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FEATURE ARTICLE

PLANTS USED IN TRADITIONAL MEDICINE AS SOURCES OF DRUGS

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INTRODUCTION

In many developing countries traditional medicine is a very important part of available medical facilities. There are many variations in the practice of traditional medicine, but plants are an important part of the medical armament of many of the traditional practitioners. Some of them use various parts of plants mainly as a supplement to other types of treatment, whereas others use preparations of plants as drugs and claim them to be efficient against various diseases. It is especially the latter use of plants, which is of interest for research concerning development of drugs.

It is a well known fact, that many plants contain pharmacologically active compounds, and at least 25% of the drugs currently used in modern Western medicine are derived from plants. A classical example is the roots of *Rauvolfia serpentina*, which has been used for centuries in Indian traditional medicine for treatment of various diseases, including mental illeness. Research, which started after the Second World War, resulted in the isolation of reserpine, an alkaloid with pronounced hypotensive effect, which was marketed in the 1950's as a remedy for hypertension. After some time an unpleasant side-effect was detected in some patients, in whom the treatment resulted in mental depressions. Investigation in to the causes of these side effects resulted in discovery of serotonin (5-hydroxy-tryptophane) as a transmittor in the brain and that reserpine caused depletion of serotonin reservoirs, resulting in mental depression. This discovery laid the foundation for development of the modern psychoactive drugs which have revolutionized mental therapy. Another example is *Catharanthus roseus*, a common tropical ornamental plant, which has been used in several developing countries as a remedy for diabetes. Studies of this plant resulted in discovery of two alkaloids, vincristin and vinblastin, which turned out to be efficient remedies for leukemia in children respectively for Hodgkins disease and choriocarcinoma.

A more recent example is *Psoralea corylifolia*, a plant which already in 1500 B.C. was recorded as a remedy for vitiligo in Papyrus Ebers. This plant has been found to contain xanthotoxin, a substance, which recently has been introduced in modern medicine as

a remedy for psoriasis.

In China, the plant *Artemisia annua* has been used for centuries for the treatment of malaria. The active compound has recently been isolated and identified as a sesquiterpene derivative, called artemisinine. This compound has in Chinese investigations been found to be effective for the treatment of malaria. Thus one report claims the total recovery of 1511 cases of infection with *Plasmodium vivax* and of 558 cases infected with *P. falciparum*. This compound is now used clinically in China and is under intensive investigation in many Western countries.

A PROGRAM FOR STUDIES OF PLANTS USED IN TRADITIONAL MEDICINE

There are, thus, good reasons to believe that plants used in traditional medicine can serve as basis for the development of new drugs and that it is worth while for developing countries to study the plants used by traditional healers, with the object of developing indigenous drugs from locally available sources. Isolation, identification and pharmacological evaluation of pharmacologically active constituents of plants is, however, not an easy task and research in this field is both time consuming and expensive. It also requires the cooperation of specialists in botany, chemistry and pharmacology.

The organization of a research program for studies of plants used in traditional medicine is outlined below.

1. Inventory and Botanical Identification

The program must start with an inventory of the plants used. To do this it is necessary to gain the confidence of the traditional healers, which often is difficult, as they are suspicious of competition and often, as a part of their training, have sworn an oath not to reveal their knowledge to outsiders. This problem has to be solved differently depending on the local circumstances. It might be possible to work through missionaries who have gained the confidence of the local population, including the healers. Example of this approach are found in inventories performed by Haerdi (1) in Tanzania and by Sandberg (2) in The Central African Republic. In an inventory in Northearn Tanzania (3,4,5) the author in cooperation with Tanzanian counterparts used the Party Organization to get in touch with the healers. The Governing Party in Tanzania is very well organized. The smallest unit is a so called ten-house leader, which is supervising ten households and thus knows if a traditional healer is a member of this group. Through the party a message was sent to the districts and villages we intended to visit and the ten-house leaders were asked to summon the healers for interviews and at the same time inform them that this investigation would not constitute a threat to their professional activities, but that their cooperation would be of great value to the country. This worked very well and the healers were surprisingly cooperative and apparently gave correct information, as we got many dupiclates of the same plant from healers in different villages. It was also found that about 90% of the plants we recorded had previously been

reported as medicinal plants in Eastern and Southern Africa.

In a study which we at present are conducting in Somalia, our Somalian counterparts have solved the problem in a different way. They have employed healers as consultants to the Faculty of Medicine at their National University. This enables us not only to get information of all the plants these healers use, but also to get in touch with other healers, who are more willing to discuss their practice with a colleague than with a Western-trained physician.

In the interviews the healers should be asked to show the plants and to describe what part of the plant they use, how the remedy is prepared, what symptoms are treated and what dose and regimen they prescribe. Botanical specimens should be taken, to ensure subsequent identification of the plant. This requires the cooperation of a trained botanist. Samples of the plant parts used may also be taken for future screening of pharmacological activity or other tests to verify the claimed medical use. These samples must be conserved by drying quickly. This is best accomplished by spreading them in the sun. Precise record keeping is of course very important to avoid mixing of herbarium specimens and samples, which can cause great confusion and troubles in future work.

Following the field work, the next task will be botanical identification of the specimens. This is very important as only correct botanical identification will ensure that more material of the same plant can be collected, if need be, in the future. The botanist should also be asked to provide all synonyms of the name. This is necessary for conducting searches in the literature, for information about the chemical constituents and pharmacological properties of the plants.

2. Studies of the Literature

The literature search can be based on Chemical Abstracts, where the plant names can be directly used for the search. Farnsworth et al. (6,7) have developed a computer base for information about use of plants in traditional medicine, pharmacological effects of extracts of the plants and compounds isolated. This base, called NAPRALERT, is available upon request to Prof. Norman Farnsworth, The University of Illinois at Chicago, Program for Collaborative Research in the Pharmaceutical Sciences. Box 6998, Chicago, Illinois 60680, U.S.A. The fee for the search is dependant on the amount of information available in the database.

Already at this stage, information of importance to a developing country can be obtained. A plant may be found to be known to contain harmful substances, e.g. pyrrolizidine alkaloids, which should prompt advice to be given to the healers not to use that plant. It might also be found that a plant contains compounds which verify the claimed efficacy of the plant. Then this plant can be directly exploited for production of a drug.

3. Pharmacological Screening

The most common experience is that very little is known about the plant. The next step in the program will then be to decide

which of these plants will be profitable to subject to further studies. This is the most difficult part of the program and no really good methods are available. Several approaches are possible:

3.1. Animal experiments directly related to the claimed effect:

An extract of the plant might be tested in an animal experiment. This is an attractive approach, which, however, often is difficult to apply. The reasons for this can be difficulties to find a suitable test system. It can also be a problem to choose what to test for, if the plant is reported to be used against several diseases. This approach is time-consuming and expensive, as a laboratory has to be set up and many different tests have to be tried.

3.2. General screening for pharmacological effects:

Another approach is a general screening for pharmacological effects of the extract. This approach disregards the information about the use of the plant obtained by the healer but can have the advantage of being quick and to require only small amounts of extract for the test. A test which is almost ideal for this purpose is the isolated-guinea-pigileum test according to Rosell et al. (8,9). In this test the extract is tested for its ability to contract the ileum or to inhibit artifically induced contractions. The guinea pig ileum is a piece of smooth muscle, innervated by at least 10 different nerve systems and the responses in the test can thus be the result of interference of the active compound(s) in the extract with any of these nerve systems or with the smooth muscle itself. The test is thus able to pick up many different pharmacological activities. The drawback of the test is that it gives only an indication of the presence of pharmacologically active compounds but no information whether this activity is useful medically or not. Another test in this category is the "hippocratic screening" introduced by Malone (10), where the extract is administered intraperitioneally to intact rats, which are then observed at regular intervals and their reactions and behaviour recorded according to a special scheme, involving over 50 different parameters, such as mobility, breathing, lacrimation, salivation, pupil size, ptosis, tail erection, body temperature, hyperemia, cyanosis, micturation, diarrhoea etc. This test is very time consuming as it requires observations of each animal for a whole day, followed by observations once a day for one week and finally autopsy of the animal. Also the requirements of material for testing is rather high.

3.3. Observation of healer's practice and clinical evaluation:

Another approach for choosing plants for further studies is to have a physician, trained in clinical pharmacology, observe the practice of a traditional healer. Such observations would indicate which plants are likely to be clinically effective and the physician would also have an opportunity to observe if the treatment has any side effects. Following such observations, extracts of the plants would then be subjected to toxicological studies, whereupon proper clinical evaluation could be started. Patients would be asked if

they would prefer treatment with a traditional remedy or with Western drugs. As many people in developing countries usually have a strong belief in traditional medicine, it should not be difficult to find patients willing to paticipate in such a clinical evaluation, which should be performed in a hospital and include placebo in a double blind test. We are preparing for such studies in Somalia and a Somalian physician has been trained in clinical pharmacology in Sweden and is now starting observations of a healer's practice in Somalia. The advantage of this approach is that clinical efficacy of the plant would have been been established before the search for active constituents is started, which gives a stronger motivation for this expensive and time consuming work.

In China the experience of clinical evaluation of crude extracts of traditional medicinal plants are quite extensive. There are very old written documents about the use of medicinal plants. They have been used for many generations in exactly the same way and these plants can therefore be considered quite safe. In Africa the situation is different as no old written records on the use of the plants are available. It is also known that plants used in African traditional medicine sometimes have caused poisoning of the patients. Clinical evaluation of African medicinal plants must therefore be performed with great caution.

3.4 Choice of solvent for extraction:

Most healers use aqueous extracts of their plants, obtained by boiling or by soaking the ground plant parts in water, followed by filteration to remove the remaining plant material. For evaluation of the efficacy of the plants one must therefore assume that the active constituents are extractable by water and water should therefore be the solvent of choice for extraction of the plants. Employment of organic solvents, which is desirable from the chemist's point of view (see below), might lead to failure to discover any pharmacological activity of the plant if the active constituents are extremely polar.

4. Isolation and Identification of Pharmacologically Active Constituents:

As discussed above water should be used for extraction of the plant material. This causes difficulties for the chemical work as aqueous extracts are very complicated and difficult to handle. We have therefore developed a scheme for preliminary chemical characterization of the chemical properties of the pharmacologically active compounds of an aqueous plant extract (11). This scheme is outlined in Fig.1. A solution of a lyophilized aqueous extract is subjected to heat under the influence of alkali and acid. If the activity is retained, this indicates that the active compounds are stable to such treatments. Filteration of a solution of the extract through a column of Sephadex, followed by pharmacological testing of the two fractions obtained, gives information about the molecular size of the active compounds. Ion exchanger experiments give information of the charge of the compounds and extraction with organic solvents about the polarity. Evaluation of the results of

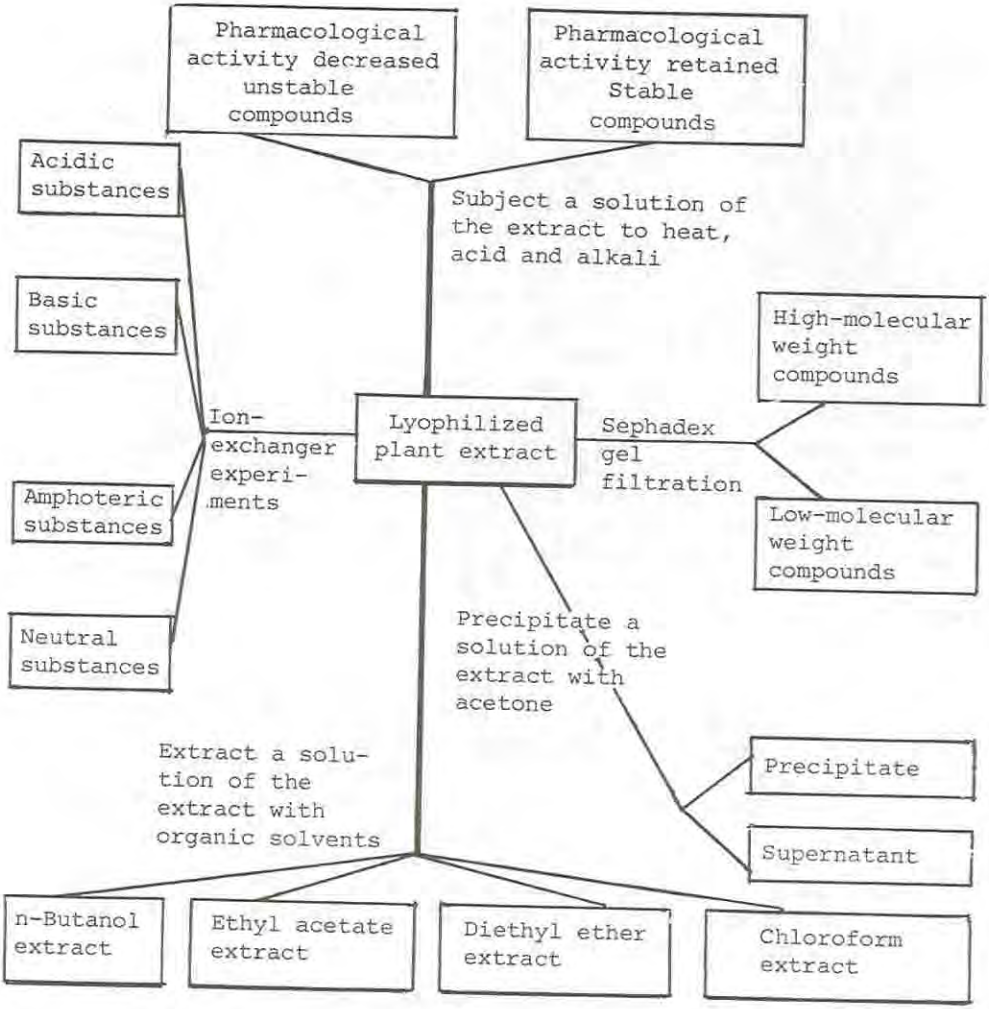

Fig. 1 Scheme for preliminary chemical characterization of the chemical properties of the pharmacologically active compounds of an aqueous plant extract.

these tests forms a base for development of a suitable isolation procedure, which must be monitored by pharmacological tests. If the pharmacological activity is solely retained in the supernatant or in the precipitate obtained on acetone precipitation of a solution of the extract, this procedure is often a convenient first step for purification. For charged compounds ion exchangers are very useful. The active material can be adsorbed and all the impurities washed out of the column before elution of the desired compounds. For compounds of higher molecular weight, gel filtration is often very useful. In most cases various chromatographic methods must be employed for the final purification.

5. Experiences with the Method:

As the isolation procedure must be monitored by pharmacological tests, the test-procedure must meet certain requirements. If the test is very timeconsuming and requires big amounts of material it becomes the bottle-neck of the isolation work. An ideal test system for this purpose should be simple and quick to perform and require very small amounts of material. In vitro tests are therefore more preferable than in vivo tests on whole animals. Before attempting an isolation procedure it might be well worth to spend some time in finding a correlation between a more cumbersome test, originally used for establishing pharmacological activity of the plant extract, and a more simple test which can be used to monitor the isolation procedure. An almost ideal test for this purpose is the isolated-guinea-pig-ileum test (see above). This test is very quick. A skilled technician can easily test more than 20 samples in one day, and it requires only mg or µg amounts of the tested fractions. Using our scheme for preliminary characterization of chemical properties in combination with the guinea-pig-ileum test, has enabled us to devise isolation procedures for a variety of pharmacologically active compounds, e.g. quaternary ammonium compounds (11), triterpene saponins (12), biogenic amines (13), cathechins and new 1,3,-diaryl-propan-2-ol derivatives (14).

6. Pharmacological Studies on Isolated Compounds:

To evaluate the medicinal value of isolated compounds these must be subjected to intense pharmacological studies, aiming at clarification of the mechanism for their activities. This requires access to gram-quantities of pure substance as a contrast to the small amounts (usually less than 50 mg) required for identification or structure determination. To obtain them one has to consider scaling up of the original isolation procedure or synthesis of the compound. If the structure is not too complicated synthesis might be preferable. Scaling up of the isolation procedure might require collection of 50 - 100 kg of plant material, working up of which requires access to a small factory or a pilot plant.

7. Toxicology, Clinical Evaluation and Production of Drugs:

These steps in the program for studies of plants used in traditional medicine are standard procedures in the development of new drugs. They require very big resources and can not be undertaken by a university department. However, when the program has been brought successfully to stage 6. (see above) it should not be difficult to find a pharmaceutical company willing to enter the project.

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