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Engineering S. cerevisiae with the deletion of endogenous glucosidases for the production of flavonoid glucosides

Glycosylation of flavonoids is a promising approach to improve the pharmacokinetic properties and pharmacological activities. However, chemical glycosylation remains restricted by such disadvantages as poor regio- and stereoselectivities, and large-scale application of whole-cell glycosylation is still hampered by inefficient UDP-sugar formation. Using a combinatorial approach, an engineered *Saccharomyces cerevisiae* strain was constructed to enhance the production of flavonoid glucosides.

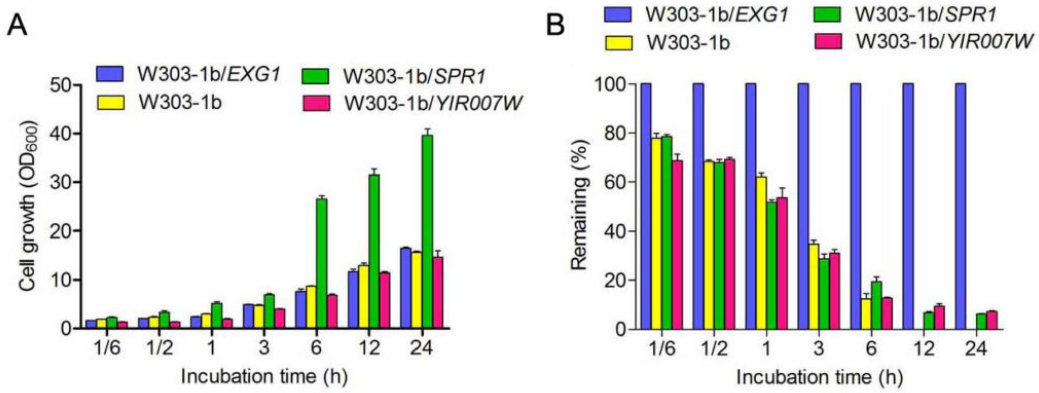

Fig. 1. Hydrolytic activity to luteolin 7-O-glucoside in strains with the deletion of glucosidases. (a) Biomass (OD600). (b) The remaining rate of luteolin 7-O-glucoside in the liquid medium. The values are presented as the means, and the error bars show the SD (n=3).

Firstly, a suitable glucosyltransferase (SbGT) were obtained from *Scutellaria baicalensis* Georgi. Then, three glucosidase genes (*EXG1*, *SPR1*, *YIR007W*) were knocked out using homologous integration, and the *EXG1* gene was determined to be the decisive gene of *S. cerevisiae* in the process of hydrolysing flavonoid glucosides. To further enhance the potential glycosylation activity of *S. cerevisiae*, two genes encoding phosphoglucomutase (PGM2) and UTP-glucose-1-phosphate uridylyltransferase (UGP1) involved in the synthetic system of uridine diphosphate glucose (UDPG) were over-expressed in *S. cerevisiae*. Finally, an engineered yeast strain was constructed to enhance the production of flavonoid glucosides by combining the expression of *SbGT*, *PGM2*, and *UGP1* with the deletion of glucosidases.

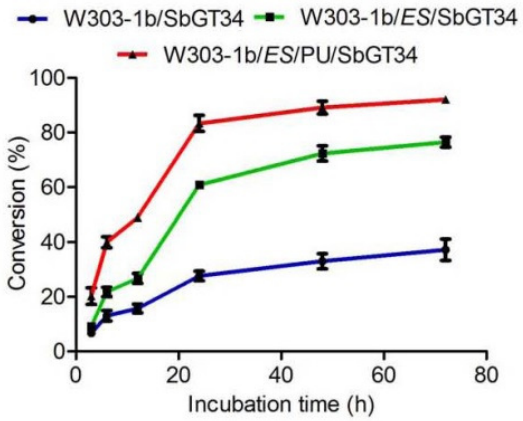

Fig. 2. Differences in the level of scutellarein 7-O-glucoside produced by strains W303-1b/SbGT34, W303-1b/ESΔ/SbGT34 and W303-1b/ESΔ/PU/SbGT34 over time. Strains were incubated with 0.2 mM scutellarein. The values are presented as the means, and the error bars show the SD (n=3).

Consequently, the resulted engineered strains were assayed for whole-cell biotransformation of scutellarein, and approximately 4.8 g (1.2 g/L) of scutellarein 7-*O*-glucoside was produced in 4 L of medium after 54 h of incubation in a 10-L fermenter while being supplied with ~ 3.5 g of scutellarein. Most important, this platform without glucosidase activity could be used to modify a wide range of valued plant secondary metabolites and to explore of their biological functions using whole-cell *S. cerevisiae* as a biocatalyst.

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