Summary

Infections by soil-transmitted helminths threatens about 1.5 billion people in tropical and subtropical regions around the world. Main reasons for helminthiasis are poor sanitary conditions and the limited access to anthelmintic treatments in developing countries. Also in industrial countries, an increasing number of drug resistant helminths in animals, especially livestock, is an emerging problem.

For identification of new anthelmintic natural products as lead compounds, the systematic investigation of traditionally used plants against helminths, followed by bioactivity-guided fractionation, identification of the active principle and investigation of the underlying anthelmintic mechanisms can comprise a possible strategy to combat these problems. The present study investigated two traditionally used plants using the the free-living and non-parasitic nematode *Caenorhabditis elegans* as model organism, as it is closely related to parasitic nematodes.

Extracts from the bark and leaves of *Ailanthus altissima*, also known as tree of heaven, are traditionally used to treat gastroenteritis and infections caused by helminths. A methanol-water (7:3, v/v) extract of the primary stem bark irreversibly inhibited the reproduction of *C. elegans* L4 larvae. The effect was strongly dependent on the treated larval stage as L3 larvae and adults were less affected. By bioactivity-guided fractionation the quassinoids ailanthone and 13,18-dehydroailanthinone were identified as active compounds. In contrast, 13,18-dehydroglaucarubinone did not show any bioactivity, which might be caused by the presence of a hydroxyl-group in the C-15 ester substituent. Further investigations with the quassinoids bruceine A from *Brucea javanica* and quassin from *Quassia amara* revealed that polarity of the substances is important for bioactivity, as well. Further investigations concerning the structure-activity relationships with a bigger set of quassinoids is to be performed in future works. Using ultra-sectioning and atomic force microscopy of treated *C. elegans* showed severely damaged germ cells and rachis, which led to none or only poorly developed oocytes. It is hypothesized that these damages led to the activation of the transcription factor DAF-16, which plays a major role in the nematode's response to stress. A regulation *via* the respective insulin/insulin-like IGF-1 pathway by using deletion mutants of DAF-16 and the receptor DAF-2, respectively, was not observed.

The West African plant *Combretum mucronatum* contains oligomeric procyanidins as active principle with nematicidal activity against *C. elegans* and parasitic feline roundworm (*Toxocara cati*) and canine whipworm (*Trichuris vulpis*). To get further insights into the underlying mode of action, non-directed mutagenesis by ethyl methanesulfonate was performed, leading to the identification of two mutants with a reduced sensitivity to *C. mucronatum* extract. However, the mutants did not show increased resistance against the tannin-rich extracts of *Rhododendron ferrugineum* and *Rumex acetosa*. Whole genome sequencing of the two mutants revealed that a large part of the encoded proteins from

mutated genes were associated with the membrane and transmembrane region. To determine whether distinct proteins are targets of oligomeric procyanidins, deletion mutants with the respective mutated genes were chosen for further mortality assays with *C. mucronatum* extract. Only one mutant carrying a deletion of the gene *F53F8.3* showed increased resistance against oligomeric procyanidins, but the effect was not observable anymore following outcrossing. Subsequently, the targets of oligomeric procyanidins from *C. mucronatum* extract on *C. elegans* remains unknown.

In conclusion, the findings of this study provide a base for further investigations to elucidate the mode of action of oligomeric procyanidins and quassinoids in *C. elegans*.