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Sanguinarine Blocks Cytokinesis in Bacteria by Inhibiting FtsZ Assembly and Bundling†

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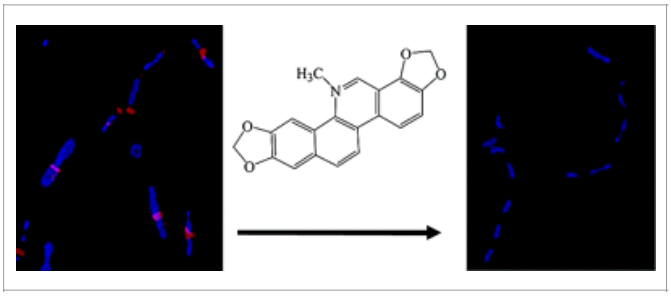
Abstract:



Bacterial diseases are among the leading causes of human death. The development of antibiotic resistance greatly contributes to the high mortality rate, and thus, the discovery of antibacterial drugs with novel mechanisms of action is needed. In this study, we found that sanguinarine, a benzophenanthridine alkaloid, strongly induced filamentation in both Gram-positive and Gram-negative bacteria and prevented bacterial cell division by inhibiting cytokinesis. Sanguinarine did not perturb the membrane structure in *Escherichia coli*. However, it perturbed the cytokinetic Z-ring formation in *E. coli*. In addition, sanguinarine strongly reduced the frequency of the occurrence of Z rings/micrometer of *Bacillus subtilis* length but did not alter the number of nucleoids/micrometer of cell length. The results suggested that sanguinarine inhibited cytokinesis in *B. subtilis* by inhibiting Z-ring formation without affecting nucleoid segregation. Sanguinarine inhibited the assembly of purified FtsZ and reduced the bundling of FtsZ protofilaments *in vitro*. Further, the interaction of sanguinarine to FtsZ was investigated using size-exclusion chromatography, an extrinsic fluorescent probe 1-anilinonaphthalene-8-sulfonic acid, and tryptophan fluorescence of mutated FtsZ (Y371W). Sanguinarine was found to bind to FtsZ with a dissociation constant of 18-30 μM. The results together show that sanguinarine inhibits bacterial division by perturbing FtsZ assembly dynamics in the Z ring and provide evidence in support of the hypothesis that the assembly and bundling of FtsZ play a critical role in bacterial cytokinesis. The results suggest that sanguinarine may be used as a lead compound to develop FtsZ-targeted antibacterial agents.

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