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Manufacturing Flavonoids: Occurrence, Significances, Limitations and their Production in Non-Native Hosts Using System Engineering

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COLUMN ARTICLE

Flavonoids are the most ubiquitous secondary metabolites produced in plants [1-3]. The production of flavonoids occurs in cytosol after making their way from endoplasmic reticulum and plastids [1]. More than 8,000 naturally occurring flavonoids have been identified and most of them are common in higher plants [4-7] and deposited in fruits, vegetables, nuts, seeds, stems, flowers, roots, bark, tea, wine and coffee which makes them the common constituents of our daily diet [8]. Numerous health promoting effects of these flavonoids makes them an indispensable component for the applications as nutraceuticals, pharmaceuticals and cosmeceuticals. Anti-inflammatory, anti-oxidative, anti-bacterial, anti-tumorigenic, anti-carcinogenic properties are some of the beneficial activities of flavonoids to name a few [9-11].

Although plants are the natural sources of flavonoids, their large-scale production by plant extraction for drug development is a challenge [11]. Similarly, difficulties are expected using tissue culture and chemical synthesis, making it difficult to conduct systematic experiments to elucidate their biological activity. In recent years, introduction and expression of natural plant pathways in non-native hosts such as *E. coli* and other microorganisms have proven to bear sustainable alternative [11-13]. However, pathway elucidation and subsequently the validation there of play an important role for the successful production of flavonoids in the selected heterologous host organisms. In these approaches, *E. coli* transformant containing flavonoid producing phenyl propanoid pathway gene assembly from plants were employed and inexpensive starting materials were supplied to the culture medium to produce a more valuable flavonoids (Figure 1) [14-16].

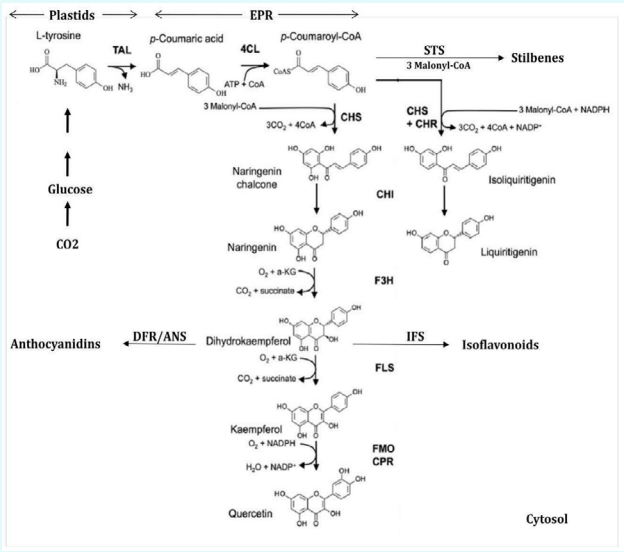

Figure 1: Phenylpropanoid pathway for the biosynthesis of the flavonoids in plants. TAL: tyrosine ammonia-lyase; 4CL: 4-coumaroyl-CoA lyase; CHS: chalcone synthase; CHR: chalcone reductase; CHI: chalcone isomerase; F3H: flavanone 3-hydroxylase; FLS: flavonol synthase; FMO: flavonoid-3'-monooxygenase; CPR: cytochrome P450 reductase; STS: stilbene synthase; DFR: dihydroflavonol reductase; IFS: isoflavone synthase; and ANS: anthocyanidin synthase.

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Though it is still challenging, we have come a long way to be able to synthesize a particular bioactive flavonoid using *E. coli*. Choosing the right production host, media optimization, enzyme engineering, promoter engineering, vector engineering, silencing/deleting the co-factors and energy sucking unwanted genes, and enhancing the malonyl-CoA pool may further contribute to the increase in the flavonoid's industrial yield starting from glucose or other cheap raw materials.

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