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PHARMACOLOGICAL CHARACTERIZATION OF MONOTERPENES WITH POTENTIAL NEMATODICIDAL ACTIVITY IN RUMINANTS

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The search for novel alternatives to control gastrointestinal nematodes (GI) in ruminants is relevant in a scenario of increased anthelmintic resistance. The use of monoterpenes may enhance the effectiveness of existing synthetic anthelmintic drugs. However, it is necessary to study the potential pharmacological interactions and the fate of these compounds after their administration to ruminants. This work evaluated *in vitro* the effects of monoterpenes on the processes of drug metabolism and intestinal accumulation and the *in vivo* pharmacokinetics interactions between the best "candidate" and synthetic anthelmintics. In Phase 1, the intestinal accumulation of Rhodamine 123 (Rho123), a P-glycoprotein substrate, was studied in cattle ileum explants in the presence or absence of carvone (CNE), geraniol (GNL) and citral (CTL). 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. The presence of CNE and GNL increased the accumulation of Rho123 in the ileum explants by 66 % and 46 % respectively ($P<0.05$). CNE, GNL and CIT reduced the CYP-dependent metabolism between 43 and 91 % ($P<0.05$) and the FMO dependent metabolism between 69 and 84 % ($P<0.05$). Additionally, in Phase 2, two separate experiments evaluated *in vivo* interaction of CNE-ivermectin (IVM) and GNL- albendazole (ABZ) in lambs. For the CNE-IVM assay, lambs were treated with either IVM (subcutaneous, 0.2 mg/kg) or IVM in combination with CNE (100 mg/kg, three oral doses every 24 h). In the GNL-ABZ trial, two experimental groups were treated with ABZ (5 mg/kg, orally) or, ABZ and GNL (100 mg/kg, two oral doses administered at -1 and 9h post-administration of ABZ) respectively. Blood samples were serially collected, and plasma levels of each compound were determined by HPLC. No undesirable effects were observed after the oral administration of CNE or GNL. In both trials, no changes were observed in the pharmacokinetic parameters of the synthetic anthelmintics after their administration combined with the monoterpenes. The highest plasma concentrations of CNE and GNL were between 3,04 and 5.27 µg/mL which are several times below the effective *in vitro* concentrations against GI reported in the literature. Although the presence of monoterpenes did not increase the plasma concentrations of IVM and ABZ, the lack of negative pharmacokinetic interactions gives these combinations an important pharmacological value to study their potential antiparasitic effect. The integration of *in vitro and in vivo* assays are critical for the design of successful alternative pharmacological tools based on the use of bioactive phytochemicals.