Journal of Ethnopharmacology 122 (2009) 177–183

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jethpharm

Review

How scientific is the science in ethnopharmacology? Historical perspectives and epistemological problems

Jürg Gertsch*

Department of Chemistry and Applied Biosciences, ETH Zürich, Wolfgang-Pauli-Str. 10, CH-8093 Zürich, Switzerland

ARTICLE INFO

Article history:
Received 24 November 2008
Received in revised form 4 January 2009
Accepted 4 January 2009
Available online 10 January 2009

Keywords:
Ethnopharmacology
Epistemology
Methodology
In vitro bioassays
Concentration–effect
Philosophy

ABSTRACT

This commentary is based on a general concern regarding the low level of self-criticism (-evaluation) in the interpretation of molecular pharmacological data published in ethnopharmacology-related journals. Reports on potentially new lead structures or pharmacological effects of medicinal plant extracts are mushrooming. At the same time, nonsense in bioassays is an increasing phenomenon in herbal medicine research. Only because a dataset is reproducible does not imply that it is meaningful. Currently, there are thousands of claims of pharmacological effects of medicinal plants and natural products. It is argued that claims to knowledge in ethnopharmacology, as in the exact sciences, should be rationally criticized if they have empirical content as it is the case with biochemical and pharmacological analyses. Here the major problem is the misemployment of the concentration–effect paradigm and the overinterpretation of data obtained *in vitro*. Given the almost exponential increase of scientific papers published it may be the moment to adapt to a falsificationist methodology.

Contents

> The great tragedy of Science – the slaying of a beautiful hypothesis by an ugly fact. Thomas Henry Huxley [1825–1895]

Natural products are promising candidates for drug discovery and they still continue to play an important role in future small organic compound drug development programs (Newman and Cragg, 2007). While the typical industrial drug discovery process makes use of medium and high-throughput bioassay screening platforms to find promising compounds for a particular target, ethnopharmacology goes the opposite way; anecdotal efficacy of medicinal plants is put to test in the laboratory. The ethnopharmacologist tries to understand the pharmacological basis of culturally important plants. This approach is currently employed to study the pharmacopoeias of Traditional Chinese Medicine (TCM), the European pharmacopoeias, or the numerous medicinal plants from traditional ethnic groups. Thus, ethnopharmacologists typically use the working hypotheses derived from anthropological fieldwork, i.e. plant extract X is used in the cultural context Z to cure diseases A–D. Therefore, ethnopharmacology research is transdisciplinary (Etkin and Elisabetsky, 2005), touching on areas like cultural anthropology, ethnobiology, and as the name implies, pharmacology.

While cultural anthropologists have already pointed out the often insufficient quality of the ethnographic part in ethnopharmacology (Etkin, 1993; Soejarto, 2005), there is an increasing problem with the pharmacological part as will be discussed below. Reports on pharmacological effects of medicinal plants are growing almost exponentially. However, in the last 20 years few significant

* Tel.: +41 44 633 73 74.
E-mail address: juerg.gertsch@pharma.ethz.ch.

0378-8741/$ – see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.jep.2009.01.010

discoveries have been made. This may in part be based on the fact that the many of most relevant plant constituents, including the psychoactive, poisonous, and antitumor natural products, have already been found and we have to work harder to find yet another molecule that will change the world. As Moerman (2008) recently put it, "the low-hanging fruits have already been picked". Instead of working harder to find a significant natural product or a medicinal plant with outstanding pharmacological properties, ethnopharmacologists dwell in the shallow waters of insignificant bioactivities obtained in often meaningless bioassays. As a consequence, the risk of overinterpreting pharmacological data, in particular from *in vitro* assays, is much bigger today than it used to be during the beginning of ethnopharmacology where pharmacology was almost exclusively carried out *in vivo*.

1. The past golden days of ethnopharmacology

Ethnopharmacology was initiated by the missionaries in the colonies interested in the use of pharmacologically active plants, like the Jesuits in 16th century Latin America (Anagnostou, 2005). Molecular ethnopharmacology was later established by scientists like Luis Lewin [1850–1929], Carl Hartwich [1851–1917], Alexander Tschirch [1856–1939] and Richard Evans Schultes [1915–2001], who contributed to the study of the chemistry of pharmacologically active plants and their cultural importance. Throughout that time, anthropologists worked together with chemists and biochemists often leading to fruitful collaborations, like the famous one between Johann Wolfgang von Goethe [1749–1832] and Friedlieb Ferdinand Runge [1794–1867] resulting in the isolation of caffeine or between Robert Gordon Wasson [1898–1986] and Albert Hofmann [1906–2008], resulting in the isolation of psilocybin from psychoactive mushrooms. In fact, early ethnopharmacologists made milestone discoveries, such as the elucidation of the pharmacological principles in foxglove (*Digitalis* spp.), poppy (*Papaver somniferum* L.), curare (mixture of plants including *Chondodendron tomentosum* Ruiz & Pav. and *Strychnos* spp.), the finding of the first antimalarial quinine from *Cinchona* spp., and the spectacular elucidation of the pharmacology of psychedelic plants. Typically, ethnopharmacological discoveries started with field observations and ended in new pharmacological insights. The use of tobacco as a stimulant was first observed in Latin America by the early colonialists and the seeds of *Nicotiana tabacum* L. where brought to Europe from Brazil in 1560 by Jean Nicot de Villemain. Nicotine was isolated and its structure determined in the 19th century. The pharmacologist Otto Löwi [1873–1961] then discovered the pharmacological basis of nicotine action and for the first time described the nicotinergic acetylcholine receptor, which is blocked by curare, a South American arrow poison (vide supra). Without any doubt, Latin American ethnopharmacology has indirectly contributed to the discovery of the cholinergic system. Similarly, aspirin was developed based on ethnopharmacological studies with the bark of the willow tree (*Salix* spp.), which has been used traditionally in Europe to treat fever and inflammation. Another more recent example of model research in ethnopharmacology is the work on the Chinese antimalarial plant *Artemisia annua* L., which has resulted in the recent development of artemisinin, a sesquiterpene with a trioxane peroxide bond, into the new clinical semisynthetic antimalarial agent artemether (formulated in Coartem® and Riamet®) (Kuhn and Wang, 2008).

Ethnopharmacology has witnessed a revival in the 1980s, probably culminating in the founding of the bioprospecting company Shaman Pharmaceuticals Inc. in 1987. Disappointingly, the overwhelming wealth of ethnopharmacological knowledge under investigation did not yield any new discovery of major importance to humanity and no blockbuster was discovered in the process. As one consequence, Shaman Pharmaceuticals Inc. went bankrupt in 2001 (Clapp and Crook, 2002). During that time, the overall awareness of the importance of biodiversity became a topic at the Rio summit in 1992 and the Convention on Biological Diversity (CBD) was originally signed by more than 150 nations and is now ratified by more than 175 countries in the world. The CBD (http://www.biodiv.org) and the Bonn guidelines (http://www.cbd.int/abs/bonn.shtml) now provide new directions for bioprospecting. Despite a new awareness of the importance of intellectual property among the ethnic groups in which ethnopharmacological studies are being carried out and the emerging critical attitude towards ethnopharmacology in general, numerous researchers started to engage in fieldwork throughout the 1990s and the beginning of the 21st century.[1] Ethnopharmacological studies are often driven by the aim of preserving traditional knowledge, to understand the pharmacological basis of herbal medicines, or with the aim of finding a valid reason to guard the rainforests or to engage in conservation (Kim, 2005). Alternatively, bioprospecting is continued by both academic groups and the industry in order to find new leads, probably inspired by the achievements of the early days of ethnopharmacolgy. Much of the data currently generated by ethnopharmacologists worldwide is being published in specialized journals, such as the Journal of Ethnopharmacology. In fact, the amount of papers published in Journal of Ethnopharmacology has more than doubled from 2003 to 2005, reflecting the continuing strong interest in this field. An almost exponentially growing number of reports about apparently interesting and meaningful findings in the field of ethnopharmacology, in particular in the pharmacological area, call for a critical assessment.

2. Are we facing a problem in contemporary ethnopharmacology?

The Journal of Ethnopharmacology has managed to increase its impact factor from 1.4 in 2004 to 2.0 in 2007, suggesting that the quality of the published work has increased over the last years (*vide infra*). However, as in other journals, the number of papers with inconclusive scientific datasets and incoherent experimental approaches has increased too. In the case of ethnopharmacology, this is generally not because of the natural product chemistry component (where molecular structures can be elucidated or falsified based on physicochemical parameters) but because of the molecular pharmacological data, where the spectrum of interpretation and speculations seems to be endless. While there are numerous examples of meaningful descriptions of the pharmacological actions of natural products, some of which have even led to therapeutic applications (Newman and Cragg, 2007), there is a tendency to attribute an apparently pharmacological effect to almost every plant extract and natural product. If there are no clear standards, bioassays with extracts or compounds may present numerous pitfalls which, if unspotted, lead to wrong conclusions (*vide infra*). This problem has been recognized by the editorial board of the Journal of Ethnopharmacology (Verpoorte, 2006), suggesting to set standards for different areas of medicinal plant research (Verpoorte, 2008). Yet increasingly, experimental problems are not spotted by peer reviewers due to limited time or expertise in the relevant field. In the ethnopharmacology and pharmacognosy literature we find thousands of claims of bioactive natural products and extracts with potential therapeutic applications. But hopes and promises are rarely tested on a rational basis. Few claims made from *in vitro* observations stand the test *in vivo*. Instead of trying to falsify theories (e.g. compound X can treat disease Y) ethnopharmacologists prefer to change to other projects and thus fabricate new theories.

[1] Including this author.

Ultimately, the noise produced by publishing nonsense *in sensu stricto* inhibits the progress of science. This problem seems to be particular inherent to academic research.

Intriguingly, pharmaceutical companies or professional organisations dedicated to bioprospecting cannot survive solely on claims of potential therapeutic agents, because their long-term prosperity depends on effective and successful clinical candidates. Thus, the success of drug discovery depends on the stringent criteria that help to avoid development of false positive candidates. Drug discovery lacks mathematical precision and ethnopharmacology is certainly not an exact science and interpretations are often ambiguous. Clearly, ambiguous claims lack objectivity and are potentially subject to wrong assertions. But do we care? In academia we often do not detect false positives when they fit our theory. Instead of trying to falsify theories we desperately try to prove them right and run the risk of being uncritical with our data. This is reflected by the ever-increasing number of research articles. In analogy to economics, an exponential growth of scientific claims in circulation results in a fall in their value and/or raises the expectations for quality. Of course, there are some notable exceptions where ethnopharmacologists collect data in the field (ethnomedical basis) and then carry out *in vitro* studies (with respect to a potential mechanism of action) as well as *in vivo* studies, in order to corroborate a potential therapeutic efficacy. Such examples are provided, e.g. by the state of the art research on the medicinal plant *Curcuma longa* L., which may hold great therapeutic promise to treat inflammation and certain types of cancer (Goel et al., 2008) or the studies conducted with the Thundergod vine (*Tripterygium wilfordii* Hook F.) a Chinese medicinal plant for the potential therapeutic use in rheumatoid arthritis (reviewed in Schmidt et al., 2007). Only an in-depth analysis of the efficacy of these plants in the treatment of malignancies will eventually provide a scientific basis for their evaluation. Unfortunately, many medicinal plant projects never pass beyond the *in vitro* analysis and anecdotal evidence is often short-circuited with *in vitro* findings (Fig. 1). In contemporary ethnopharmacology we are facing a problem because we talk about human health but often mean cellular effects observed *in vitro*. Because ethnopharmacology has

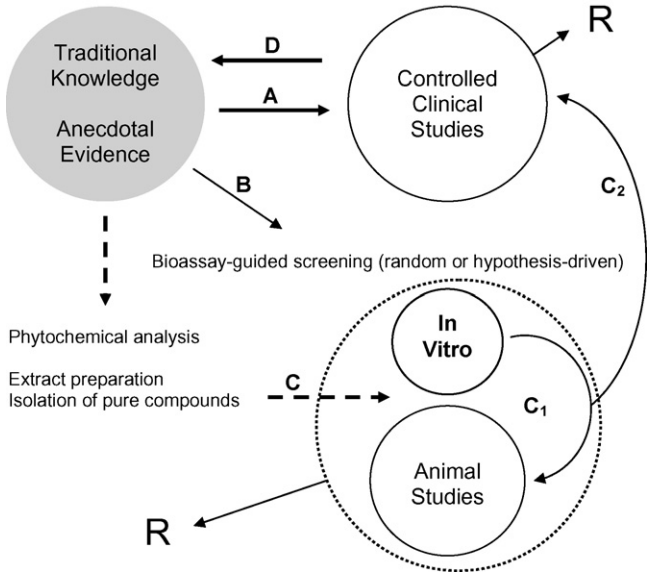

Fig. 1. Interfaces for falsification in the process of ethnopharmacological evaluation. Traditional herbal drugs can either be directly assessed in clinical trials (A), used as a basis for bioprospecting (B), or subjected to *in vitro* studies related to the ethnopharmacological indication (C). (A) and (C) are hypothesis-driven. Empirical data obtained from (B) and (C) then pass through (C_1) and (C_2) where pharmacological hypotheses can be refuted based on *in vitro* and animal studies (R). However, only randomized double-blind placebo-controlled clinical studies allow for confirmation (D) or refutation (R) of anecdotal evidence (traditional knowledge).

empirical elements it can and should be criticized in order to foster the discussion about how to improve its scientific quality.

3. A philosophical problem

The obvious question is whether there is general agreement on what is meaningful in ethnopharmacology? To a certain extent, this is a philosophical question as all depends on the way we perceive the evolution of scientific knowledge. Just as physics was constantly challenged by philosophical reasoning during its early development we need a philosophical basis in the life sciences to establish an epistemology (theory of knowledge). If there is something like a normal science called ethnopharmacology in the sense of Kuhn's (1974) definition of normal science we have to ask what the essence of this science is. Is ethnopharmacology dedicated to the inventarization of potentially bioactive principles in a cultural context or is the scope more scientific and aims to describe pharmacological effects to make claims about indigenous health care systems? While philosophers like Karl Popper [1902–1994] and Imre Lakatos [1922–1974] believed in objective knowledge as being important to the progress of science, Paul Feyerabend [1924–1994], Poppers most rebellious pupil, proposed that science is an unorganized and essentially anarchistic enterprise (Feyerabend, 1991). He realized that in science there is a tension between truth and freedom. Feyerabend was not renouncing the search for truth, or implying that we can preserve freedom by repealing physical laws. He wanted to encourage competition rather than monopoly in epistemology. Feyerabend also criticized that scientists tend to make claims to truth well beyond their actual capacity (Feyerabend, 1975) and thereby impose theories or laws of science upon society. Feyerabend's view on the progress of science adequately portrays what is actually happening in our laboratories because our scientific objectives are as diverse and obscure as human nature. On the other hand, the Popperian methodology of conjecture and refutation is an approach that describes the way theoretical physicists may do science but only partly applies to the life sciences. Popper's epistemiological philosophy and views on scientific method may therefore not be practical overall and there may be many theoretical problems (Stamos, 2007), but his critical rationalism should be useful to the working scientist as it will improve our research. According to Popper, science should aim to not verify hypotheses (at a methodological level) but to falsify them, which makes him a post-positivist verificationist. Verificationism is the doctrine stating that all truths are knowable, based on the verificationist principle proposed by the logical positivist Sir Alfred Jules Ayer [1919–1989]. Ayer greatly influenced philosophy of science as his work was devoted to exploring different facets of claims to knowledge, in particularly perceptual knowledge and knowledge that depends on inductive reasoning. He is known for popularising the verification principle in his book "Language, Truth, and Logic" (Ayer, 1936).There are different schools of verificationism, such as empiricism, positivism, and pragmatism, all of which have greatly influenced epistemology in science. Ethnopharmacology often employs the reasoning of pragmatism. It is argued that the theoretical knowledge about things is directly related to the way we live and experience our environment. The epistemology of early pragmatism was influenced by Darwinian thinking and by the biological idealism proposed by Arthur Schoppenhauer [1788–1860]. What an organism believes may differ from what is actually true and still be beneficial to the organism. The promotion of indigenous health care systems based on verificationist principles is popular in ethnopharmacology but has epistemological problems. It can be argued that the verification principle is self-refuting in that its axioms are neither empirically verifiable nor logic, e.g. Fitch's paradox of knowability demonstrates that the verificationist claim (all truths are knowable) leads to "epistemic collapse", i.e. everything

which is true is (actually) known (Fitch, 1963; Marton, 2006). In ethnopharmacology, verificationism leads to the conclusion that certain believes and metaphysical concepts (e.g. plant A brings good fortune and plant B can be used to deter witches) need to be ruled out as meaningless (not verifiable). Popper's critique of verificationism was about the problem of inductive logic, a problem also inherent in the life sciences. In my opinion, Popper's views on scientific method should be useful to ethnopharmacology because the normally applied verificationism of plausible hypotheses in ethnopharmacology and the overall strong inductive thinking often lead to uncritical conclusions drawn from verifiable scientific experiments, like, e.g. plant extract X kills cancer cells *in vitro* and therefore is an anticancer agent. To falsify this hypothesis we would have to bring the experiment to the next stage of *in vivo* experiments because cancer is a phenomenon observed *in vivo*. In this commentary, it is also argued that we are currently facing a dilemma, which is based on the exponentially increasing number of published claims (pseudo-theories) and the segregation of knowledge into first class (in-depth) and second class (superficial) science. The latter is largely based on the way we perform experiments and the lack of critical analysis of *in vitro* data. It will be argued that *in vitro* data cannot always be used to verify or refute an observation made in the field and that *in vitro* data may be misleading.

4. Misemployment of the concentration–effect paradigm – fact or artefact?

Much of the problem of the malpractice of scientific method in the pharmacology part of ethnopharmacology is based on carelessly carried out bioassays. Far too often, outrageously high concentrations of an extract or a natural product are used to identify a pharmacological response. The concentration–effect paradigm in pharmacology states that the dose–response is an indication of pharmacological efficacy. This paradigm has also been adopted in *in vitro* assays where a concentration–effect response is the "golden standard". What is the basis of this criticism? It is best summarized by the statement that inductive reasoning without critical rationalism may lead to wrong assertions. For example, it is wrong to conclude that natural radioactivity (earth radiation) is responsible for the death of people only because one can show in an experiment that radioactivity is lethal. It is, of course, a question of concentration. We all know the dictum of Paracelsus [1492–1541] that "the dose makes the poison". Analysing claims of meaningful and significant effects observed in cellular assays with extracts (mostly herbal extracts) but also single compounds shows that there are strikingly different opinions about which concentrations are substantial with regard to meaningful effects.

To provide an example, Palu et al. (2008) investigated commercial noni fruit concentrates obtained from the fruits of *Morinda citrifolia* L. and they found that 1.5 mg/ml (!) of their extract activates the cannabinoid type-2 (CB_2) receptor but inhibits the type-1 (CB_1) receptor. There are two problems. First, it is unusual and problematic to apply 1.5 mg/ml of an extract to a radioligand assay because typically 10 μg/ml are enough to detect a positive signal, i.e. displacement (Gertsch et al., 2008). For instance, a *Cannabis sativa* L. extract (2% THC) results in a K_i value of <100 ng/ml (!), meaning that more than 50% of the radioligand is displaced by less than 1 μg. Thus, the authors are out of the expected experimental range by a factor of more than 1000. Second, Palu et al. measure effects on radioligand binding to a receptor without being able to determine an IC_{50} value, but draw conclusions about activation or inhibition of that receptor, not realizing that binding effects (and in this case they are not even well established) do not inevitably enlighten us about the activation or inhibition of a g-protein coupled receptor (GPCR). The actual problem is the claim derived from this study, namely that noni fruit extract activates the CB_2 receptor (as stated in the abstract). If we care about objective knowledge we have to say that this claim is not scientifically meaningful and can be refuted.

A second example is the apparent usefulness of *Uncaria tomentosa* (Willd.) DC (cat's claw) extracts in the treatment of cancer as suggested by different investigations (Riva et al., 2001; Akesson et al., 2003; De Martino et al., 2006), although the effects were observed in the mg/ml range *in vitro* (!), which is clearly inacceptable. As a consequence, other researchers have tried to identify the anticancer agents in *Uncaria tomentosa* (Willd.) DC. and reported oxindole alkaloids with antiproliferative IC_{50} values close to 100 μM which they considered to be potent (Bacher et al., 2006). A third example is the conclusion made by Hostanska et al. (2005) that extracts of black cocosh (*Cimicifuga racemosa* L.), commonly used to treat hot flashes and other symptoms associated with menopause, may also represent a novel therapeutic approach for the treatment of prostate cancer only because such extracts kill cancer cells *in vitro* with IC_{50} values between 35 and 60 μg/ml.

The potency of these effects is questionable when taking into account that the therapeutic anticancer agent paclitaxel (Taxol®) from *Taxus brevifolia Nutt.* exhibits low nM IC_{50} values in the same cell lines (i.e. it is 50,000 times more potent than *Uncaria* alkaloids) (Altmann and Gertsch, 2007). Unfortunately, the conclusions of such studies will be adopted uncritically and cited by other scientists who do not read the paper carefully.

In ethnopharmacology, we need to understand that concentration determines meaning. Unfortunately, there are no standards beyond the cut-off concentrations commonly used at industry ($EC_{50} \leq 10$ μM for pure compounds). Scientists working with natural products need to realize that the molecular architecture (carbon scaffold, heteroatoms, functional groups, multiple stereocenters, etc.) of natural products greatly facilitates protein interactions probably because natural products have been phylogenetically selected in a protein environment. Therefore, protein binding interactions of natural products may not be linear with concentration but exponential. This means that high concentrations are always likely to generate a response as multiple proteins are targeted. Thus, in theory, a natural product may have a critical concentration at which it binds almost non-selectively to proteins. This is the reason why plant polyphenols (tannins) tan animal skin to leather. At the molecular scale this phenomenon is probably also true for phenolic compounds and soluble proteins. Good examples are the "frequent hitters" quercetin, apigenin, and curcumin.[2] These interesting phenolic natural products interact with many proteins *in vitro* and appear to have multiple therapeutic effects without being toxic. For example, despite intensive research on curcumin, which is derived from the spice and medicinal plant *Curcuma longa* L. (Aggarwal and Harikumar, 2008), it is still somewhat obscure whether the numerous bioactivities found at μM concentrations are meaningful to human health because the bioavailability of this highly promising natural product appears to be very limited and only nM plasma concentrations are detected *in vivo* (Villegas et al., 2008). The same is true for many other natural products.

Here the emerging question is "what is meaningful?" It is somewhat more complicated than "the more potent the better" as apparently weak compounds may act synergistically (e.g. in an extract) on the same signalling pathway and lead to meaningful pharmacological effects *in vivo* despite their moderate binding affinities to particular targets (Schmidt et al., 2007). However, this appealing concept of "natural product triggered network pharmacology" needs to be proven. It would be too simple to believe that this is the general way plants cure. It is feasible that extract components may just as well act antagonistically to each other. Thus,

[2] Each of these natural products has more than 350 entries in PubMed NCBI (www.pubmed.com) describing their in vitro pharmacological effects.

it is time to abandon the maybe naïve belief that phytomedicines are good therapeutics *per se* as they can be completely ineffective or not more pharmacologically effective than a common vegetable. Alternatively, we should not ignore the possibility that many medicinal plants could be simply mediators of a significant "meaning response" (placebo effect) in a cultural context (for elaboration on this topic, see Moerman and Jonas, 2002) and do not contain pharmacologically active molecules, at least not for the disease indicated by the ethnomedical data. If there are common denominators in plants that have therapeutic effects we need to describe them. With regard to meaningful concentrations in bioassays, we should ask the question whether *in vitro* effects observed at extract concentrations >50 μg/ml or compound concentrations >5 μM are meaningful in the particular bioassay context or whether other common plant extracts or natural products would cause the same effect. A superficial analysis of concentrations used in ethnopharmacology research articles published in the journals: Journal of Ethnopharmacology, Journal of Natural Products, Planta Medica, Phytotherapy Research, Life Sciences, and Biochemical Pharmacology shows that there are numerous examples where ≥200 μg/ml of extracts and ≥20 μM of single substance are used. For the reasons outlined above, such concentrations are likely to be artificial despite of yielding reproducible effects. Even worse, such high concentrations may trigger non-physiological effects resulting in artefacts. As bioassays are increasingly specialized it should be helpful to include both positive and negative (!) controls to set the standards for meaningfulness. Negative controls could be plant extracts from vegetables and common natural products such as quercetin. In addition, we need to think about the possibility that *in vitro* data can be misleading because certain natural products are metabolized and the pharmacokinetics of the individual natural products are often totally ignored. For instance, it makes no sense to test glycosylated compounds *in vitro* because they are likely to be metabolized *in vivo* by the intestinal flora. It would be extremely helpful if more pharmacokinetic studies could be performed with plant constituents. For *in vivo* studies it is questionable whether pharmacological effects detected with doses of 200 mg/kg or more, as sometimes found in research articles, are of any practical use. To overcome the poor pharmacokinetics, plant extracts are sometimes injected intraperitoneally or intravenously, thus moving away from the ethnomedical application. Even if, e.g. a significant anti-inflammatory effect of an extract is observed at 200 mg/kg after peroral application, it will most likely not be of any practical use. Moreover, the toxicology of such high concentrations is seldom sufficiently well studied in animal experiments. Thus, reproducible datasets and statistically significant effects can be meaningless when contextually falsified. There are, of course, numerous encouraging examples of ethnopharmacological studies in which peroral dose–response effects of plant extracts are compared to a positive control (e.g. Piato et al., 2008).

5. Sociocultural consequences of artefact research in ethnopharmacology

Since the use of medicinal plants is a widely accepted therapeutic strategy for millions of people uncritical scientific reports in the field of ethnopharmacology and pharmacognosy may easily have an impact on society. Often, the marketing departments of agencies selling botanical therapeutics make use of uncritical positive claims published in scientific journals but ignore negative claims. The problem was recently addressed by Gómez Castellanos et al. (2008) with the case of red lapacho (*Tabebuia impetignosa*, syn. *Tabebuia avellanedae* Lor. ex Griseb.), which is also sold as "miracolous botanical therapeutic" to treat cancer. Much of the excessive optimism is based on preliminary laboratory data showing that some of its constituents (lapachol and derivatives) exert cytotoxic and antimetastatic effects. However, Müller et al. (1999) reported that the *in vitro* cytotoxic effects observed with these potentially interesting compounds are due to damage to the cell membranes rather than interaction with defined targets. Regardless of this important finding, sophisticated studies on the signal transduction of the cytotoxic and pro-apoptotic effects of lapachone and derivatives were carried out *in vitro* by Choi and colleagues in Korea, leading to many scientific publications, which will not be cited here. In case that our *in vitro* studies on the molecular mechanisms of action of natural products cannot be correlated with therapeutic (i.e. physiological) effects because these compounds are simply not potent enough *in vivo* or physiologically ineffective, or we cannot define new cellular mechanisms (interaction of this compound with a particular protein target), we probably have to talk about *in vitro* "artefact research". Importantly, at cytotoxic concentrations of any natural product (be it relevant or irrelevant) there will nonetheless be an array of secondary cellular effects that can be described *in vitro*, probably leading to numerous incoherent publications. The sociocultural consequence of such research is that potentially money has been wasted.

6. Popper's critical rationalism is setting standards

The essential elements of scientific method are curiosity (hypotheses), operations (experiments), repeatable observations (empirical data), establishment of models (theories), and reproduction or falsification of models by the scientific community. The obvious weak point in ethnopharmacology is the latter. We may know when a hypothesis or theory is wrong when it can be proved wrong. Popper and Miller (1983) showed that evidence supposed to partly support a theory can in fact only be neutral to, or countersupports the theory. But do we like to falsify our theories? Most probably this Popperian approach is not very popular among scientists who are under pressure to publish. On the contrary, we are the sellers of our ideas and data. In an 'inflation-driven' scientific environment the currency (scientific publications) is devaluated as the amount of currency increases, which motivates us to publish as many claims as possible. As Murray (2001) put it, the plethora of *ad hoc* (not universal) hypotheses indicates that biologists are reluctant inductivists in that the search for generalization does not have a high priority. Biologists test their hypotheses (theories) by verification. Theoretical physicists, in contrast, are deductive unifiers and test their explanatory theories by falsification. In inductive reasoning, one makes a series of observations and infers a new claim based on them. This process mirrors what is going on in the life sciences (including ethnopharmacology). We test extracts and compounds in biological assays (*in vitro*, high content cellular assays, *ex vivo*, *in vivo*) and infer new therapeutic applications from reproducible data. Alternatively, we intend to verify or even validate the ethnomedical use of plants in traditional societies. Too often we forget that only a well-performed randomized placebo-controlled double-blind clinical trial is able to refute a theory that extract or compound X cures disease Y. In drug discovery this is of course the very last step in the process (Fig. 1). Interestingly, Graz et al. (2007) have proposed a cost-effective protocol for clinical studies in ethnopharmacology, which may be a good starting point to verify or refute anecdotal evidence. Nonetheless, ethnopharmacologists may be tempted to accept the anecdotal evidence reported by traditional healers as true and take it as scientific evidence for the efficacy of a certain medicinal plant. A short excursion into the Renaissance herbal books of the 16th Century, which were largely based on Dioscorides *de Materia Medica*, should be enough to teach us that anecdotal evidence is bad evidence because the often unrelated numerous claims about the medicinal effects of herbal medicines, and in particular animal and inorganic medicines, have to a cer-

tain extent already been refuted by modern molecular medicine. Interestingly, the herbal drugs listed in the modern Pharmacopoeias are recognized as exerting beneficial effects, largely based on traditional evidence reinterpreted by modern pharmacological data, but only partly based on sound clinical evidence. Thus, traditional medicine based on non-toxic herbal drugs has the clear benefit of a kind of cultural validation over time, independently of the question whether this process is based on rational decisions.

On the other hand, the rational drug development process passes through several stages at which hypotheses can be refuted (Fig. 1). If an agent is active against a protein it needs to be active against that protein within the cell; it needs to be active in the primary cells and tissues; it needs to be active in an animal model, etc. In academia, we are often far away from trying to falsify our conclusions by bringing the experiment to the next stage of complexity. The result is the fabrication of unscientific hypotheses and theories. Is it correct to talk about an antimalarial activity of an extract when the readout is derived from an *in vitro* model? Is a compound an anticancer agent only because it kills cancer cells *in vitro*? If compound X shows anticancer effects in different *in vitro* models but is completely inactive *in vivo* because it is not bioavailable or metabolized we have the possibility of improving its chemical properties such that it becomes a therapeutic candidate. If an extract (e.g. medicinal plant extract) shows anti-inflammatory effects *in vitro* but is ineffective *in vivo* (inflammation is an *in vivo* phenomenon) there is probably not much we can do about it. Unfortunately, some researchers in ethnopharmacology still believe in the "good herbal medicine" that has to be effective somehow (e.g. Wayland, 2004) – thus, they search until they find something and subsequently claim that what they have found is a proof of the effectiveness of that particular plant. To set standards we have to realize that we need to collaborate with each other to obtain a critical amount of sound data on the chemistry and pharmacology of a plant which allows us to judge whether this plant may be useful for (1) the isolation of new bioactive chemical entities, (2) the development of botanical drugs, (3) the development of dietary supplements or food additives, or (4) the development of cosmeceuticals. Potential academic and industrial collaborations should include expert laboratories from different fields, including natural product chemistry, *in vitro* bioassays (screening, target identification), biopharmacy (pharmacokinetics), animal experiments (verification, knockout models, *in vivo* efficacy), and clinical studies. Too often, ethnopharmacology laboratories do not collaborate with trained pharmacologists but engage themselves in the development of *in vitro* assays and animal studies. This may lead to poor methodology and uncritical assessment. On the other hand, professional collaborations allow us to ensure that the same or similar data can be generated in independent setups, which is the essence of science. Alternatively, datasets need to be refuted. Popper's critical rationalism teaches us the difference between metaphysics and science and that we can only do science when being generally critical with datasets, i.e. datasets need to have a falsifiability status. Have we recently tried to refute our hypotheses experimentally? We have to agree with Psarros (1997) that while there is no deny that in the natural sciences many questions are settled empirically, the reduction of the scientific enterprise to falsificationism is a shortcoming because it does not answer the question about the conditions for successful action. We also have to agree with Lakatos (1978) that in practice scientists often do not abandon their theories only because some new experimental data refute them. Thus, falsifiability is contextual. According to Lakatos, the typical unit of science is not an isolated hypothesis, but a research program, consisting in theories and heuristics. The fact that the inexact science of ethnopharmacology does not generally have predictive theories does not constitute proof that it cannot have them. On the contrary, we should attempt to formulate predictive theories based on critical rationalism. We also should adopt Lakatos' definition of science as a research program with clear objectives rather than individual PhD theses or projects. The incentive to do science should be scientific insights and promotion of knowledge – our contribution to mankind. I admit that this is to put lipstick on the pig and that these high ideals simply do not match reality. We are all under the pressure to publish our research data and the number of annual publications directly impacts our funding situation. We can only hope that there will be a way out of this. In a recent Nature Medicine editorial it was proposed that each scientist should only be allowed to publish 20 papers in his/her entire career (Nat. Med. 13, 1121, 2007), which would naturally lead to a dramatic reduction of noise and announcement of incremental data. Even though this idea is not realistic it is nonetheless appealing and reflects the current malpractice of publishing *ad hoc* findings as a means of increasing the contemporary scientist's portfolio (which typically contains research papers, funding, patents, reviews, etc.). Only when researchers start to try to falsify or refute their observations and subsequently announce grown-up theories will we see an improvement in scientific quality and a more efficacious promotion of knowledge. In my opinion this is urgently needed in ethnopharmacology. To quote Popper (1959): "The game of science is, in principle, without end. He who decides one day that scientific statements do not call for any further test, and that they can be regarded as finally verified, retires from the game."

Acknowledgments

I would like to thank the following colleagues for lively and critical discussions and for constructive comments and corrections: Thomas Baumann, University of Zurich, Switzerland; Michael Heinrich, University of London, England; Marco Leonti, University of Cagliari, Italy, Dan Moerman, University of Michigan, USA; Wolfgang Schühly, Universtiy of Graz, Austria; Peter Taylor, IVIC, Venezuela.

References

Aggarwal, B.B., Harikumar, K.B., 2008. Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. International Journal of Biochemistry & Cell Biology 41, 40–59.

Akkeson, C., Lindgren, H., Pero, R.W., Leanderson, T., Ivars, F., 2003. International Immunopharmacology 3, 1889–1900.

Altmann, K.H., Gertsch, J., 2007. Anticancer drugs from nature – natural products as a unique source of new microtubule-stabilizing agents. Natural Product Reports 24, 327–357.

Anagnostou, S., 2005. Jesuits in Spanish America: contributions to the exploration of the American materia medica. Pharmacy in History 47, 3–17.

Ayer, A.J., 1936. Language, Truth and Logic. Victor Gollancz Ltd., London.

Bacher, N., Tiefenthaler, M., Sturm, S., Stuppner, H., Ausserlechner, M.J., Kofler, R., Konwalinka, G., 2006. Oxindole alkaloids from *Uncaria tomentosa* induce apoptosis in proliferating, G0/G1-arrested and bcl-2-expressing acute lymphoblastic leukaemia cells. British Journal of Haematology 132, 615–622.

Clapp, R.A., Crook, C., 2002. Drowning in the magic well: Shaman Pharmaceuticals and the elusive value of traditional knowledge. The Journal of Environment & Development 11, 79–102.

De Martino, L., Martinot, J.L., Franceschelli, S., Leone, A., Pizza, C., De Feo, V., 2006. Proapoptotic effect of *Uncaria tomentosa* extracts. Journal of Ethnopharmacology 107, 91–94.

Etkin, N.L., 1993. Anthropological methods in ethnopharmacology. Journal of Ethnopharmacology 38, 93–104.

Etkin, N.L., Elisabetsky, E., 2005. Seeking a transdisciplinary and culturally germane science: the future of ethnopharmacology. Journal of Ethnopharmacology 100, 23–26.

Feyerabend, P.K., 1975. Against Method. Humanities Press, London.

Feyerabend, P.K., 1991. Three Dialogs of Knowledge. Wiley–VCH, Weinheim.

Fitch, F., 1963. A logical analysis of some value concepts. The Journal of Symbolic Logic 28, 135–142; reprinted in Salerno (Ed.), New Essays on the Knowability Paradox, Oxford: Oxford University Press.

Gertsch, J., Leonti, M., Raduner, S., Racz, I., Chen, J.Z., Xie, X.Q., Altmann, K.H., Karsak, M., Zimmer, A., 2008. Beta-caryophyllene is a dietary cannabinoid. Proceedings of the National Academy of Sciences USA 105, 9099–9104.

Goel, A., Jhurani, S., Aggarwal, B.B., 2008. Multi-targeted therapy by curcumin: how spicy is it? Molecular Nutrition & Food Research 52, 1010–1030.

Gómez Castellanos, J.R., Prieto, J.M., Heinrich, M., 2008. Red Lapacho (Tabebuia impetiginosa) – a global ethnopharmacological commodity? Journal of Ethnopharmacology (ahead of print).
Graz, B., Elisabetsky, E., Falquet, J., 2007. Beyond the myth of expensive clinical study: assessment of traditional medicines. Journal of Ethnopharmacology 113, 382–386.
Hostanska, K., Nisslein, T., Freudenstein, J., Reichling, J., Saller, R., 2005. Apoptosis of human prostate androgen-dependent and -independent carcinoma cells induced by an isopropanolic extract of black cohosh involves degradation of cytokeratin (CK) 18. Anticancer Research 25, 139–147.
Kim, H.S., 2005. Do not put too much value on conventional medicines. Journal of Ethnopharmacology 100, 37–39.
Kuhn, T., 1974. Second thoughts on pradigms. In: Stuppe, F. (Ed.), The Structure of Scientific Theories. University of Illinois Press, Urbana, USA, pp. 459–482.
Kuhn, T., Wang, Y., 2008. Artemisinin – an innovative cornerstone for anti-malaria therapy. Progress in Drug Research 66, 385–422.
Lakatos, I., 1978. The Methodology of Scientific Research Programmes: Philosophical Papers, vol. 1. Cambridge University Press, Cambridge, England.
Marton, P., 2006. Verificationists versus realists: the battle over knowability. Synthese 151, 81–98.
Moerman, D.E., Jonas, W.B., 2002. Deconstruction the placebo effect and finding the meaning response. Annals of Internal Medicine 136, 471–476.
Moerman, D.E., 2008. Personal Communication at the 10th International Congress of Ethnopharmacoloy, 16–19th September, Sao Paulo, Brazil.
Müller, K., Sellmer, A., Wiegrebe, W., 1999. Potential antipsoriatic agents: lapacho compounds as potent inhibitors of HaCaT cell growth. Journal of Natural Products 62, 1134–1136.
Murray Jr., B.G., 2001. Are ecological and evolutionary theories scientific? Biological Reviews of the Cambridge Philosophical Society 76, 255–289.
Nature Medicine Editorial, 2007. Ticket scalpers. Nature Medicine 13, 1121.
Newman, D.J., Cragg, G.M., 2007. Natural products as sources of new drugs over the last 25 years. Journal of Natural Products 70, 461–477.
Palu, A.K., Kim, A.H., West, B.J., Deng, S., Jensen, J., White, L., 2008. The effects of *Morinda citrifolia* L. (noni) on the immune system: its molecular mechanisms of action. Journal of Ethnopharmacology 115, 502–506.
Piato, A.L., Detanico, B.C., Jesus, J.F., Lhullier, F.L., Nunes, D.S., Elisabetsky, E., 2008. Effects of Marapuama in the chronic mild stress model: further indication of antidepressant properties. Journal of Ethnopharmacology 118, 300–304.
Popper, K., 1959. The Logic of Scientific Discovery. Harper and Row, London.
Popper, K., Miller, D., 1983. A proof of the impossibility of inductive probability. Nature 302, 687–688.
Psarros, N., 1997. Critical rationalism in the test tube? Journal for the General Philosophy of Science 28, 297–305.
Riva, L., Coradini, D., Di Fronzo, G., De Feo, V., De Tommasi, N., De Simone, F., Pizza, C., 2001. The antiproliferative effects of Uncaria tomentosa extracts and fractions on the growth of breast cancer cell line. Anticancer Research 21, 2457–2461.
Schmidt, B.M., Ribnicky, D.M., Lipsky, P.E., Raskin, I., 2007. Revisiting the ancient concept of botanical therapeutics. Nature Chemical Biology 7, 360–366.
Soejarto, D.D., 2005. Ethnographic component and organism documentation in an ethnopharmacology paper: a "minimum" standard. Journal of Ethnopharmacology 100, 27–29.
Stamos, D.N., 2007. Popper, laws, and the exclusion of biology from genuine science. Acta Biotheoretica 55, 357–375.
Verpoorte, R., 2006. Setting standards! Journal of Ethnopharmacology 106, 289.
Verpoorte, R., 2008. Setting standards: diabetes. Journal of Ethnopharmacology 115, 161–162.
Villegas, I., Sánchez-Fidalgo, S., Alarcón de la Lastra, C., 2008. New mechanisms and therapeutic potential of curcumin for colorectal cancer. Molecular Nutrition & Food Research 52, 1040–1061.
Wayland, C., 2004. The failure of pharmaceuticals and the power of plants: medicinal discourse as a critique of modernity in the Amazon. Social Science & Medicine 58, 2409–2419.