Metabolic engineering of robust industrial strains for *de novo* resveratrol production from sole carbon sources for application in process-like conditions

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For industrial applications, the search for robust microorganisms is essential to design sustainable processes. In addition to the wide range of uses in the food industry, *S. cerevisiae* is used as a robust cell factory to produce many chemicals of interest to society, from biofuels to high-value natural products. Resveratrol is a phenolic antioxidant compound, usually extracted by a complex and low-efficiency process from grapes or the roots of Japanese knotweed, and therefore being dependent on the supply of plant resources, as well as environmental factors. It can also be synthesized chemically through a complex and polluting method. In this sense, its production through microbial biosynthesis can side these drawbacks, being however mainly produced at the cost of expensive substrates as p-coumaric acid. *De novo* resveratrol production from glucose has been recently reported in a laboratory strain[1]. In this work, multiple robust industrial diploid strains were successfully engineered with resveratrol central pathway (*PAL2*/*C4H*/*CL2*/*VST1*) using CRISPR/Cas9 system for its *de novo* production through phenylalanine using glucose as sole carbon source. Top-producing strains revealed a resveratrol titre ca. 25% higher when compared to a laboratory strain using the same glucose concentration. Strains were screened in both batch and fed-batch conditions, revealing promising performance for scale-up application. This work aims for the construction of a fully engineered robust yeast strain for resveratrol production for industrial application.

1 Li et al. (2016) *Sci. Rep.* 6:36827

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