

TREATMENT OF TAPEWORM INFECTIONS; AN OLD DRUG AND ITS REPLACEMENTS

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This lecture is dealing with the old botanical drugs: Rhizomes of *Dryopteris* ferns, the use of them in treatment of tapeworm infections, and their replacements. They were used in antiquity, seem to have been forgotten for centuries, but rediscovered in the 18th century. The Swiss brothers Peschier made the first galenical preparation of *Dryopteris filix-mas* in 1825, an ethereal extract of its rhizome.

Since then a fairly great numbers of scientists have studied the raw drug and the extract. Botanists and pharmacognosists have studied different species of the ferns. The ways of making the extract have been topics for galenic pharmacy. The constituents of the extract have been thoroughly studied in organic chemistry. Analytical chemistry has been involved in attempts to standardize the extract. The use of it in medicine and its mode of action have been studied by pharmacologists.

What have been the results of all this research? Studies in botany and pharmacognosy have shown that other species of the *Dryopteris* genus also have constituents that are active against tapeworms. Two subspecies of *Dryopteris austriaca*, subsp. *dilatata* and subsp. *eu-spinulosa*, have been especially interesting, as they yield extracts that seem to be more effective than extracts of *Dryopteris filix-mas*. Rhizomes of *Dryopteris austriaca* in addition to rhizomes of *filix-mas* have been embodied in the Finnish pharmacopoeia. In the USA *Dryopteris marginalis* has besides *filix-mas* been the source of the official drug.

Much work in galenic pharmacy has been aimed at producing more concentrated extracts. The Swiss pharmacopoeia (Ed. V) contains the preparation *Extractum Filicis concentratum* which is the so-called *baryt crude filicin*.

The most impressive work has been done in organic chemistry, in studies on the constituents of the rhizome and the extract. The basic work was carried out by the German chemist *Boehm* around the year 1900. He isolated several constituents and revealed the structure of some of them. They turned out to be derivatives of the phenol *phloroglucinol*, with a side-chain of butyric acid. The main constituents contain two rings linked by a methylene bridge, but compounds with three and four rings have also been found. The Finnish chemists *Penttilä* and *Sundman* and others have shown during the 1960s that the butyric group may be substituted with acetyl or propionyl groups. Today the constituents are called "*dryopteris acylphloroglucinols*".

Many studies have tried to clarify the vermifugal effects of the constituents of the extract. For some years the *filixic acid* was considered the most effective substance. Works by *Mühleman* and by *Hörhammer* and *Spagl* during the 1940s and 50s have shown that *flavaspidic acid* has the lowest DL50 tested on *Tubifex*, a small worm. In Finland *Anttonen* has used pure flavaspidic acid to expel tapeworms from 76 patients, with success in 65 cases.

The extract was usually effective against tapeworms, but it also turned out to be poisonous. From the last part of the 19th century many scientists have tried to find methods to standardize the extract. Some pharmacopoeias have included variations of *Fromme's* chemical method for the determination of *crude filicin*, which gives a measure of the content of acidic compounds in the extract. The method is highly questionable, as a number of researchers have found no correlation between results of it and the effect on different test organisms.

Some fifty years ago the author found that *paper chromatography* could be a useful method to separate the acylphloroglucinols in the extract. What was more interesting, the method could be used to measure the amount of *flavaspidic acid* in the drug and the extract. Some measures had to be taken. To avoid forming of chelates between the phenols and traces of metals, the paper was impregnated with a solution of EDTA. The stationary phase was formamide which contained an ascorbic acid buffer, to avoid oxidation of the flavaspidic acid. The mobile phase was a mixture of chloroform and petrol ether. After chromatography the flavaspidic acid spot was eluted from the paper and the extinction read in ultraviolet. The content of flavaspidic acid in 8 different extracts were found to be from 4.3 to 7.4 per cent.

However, from the 1960s there was less need for analysing the extract. German pharmaceutical producers introduced *niclosamide* and later *praziquantel* in the treatment of helminthiasis. These substances have more or less replaced the old extract.

In Finland helminthiasis has been a real health problem. The country is known as “the land of thousand lakes”, and many Fins have loved fishing and eating raw fish. Some of them have been struck by *anemia perniciosa*, because the fish tapeworm, *Diphyllobothrium latum*, deprives them of vitamin B₁₂. In 1960 it was estimated that 800 000 Fins had fish tapeworms.

A new acylphloroglucinol, *desaspidin*, was isolated from *Dryopteris austriaca* by Aebi, Kapoor and Büchi in the 1950s, and about the same time in the research laboratory of the Finnish firm *Medica* by Pentillä and Sundman, who also synthesized it. Östling has explained in a Nordic medical journal that desaspidin was tried on more than 2 000 persons infected with fish tapeworm in 1959-60, with positive results in about 90 per cent of the patients. The doses were 200 to 400 mg desaspidin. In one of the cases, an adult male, 16 worms were expelled, with a total length of 330 meters (about one thousand feet)!

In 2006, through kind individuals in Finland the author was brought into contact with Mr. Jaakko Honkavaara, a former Vice President, Quality Management, who had worked for Finnish pharmaceutical industry for 40 years. He explained that synthetic desaspidin was introduced on the market in 1961, in the form of tablets. However, the production was discontinued around 1980. The reason? The market had disappeared. Most people had stopped eating raw fish about that time. Campaigns against eating raw fish must have been fruitful.