Biosynthetic production of curcuminoids

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Curcuminoids are natural phenylpropanoids from plants that have been reported as potential cancer-fighting drugs. Nevertheless, these compounds present a poor bioavailability. Cellular uptake is low and curcuminoids are quickly metabolized once inside the cell, requiring repetitive oral doses to achieve an effective concentration for therapeutic activity [1].
Herein, we report an engineered artificial pathway for the production of curcuminoids in *Escherichia coli*. *Arabidopsis thaliana* 4-coumaroyl-CoA ligase and *Curcuma longa* diketide-CoA synthase (DCS) and curcumin synthase (CURS1) were used and 188 μM (70 mg/L) of curcumin was obtained from ferulic acid [2]. Bisdemethoxycurcumin and demethoxycurcumin were also produced, but in lower concentrations, by feeding *p*-coumaric acid or a mixture of p-coumaric acid and ferulic acid, respectively. Additionally, curcuminoids were produced from tyrosine through the caffeic acid pathway. To produce caffeic acid, tyrosine ammonia lyase from *Rhodotorula glutinis* and 4-coumarate 3-hydroxylase from *Saccharothrix espanaensis* were used [3]. Caffeoyl-CoA 3-O-methyl-transferase from *Medicago sativa* was used to convert caffeoyl-CoA to feruloyl-CoA. Using caffeic acid, p-coumaric acid or tyrosine as a substrate, 3.9, 0.3, and 0.2 μM of curcumin were produced, respectively.
This is the first report on the use of DCS and CURS1 *in vivo* to produce curcuminoids. In addition, curcumin, the most studied curcuminoid for therapeutic purposes and considered in many studies as the most potent and active, was produced by feeding tyrosine using a pathway involving caffeic acid. We anticipate that by using a tyrosine overproducing strain, curcumin can be produced in *E. coli* without the need of adding expensive precursors to the medium, thus decreasing the production cost. Therefore, this alternative pathway represents a step forward in the heterologous production of curcumin using *E. coli.* Aiming at greater production titers and yields, the construction of this pathway in another model organism such as *Saccharomyces cerevisiae* is being considered.

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