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SCIENCE DIRECT
Journal of Ethnopharmacology 101 (2005) 338–339
Journal of ETHNO-PHARMACOLOGY
www.elsevier.com/locate/jethpharm

Letter to the Editor

Screening of traditional herbal medicine: First, do a retrospective study, with correlation between diverse treatments used and reported patient outcome

Sir,

Here are some thoughts about research methods, inspired by our experience in Mali.

In the search for new treatments, systematic screening of natural products has so far yielded relatively few results. Are there any other major drugs waiting to be discovered in the plant kingdom? If so, what is the best method to find them quickly?

Take the case of malaria: Modern antimalarial drugs have been developed from only two plants, *Cinchona* spp. and *Artemisia annua*. Antimalarial properties of *Cinchona*, from which quinine is still extracted, were found about 400 years ago, after the introduction of malaria in South America, the tree's native habitat. As for *Artemisia annua*, this fragile source of artemisinin and derivatives, its effectiveness has long been well known in China; it has been recommended for intermittent fevers in classical Chinese medical textbooks for 1500 years (Willcox et al., 2004).

In our example of malaria research, the problem is not to find natural products with in vitro activity against *Plasmodium falciparum*. Hundreds of them have been found, thanks to random screening and ethnobotanical studies. The problem is that, in this ocean of hopes, we have found no real breakthrough. Why? One major difficulty seems to be that an active molecule (in vitro) has very little chance of displaying, in further animal and human studies, an adequate absorption, phamaco kinetic and adverse-effect profile. As a result, we waste a lot of time and resources studying compounds that ultimately prove useless.

The selection of the plants (including the method of preparation, administration and dosage), at the beginning of the research process, i.e. before the pre-clinical phase, is very important; it needs to be conducted with more stringent exclusion criteria. We suggest that "ethno medical" research in the form of an observational retrospective clinical study (retrospective treatment-outcome study-RTO study) should be conducted before laboratory screening and before prospective clinical study of traditional medicine.

An RTO study is conducted with a questionnaire applied to a representative sample of a population. Inclusion criteria are built on syndromic definitions used for clinical decisions in district health centres (in the example of malaria: national guidelines for malaria treatment where blood tests are not available). The recall period is kept short (2 weeks for an uncomplicated malaria episode) for accuracy. A convenient unit of enquiry is the household, where a mini-focus group is conducted when a family member has met inclusion criteria. Patient progress under various treatments (modem and/or traditional, at home and/or with traditional heater and/or in modem health services, substances used) is recorded, then analysed with adjustment for confounding factors (disease severity estimates, time to treatment, socio-demographic data and mixed treatments including traditional and moderns drugs). If a given traditional treatment (e.g. a plant preparation) is, when used alone, systematically followed by a rapid and complete cure, with no failure or important side effects, the chances are high that the product deserves further scrutiny.

The advantage of conducting RTO studies as described above, before pre-clinical research and before choosing plants of interest for prospective studies, is that a product selected through this process has a relatively high chance of appearing again, after the long road of standard research process, as safe and effective in humans. Information about traditionally known side-effects, incompatibilities and limitations (including experience with small children and pregnant women) are precious signs for further research in toxicology. RTO studies could avoid many of the fruitless laboratory and Phase I research efforts, if they are designed with sufficient power to detect correlations between patient progress and different traditional treatments. The latter may be numerous, even in a small area, thus making large study samples necessary (in order to obtain meaningful groups for correlation tests like Chi-square or Fisher's exact), but it might well be worth the trouble.

In our experience in Mali (supported by the Swiss Development and Cooperation Agency), with a sample of 952 households in two rural districts, 66 plant species were mentioned and identified as treatments for malaria. In the analysis of traditional treatments taken alone (no concomitant use of modem treatments), the plants quoted with the highest frequency (*Nauclea latifolia*, *Cochlospermum tinctorium* and *Securidaca longepedunculata*) were not the ones whose use was followed by the best patient progress, hence supporting the hypothesis that RTO studies may produce results different from ethnobotanical research. We tested the eight plants

0378-8741/$ – see front matter
doi:10.1016/j.jep.2005.07.008

with best clinical outcomes and found medium to high in vitro activity against chloroquine-resistant *Plasmadium falciparum* cultures (IC50 ranging from 18.3 down to 1.0 μg/ml for crude extracts) (Swiss Tropical Institute, Basel). One of these plants is being tested in a prospective observational clinical trial, whose preliminary results are promising. So only now, after an RTO study, are we beginning the usual research process: laboratory screening and prospective trials, with designs used in Tanzania (Matthies et al., 1999), Uganda (Willcox, 1999), and elsewhere (Willcox et al., 2004).

In summary, as a complement to ethnobotanical research, before laboratory screening and prospective studies, a field survey in the form of an observational, retrospective clinical study of treatments used and their outcomes, with careful adjustment for confounding factors, may help to select active local products with promising safety and effectiveness profiles.

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25 March 2005