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Title

De novo curcuminoids production in engineered *Escherichia coli*

Authors and Affiliation

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Abstract (1500/1800 characters)

Curcuminoids are a mixture of polyphenolic compounds (curcumin, bisdemethoxycurcumin and demethoxycurcumin) produced in the plant *Curcuma longa* with several therapeutic properties, including anticancer, anti-inflammatory, among others. Given this great potential, the curcuminoids market size is expected to reach $369M by 2033 with 11.3% CAGR [1]. However, these compounds are present in low amounts, accumulate during long growth periods, and their purification is environmentally unfriendly, expensive and difficult originating low yields and purity [2]. Hence, their biosynthesis by engineered microbes using synthetic biology has emerged as a potential competitive alternative. In the past, we developed for the first time a biosynthetic pathway in *E. coli* to produce curcumin, the curcuminoid with the highest therapeutic potential, from tyrosine, obtaining the highest production titers reported (43.2 µM curcumin, 125.8 µM total curcuminoids) [3,4]. This opened the door to produce curcumin from simple carbon sources which will be key at an industrial scale. In this study, we used a tyrosine overproducing *E. coli* strain to produce curcuminoids from glucose. Also, the previously constructed combinatorial biosynthetic pathway [3] was modified to overexpress more efficient enzymes for specific steps [5], including 4-hydroxyphenylacetate 3-hydroxylase units B/C from *Salmonella enterica* and *Pseudomonas aeruginosa*, that convert the highly accumulated coumaric acid into caffeic acid, and feruloyl-CoA synthase from *Sphingobium sp.*, that converts the hydroxycinnamic acids to CoA esters, having higher affinity to ferulic acid. All these modifications allowed to obtain the highest titers of curcumin reported so far from glucose with low amounts of the other curcuminoids being produced (> 250 µM curcumin, 12 µM total curcuminoids).

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