ETHNOPHARMACOLOGY AND HEALTH CARE IN THE DEVELOPING WORLD

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Summary

Pharmacology has always played a part in ancient medical traditions. Some of these traditions are still very vital and play a similar role in providing health care as does western medicine. Numerous examples suggest that exploring traditional pharmacopoeia is a productive way to identify leads, such as *Physostigma venenosum, Strophantus spp., Camptotheca acuminata, Huperzia serrata, Carapichea ipecacuanha* and *Artemisia annua*. As the demand for botanical and animal products is increasing and most of the new products are harvested from the wild, questions of biodiversity and sustainability become important. Three examples of prominent medicinal plants (*Taxus brevifolia, Rauvolfia spp. and Prunus africana*) reveal both the difficulties involved, and the biological and social implications, of drug discovery. Further, indigenous models of preserving biodiversity as possible solutions to these problems are presented.

In developing countries issues of drug safety and efficacy are increasingly important, including the distribution of substandard and counterfeit medicines that occur as a consequence of human error, negligence and inadequate resources. Pharmaceutical anthropology attempts to provide the socio-cultural explanations for these problems by exploring the relationships between people and medicines. Inquiries address improper drug use and growing demand, as well as skepticism about western pharmaceuticals. The problem of increased availability of drugs in the formal and informal sectors and how this correlates to accessibility for the growing poor is also discussed.

1. Introduction

Every medical system has various means to diagnose and cure illness—manual techniques such as massages, larger and smaller surgical operations, baths, spiritual therapies, and so on. Drawing from the history of medicine, there are numerous indications of the profound knowledge of some of these systems. In the Papyrus Ebers, which was found in an Egyptan grave dated around 1600 B.C., surgical interventions are described. Skulls from 2500 B.C. were found which had sophisticated dental bridges and fillings, showing the high standards of dentistry at that time. In ancient Indian texts almost 3000 years old elaborate surgical instruments are illustrated that suggest proficiency in this science. In the tici-amatl, medical books from the Aztecs that were written down by Bernardino de Sahagun in the sixteenth century, detailed descriptions of pathology and anatomy were found suggesting the high medical standard of this people. Medical thangkas (paintings on textile) which are used in Tibetan medicine show interesting depictions of anatomy, diagnosis and materia medica. The models of these thangkas which are still in use today are estimated to originate from the seventeenth century, a period where in western medical history the circulation of the blood by William Harvey had just been discovered.

Some of these ancient medical traditions are still very vivid and play a similar role in providing health care as does western medicine. Indeed, often two or more medical systems exist side by side and are used by the people in parallel. Several of these “traditional” systems, such as Traditional Chinese Medicine or Ayurveda have been successfully established also in western contexts and play a vital role in what is called complementary or alternative medicine. Pharmacology was always part of these medical traditions, but not necessarily the most important one. In many of these traditions diet, life-style, rituals or religious beliefs are equivalent to botanical, animal or mineral medicines.

The acceptance of a medical system by a population is formed by cultural and social factors, and many aspects of traditional medicine are not easily conveyed from one system to another. It appears that plants and other materia medica are one of the few aspects that can be transferred without necessarily considering these aspects. When studying indigenous medicine, therefore, the focus often lies on ethnopharmacology. WHO and other transnational organizations have consequently placed medicinal plants, their safe use, their efficacy and conservation in the area of public health policy. WHO has developed guidelines for the assessment of botanical medicines and is sponsoring clinical trials in many developing countries. It has urged its Member States to make a systematic inventory and assessment of medicinal plants and to introduce measures for

the regulation and control of medicines. It has also published monographs on selected medicinal plants from various countries. In three volumes more than 80 plants used in traditional medicine are described in detail, with vernacular names, purity tests, major chemical constituents, pharmacology, medicinal uses and so on.

However, the use of traditional medicinal plants in many countries and regions is highly dependant on the personal experience of traditional practitioners. Medical knowledge is often passed on for many generations within families, thus producing a very individual expertise. On the other hand each medical practitioner also operates within a cultural and social framework; especially health sciences could not function without ensuring certain standards that are understood by all their customers.

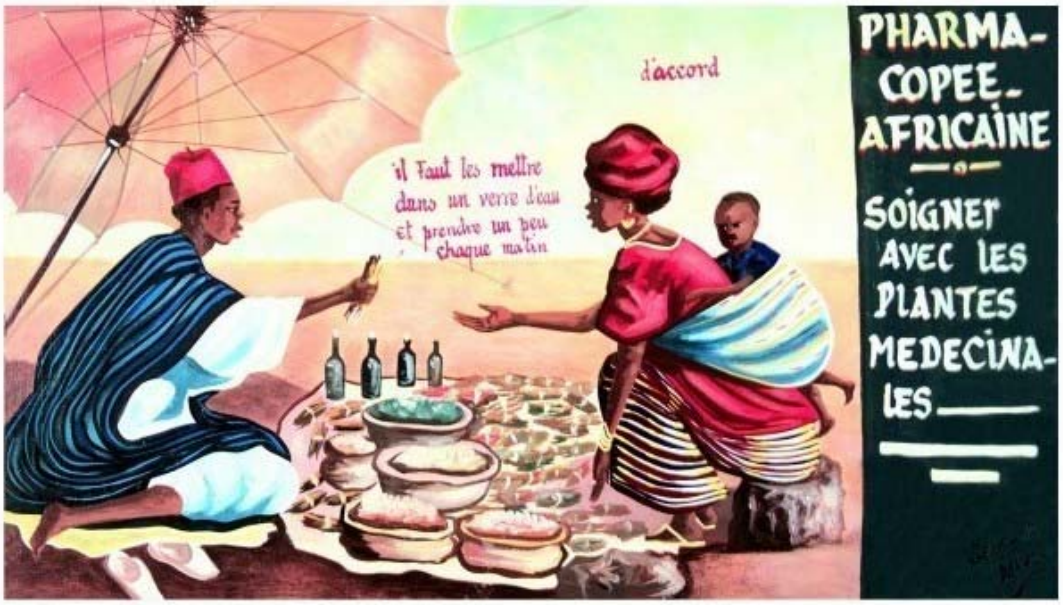

Figure 1. Painted advertisement of a traditional pharmacist, Dakar, Senegal

When discussing ethnopharmacology and its role in developing countries, several issues are important, particularly:

- Indigenous plants and their importance for western medicine, biodiversity and how it can be sustained,
- safety and efficacy of western medicines, and
- pharmaceutical anthropology.

2. Indigenous Plants in Western Medicine

It is estimated that more than 30% of recently introduced drugs are directly or indirectly of natural origin, many of them deriving from poor countries. About 60% of the antibiotics and antitumor drugs are natural products or are derived from natural products. While there are different approaches to finding new interesting active compounds such as random screening, studying traditional medicines is one important

approach to lead-finding. The following are only a few examples of the power of natural products to uncover new therapeutic agents and define novel drug targets.

2.1. Plants from Indigenous African Medical Systems

Catharanthus roseus (L.) G. Don (Apocynaceae), for example, has been used against diabetes and "heart-diseases" in Africa. It was first mentioned in the seventeenth century by Etienne de Flacourt-Bizet in his "*Historie de la Grande isle Madagascar*". Indigenous to Madagascar, it is now widespread in all tropical regions of the world. Due to a coincidence the anti-carcinogenic properties of the main alkaloids, vincristine and vinblastine, were discovered in the late 1950s. Vincristine, vinblastine and their semi-synthetic derivatives are now used for acute leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, breast cancer, uterine and cervical cancer, bronchial cancer and Kaposi's sarcoma. (see *Plants as a Source of Anti-Cancer Agents*).

The West-African Kalabarbean *Physostigma venenosum* Balf. (Fabaceae) is employed by the local population as an ordeal poison, *esere*. It was discovered by western science relatively late in the mid nineteenth century, because, like many other African poisonous plants, the knowledge about the plant was kept secret from white missionaries and colonialists. Physostigmine was isolated for the first time in 1860 and by 1876 the substance was successfully being used by Laqueur in cases of glaucoma, its later main indication. Nowadays the liana can still be found in Central African markets where it is sold for medicinal purposes. Physostigmine, or eserine, is an antidote to strychnine, nicotine, curare and atropine. It has been replaced by synthetic anticholinesterases (neostigmine and pyridostigmine). Their therapeutic indications today are myasthenia gravis, post-operative intestinal or bladder atony and post-operative recovery after curarization. A future potential use may lie in its ability to improve cognitive function, which could be beneficial in Alzheimer's disease.

Strophantus spp. (Apocynaceae), of which about 30 species are known in Africa, are the most interesting plants. First employed as hunting poisons, their alkaloids were once important pharmaceuticals in medicine. *Strophantus* was the first effective and highly toxic plant discovered by Europeans in Africa. First mentioned in the fifteenth century it took almost 300 years until the plant source was documented scientifically. Strophantine has been on the market since 1887 and is used as a cardiac medicine. Albert Fraenkel was the first person to introduce intravenous strophantine therapy in 1905/1906, a technique which was later declared as "one of the greatest advances in medicine in the twentieth century". *Strophantus* still remains a source of ouabaine, a cardiac glycoside that is used as a heart tonic in emergency medicine because of its rapid onset and short duration of action.

2.2. Plants from other Medical Traditions

Several other medical traditions are also precious intellectual reservoirs for the development of new pharmaceuticals, particularly when the knowledge has been written down for centuries. Traditional Chinese medicine, for example, gave rise to new plant-derived anticancer and anti-malarial drugs. Anti-tumor activities of Camptothecin from *Camptotheca acuminata* Decne (Nyssaceae) were discovered in the early 1950s; in 1966

the findings were first published by M.E. Wall and M.C. Wani. Camptothecin is efficient against a variety of solid tumors which have been unaffected by most cancer therapeutics. Some Camptothecin analogs have also been shown to have antiparasitic properties against trypanosomes and plasmodium parasites. In preclinical studies its derivative irinotecan was effective against neuroblastoma. The major clinical contribution of camptothecin and taxol is that they are founding members of drug classes with novel and previously unpredicted mechanisms of action.

Huperzine A, an acetycholinesterase inhibitor from *Huperzia serrata* (Thunb) Trevis (Lycopodiaceae) is a clinical candidate for treating Alzheimer's disease and other acute and chronic neurodegenerative disorders (see *The Search for Plants to Manage Neurodegenerative Diseases*). In Traditional Chinese Medicine *Huperzia serrata* (Qian Ceng Ta) has been used for centuries to treat fever, inflammation, blood disorders and schizophrenia. Its second name, Jin Bu Huan "more valuable than gold", hints at the powerful analgesic and antipyretic properties of the plant. Clinical trials in China have shown a significant improvement in memory of aged people and patients with Alzheimer's disease. In the USA, huperzine A, but it is sold as a dietary supplement for memory loss and mental impairment. In recent pharmacologic studies it has been shown to be effective as a prophylactic drug against nerve gas poisoning, thus being a potential protective agent against chemical weapons.

In South America the root of the highly effective Ipecacuanha (*Carapichea ipecacuanha* (Brot.) L. Andersson) (Rubiaceae) was specifically used in indigenous medicine against dysentery. The plant was discovered by one of the founders of tropical medicine, Willem Piso (1611-1678), who published his findings in his pioneering work "De Indiae utriusque" in 1658. It took 30 years until the root was first used in Europe and until 1913 to verify scientifically what had been already proven empirically 250 years before: that emetine, the main alkaloid of Ipecacuanha, is effective against *Entamoeba histolytica*. Today emetine is used in emergency medicine in cases of poisoning to trigger vomiting in small children.

Most of the medicinal plants which are or were important for bio-medicine originate from what are now developing countries. These countries, however, rarely benefited from their traditional knowledge. While pharmaceutical and chemical industries have their products patented, the necessary basic knowledge is often seen as a public property. Furthermore, the most important research goals of the pharmaceutical industry are to create new therapeutics for western countries and not for developing countries. Many conditions that especially effect poor developing countries—tropical and infectious diseases which cause severe suffering and millions of deaths every year—are the very diseases that pharmaceutical companies are often not interested in developing drugs against. Of the 1393 new drugs that were approved between 1975 and 1999, only 16 (just over 1%) were specially developed for tropical diseases and tuberculosis—diseases which account for more than 11% of the global disease burden. In this respect, the following example of a drug against malaria, *Artemisia annua*, is an exception.

2.3. The Case of *Artemisia annua* L.

Malaria is one of the most devastating diseases in developing countries. The vast

majority of deaths from malaria occur in sub-Saharan Africa, where the disease also presents major obstacles to social and economic development. It is estimated that there are at least 300 million acute cases of malaria each year worldwide, resulting in more than a million deaths. Around 90% of these deaths occur in Africa, mostly in young children. Morbidity and mortality in malaria is rising because of multi-drug resistant *Plasmodium falciparum* and due to delay in receiving adequate medication.

A new anti-malaria drug has been introduced over the past decade which has been used in traditional Chinese medicine for hundreds of years to treat fever and malaria. Artemisinin was isolated from *Artemisia annua* L. (Asteraceae) (qinghaosu or sweet or annual wormwood). It is structurally distinct from all other anti-malarials and acts at early trophozoite and ring stages. Since the 1970s, when the active principle was identified and the structure elucidated, many derivatives have been produced. Artemisinin has many advantages: it acts rapidly, it has surprisingly few adverse effects, it reduces gametocyte carriage and thus diminishes transmission, and provides protection against multi-drug resistant malaria parasites. A disadvantage is the occurrence of recrudescenses when given in short course monotherapy which makes the combination with longer-acting anti-malarial drugs advisable.

To delay drug resistance, artemisinin derivatives are often combined with standard anti-malarials. This also has the advantage that the treatment can be taken in a shorter course (three days). If artemisinin is given alone a seven day treatment has to be completed, a fact that significantly decreases compliance. Artemisinin-based combination therapies (ACTs) are recommended for countries which experience resistance to conventional monotherapies. They are, however, quite costly compared to monotherapies. In its initiative Roll Back Malaria (RBM), WHO has entered into a special pricing agreement with Novartis, the manufacturer of artemether-lumefantrine. Novartis agreed to produce the drug at cost price for use in the public sector in malaria-endemic countries.

Malaria in adults could also be treated by locally prepared medications from *A. annua* plants. These medications have the advantage that they are cheap, they could be produced locally and could provide people in inaccessible areas with medication, where health facilities are not available. A study showed that the bioavailability of artemisinin from tea preparations may exceed that from pure artemisinin tablets. It seems that other constituents—particularly flavonoids—enhance the antiplasmodic activity of artemisinin. With the use of locally prepared preparations, however, is the serious risk of inducing resistance against this drug, especially when insufficient doses are used.

Delay in treatment, often caused by the lengthy distance to the next health facility, is regarded as a significant factor in high child mortality. Many malaria patients, however, are not able to take medication by mouth. Especially in remote areas where injectable drugs are not available, this can be fatal. Severe malaria can progress within hours to a life-threatening condition. Artesunate, a derivative of artemisinin, has the advantage that it can be given parenterally in the form of suppositories. Rectal artesunate is especially valuable for patients with acute malaria who cannot take oral medication and where parenteral anti-malarial treatment is not available. It has been selected by WHO as a candidate for emergency administration to provide an initial anti-malarial cover indicated by clinical improvement and rapid fall in the density of parasitaemia. It gives

the patient and caretakers time to see a health facility which provides adequate parenteral treatment with a standard anti-malarial. Artesunate suppositories can be given safely by caretakers with little training.

Artemisinin derivatives could also be used in the treatment and control of schistosomiasis. Because of the potential problem of praziquantel (the drug of choice) resistance, the search for alternative drugs for the treatment and control of this disease is continuing. Artemether exhibits maximum activity against the liver stages of *S. japonicum* and *S. mansoni*. Thus it could be used as an additional tool in the control of schistosomiasis. This approach, however, has to be considered carefully because of the risk of developing resistance against local *Plasmodium***.**

3. Biodiversity and Sustainability

There is an increasing demand for botanical and animal products for the national markets. These products are partly cultivated, but most of them come from wild collections. These medicines are usually cheaper than western medicines, more accessible and very popular with the local population.

Often these pharmaceuticals are produced on a small scale by local manufacturers. Sometimes there are also large markets, such as in Mexico, Nepal, northern India and China, that provide medicines for the local urban population and for export. Thousands of tons of medicines are often sold in these countries every year.

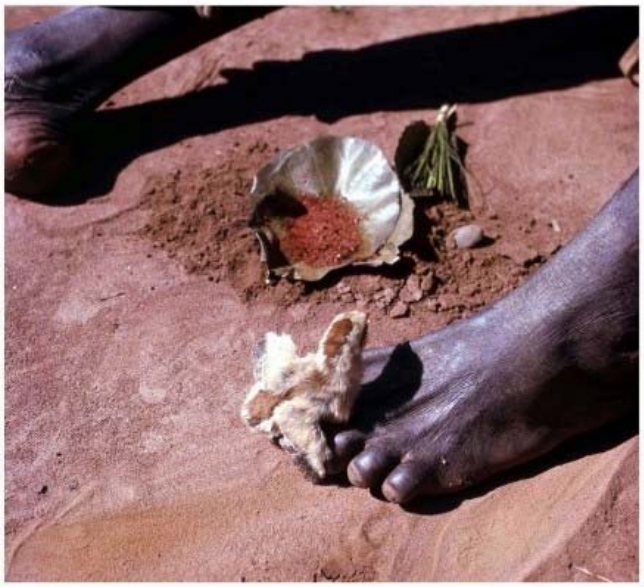

Figure 2. The oracle poison *benge (Strychnos icaja)* is administered to a chicken for consultation of the oracle. (Photograph Armin Prinz)

Furthermore, a great threat for biodiversity is the international marketing of medicinal plants. Specific drugs, especially in Africa and South-America, are often directly harvested and exported from western pharmaceutical companies. Because chemical synthesis of complicated structures is often difficult, many important drugs have to be

obtained either by cultivation or collection from the wild. Over-harvesting of raw material, however, may lead to the extinction of endangered species and the destruction of natural habitats and resources. Three examples, one from North America and two from Africa will illustrate these problems and also reveal the political and social implications of these issues.

3.1. *Taxus brevifolia* and Biodiversity

In the 1960s random screenings of plant samples for new substances that could possibly be used in therapy against cancer were carried out under supervision of the National Cancer Institute and the United States Department of Agriculture. Taxol from *Taxus brevifolia* Nutt. (Taxaceae) was one of the promising substances found. It was first isolated in 1966 and showed outstanding activities against various tumor cell lines. In 1984 clinical studies were started. In 1992 permission to market taxol was received for the treatment of refractory ovarian cancer and subsequently it was approved for treating metastatic breast and lung cancers and Kaposi's sarcoma. Since the inclusion of taxol in the treatment regimen for ovarian cancer, the survival rate has more than doubled. The success with taxol (and also camptothecin, see previous section) largely comes from the prolongation and improvement of the quality of human life.

In order to enable clinical testing, for years the only way to have access to taxol was to shed the bark of more than sixty year old Californian yew trees which were damaged irreversibly by the harvesting procedure. Furthermore, relevant compounds are obtainable only in small amounts. The danger of the overuse of existing supplies was imminent. American environmentalists protested against the cutting down of the trees but their objections were rejected by the US authorities. The problem could partly be solved by producing semi-synthetic derivates of taxol from other *Taxus* species, especially the European *Taxus baccata L.* (Taxaceae). As a consequence, the supply of taxol is now assured. The question, however, has to be asked what would have happened if a plant with a similar pharmaceutical value originating from a developing country or a country without strong democratic institutions gained worldwide importance?

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