ABSTRACT

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Training Workplace	Department of Biochemical Sciences
Doctoral Degree Program	Xenobiochemistry and Pathobiochemistry
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Title of Doctoral Thesis	The use of transcriptomic analysis in study of drug-resistance in nematodes

Haemonchosis, an infection of ruminants caused by the nematode Haemonchus contortus, negatively affects animal health and the economics of livestock production. Although anthelmintics are a basic tool in the treatment of haemonchosis, their efficacy is rapidly decreasing due to drug resistance development. Increased inactivation and efflux of anthelmintics associated with higher transcription of xenobiotic metabolizing enzymes (XME) belong to a significant drug-resistance mechanism. However, information about XME in H. contortus is still limited. The aim of this study was to increase knowledge about the mechanism of drug resistance in the parasitic nematode H. contortus, focusing on the analysis of constitutive expression of selected XME throughout the life cycle and comparing changes in expression between strains with different levels of resistance and after exposure to selected anthelmintics. In the genome of H. contortus, 46 members of short-chain reductases/dehydrogenases (SDR) and 22 members of aldo-keto reductases (AKR) were identified, whose constitutive expression was analyzed in eggs, larvae, and adults and compared in an anthelmintic-sensitive and resistant strain. Increased expression of akr19 in the resistant strain and after contact with sublethal doses of flubendazole (FLU) suggests its potential involvement in drug resistance. Deactivation of FLU by free-living stages was demonstrated and more effective reduction was observed in larvae and females of the resistant strain. Analysis of changes in the expression of UDP-glycosyltransferases (UGT) throughout the life cycle showed a higher expression of most UGT in juvenile stages compared to adults, with ugt368b2 as a suitable candidate for further investigation. Exposure of adults to albendazole (ABZ) led to a significant induction of several XME, which may contribute to more efficient anthelmintic metabolism. Exposure of free-living stages to sublethal doses of ABZ during development induces changes in UGT and Pgp gene expression, some of which are stable throughout the nematode life cycle and are transmitted to the next generation.