The dual anthelmintic potential for triterpenoids in the treatment of blood and liver flukes

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Abstract

The ability to rapidly identify chemotherapies with activity against a diverse range of disease-causing pathogens is a major driving force in drug discovery. For example, compounds with dual activity against both liver and blood flukes could improve the economic and biomedical burdens associated with the neglected infectious diseases schistosomiasis and fascioliasis. In the UK alone, infection with *Fasciola hepatica* (liver fluke) leads to the loss of over £300 million per annum in the livestock sector. Furthermore, chronic infection with *Schistosoma* (blood fluke) worms results in the deaths of 200,000 people per annum. In the absence of immunoprophylactic vaccines, these figures clearly demonstrate an urgent need to maintain existing or identify new chemotherapies for sustaining anthelmintic control.

For *F. hepatica* control, triclabendazole (TCBZ) is the only drug on the market that kills both adult and juvenile stages of the parasite. In schistosomiasis, praziquantel (PZQ) is the only registered drug active against all human-infective schistosome species. Unfortunately, PZQ is ineffective against juvenile worms, often requiring repeat treatment in endemic areas. Furthermore, TCBZ resistant (or less susceptible) liver flukes have been found in all continents where fascioliasis is endemic and there is increasing concern that PZQ insensitive (or resistant) blood flukes could also be developing. Therefore, single-compound fascioliasis and schistosomiasis control strategies are unlikely to be sustainable presenting a strong impetus for identifying new anthelmintics.

In this study, we continued our search for anthelmintic products derived from plants. Specifically, we screened twenty triterpenoids for activity against juvenile and adult lifecycle stages of both liver and blood fluke parasites. Of these twenty, one compound had an overlapping effect on both parasites in all stages of the lifecycle examined. This compound, 700015, resulted in gross disruption to the tegument of both species and affected both neoblast proliferation as well as oviposition within *S. mansoni* adult worms. Initial investigations into cell cytotoxicity suggests that this compound is not particularly cytotoxic to bovine MDBK or human HepG2 cells. We have demonstrated that naturally derived triterpenes have the potential as future drug candidates to treat both liver and blood flukes.