 528-532. Cited 605 times.
doi: 10.1038/nature12051

View at Publisher

60 Pateraki, I., Andersen-Ranberg, J., Hamberger, B., Heskes, A.M., Martens, H.J., Zerbe, P., Bach, S.S., (...), Hamberger, B.
Manoyl oxide (13R), the biosynthetic precursor of forskolin, is synthesized in specialized root cork cells in Coleus forskohlii

(2014) *Plant Physiology*, 164 (3), pp. 1222-1236. Cited 47 times.
http://www.plantphysiol.org/content/164/3/1222.full.pdf
doi: 10.1104/pp.113.228429

View at Publisher

61 Pateraki, I., Andersen-Ranberg, J., Jensen, N.B., Wubshet, S.G., Heskes, A.M., Forman, V., Hallström, B., (...), Hamberger, B.

Total biosynthesis of the cyclic AMP booster forskolin from Coleus forskohlii (Open Access)

(2017) *eLife*, 6, art. no. e23001. Cited 7 times.
https://elifesciences.org/content/6/e23001-download.pdf
doi: 10.7554/eLife.23001

View at Publisher

62 Pelot, K.A., Mitchell, R., Kwon, M., Hagelthorn, D.M., Wardman, J.F., Chiang, A., Bohlmann, J., (...), Zerbe, P.

Biosynthesis of the psychotropic plant diterpene salvinorin A: Discovery and characterization of the Salvia divinorum clerodienyl diphosphate synthase

(2017) *Plant Journal*, 89 (5), pp. 885-897. Cited 6 times.
http://www.blackwellpublishing.com/journals/TPJ
doi: 10.1111/tpj.13427

View at Publisher

63 Peters, R.J.

Two rings in them all: The labdane-related diterpenoids

(2010) *Natural Product Reports*, 27 (11), pp. 1521-1530. Cited 154 times.
doi: 10.1039/c0np00019a

View at Publisher

64 Pompon, D., Louerat, B., Bronine, A., Urban, P.

Yeast expression of animal and plant P450s in optimized redox environments

(1996) *Methods in Enzymology*, 272, pp. 51-64. Cited 448 times.

View at Publisher

65 Riley, A.P., Groer, C.E., Young, D., Ewald, A.W., Kivell, B.M., Prisinzano, T.E.

Synthesis and κ-opioid receptor activity of furan-substituted salvinorin A analogues (Open Access)

(2014) *Journal of Medicinal Chemistry*, 57 (24), pp. 10464-10475. Cited 26 times.
http://pubs.acs.org/jmc
doi: 10.1021/jm501521d

View at Publisher

66 Ro, D.-K., Ehlting, J., Douglas, C.J.

Cloning, functional expression, and subcellular localization of multiple NADPH-cytochrome P450 reductases from hybrid poplar

(2002) *Plant Physiology*, 130 (4), pp. 1837-1851. Cited 70 times.
doi: 10.1104/pp.008011

View at Publisher

67 Scheler, U., Rothe, K., Manzano, D.
Engineering the biosynthesis of carnosic acid and carnosol in yeast
(2016) *Nat. Commun.*, 7, p. 12942.

68 Schellenberg, R.

Treatment for the premenstrual syndrome with agnus castus fruit extract: Prospective, randomised, placebo controlled study

(2001) *British Medical Journal*, 322 (7279), pp. 134-137. Cited 205 times.

View at Publisher

69 Shults, E.E., Mironov, M.E., Kharitonov, Yu.V.

Furanoditerpenoids of the labdane series: Occurrence in plants, total synthesis, several transformations, and biological activity

(2014) *Chemistry of Natural Compounds*, 50 (1), pp. 2-21. Cited 9 times.
http://www.kluweronline.com/issn/0009-3130
doi: 10.1007/s10600-014-0861-8

View at Publisher

70 Smith III, A.B., Toder, B.H., Carroll, P.J., Donohue, J.

Andrographolide: an X-ray crystallographic analysis

(1982) *Journal of Crystallographic and Spectroscopic Research*, 12 (4), pp. 309-319. Cited 27 times.
doi: 10.1007/BF01159047

View at Publisher

71 Teoh, K.H., Polichuk, D.R., Reed, D.W., Covello, P.S.

Molecular cloning of an aldehyde dehydrogenase implicated in artemisinin biosynthesis in Artemisia annua

(2009) *Botany*, 87 (6), pp. 635-642. Cited 128 times.
http://article.pubs.nrc-cnrc.gc.ca/RPAS/rpv?hm=HInit&calyLang=eng&journal=cjb&volume=87&afpf=b09-032.pdf
doi: 10.1139/B09-032

View at Publisher

72 Tesso, H., König, W.A.

Terpenes from Otostegia integrifolia

(2004) *Phytochemistry*, 65 (14), pp. 2057-2062. Cited 17 times.
doi: 10.1016/j.phytochem.2004.03.012

View at Publisher

73 Trikka, F.A., Nikolaidis, A., Ignea, C., Tsaballa, A., Tziveleka, L.-A., Ioannou, E., Roussis, V., (...), Makris, A.M.

Combined metabolome and transcriptome profiling provides new insights into diterpene biosynthesis in S. pomifera glandular trichomes

(2015) *BMC Genomics*, 16 (1), art. no. 935. Cited 8 times.
http://www.biomedcentral.com/bmcgenomics
doi: 10.1186/s12864-015-2147-3

View at Publisher

74 Webster, D.E., He, Y., Chen, S.-N., Pauli, G.F., Farnsworth, N.R., Wang, Z.J.

Opioidergic mechanisms underlying the actions of Vitex agnus-castus L.

(2011) *Biochemical Pharmacology*, 81 (1), pp. 170-177. Cited 29 times.
doi: 10.1016/j.bcp.2010.09.013

View at Publisher

75 Wubshet, S.G., Tahtah, Y., Heskes, A.M., Kongstad, K.T., Pateraki, I., Hamberger, B., Møller, B.L., (...), Staerk, D.

Identification of PTP1B and α-Glucosidase Inhibitory Serrulatanes from Eremophila spp. by Combined use of Dual High-Resolution PTP1B and α-Glucosidase Inhibition Profiling and HPLC-HRMS-SPE-NMR

(2016) *Journal of Natural Products*, 79 (4), pp. 1063-1072. Cited 13 times.
http://pubs.acs.org/journal/jnprdf
doi: 10.1021/acs.jnatprod.5b01128

View at Publisher

76 Wuttke, W., Jarry, H., Christoffel, V., Spengler, B., Seidlová-Wuttke, D.

Chaste tree (Vitex agnus-castus) - Pharmacology and clinical indications

(2003) *Phytomedicine*, 10 (4), pp. 348-357. Cited 127 times.
www.urbanfischer.de/journals/phytomed
doi: 10.1078/094471103322004866

View at Publisher

77 Xu, M., Hillwig, M.L., Prisic, S., Coates, R.M., Peters, R.J.

Functional identification of rice syn-copalyl diphosphate synthase and its role in initiating biosynthesis of diterpenoid phytoalexin/allelopathic natural products

(2004) *Plant Journal*, 39 (3), pp. 309-318. Cited 96 times.
doi: 10.1111/j.1365-313X.2004.02137.x

View at Publisher

78 Yao, J.-L., Fang, S.-M., Liu, R., Oppong, M.B., Liu, E.-W., Fan, G.-W., Zhang, H.

A review on the terpenes from genus vitex

(2016) *Molecules*, 21 (9), art. no. 1179. Cited 4 times.
http://www.mdpi.com/1420-3049/21/9/1179/pdf
doi: 10.3390/molecules21091179

View at Publisher

79 Yee, N.K.N., Coates, R.M.

Total Synthesis of (+)-9,10-syn-and (+)-9,10-anti-Copalol via Epoxy Trienylsilane Cyclizations

(1992) *Journal of Organic Chemistry*, 57 (17), pp. 4598-4608. Cited 60 times.
doi: 10.1021/jo00043a014

View at Publisher

80 Zerbe, P., Hamberger, B., Yuen, M.M.S., Chiang, A., Sandhu, H.K., Madilao, L.L., Nguyen, A., (...), Bohlmann, J.

Gene discovery of modular diterpene metabolism in nonmodel systems

(2013) *Plant Physiology*, 162 (2), pp. 1073-1091. Cited 76 times.
http://www.plantphysiol.org/content/162/2/1073.full.pdf+html
doi: 10.1104/pp.113.218347

View at Publisher

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