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Mini-review

Ethnopharmacology: quo vadis? Challenges for the future



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A B S T R A C T

It is well-known that humans have used medicinal plants for millennia, but as a defined field of scientific research called ethnopharmacology, it has a relatively short history. It is linked to the development of pharmacology in the 19th century (as exemplified in the work of Claude Bernard linking the explorers' observations on traditional uses of medicines and toxins) and to fascination with psychoactive drugs in the 1960s. This fascination gave rise to what we now call ethnopharmacology, a term first used as recently as 1967. With thousands of ethnopharmacological articles published each year now, the field has expanded greatly. It nowadays covers a wide range of topics based on the anthropological, historical and other socio-cultural studies of local and traditional plants, fungi and animals; as well as the biological and clinical studies of resources used as medicines, toxins, foods, among other applications. It is one of the few fields in science truly transdisciplinary and it is a key bridge between socio-cultural and the natural/medical sciences. More importantly, ethnopharmacological research is crucial for the improvement of livelihood, health and wellbeing of humans.

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Introduction

There is no doubt that ethnopharmacology is a thriving discipline, as now established journals publish thousands of articles in this field of research. While there are not many institutes carrying the term in their name, many groups working in pharmacy, biology, and chemistry, among other disciplines, publish in the field. It is impressive for an area of study with a surprisingly short history.

Ethnopharmacology is, by definition, a scientific approach to the study of the biological activities of any preparation used by humans, which have, in a very broad sense, either beneficial or toxic or other direct pharmacological effects. As such, it is not about describing (generally local or traditional) uses, but about the combined broad anthropological and pharmacological-toxicological study of these preparations.

Studies describing the use of useful plants are generally included in this definition, but these are generally conducted with the goal of leading to an experimental study of botanical drugs (Heinrich et al., 2009).

To the best of our knowledge the term 'ethnopharmacology' was first used in 1967 by Efron and colleagues who used it in the title of a book on hallucinogens: *Ethnopharmacological Search for Psychoactive Drugs* (Efron et al., 1970; Holmstedt, 1967). This term was proposed much later than the term ethnobotany, coined in 1896 by American botanist William Harsberger when describing the study of human plant use. Both ethnopharmacology and ethnobotany investigate the relationship between humans and plants in all its complexity. Or as Daniel E. Moerman from the University of Michigan-Dearborn put it: "Essentially ethnopharmacology is the examination of non-Western (not mine) medicinal plant

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use in terms of Western (my) plant use" (Daniel E. Moerman, personal communication, September 15, 2013). Here the pharmacological aspect is less at the center.

It would not be appropriate to limit this discussion to the period after 1967. Plants and animal-based medicines are an integral part of indigenous medical systems in many regions of the world, and form a part of the traditional knowledge of a culture. Any study involving the documentation and systematic study of local and traditional uses of a plant or taxa is one with an ethnopharmacological context. Explorers, missionaries, merchants, and knowledgeable experts in the respective healing tradition describe the uses of such medicinal plants, which may form a basis for ethnopharmacology-based drug development. For centuries this knowledge has been widely used as a starting point for drug development, and once an initial lead is found, many researchers no longer consider this knowledge to be of relevance for drug discovery programmes. In the context of today's ethnopharmacology the focus has certainly also moved to understand the benefits and risks of commonly used local and traditional plants with the aim of contributing to a better and safer uses of such resources (Heinrich, 2006; 2009).

In a modern biological and biomedical context, ethnopharmacology requires an integration of pharmacological, or other natural science, approaches with research on local and traditional uses. Hence, Claude Bernard (1813-1878), one of the founding fathers of pharmacology and physiology, is rightfully seen as one of the first researchers to conduct what today we would call an ethnopharmacological study. His interest was on the study of curare and the reasons behind why it was non-toxic if applied orally. He wrote (Bernard, 1966): 'One of the facts noted by all those who reported on curare is the lack of toxicity of the poison in the gastrointestinal tract. The Indians indeed use curare as a poison and as a remedy for the stomach' (p. 93). This is also linked to the way curare is prepared and applied. Bernard also stated: 'If curare is applied into a living tissue via an arrow or a poisoned instrument, it results in death more quickly if it gets into the blood vessels more rapidly. Therefore death occurs more rapidly if one uses dissolved curare instead of the dried toxin' (Bernard, 1966: 92). Bernard also was able to demonstrate that the animals did not show any nervousness and no sign of pain. The main sign of death induced by curare is muscular paralysis. If the blood flow in the hind leg of a frog is interrupted using a ligature without interrupting the innervations, and it is poisoned via an injury of the hind leg, it retains its mobility and the animal does not die from curare poisoning (p. 115). These and subsequent studies allowed a detailed understanding of the pharmacological effects of curare on other respiratory paralysis. This is an ethnopharmacological analysis of traditional practice using 19th century state-of-the-art biomedical science.

The principal compound responsible for this activity was isolated for the first time from *Chondrodendron tomentosum* Ruiz and Pav., and in 1947 the structure of the bisbenzylisoquinoline alkaloid, D-tubocurarine was determined. Finally, tubocurarine's structure was resolved using NMR in the 1970 decade showing that it has only one quaternary nitrogen. Currently, in many European countries tubocurarine is sporadically used, for example, in France it is still used for

muscle relaxation during surgery (Heinrich, 2010). In a similar argumental line, 19th century research of phantastica and hallucinogenic substances played a crucial role in the development of psychopharmacology/neuropharmacology (Holmstedt, 1967)

Any form of empirical use and 'medical testing' of a plant for novel uses may be considered an ethnopharmacological approach. Foxglove, *Digitalis purpurea* L., Scrophulariaceae, was used by an English housewife to treat dropsy currently known as edema, and was then explored more systematically for its medical properties by the physician William Withering (1741-1799). He used the orally transmitted knowledge of British herbalism in order to develop a medicine used by conventional medicine. Prior to such studies, herbalism was more of a clinical practice interested in the patient's welfare, and less of a systematic study of the uses and chemical properties of medicinal plants.

These two historical examples are among the many success stories of an ethnopharmacology driven drug development strategy, albeit the earlier ones were not called so at the time. Numerous other examples could be listed including most recent developments on *Galanthus* spp./*Leucojum* spp. (galanthamine), *Croton lechleri* Muell. Arg. (Crofelemer), *Euphorbia peplus* L. (Peplin) and *Cannabis sativa* L. (Sativex®), to name just a few examples (Heinrich, 2010). Clearly, natural products remain one of the most important sources, even maybe the most important one, of new drug leads. More than half of new products commercially launched are natural products, their derivatives or mimetics (Chin et al., 2006).

Similar examples could be cited from other medical traditions but, more importantly, the above-mentioned examples show that the coining of the term ethnopharmacology actually offered focus and a clear concept of a field of research interested in the interface of traditional and local medical use of plants and their biological characteristics. It also replaced the many other terms previously used like *Pharmakoethnologie* used already by Tschirch (1910) in his classic '*Handbuch der Pharmakognosie*' or *pharmacoetnologia* or *aboriginal botany*.

So how did the term and the concept the term represents come about? Even though the term itself is less than 50 years old, in fact its origin is not well known as one would expect. This article is more than anything a call for more research into the short history of this field. A critical appraisal of the term would be well warranted. After its initial use in the context of hallucinogenic plants the term was only occasionally used until 1979, when Laurent Rivier and Jan Bruhn founded the *Journal of Ethnopharmacology*. With this event, the scope was broadened to "a multidisciplinary area of research concerned with the observation, description, and experimental research of indigenous drugs and their biological activity" (Rivier and Bruhn, 1979). Thirty-five years later, many journals (including the *Revista Brasileira de Farmacognosia* or *Brazilian Journal of Pharmacognosy*) publish ethnopharmacological research and give testimony to the thriving research interest in how we humans use plants as medicine, food, as toxins or as a veterinary ailment. A much larger share of articles focus on the biological and pharmacological activity of locally and traditionally used medicinal plants, studies analyzing the

local and traditional uses, as well as historical ones, still are an important part of what constitutes 'ethnopharmacology'.

We continue to have a very complex and critical debate regarding who benefits from this research and how we best follow ethical guidelines, which in this field are most prominently, based on the Convention on Biological Diversity (Rio Convention, 1992) and subsequent agreements as the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization (ABS) to the Convention on Biological Diversity (2010). As pointed out previously, research in the field is thriving and there are tremendous opportunities maybe most importantly in the context of developing a rational scientific basis for using such local and traditional resources.

With this development in mind I need to highlight that, as in all disciplines, the debate also is very much about what constitutes good quality in the field. In this regard we have numerous challenges exacerbated by the multidisciplinary nature of what today constitutes ethnopharmacology. Thus key challenges are often related to scientific precision and accuracy; thus ascertaining that the scientific results are scientifically reliable and reproducible. I just want to remind us of key challenges, and how to achieve them continues to be an essential debate (Heinrich and Verpoorte, 2014):

- The botanical authenticity and details about how this was achieved needs to be authenticated (*e.g.* Bennett, 2014; Rivera et al., 2014).
- Ethnopharmacology is about linking local/traditional uses with biologic and biomedical studies. Therefore, it is crucial to base research on a very sound understanding of these uses and the importance of the plants in a community (Heinrich et al., 2009)
- No study makes sense, if it is not supported on a chemical and analytical base, and the description of extracts. We have particular challenges and as much information as possible on an extract and its composition is an essential element of all ethnopharmacological studies (*e.g.* Sheridan et al., 2012)
- There are many challenges in the context of pharmacology, but again it is crucial that pharmacological research uses state-of-the-art approaches. The models and doses used must be of physiological and/or pharmacological relevance, and the studies have to be conducted based on the existing standards (*e.g.* Cos et al., 2006; Verspohl, 2002 among others). One could write pages on what constitute minimum standards for pharmacological studies on plants. There are trivial points, we all need to remember: the proper use of positive and negative controls, the use of a dose range which is of pharmacological relevance, and appropriate dosing regimens and modes of application in *in vivo* studies.

In essence, the wider challenge lies in the need not only to understand, and properly describe, botanical and phytochemical aspects of the drugs studied, but also using a robust, state-of-the-art and fully reproducible methodology, relevant to the question asked. To cite just one of the many problems found in literature, a general *in silico* or *in vitro* assay for antioxidant activity is used and then conclusions are drawn on the potential beneficial effects in case of, for example,

Alzheimer's disease or other chronic forms of dementia. The assays used in this example bear no pharmacological relevance for the conditions studied, but provide general data on the generic, and thus edibility, anti-oxidant activity of a botanical drug. The later is also of scientific interest, but not in the context of treating a disease.

Lastly one also needs to consider how much of a mechanistic understanding such a study provides and a more detailed understanding of the underlying modes of action and the drug's specific targets provides a much better basis for evidence-based evaluation than a general screening.

To conclude this short and very general view on the state-of-the-art in ethnopharmacology, we will need to pay much more attention to the methods we use and to the particular challenges of a multidisciplinary field of research. Ethnopharmacology can make very important contributions to science and is of interest in practically all countries of the world, especially to those undergoing a fast economic development and the associated cultural and social changes. Consequently, it is our task to make this research meaningful and strive for the best practice (Gertsch, 2009). More than 150 years ago Claude Bernard set such standards, which we need to follow in his and other researchers who have formed this field tradition.

Conflicts of interest

The authors declare no conflicts of interest.

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