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**Background:** Filamentous fungi are important producers of secondary metabolites, low molecular weight molecules that often have bioactive properties. Calbistrin A is a secondary metabolite with an interesting structure that was recently found to have bioactivity against leukemia cells. It consists of two polyketides linked by an ester bond: a bicyclic decalin containing polyketide with structural similarities to lovastatin, and a linear 12 carbon dioic acid structure. Calbistrin A is known to be produced by several uniseriate black Aspergilli, *Aspergillus versicolor*-related species, and Penicillia. *Penicillium decumbens* produces calbistrin A and B as well as several putative intermediates of the calbistrin pathway, such as decumenone A-B and versiol.

**Results:** A comparative genomics study focused on the polyketide synthase (PKS) sets found in three full genome sequence calbistrin producing fungal species, *P. decumbens*, *A. aculeatus* and *A. versicolor*, resulted in the identification of a novel, putative 13-membered calbistrin producing gene cluster (*calA* to *calM*). Implementation of the CRISPR/Cas9 technology in *P. decumbens* allowed the targeted deletion of genes encoding a polyketide synthase (*calA*), a major facilitator pump (*calB*) and a binuclear zinc cluster transcription factor (*calC*). Detailed metabolic profiling, using UHPLC-MS, of the ∆*calA* (PKS) and ∆*calC* (TF) strains confirmed the suspected involvement in calbistrin productions as neither strains produced calbistrin nor any of the putative intermediates in the pathway. Similarly analysis of the excreted metabolites in the ∆*calB* (MFC-pump) strain showed that the encoded pump was required for efficient export of calbistrin A and B.

**Conclusion:** Here we report the discovery of a gene cluster (*calA*-*M*) involved in the biosynthesis of the polyketide calbistrin in *P. decumbens*. Targeted gene deletions proved the involvement of *CalA* (polyketide synthase) in the biosynthesis of calbistrin, *CalB* (major facilitator pump) for the export of calbistrin A and B and *CalC* for the transcriptional regulation of the *cal*-cluster. This study lays the foundation for further characterization of the calbistrin biosynthetic pathway in multiple species and the development of an efficient calbistrin producing cell factory.

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