Investigation of a novel *O-demethylase* acting upon polymethoxyflavones

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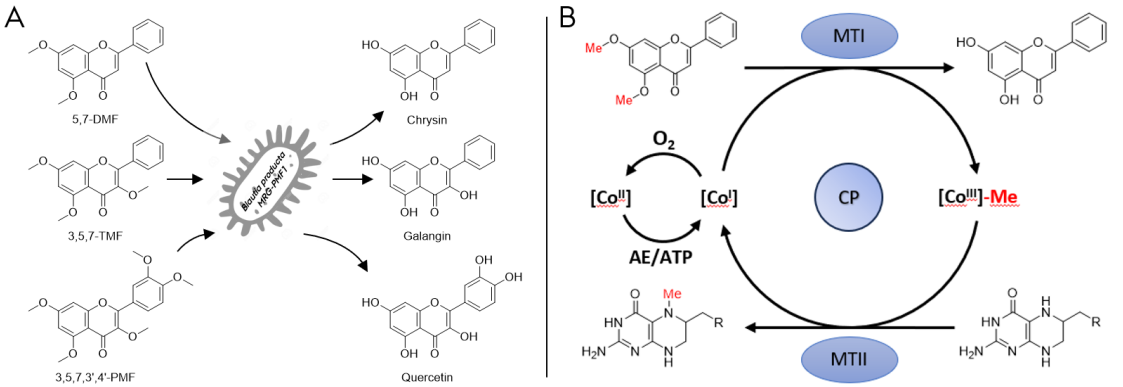
Natural products are a rich source of compounds with a plethora of bioactivities including anti-microbial, anti-cancer, anti-viral, anti-diabetic, anti-inflammatory, etc[1]. Flavonoids constitute a family of natural products with a broad variety in structure and activity. The flavonoid backbone is often highly substituted by functionalities of hydroxy, methoxy, or glycosylation which dictates their bioactivity. The potential of Flavonoids in therapeutics is however limited by their bioavailability due to low aqueous solubility and membrane permeation[2].

Recently, our collaborator, Jeahong Han, discovered a gut microbe, namely *Blautia producta* MRG-PMF1, capable of catalyzing the demethylation of polymethoxyflavones and structurally related non-natural products[3-5] (**Fig. 1A**).



The observed demethylation is highly believed to be catalyzed by the vitamin B12-dependent methyltransferase/corrinoid protein complex, ultimately shuffling methyl groups to acceptors such as tetrahydrofolate (**Fig. 1B**). We aim to characterize the enzymatic system *in vitro* and utilize the natural activity towards natural product scaffolds to generate catalysts with very high selectivity and specificity - generating reactive hydroxy groups on which further modifications can be accomplished by e.g., glycosylation.

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