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Pseudolaric Acid B as a new class of microtubule destabilizing agent and an effective anti-tumor compound *in vivo*

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Pseudolaric acid B (PAB) is the major constituent in *pseudolarix kaempferi* that has been used as an anti-fungal remedy in traditional Chinese medicine. We purified PAB to apparent homogeneity and showed that it exhibits potent growth inhibition towards a panel of cancer cell line (average IC_{50}=1 μM). PAB also induces cell cycle arrest at G_2-M transition, leading to apoptosis. Detail analysis of the mode-of-action revealed that cellular microtubule networks were disrupted by PAB treatment. Chromatin condensation was observed in PAB-treated cells. Nonetheless, mitotic spindles apparatus failed to form. Taken together, these data suggested that microtubules were destabilized by PAB treatment, resulting in mitotic arrest. On the other hand, polymerization of purified bovine brain tubulin is dose-dependently inhibited by PAB, suggesting that tubulin is the direct target of PAB. However, PAB did not displace [^{3}H]colchicine in the competition binding assay, suggesting that PAB interacts with tubulin through a novel binding site. Most importantly, unlike other members of microtubule-targeting compounds such as colchicine and taxol, PAB circumvents multidrug resistance phenotype, and displays remarkable potency in cells overexpresing P-glycoprotein pump. Finally, we showed that PAB is an effective anti-tumor agent in vivo as evaluated by the murine xenograft tumor model.