Fermentation and purification strategies for the production of betulinic acid and its lupane-type precursors in Saccharomyces cerevisiae - DTU Orbit (29/11/2018)

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Microbial production of plant derived, biologically active compounds has the potential to provide economic and ecologic alternatives to existing low productive, plant-based processes. Current production of the pharmacologically active cyclic triterpenoid betulinic acid is realized by extraction from the bark of plane tree or birch. Here, we reengineered the reported betulinic acid pathway into S. cerevisiae and used this novel strain to develop efficient fermentation and product purification methods. Fed-batch cultivations with ethanol excess, using either an ethanol-pulse feed or controlling a constant ethanol concentration in the fermentation medium, significantly enhanced production of betulinic acid and its triterpenoid precursors. The beneficial effect of excess ethanol was further exploited in nitrogen-limited resting cell fermentations, yielding betulinic acid concentrations of 182 mg/L and total triterpenoid concentrations of 854 mg/L, the highest concentrations reported so far. Purification of lupane-type triterpenoids with high selectivity and yield was achieved by solid-liquid extraction without prior cell disruption using polar aprotic solvents such as acetone or ethyl acetate and subsequent precipitation with strong acids. This study highlights the potential of microbial production of plant derived triterpenoids in S. cerevisiae by combining metabolic and process engineering. This article is protected by copyright. All rights reserved.

**General information**
State: Published
Organisations: Novo Nordisk Foundation Center for Biosustainability, iLoop, Research Groups, Applied Metabolic Engineering, RWTH Aachen University, Technical University of Dortmund
Contributors: Czarnotta, E., Dianat, M., Korf, M., Granica, F., Merz, J., Maury, J., Baallal Jacobsen, S. A., Förster, J., Ebert, B. E., Blank, L. M.
Pages: 2528-2538
Publication date: 2017
Peer-reviewed: Yes

**Publication information**
Journal: Biotechnology and Bioengineering
Volume: 114
Issue number: 11
ISSN (Print): 0006-3592
Ratings:
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): CiteScore 4.07 SJR 1.372 SNIP 1.186
Web of Science (2017): Impact factor 3.952
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 4.14 SJR 1.447 SNIP 1.178
Web of Science (2016): Impact factor 4.481
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): CiteScore 4.44 SJR 1.632 SNIP 1.355
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): CiteScore 4.16 SJR 1.612 SNIP 1.395
Web of Science (2014): Impact factor 4.126
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): CiteScore 4.44 SJR 1.637 SNIP 1.427
Web of Science (2013): Impact factor 4.164
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): CiteScore 4.04 SJR 1.62 SNIP 1.364