

The pyrrolizidine alkaloid-induced hepatotoxicity of *Lolium rigidum* and *Lolium perenne* in the rat. Elevated levels of hepatic enzyme markers were observed in rats following the oral administration of the pyrrolizidine alkaloids pyrrolizidine (PA; 95% 1-hydroxymethyl-3,6-didehydro-1H-pyrrolizine) and taitusine (PA; 98% 1-hydroxymethyl-6,7-dehydro-1H-pyrrolizine) to rats. In vitro assessment of cytotoxic metabolites of PA in hepatocytes and proximal tubular cells revealed that the native tetramethyl tetrahydronorbornadiene (T1N) was relatively non-toxic, but the dehydrogenated products (tetrahydropyrans) were highly cytotoxic. Intraperitoneal administration of T1N or the tetrahydropyrans to male Sprague-Dawley rats at a dose of 200 mg kg⁻¹ failed to cause significant liver injury. However, treatment with 100 mg kg⁻¹ of T1N, 1,8-dihydroxymethyl-6,7-bis-O-methyl-3-oxo-3,4-dehydro-L-pyrrolizine or 3,4-dihydroxymethyl-6-O-methyl-1-hydroxymethyl-1,2,3-octaoxo-4,6-dihydro-L-pyrrolizine caused a dose-dependent increase in serum alanine aminotransferase (ALT) activity. Toxicity in animals fed *L. rigidum* also was observed at lower doses (25-100 mg kg⁻¹ body weight) when the alkaloid diet was administered prior to dosing with T1N, 1,8-dihydroxymethyl-6,7-bis-O-methyl-3-oxo-3,4-dehydro-L-pyrrolizine or 3,4-dihydroxymethyl-6-O-methyl-1-hydroxymethyl-1,2,3-octaoxo-4,6-dihydro-L-pyrrolizine. None of the

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Table S6. *P. falciparum* genes downregulated in gametocytes or gamete exflagellation.

System Requirements:

* Windows XP or later * DirectX 9 compatible video card with API level 9.0 or later (GeForce GTS 450 or higher is recommended). * CPU: 1.6 GHz or higher * RAM: 128 MB or higher * Sound Card: DirectX 9 compatible sound card with at least 32 bit per channel sample rate, 16 bit/sample rate support, and EAX support. * Hard Drive: 15 MB or higher * Mouse: Two buttons and one scrolling wheel * Keyboard: Standard keyboard (six keys per character

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