



Detection of antileukemia metabolites from *P. limosum* integrating genome mining, metabolomic analysis and cytotoxicity assays

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Highlights: Chemical dereplication and genome mining approaches were applied to detect cytotoxic metabolites produced by *P. limosum* CMLD 19 with anticancer potential against human leukemia cells. During the ongoing study, metabolites such as fumitremorgin and triprostatin were detected in the rice extract of *P. limosum* which showed 80% of cell inhibition for different human leukemia cell lines.

Natural products derived from microorganisms represent a promising source for discovering of cytotoxic compounds with anticancer potential. In this context, this study aimed to combine bioguided metabolomic analysis and genome mining of *P. limosum* CMLD 19 (an endophytic fungus isolated from the Atlantic Forest) as a strategy to screen bioactive compounds against human leukemia cells. The whole genome sequencing from the strain was obtained and submitted to the FungiSmash 6.0 platform for Biosynthetic Gene Clusters (BGCs) prediction. The analysis from *P. limosum* genome revealed 44 biosynthetic gene clusters (BGC's), including the hybrid cluster 39.1 (mixed pathway) which exhibited 55% of similarity to BGC's responsible for encoding the production of the known metabolites: fumitremorgin, triprostatin, breviamide and verrucologen. *P. limosum* was then cultivated in different culture media growth (YES, BD and rice). The corresponding organic extracts were submitted to biological activity assays against different leukemia cell. More than 80% of cell inhibition was observed for the rice extract on Jurkat and Kasumi-1 cell lines. Through manual and automated chemical dereplication performed at GNPS platform, the metabolites fumitremorgin C, triprostatin A and B and verrucologen were detected and annotated. These compounds have anticancer activities described against different types of cancer cell lines. However, there is no evidences linking these compounds to activities against leukemia. These results point towards compounds produced by *P. limosum* with potential for cytotoxic activity against leukemia to be further investigated. Thus, the rice extract was scaled up and the target metabolites will be isolated for structural elucidation and confirmatory biological assays of cellular activity and mechanism of action.

