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Title: Mechanism of Resistance to Camptothecin, a Cytotoxic Plant Secondary Metabolite, by *Lymantria* sp. Larvae

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Abstract: Camptothecin (CPT), a monoterpene indole alkaloid, is a potent inhibitor of eukaryotic topoisomerase I (Top 1). Because of this property, several derivatives of CPT are widely used as chemotherapeutic agents. The compound is produced by several plant species, including *Nothapodytes nimmoniana* (Family: Icacinaceae) presumably as a deterrent to insect pests. Here, we report, a lepidopteran larva, *Lymantria* sp. of Lymantriidae family which feeds voraciously on the leaves of *N. nimmoniana*, without any adverse consequences. Larval body weight and molting period were unaffected despite captive feeding of the larva with CPT enriched leaves. Mass spectrometric analysis indicated that nearly 46% of the ingested CPT was excreted while the rest was sequestered predominantly in the exuviae and setae (~35%). Although most of the CPT was in the parental form as found in the plant, traces of inactive, sulfated forms of CPT were recovered from the larva. Compared to that in plant, there were no critical mutations at the CPT binding domain of the insect's Top 1. The gut pH of the larva was alkaline (pH 10.0). The alkaline gut environment converts CPT from its active, lactone form to inactive, carboxylate form. It is likely that such conversion might help the larva to reduce the overall burden of CPT in its gut. We discuss the results in the context of the mechanisms of resistance adapted by insects to plant toxins.

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