WAAVP 2021

Book of Abstracts

P-3025

Monoterpenes as potential tools to improve the activity of synthetic anthelmintics: pharmacological screening of their effects on drug metabolism and intestinal accumulation

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Abstract

The search for novel alternatives to control gastrointestinal nematodes in ruminants is relevant considering the increasing of anthelmintic resistance. The use of monoterpenes may contribute to improving parasite control by enhancing the effectiveness of existing synthetic anthelmintic drugs. The work described here evaluated *in vitro* the effects of monoterpenes on the processes of drug metabolism and intestinal accumulation and additionally, the anthelmintic activity of the best "candidate". In Trial 1 the intestinal accumulation of Rhodamine-123 (Rho123), a P-glycoprotein substrate, was studied in cattle ileum in the presence or absence of carvone (CNE), geraniol (GNL), citral (CTL), anethole (ANT), carvacrol (CVC) and thymol (TML). The effect of CNE, GNL and CTL on flavin-containing monooxygenase (FMO) and cytochrome P450 (CYP) dependent metabolism was assessed in sheep liver microsomes measuring specific enzyme activities. Among the monoterpenes tested, only the presence of CNE and GNL increased the accumulation of Rho123 by 73 % and 44 % respectively ($P<0.05$). CNE, GNL and CIT reduced the CYP-dependent metabolism between 29.5 and 91 % ($P<0.05$) and the FMO dependent metabolism between 46 and 84 % ($P<0.05$). Additionally, in a separate experiment (Trial 2), the anthelmintic activity of the best monoterpene "candidate" was evaluated in lambs. *S*ix lambs artificially infected with 2000 *Haemonchus. contortus* larvae each were treated with CNE (the best candidate from Trial 1) at 100 mg/kg orally, four times every 24 h. The fecal eggs count (FEC) reduction was measured at 7, 14 and 21 days post-administration of the first dose of CNE. The FEC reduction after the *in vivo* administration of CNE to infected lambs was 85 % (7 d), 88 % (14 d) and 82 (21 d). Integrated in-*vitro-in vivo* assays are critical for the design of successful alternative parasite control strategies based on the use of bioactive phytochemicals.