In silico profiling of *Escherichia coli* and *Saccharomyces cerevisiae* as terpenoid factories

An analysis of the most prominent heterologous hosts

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Our focus was set on the *in silico* analysis of metabolic networks of the most prominent heterologous hosts *E. coli* (gut bacterium) and *S. cerevisiae* (baker's yeast) relating to the efficient supply of isopentenyl diphosphate (IPP). IPP is the common terpenoid precursor, which is produced by the microbes themselves naturally. Microbes producing IPP in high amounts are a prerequisite to produce plant terpenoids efficiently.

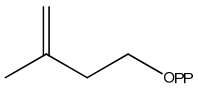

Figure 1: Isopentenyl diphosphate (IPP).

Terpenoids are a class of natural products with important medicinal and industrial applications from drugs (artemisinin, paclitaxel) to biofuel precursors (bisabolene, farnesene) to flavor compounds (patchoulol, linalool, menthol, eucalyptol).

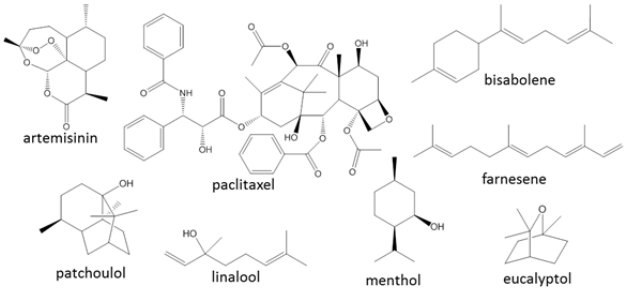

Figure 2: Diversity of terpenoids.

Several of these bioactive compounds are scarce and produced only in low amounts in plants, which makes the production in plants uneconomical and environmentally destructive. The total chemical synthesis of many terpenoids is challenging due to their complex structure and neither ecologically nor economically efficient. Alternatively, the use of a microbial platform organism for the production of terpenoids may offer the possibility of large-scale, cost-effective and environmentally friendly industrial production independent from climate or cultivation risks.

Today, *E. coli* and *S. cerevisiae* are the most widely used microorganisms for heterologous terpenoid production but terpenoid yields are still low. Thus, the aim of this study was to identify new metabolic engineering targets for an enhanced terpenoid yield.

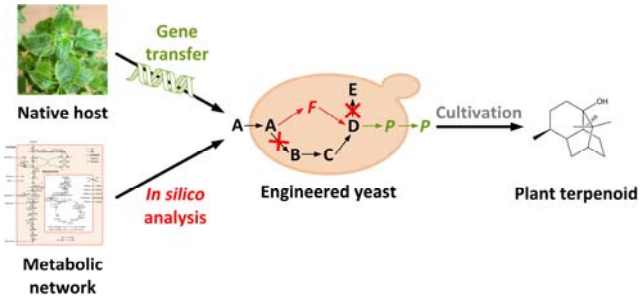

Figure 3: Schematic representation of the approach. First, terpenoid genes have to be transferred from the plant to the microbial host (*E. coli* or *S. cerevisiae*) to be able to produce plant terpenoids in microbes. Second, the metabolic network of the microbes is analyzed *in silico* to identify targets to metabolically engineer the microbial host for an enhanced terpenoid biosynthesis.

E. coli and *S. cerevisiae* use different pathways to supply IPP. The analysis of the metabolic networks revealed that the DXP pathway of *E. coli* has theoretically, based on stoichiometry, a higher potential to produce IPP in high yields than the one of yeast. Moreover, non-fermentable carbon sources have a higher potential for the production of terpenoids in high yields in comparison to sugars.

Deficiencies in energy and redox equivalents are identified in the metabolic networks and are a basis for metabolic engineering strategies. Different knockout and heterologous overexpression strategies are presented leading either to increased minimal or to an enhanced theoretical maximum terpenoid yield on different carbon sources. [1,2]

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Publikationen:

[1] Gruchattka E, Hädicke O, Klamt S, Schütz V, Kayser O: ***In silico* profiling of *Escherichia coli* and *Saccharomyces cerevisiae* as terpenoid factories**. *Microb Cell Fact* 2013, **12**:84.

[2] Abstracts of the 26th International Conference on Yeast Genetics and Molecular Biology. Frankfurt/Main, Germany. August 29-September 3, 2013. *Yeast* 2013, **30 Suppl 1**:S22-253.