Revista Brasileira de Farmacognosia
BRAZILIAN JOURNAL OF PHARMACOGNOSY
www.journais.elsevier.com/revista-brasileira-de-farmacognosia/

Original article

Are ethnopharmacological surveys useful for the discovery and development of drugs from medicinal plants?

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ARTICLE INFO

Article history:
Received 15 November 2013
Accepted 4 April 2014

Keywords:
Ethnobotany
Ethnodirected
Ethnomedicine
Traditional uses

ABSTRACT

Ethnopharmacological and ethnobotanical approaches are described in the literature as efficient to identify plants of interest for phytochemical and pharmacological studies. In the present work, we reflect on the quality of the data collected in ethno-directed studies. In accordance to the problems identified in published studies, and their theoretical and methodological underpinnings, we believe that these studies are poorly suited to contribute to the advancement of research aimed at the development of novel drugs.

Introduction

Despite the richness of the ethnopharmacological surveys performed worldwide, and the increase in knowledge of the use of natural resources by local communities (Albuquerque et al., 2012), particularly in Brazil, many of the collected data were found not to be sufficiently sound for bioprospecting purposes. In fact, the ethnopharmacological/ethnobotanical approach has been progressively losing its appeal as a tool for systematic identification of novel pharmaceutical drugs because this approach has failed to locate new species that could represent interesting candidates for further phytochemical and pharmacological studies (Gertsch, 2009). The reasons for this failure include the poor quality of many studies (Albuquerque and Hanazaki, 2006; 2009) both from a pharmacological point of view and in the data collection of ethnopharmacological surveys. From the pharmacological side, many of the problems are associated with limitations in the methods employed and misinterpretations of the bioassay results (Houghton et al., 2007; Gertsch, 2009). Nevertheless, in order to characterize the scenario we have to consider the affirmation of Gertsch (2009), which states that:

"(...) in the last 20 years few significant 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".

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0102-695X/$ - see front matter
http://dx.doi.org/10.1016/j.bjp.2014.04.003

In ethnopharmacological surveys, the problems include inadequate design for data collection, and the misinterpretation of the role medicinal plants play in the medical systems of local and indigenous communities (Etkin, 1993; Moerman, 2007; Albuquerque and Hanazaki, 2006; 2009). For instance, our current database relative to the local uses of the Brazilian medicinal flora is quite large, but it exhibits various methodological biases that limit our power of interpretation, as shown by Medeiros et al. (2013a,b). Furthermore, other authors have mentioned the fragility of taxonomic information for the species studied in ethnopharmacological studies (Bennett and Balick, 2014; Rivera et al., 2014). Considering the problems mentioned, the present manuscript focuses on issues associated with ethnobotanical/ethnopharmacological data collection of medicinal plants, a topic that has been neglected in the ethnopharmacological literature (Etkin, 1993; Reyes-García, 2010).

One should bear in mind that not all records resulting from ethnopharmacological surveys of medicinal plants can be validated from the medical point of view for several reasons: 1. Data collection does not take into consideration the full scope of the particularities of the local medical systems; 2. Records include a maladaptive culture trait (*i.e.*, therapeutic indications that do not seem to be biologically effective); and 3. Records include traits exclusively adapted to the studied population. Therefore, to promote a debate on the ethnopharmacological/ethnobotanical approach with respect to bioprospecting, henceforth designated as ethnodirected, the present article discusses the main weak points of this approach and possible alternatives to overcome its limitations, based on experiences from our research group. The topics discussed here include sampling issues, the selection of plants relevant for bioprospecting based on their popularity and versatility, and the omission of information indispensable for efficiently testing the plants.

In this manuscript we are do not consider that bioprospecting and ethnopharmacology have the same meaning, but rather we are critically reflecting on the direction commonly adopted by ethnopharmacological studies that seek to increase knowledge for the discovery of new drugs from natural products. The following considerations aim to lead to a reflection on the tools that are currently used by researchers who explicitly aim to collaborate on the above-mentioned issues.

Efficiency of the ethnodirected approach

With respect to the search for new drugs, some studies have compared ethnodirected to other approaches, the random approach in particular, which consists of randomly collecting plants for phytochemical and pharmacological screening (Balick and Cox, 1996; Khafagi and Dewedar, 2000; Oliveira et al., 2011; Slish et al., 1999; see also Cragg and Newman, 2003; 2005). In several instances the results of ethnodirected investigation are best compared to a random search for plants for specific therapeutic purposes. Khafagi and Dewedar (2000) investigated plants with antimicrobial activity that grow spontaneously in Sinai (Egypt) and found that 83% of the plants selected using the ethnodirected approach elicited such properties, while only 42% of the randomly selected plants did. Similarly, Slish et al. (1999) found that four out of 31 plants selected in Belize using the ethnobotanical approach exhibited vascular smooth muscle relaxant activity, while none among the 32 randomly collected ones exhibited this property.

However, the interpretation of the results might lead to divergent conclusions on the efficiency of the ethnodirected approach as an indicator of promising plants. For instance, Khafagi and Dewedar (2000) found that the random approach led to the identification of a larger percentage of species with strong antimicrobial activity (13.9% versus 8.3%) even though the ethnobotanical approach allowed for the identification of a larger number of plants with antimicrobial activity. Thus, one of the lessons we could draw from this example is that, in some cases, finding a small number of plants that exhibit a property of interest to a high degree might be more relevant than finding a larger number of plants with lower levels of activity. Therefore, even in cases in which the ethnopharmacological approach seems to stand out, our enthusiasm might lead us to reach unsound conclusions regarding its actual relevance for the search of new drugs. Case et al. (2006) reported on the limitations of the ethnopharmacological approach in their study on drugs used for the treatment of respiratory diseases in Manus province, New Guinea. These authors selected the informant consensus model to identify the plants with potential pharmacological activity, but found that their underlying assumptions were inadequate to predict antimycobacterial activity. Hence, they warn that ethnodirected approaches should be considered limited while wider-scoped studies are needed to elucidate their relevance or incompatibility.

Although the results from an ethnodirected approach will overlap with those of a random approach, studies indicate that there is no full agreement between the two methods in some cases. Examples can be found in the search for novel anticancer agents. Spjut (2005) reported that active species were detected more frequently (1.4- to 2.6-fold greater rate) from the group of medicinal and poisonous plants in relation to a plant species screened at random. Gyllenhaal et al. (2012) found that for many cancer cell lines, the random approach returned better results than the ethnomedical selection approach; as occurred with MCF-7 (human breast cancer) for which the random approach success rate was higher than the ethnomedical. The authors relativize their findings by arguing that the results could be due to the much higher sampling for random collections. However, according to the authors:

"The overall analysis suggests that plants collected based on ethnomedical use may in fact have a somewhat higher rate of positive bioassays on a per-species or per sample basis, although a portion of these assay results may be due to ubiquitous bioactive compounds. Ethnomedical collections in general may nevertheless play a useful role in drug discovery programs due to this elevated rate of bioactivity".

In the last two decades, few significant discoveries have been made in the field of ethnopharmacology (Gertsch, 2009). Some candidate compounds identified by the bioprospecting research-based ethnomedical approach, as developed by Shaman Pharmaceuticals, have failed, which leads to the