Medicinal Plants in Control of Protozoal Infections

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Infectious diseases are caused by prokaryotic or eukaryotic micro organisms, viruses or other sub cellularinfectious elements. Although the majority of infectious diseases from micro organisms are caused by bacteria, the other groups are nonetheless important. Inside the group of eukaryotes protozoa cause prominent infections,like malaria, trypanosomiasis, leishmanias and dysentery. Many of them do not only cause severe maladies, but also cause an imminent economic damage. Malaria e.g. is a life-threatening parasitic disease transmitted by mosquitoes. Today approximately 40% of the world's population mostly those living in the world's poorest countries is at risk of malaria. There are at least 300 million acute cases of malaria each year globally, resulting in more than a million deaths. In Africa today, malaria is understood to be both a disease of poverty and a cause of poverty.

Many attempts to eradiate infections with different types and strains of malaria parasites e.g. *Plasmodium falciparum* by control of the transmitting mosquitoesusing different insecticides like DDT failed or just reduced the number of infections in the past. Such strategies were also tried for many other infections e.g. the Chagas' disease in Central America, with similar result. Therefore, chemotherapeutic treatment after infection is still very important.

Many protozoal infections can cured by use of synthetic compounds, which are frequently used as standard drugs in our western type medicine. One of the first used compounds was quinine, a quinolinealkaloid isolated from *Cinchona succirubra*, Rubiaceae. This compound was used for a long time, but it could control the blood stages of the malaria parasite. Liver stages were not influenced, which meant no cure. Today compounds like chloroquine (Resochin® and mefloquine (Lariam®) can be used against the blood stages of the malaria parasite, while primaquine and pyrimethamin (Daraprim®) are directed against the liver stages. Some of these compounds are also used for chemoprophylaxis, preventing tourists to get a severe infection.

Since malaria is a disease which happens to occur in poorer countries and the parasites become more and more resistant against the synthetic compounds, there is a need for less resistant and especially cheaper antimalarials. The latter requirement can often be fulfilled by the use of medicinal plants growing in the particular country. Such plants are often sold on the market places and they are thus available for everybody. It is quite clear that the quality of the plant material is not always good, since there is no quality control. Additionally, no information exists about toxicity in most cases. Phytochemical research can therefore find new antimalarial leads and also help to increase the quality of the traded plants. The Chinese herb *Artemisia annua* is an example for this. The isolated sesquiterpene lactone artemisinine was

found to be very active against chloroquine resistant strains of *P. falciparum*. This compound and its semi-synthetic derivatives are already used to treat Malaria in several countries of the world.

We investigated medicinal plants, which are used against protozoal infections in Guatemala. The Asteraceae *Neurolaena lobata*, which occurs from South-Mexico throughout whole Central America up to the northern parts of the South-American subcontinent and in the Caribbean, is frequently used against Malaria, the American form of Trypanosomiasis, called Chagas' disease and dysentery, often caused by infection with *Entamoeba histolytica* or *Giardia intestinalis*. Additionally, we investigated other member of the genus Neurolaena, used in special parts of Guatemala and Mexico and some other plants often used when *N. lobata* was not available.

The investigation of Neurolaenaleaves afforded 15 different sesquiterpene lactones. A number of them were tested against *P. falciparum*, *Trypanosoma cruzi*, *Entamoeba histolytica* and *Giardia intestinalis* in *vitro*. The neurolenin type sesquiterpene lactones were found to be the most active compounds with IC_{50} values between 0.6 and 1 µM, while the also found furanoheliangolide type sesquiterpene lactones were much less active, having IC_{50} values in the range of 15 to 20 µM. Although all compounds are only moderately active in comparison to artemisinine (0.14 µM), they can certainly explain the use of the plant against Malaria, especially if one considers the high amounts found in the plant. Since sesquiterpene lactones are often display cytotoxicity, all compounds were tested on their ability to reduce tumor growth.

Interestingly the furanoheliangolides, which are almost inactive against *P. falciparumhad* the highest cytotoxicity values. These results could help to find active plants with low levels of toxic compounds. We therefore investigated different populations to select plants with high amounts of neurolenins and less amounts of furanoheliangolides.

The main neurolenins were also tested against *T. cruzi*, *E. histolytica* and *G. intestinalis*. We found considerable activities in all cases but the values found against the Chagas' disease were most promising. The IC_{90} found for the main compound neurolenin B (~5 µg/ml) clearly showed it more active than such standard compounds as e.g. nifurtimox and benznidazol.

From *Eupatorium semialatumwe* isolated eight sesquiterpene lactones and a large number of flavonoids. The bitter principles were in analogy to Neurolaena again the most active compounds. However, the activities of the sesquiterpene lactones found here were much lower than those found for *Neurolaena*. We only found IC_{50} values between 9 and 30 µM.

We also tested the sesquiterpene lactones from *Arnica montana*, a European Asteraceae, which is used externally against all kinds of inflammations. Helenaline and its ester derivatives showed IC_{50} values between 0.23 and 7.5 µM. Especially the IC_{50} of helenaline (0.23 µM) looks promising compared to artemisinine (0.14 µM). Unfortunately helenaline is very cytotoxic and it also showed cardiotoxic effects, the reason for the solely external use of *Arnica* preparations.

Currently we are working with *Erythrina addisoniae* (Fabaceae). This tree occurs in dry areas of West Africa from Sierra Leone to Nigeria. The stem and root bark of this tree is used in Ghana against different types of infections including dysentery and malaria. The genus *Erythrina* is distributed throughout all tropical areas with more than 100 species worldwide. Although the phytochemistry of several of the species is already known, not much information existsabout their pharmacology. In general most of the *Erythrina* species contain isoquinoline alkaloids and different types of isoflavones and flavanones. *E.*

addisoniae is investigated for the first time. So far we found prenylated isoflavones, pterocarpanes and flavanones. The extracts and fractions were already tested against *P. falciparum* in *vitro*. Their IC_{50} values ranged between 7 and 100 µg/ml. The first flavonoids were already tested, but their activities could not explain the promising results we got with some of the fractions, others are momentarily under investigation.