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### **Innovative medicines and quality: reverse pharmacognosy**

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In this paper we discuss an E-motive project in which Indian and Dutch farmers and veterinarians exchanged knowledge about herbs and management. This project was discussed at a workshop on the quality control of herbal therapeutics that took place in Zwolle on October 23, 2014 [1]. A major contribution came from prof. Dr. Padma Venkatasubramanian of the Institute of Trans-disciplinary Health Sciences and Technology, Bangalore, India. She suggested that currently phytotherapeutics are not standardized in line with their traditional uses and this should be critically reconsidered. This complaint is also heard from practitioners of Traditional Chinese Medicine. Venkatasubramanian spoke in favor of the so-called reverse pharmacognosy, in addition to describing what is called the reverse pharmacology by others [2].

### **Emancipation of herbal medicine**

Pharmacognosy is the discipline that is most involved in the scientific substantiation of the traditional uses of medicinal plants. After identifying specific, potent pharmacologically active substances in plants (mixtures), applications derived from tradition medicine became more reliable (more predictable) because extracts were standardized on the now well-known active ingredient(s), and the safety of these medicines could be better ensured, in particular unexpected overdoses were prevented. The usefulness of this scientific discipline for herbal medicine was not always obvious. Often the active plant compounds were isolated or synthesized and as such patented - more often derivatives of these compounds were developed that were easier to patent and were more readily available to the digestive system but these were often more powerful and more toxic. The resulting patented drugs have gained a leading position in the medical world and the unpatented spices are largely pushed out of the market. Many plants that were the basis of medicinal products developed in this way could not be used anymore by professionals in the Netherlands (such as *Digitalis* spp, *Datura stramonium*, *Hyoscyamus niger*, *Papaver somniferum*. Since 2001 also plants like *Rubia tinctorum* and *Ephedra* spp.) were taken out of the herbal markets. However some plants, such as *Salix* spp., willow bark), have made a comeback as herbal medicinal products in the EU.

In some third world countries that have their own traditional medicines there has been much opposition to the above described erosion of traditional herbal medicine which is characterized as biopiracy. Ethno-pharmacology has thus become associated with the theft of traditional knowledge. Several pharmacologists in the developing world have expressed support for better cooperation with the local traditional healers. The World Health Organization and the European Parliament have expressed support for this, but in practice, bodies such as the Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA), despite the insistence of the European parliament, contain no experts in the field of traditional medicine in their working group which is composed primarily from pharmacologists and pharmacologists.

### **Examples of reverse pharmacology**

The typical development of a medicine runs from laboratory to clinic and is very long and costly [fig.1].

Taking the other direction, from the clinic to the laboratory, effective drugs can be developed much more quickly and cheaply [fig.2].

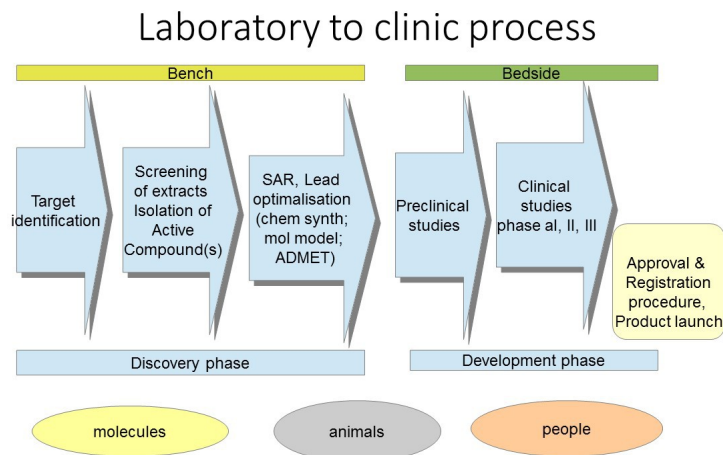


Fig. 1. In [11].  
SAR = Structure-Activity Relationship studies; ADMET = Absorption, Distribution, Metabolism and Excretion Test.

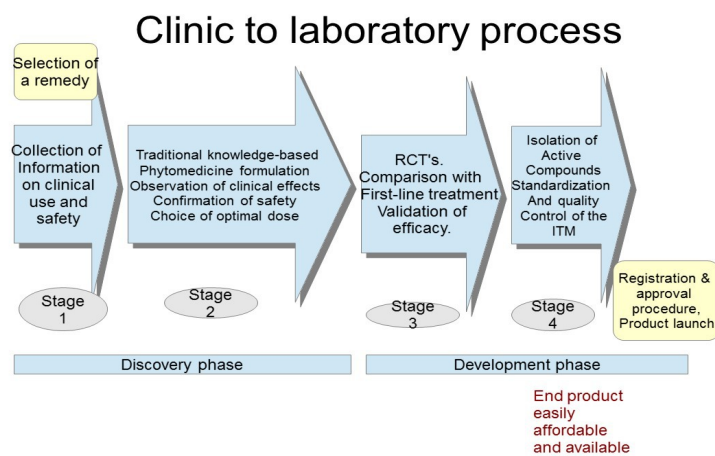


Fig. 2. In [11].  
RCT = Randomised Controlled Trial (randomized and controlled clinical study).

An example from Mali (Africa) has been described by Willcox et al from Oxford University. [3] They used four steps to develop a herbal medicine against malaria:

1. Plants were selected on the basis of the results of a retrospective study from the various traditional remedies used in Africa.
2. Clinical trials were undertaken with dose escalations to find the optimal dose of the active compound.
3. Then, this active compound was tested in a randomized clinical trial (RCT) and was compared to the regular standard of care.
4. Finally, the active components were characterized so that standardization and quality controls could

be established.

This example showed that this way of developing effective and standardized (herbal) medicines was faster and cheaper than the typical approach of screening randomly.

Using ethnobotanical knowledge can provide a significant saving on the three main hurdles in drug development: time, money and toxicity, claimed Suhr in a review [4], in which he argues that reverse pharmacology is a rational and pragmatic strategy for potential drugs discovery. As a starting point, the clinical experience of local healers is of cardinal importance. In addition, a multidisciplinary and systems biology approach is needed in which rational holistic analyses are done using the required therapeutic steps. As the safety of a herbal preparation is often supported by many years of traditional uses, further pharmaceutical development can take place in parallel with RCTs. Traditional knowledge and wisdom, modern Western medicine and high throughput screening technology (automation that allows a quick determination of whether substances or extracts exhibit certain activities) form a golden triangle in which innovative medicines with minimal toxicity risks can be quickly developed.

Pathwardan in Puna (India) said that biotechnology has made enormous progress, for example in genomics and asymmetric synthesis, but the pharmaceutical industry suffers from an innovation deficit [5]. "We have become high throughput in technology, yet have remained low throughput in thinking" is the criticism. A similar criticism comes from the Netherlands Drug Bulletin of January 2016 which contains a retrospective of 2015: "None of the discussed resources has opened a new therapeutic window even with all the cost and effort that has been associated with the development and production of these resources. For the patient there has been no progress." It was also noted that the new drugs are developed through an accelerated registration procedure under which there is insufficient data available about the side effects and safety. The evaluation of these is missing.

New drugs go to the market without innovation and without significant improvement in the risk / benefit ratio. This indicates that radical change is needed. Reductionism makes way for systems theory. It also asks for a reappraisal of traditional knowledge. Traditional medicine, however, is not static but an evolutionary sector that increasingly incorporates new techniques. Besides the relatively well-documented ayurveda and TCM (traditional Chinese medicine), there are a large number of lesser-known traditional medicines. At this time, many traditional therapies are lost when their holders die, while they could be important for everyone. As examples of reverse pharmacology Pathwardan discusses the discovery of the activity of *Rauvolfia serpentina* Benth, which later led to a whole series of new drugs. The complex tonic Chavanprash (a tonic consisting of *Emblica* fruits with honey, ghee and many herbs) was developed from Ayurveda. Also developing effective preparations of *Hypericum perforatum* was a reverse pharmacology process.

### **Reverse pharmacognosy**

A revaluation and increased participation of traditional medicinal knowledge practitioners should also have consequences for the system of quality control, according to pharmacologists from India. At present quality standards were developed unilaterally from Western technological and analytical perspectives. Shankar, Unnikrishnan and Venkatasubramanian [6], scientists at the Institute of Transdisciplinary Health Sciences and Technology, advocate the development of intercultural standards for quality, safety and effectiveness in relation to traditional healing systems. It's not just about medicines

that are practiced traditionally in India (Ayurveda, Sidda, Unani) but in fact all healing systems that are different from the western biomedical approach. The conceptual context of the treatments should always be taken into consideration. All healing systems have their specific epistemology, assumptions, hypotheses and methods. They have developed their own quality standards and parameters, which until this moment have been neglected when it came to the formulation of objective and verifiable standards for traditional medicines or drugs. Each traditional herbal medicine system in time develops its own internal quality standards in areas such as sowing and harvesting times, collection and processing. This also includes qualities that along other (subjective) ways are reflected such as in aromas and flavors and in the classic humoral classifications hot-cold, centripetal or centrifugal working and so on.

An important aspect of traditional medicine is also that almost all of these cures work with a combination of drugs and non-pharmacological interventions. Other research methods besides the traditional RCTs are needed, says Shankar et al. The cross-cultural cooperation between bio-medical scientists and experts on traditional knowledge cannot be left out. The identification of a traditional plant used should not only be done by a biologist / systematist, experts in the healing tradition must be involved. One example (out of many): the plant name Brahmi (in Sanskrit), can be used for two different botanical species, namely *Bacopa monneri* (L.) Pennell (this is Neer Brahmi) and *Centella asiatica* (L.) Urban (this is Manduka Parni).

Sometimes a plant mentioned in ancient texts can be replaced by another, in certain traditional systems. Often you see that the other plant, which is unrelated botanically, yet has very similar ingredients. One example of this was confirmed by means of a HPLC profile, concerning *Aconitum heterophyllum* Wall. (Ranunculaceae) and *Cyperus rotundus* L. (Cyperaceae). Another interesting finding was the harvest times of turmeric (*Curcuma longa* L.). Traditionally, it is required that the plant is harvested in the night. The amount of the active ingredient can be confirmed by the brine shrimp bioassay (a general test for pharmacological activity). From this assay the bio-activity of the extract in root harvested at night proved to be 1.5 times stronger than the root harvested in the daytime. The same bioassay revealed that the traditional ayurvedic preparation of *Piper longum* L., boiled in milk, was 27 times more active than the equally strong preparation in water.

The researchers note the lack of intercultural aspects in most established standards for herbal preparations such as the British Herbal Pharmacopoeia, WHO monographs and even in the Ayurvedic Pharmacopoeia of India.

Databases of traditional quality standards should be established worldwide and new technologies should be developed for the above non-analytical aspects, according to these researchers. In TCM some aspects of the traditional herb classification (like warm-cold) appear to be correlated to a pattern in their photon emission [12,13].

### **Learning from the Third World**

In the EU several traditional herbal medicinal products are registered based on their safety, but neither commercial parties involved, governments nor nonprofit institutions show much interest in organising comparative studies with standard first-line therapy. And the ever more pressing EU legislation is not helping in the emancipation of the diversity in folk medicinal herbal traditions that still exist [7]. In this regard, Europe can learn a lot from countries such as India, Vietnam and China, where the healing traditions are taken more seriously and are being supported by research. In India, the drug registration law is extended with a category of plant substances that can be developed through reverse

pharmacology, with proof of quality, safety and efficacy. [6] However, the danger now exists that large ethno-pharmacological databases are built with the sole purpose to develop drugs much faster through molecular docking and high throughput screening technologies. These drugs are developed outside their original context and therefore provide disappointing results. In this way biopiracy will merely enter a new stage, when Indian scientists, as for example Biswas [8] "sell out" ayurvedic knowledge.

Regarding the respectful treatment of traditional knowledge some guidelines have been developed by the ISE (International Society of Ethno Biology), called the 'gold standard' by Willcox, Bödeker et al in the edition of December 2015 of the Journal of Ethnopharmacology [9]. They dealt with a number of recent examples (*Prunus africana*, *Hoodia gordonii*, *Pelargonium sidoides*) that show that the classical way of patenting "inventions" is not suitable for the development or optimization of herbal medicines. A collaboration of scientists and local people that took place in Mali as outlined above is better.

Also the Dutch can learn from such projects. All too often, patients and their herbal practitioners are not taken seriously, neither are traditional herbal growers. From the moment the plant is identified and taken to the lab, the scientist with his assays will decide what the plant may or may not be used for. An all-time low is reached when scientists use their "authority" to frighten people from their traditional herbal use by identifying hazards that they have not studied [10]. After deciding that some compounds are "of concern" these scientists continue scaring people because an existing (or supposed) danger is the quickest way to research funding. Fortunately, there are more and more situations in which patients, therapists and scientists join forces in alliances that seek patient friendly solutions to health problems.

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