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Klčová, B.; Balarynová, J.; Trněný, O.; Krejčí, P.; Cechová, M. Z.; Leonova, T.; Gorbach, D.; Frolova, N.; Kysil, E.; Orlova, A.; Ihling, ?.; Frolov, A.; Bednář, P.; Smýkal, P.;
Domestication has altered gene expression and secondary metabolites in pea seed coat *Plant J.* (2024) DOI: 10.1111/tpj.16734

Abstract

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The mature seed in legumes consists of an embryo and seed coat. In contrast to knowledge about the embryo, we know relatively little about the seed coat. We analyzed the gene expression during seed development using a panel of cultivated and wild pea genotypes. Gene co-expression analysis identified gene modules related to seed development, dormancy, and domestication. Oxidoreductase genes were found to be important components of developmental and domestication processes. Proteomic and metabolomic analysis revealed that domestication favored proteins involved in photosynthesis and protein metabolism at the expense of seed defense. Seed coats of wild peas were rich in cell wall-bound metabolites and the protective compounds predominated in their seed coats. Altogether, we have shown that domestication altered pea seed development and modified (mostly reduced) the transcripts along with the protein and metabolite composition of the seed coat, especially the content of the compounds involved in defense. We investigated dynamic profiles of selected identified phenolic and flavonoid metabolites across seed development. These compounds usually deteriorated the palatability and processing of the seeds. Our findings further provide resources to study secondary metabolism and strategies for improving the quality of legume seeds which comprise an important part of the human protein diet.

Müllers, Y.; Sadr, A. S.; Schenderlein, M.; Pallab, N.; D. Davari, M.; Glebe, U.; Reifarth, M.; Acrylate-derived RAFT polymers for enzyme hyperactivation – boosting the α-chymotrypsin enzyme activity using tailor-made poly(2-carboxyethyl)acrylate (PCEA) *ChemCatChem* (2024) DOI: 10.1002/cctc.202301685

Abstract
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We study the hyperactivation of α-chymotrypsin (α-ChT) using the acrylate polymer poly(2-carboxyethyl) acrylate (PCEA) in comparison to the commonly used poly(acrylic acid) (PAA). The polymers are added during the enzymatic cleavage reaction of the substrate N-glutaryl-L-phenylalanine p-nitroanilide (GPNA). Enzyme activity assays reveal a pronounced enzyme hyperactivation capacity of PCEA, which reaches up to 950% activity enhancement, and is significantly superior to PAA (revealing an activity enhancement of approx. 450%). In a combined experimental and computational study, we investigate α-ChT/polymer interactions to elucidate the hyperactivation mechanism of the enzyme. Isothermal titration calorimetry reveals a pronounced complexation between the polymer and the enzyme. Docking simulations reveal that binding of polymers significantly improves the binding affinity of GPNA to α-ChT. Notably, a higher binding affinity is found for the α-ChT/PCEA compared to the α-ChT/PAA complex. Further molecular dynamics (MD) simulations reveal changes in the size of the active site in the enzyme/polymer complexes, with PCEA inducing a more pronounced alteration compared to PAA, facilitating an easier access for the substrate to the active site of α-ChT.

Zhang, H.; Lin, S.; Xie, R.; Zhong, W.; Wang, H.; Farag, M.

A.; Hussain, H.; Arroo, R. R.; Chen, X.; Xiao, J.; Thermal degradation of (2R, 3R)-dihydromyricetin in neutral aqueous solution at 100 ℃ *Food Chem.* **435**, 137560, (2024) DOI: 10.1016/j.foodchem.2023.137560

Abstract
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In the field of thermal degradation of flavonoids, current studies mainly focused on flavonols. However, the thermal degradation of dihydroflavonols in aqueous solution has received limited attention compared to flavonols. The single C2-C3 bonds of dihydroflavonols, which differs from the C2-C3 double bond in flavonols, may cause different degradation mechanisms. Dihydromyricetin (DMY) is a typical dihydroflavonol with six hydroxyl groups, and possesses various health effects. We explored the thermal degradation of DMY in neutral aqueous solution (pH 7) at 100 ℃. Ultra-performance liquid chromatography combined with photodiode array and electrospray ionization quadrupole-time-of-flight tandem mass spectrometric detection (UPLC-PDA-ESI-QTOF-MS/MS) provided suitable platform for exploring DMY degradation pathways, and negative ion mode was applied. Thermal treatment led to a decline in DMY level with time, accompanied by the appearance of various degradation products of DMY. Degradation mechanisms of DMY included isomerization, oxidation, hydroxylation, dimerization and ring cleavage. The pyrogallol-type ring B of DMY might be initially oxidized into ortho-quinone, which could further attack another DMY to form dimers. In addition, hydroxylation is likely to occur at C-2, C-3 of DMY or DMY dimers, which then further yields ring-cleavage products via breakage of the O1-C2 bond, C2-C3 bond, or C3-C4 bond. The 3-hydroxy-5-(3,3,5,7-tetrahydroxy-4-oxochroman-2-yl) cyclohexa-3,5-diene-1, 2-dione (m/z 333.0244) and unknown compound m/z 435.0925 were annotated as key intermediates in DMY degradation. Four phenolic acids, including 3,4,5-trihydroxybenzoic acid (m/z 169.0136, RT 1.4 min), 2,4,6-trihydroxyphenylglyoxylic acid (m/z 197.0084, RT 1.7 min), 2-oxo-2-(2,4,6-trihydroxyphenyl) acetaldehyde (m/z 181.0132, RT 2.4 min), and 2,4,6-trihydroxybenzoic acid (m/z 169.0139, RT 2.5 min) were identified as the major end products of DMY degradation. In addition, 5-((3,5dihydroxyphenoxy) methyl)-3-hydroxycyclohexa-3,5-diene-1,2-dione (m/z 261.0399, RT 11.7 min) and unidentified compound with m/z 329.0507 (RT 1.0 min) were also suggested to be end products of DMY degradation. These results provide novel insights on DMY stability and degradation products. Moreover, the heat treatment of DMY aqueous solution was found to gradually reduce the antioxidant activities of DMY, and even destroy the beneficial effect of DMY on the gut microbiota composition.

Struwe, H.; Droste, J.; Dhar, D.; Davari, M. D.; Kirschning, A.; Chemoenzymatic synthesis of a new germacrene derivative named germacrene F *ChemBioChem* **25**, e202300599, (2024) DOI: 10.1002/cbic.202300599

Abstract
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The new farnesyl pyrophosphate (FPP) derivative with a shifted olefinic double bond from C6-C7 to C7-C8 is

accepted and converted by the sesquiterpene cyclases protoilludene synthase (Omp7) as well as viridiflorene synthase (Tps32). In both cases, a so far unknown germacrene derivative was found to be formed, which we name “germacrene F”. Both cases are examples in which a modification around the central olefinic double bond in FPP leads to a change in the mode of initial cyclization (from 1→11 to 1→10). For Omp7 a rationale for this behaviour was found by carrying out molecular docking studies. Temperature-dependent NMR experiments, accompanied by NOE studies, show that germacrene F adopts a preferred mirror-symmetric conformation with both methyl groups oriented in the same directions in the cyclodecane ring.

Noleto-Dias, C.; Farag, M. A.; Porzel, A.; Tavares, J. F.; Wessjohann, L. A.; A multiplex approach of MS, 1D-, and 2D-NMR metabolomics in plant ontogeny: A case study on Clusia minor L. organs (leaf, flower, fruit, and seed) *Phytochem. Anal.* **35**, 445-468, (2024) DOI: 10.1002/pca.3300

Abstract
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Introduction: The genus Clusia L. is mostly recognised for the production of prenylated benzophenones and tocotrienol derivatives.Objectives: The objective of this study was to map metabolome variation within Clusia minor organs at different developmental stages.Material and Methods: In total 15 organs/stages (leaf, flower, fruit, and seed) were analysed by UPLC-MS and 1H- and heteronuclear multiple-bond correlation (HMBC)-NMR-based metabolomics.Results: This work led to the assignment of 46 metabolites, belonging to organic acids(1), sugars(2) phenolic acids(1), flavonoids(3) prenylated xanthones(1) benzophenones(4) and tocotrienols(2). Multivariate data analyses explained the variability and classification of samples, highlighting chemical markers that discriminate each organ/stage. Leaves were found to be rich in 5-hydroxy-8-methyltocotrienol (8.5 µg/mg f.w.), while flowers were abundant in the polyprenylated benzophenone nemorosone with maximum level detected in the fully mature flower bud (43 µg/mg f.w.). Nemorosone and 5-hydroxy tocotrienoloic acid were isolated from FL6 for full structural characterisation. This is the first report of the NMR assignments of 5-hydroxy tocotrienoloic acid, and its maximum level was detected in the mature fruit at 50 µg/mg f.w. Seeds as typical storage organ were rich in sugars and omega-6 fatty acids.Conclusion: To the best of our knowledge, this is the first report on a comparative 1D-/2D-NMR approach to assess compositional differences in ontogeny studies compared with LC-MS exemplified by Clusia organs. Results derived from this study provide better understanding of the stages at which maximal production of natural compounds occur and elucidate in which developmental stages the enzymes responsible for the production of such metabolites are preferentially expressed.

Méndez, Y.; Vasco, A. V.; Ebensen, T.; Schulze, K.; Yousefi, M.; Davari, M. D.; Wessjohann, L. A.; Guzmán, C. A.; Rivera, D. G.; Westermann, B.; Diversification of a novel α-galactosyl ceramide hotspot boosts the adjuvant properties in parenteral and mucosal vaccines *Angew. Chem. Int. Ed.* **63**, e202310983, (2024) DOI: 10.1002/anie.202310983

Abstract

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The development of potent adjuvants is an important step for improving the performance of subunit vaccines. CD1d agonists, such as the prototypical α-galactosyl ceramide (α-GalCer), are of special interest due to their ability to activate iNKT cells and trigger rapid dendritic cell maturation and B-cell activation. Herein, we introduce a novel derivatization hotspot at the α-GalCer skeleton, namely the N-substituent at the amide bond. The multicomponent diversification of this previously unexplored glycolipid chemotype space permitted the introduction of a variety of extra functionalities that can either potentiate the adjuvant properties or serve as handles for further conjugation to antigens toward the development of self-adjuvanting vaccines. This strategy led to the discovery of compounds eliciting enhanced antigen-specific T cell stimulation and a higher antibody response when delivered by either the parenteral or the mucosal route, as compared to a known potent CD1d agonist. Notably, various functionalized α-GalCer analogues showed a more potent adjuvant effect after intranasal immunization than a PEGylated α-GalCer analogue previously optimized for this purpose. Ultimately, this work could open multiple avenues of opportunity for the use of mucosal vaccines against microbial infections.

Mejía-Manzano, L. A.; Ortiz-Alcaráz, C. I.; Parra Daza, L. E.; Suarez Medina, L.; Vargas-Cortez, T.; Fernández-Niño, M.; González Barrios, A. F.; González-Valdez, J.; Saccharomyces cerevisiae biofactory to produce naringenin using a systems biology approach and a bicistronic vector expression strategy in flavonoid production *Microbiology Spectrum* **12**, e03374-23, (2024) DOI: 10.1128/spectrum.03374-23

Abstract
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Naringenin is the central flavonoid in the biosynthesis of several bioactive compounds and presents a growing demand for its nutraceutical properties. Naringenin extraction from plants is non-viable due to low yields, and microbial platforms could represent a controlled and sustained alternative to produce it using several metabolic engineering tools. This study shows the naringenin production in Saccharomyces cerevisiae from glucose through a combined approach of systems biology, enzyme criteria selection, and a molecular engineering strategy. In silico prediction using a mixed integer linear programming (MILP) algorithm showed that the phenylpropanoid pathway was the shortest and most viable metabolic pathway. Two biscistronic constructs were generated using the PTV-1 2A peptide sequence, and a naringenin biofactory was assembled with the phenylalanine ammonia-lyase/tyrosine ammonia-lyase genes encoding phenylalanine/tyrosine ammonia-lyase (Rhodobacter capsulatus), 4-coumaroyl (4 Cl) encoding a p-coumaroyl-CoA ligase (Solanum lycopersicum), CHS encoding chalcone synthase (Hypericum androsaemum), and CHI encoding a chalcone isomerase (Glycine max). Naringenin productivity in batch fermentation was about 40.67 ± 3.47 µg/Lh with a 6.10 ± 0.52 mg/L titer (22.41 ± 1.91 µM) and a 3.26 ± 1.36 mg/g yield (YP/S) with the detection of additional flavonoids. The obtained concentration is better than other related works in diverse engineered microorganisms. The results suggest a successful and optimizable alternative for the heterologous flavanone production in yeast combined with bicistronic expression

mediated by a 2A peptide sequence for the first time. This strategy supports the production of extensive routes for other nutraceutical compounds. IMPORTANCE Flavonoids are a group of compounds generally produced by plants with proven biological activity, which have recently beeen recommended for the treatment and prevention of diseases and ailments with diverse causes. In this study, naringenin was produced in adequate amounts in yeast after in silico design. The four genes of the involved enzymes from several organisms (bacteria and plants) were multi-expressed in two vectors carrying each two genes linked by a short viral peptide sequence. The batch kinetic behavior of the product, substrate, and biomass was described at lab scale. The engineered strain might be used in a more affordable and viable bioprocess for industrial naringenin procurement.

Jaimez, R. E.; Barragan, L.; Fernández-Niño, M.; Larreal B, O. J.; Flores, B.; Pod Production Dynamics and Pod Size Distribution of Theobroma cacao L. Clone CCN 51 in Full Sunlight *International Journal of Agronomy* **2024**, 1-9, (2024) DOI: 10.1155/2024/4242270

Abstract
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Cacao fruit production dynamics vary from one location to another and are conditioned by the number of pods produced per tree. During cocoa pod development, the strength of the carbon sink varies depending on the demand exerted by the pods, which is proportional to the size. The relationship between cocoa pod production dynamics and size distribution is still poorly understood. Dissecting this relationship is an important step toward further improving cocoa crop management. In this study, the annual yield dynamics and quantity of cocoa pods produced by popular, highly productive, and widespread clone CCN 51 were investigated, based on six size classes observed during its fructification. Growth parameters were determined as weekly increments of pod length and diameter, whereas daily increments were estimated using the logistic Richards model. The fruiting cycle was characterized by the coexistence of fruits of various sizes where the number of pods belonging to each size class changes throughout the fruiting season. Fruit production varied following a seasonal pattern, reaching a maximum of 36 pods/tree, in trees cultivated in full sunlight, of which approximately 55% matured and were harvested. The peak carbon sink demand occurs when the tree pods have the highest numbers of pods. During this period, 65% of the pods had lengths between 5 and 15 cm, which corresponds to the period of the highest pod growth rate. The average length values of the harvested pods were generally below 23 cm and rarely exceeded 7 pods/tree. The Richard model proved to describe accurately the pod growth rates for CCN 51. This represents a promising tool to determine pod growth in other cultivars of relevance for the cocoa industry, which is essential to improve cocoa crop management.

Hussain, H.; How can we unlock the full potential of marine biological resources for novel drug discovery in an effective and ethical way? *Expert Opinion on Drug Discovery* **19**, 125-130, (2024) DOI: 10.1080/17460441.2023.2285402

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Herrera-Rocha, F.; León-Inga, A. M.; Aguirre Mejía, J. L.; Rodríguez-López, C. M.; Chica, M. J.; Wessjohann, L. A.; González Barrios, A. F.; Cala, M. P.; Fernández-Niño, M.; Bioactive and flavor compounds in cocoa liquor and their traceability over the major steps of cocoa post-harvesting processes *Food Chem.* **435**, 137529, (2024) DOI: 10.1016/j.foodchem.2023.137529

Abstract
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The production of fine-flavor cocoa represents a promising avenue to enhance socioeconomic development in Colombia and Latin America. Premium chocolate is obtained through a post-harvesting process, which relies on semi-standardized techniques. The change in the metabolic profile during cocoa processing considerably impacts flavor and nutraceutical properties of the final product. Understanding this impact considering both volatiles and non-volatile compounds is crucial for process and product re-engineering of cocoa post-harvesting. Consequently, this work studied the metabolic composition of cocoa liquor by untargeted metabolomics and lipidomics. This approach offered a comprehensive view of cocoa biochemistry, considering compounds associated with bioactivity and flavor in cocoa liquor. Their variations were traced back over the cocoa processing (i.e., drying, and roasting), highlighting their impact on flavor development and the nutraceutical properties. These results represent the basis for future studies aimed to re-engineer cocoa post-harvesting considering the variation of key flavor and bioactive compounds over processing.