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Original article

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

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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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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

suggestion that an ethnodirected approach is not feasible for the development of novel drugs (Clapp and Crook, 2002). By contrast, the random approach has made effective contributions to the development of drugs, many of which are still available for the treatment of various diseases. One example is the search for new anticancer drugs conducted by the National Cancer Institute (NCI) of the United States. They employed the random approach in a program developed in the 1960s, resulting in several agents of clinical relevance such as *"taxanes and camptothecins, but their development into clinically active agents spanned a period of some 30 years, from the early 1960s to the 1990s"* (Cragg and Newman, 2005). Between 1960 and 1982 the NCI investigated about 35,000 plants before the program was suspended (Beutler et al., 2012). According to Cragg and Newman (2005):

"This plant collection program was terminated in 1982, but the development of new screening technologies led to the revival of collections of plants and other organisms in 1986, with a focus on the tropical and sub-tropical regions of the world".

The examples described above raise a question: why do scientists still assert so strongly the benefits of the ethnodirected approach versus the random one when its application in practice does not lead to significant advances in the development of particular drugs? Why do they keep on conducting studies aimed at making lists of species and therapeutic indications? We cannot give definite answers to these questions but we hypothesize that the ethnodirected approach is perhaps only useful for particular types of diseases. Only well-conducted and rigorous ethnopharmacological/ethnobotanical studies might clarify these issues.

Influence of sampling and informant selection

Ethnodirected studies of medicinal plants quite often exhibit sampling problems causing bias in their results. During the review of studies conducted in Brazil, Medeiros (2012) found that most of them had patent sampling flaws, the most frequent being the following: 1. lack of information on the universe (U) or sample (N) on which the survey of the human communities was grounded; and 2. lack of information on the U or N of a specific group (*e.g.*, folk healers), in intentional samples based on specialists from the studied communities.

Therefore, studies seeking to investigate the knowledge possessed by "local specialists" (*e.g.*, folk healers) must establish with full certainty that they are truly dealing with such. Contrariwise, when there are no well-defined criteria for intentional selection the results might not reflect the investigators' desires. Similarly, studies that rely on the informants' consensus as an indicator of the most significant or popular species must take care to ensure an appropriate application of that model and select truly representative samples of the community. Conversely, non-representative samples might point certain plants as the most popular or versatile therapeutic indications when they are actually not.

In addition, many studies have shown that the local knowledge on medicinal plants is not homogeneous, but rather it varies among the actors of a local community according to their age, gender, income, social role and intra-cultural acculturation differences (Voeks and Leony, 2004; Voeks, 2007; Camou-Guerrero et al., 2008). In such cases, the social actors who provide us information ought to be accurately identified to increase the success of selecting plants for bioprospecting purposes. For instance, investigators who focus on gender and age tend to emphasize the role of women and elders because they are considered to possess greater knowledge on medicinal plants. According to such authors, the reason that women possess such knowledge is attributed to their role in home and family care, and in the case of the elderly the reason is attributed to their longer interaction with the environment (Begossi et al., 2002; Voeks and Leony, 2004; Silva et al., 2011).

Such patterns must not be misinterpreted and then be used as criteria for informant selection in later studies. Indeed, some authors have shown that the "stock of knowledge" of individuals from different age ranges might differ and that the knowledge of older individuals might actually be in decline (Silva et al., 2011). As a consequence, the assumption that older individuals are systematically better "informants" for studies of medicinal plants might be mistaken because people appear to employ different repertoires of medicinal plants according to their age.

As regards to gender, some studies, such as the one conducted by Voeks and Leony (2004) in Brazilian rural communities, have emphasized the role of women because they are considered to possess greater knowledge of medicinal resources compared with men. However, other studies, such as the ones by Giraldi and Hanazaki (2010) and Poderoso et al. (2012), conducted in communities in Southeastern Brazil, have shown that such differences might not occur. Authors who have found differences suggest that they are associated with the role women play as homemakers, which place them in charge of the family's basic healthcare, while men focus on other activities.

Based on the roles the various social actors play and their knowledge of health care, we formulated the following suggestions for sample selection to optimize bioprospecting strategies: 1. Researchers should clearly establish the goals they aim to attain, *e.g.*, *"Do I want to study one single and well-defined therapeutic activity, or the full range of knowledge of the local medical system?"*; 2. Consideration of age, gender and social function of individuals particular relevance in the selection of the informants who might effectively supply the expected information; and 3. Although thorough knowledge of the existing international literature on the subject is necessary to give support to the study design, investigators should be careful not to restrict the sample as previous patterns detected in the literature. At times, time and financial restrictions induce us to look for faster strategies without taking into consideration that such behavior might impair the power of inference for the data.

Searching for the most popular plants as a bioprospecting tool

Most ethnodirected studies identify the plants mentioned by the largest number of individuals, the most versatile plants (the ones with many potential therapeutic uses), or a combination of both criteria as the most interesting for

bioprospecting purposes. The ethnobiological literature describes a wide variety of quantitative indicators to establish such indications (Medeiros et al., 2011), which are often used; however, awareness of their limitations is appropriate. The first criterion has proven to be inadequate in some studies seeking to confirm the pharmacological activity of certain plants based on the traditional knowledge, as in the above-mentionedstudy by Case et al. (2006). The authors used the informants' consensus to select species from New Guinea of potential pharmacological interest for the treatment of respiratory diseases; however, they did not find such activity in the plants with highest levels of consensus. Many of the quantitative indicators suggested by the scientific literature were proposed with the purpose of revealing plants important for a given culture. The authors that applied those indices to indicate potential species for bioprospecting efforts were based on the idea that a plant relevant for a culture, with great cultural consensus is more likely to present biological activities. Furthermore, most of these indices do not consider the particularities of the plants used in mixtures.

The expectation in the use of the above-mentioned criteria is usually to obtain the same lists of plants as reported in previous studies, oftenly highly popular exotic or native plants with wide local distribution. For that reason, paying attention to plants that are mentioned less frequently might be relevant for bioprospecting because low popularity is not a synonym for lack of efficacy. The high presence and importance of a plant in a local medical system is not necessarily linked to its pharmacological effect, but can be due several other factors. Moerman (2007) discusses that a plant used for treatment can be widespread in a community and may not contain any biologically active compounds. Instead, the symbolic meaning of the treatment within the culture can alter the patient's physiology, acting similar to a "placebo," and appears effective because of the cultural validation and the local belief in its effectiveness. In addition, ecological factors, such as environmental and seasonal availability, can influence the importance of medicinal plants. For example, Molares and Ladio (2009) mentioned that species located geographically closer to a community may be used more oftenly, imparting greater importance to this group of plants.

The data on less popular plants, inadequately disseminated within a social group for several reasons, might provide valuable information for bioprospecting strategies. For instance, Reyes-García et al. (2008) observed that the low prestige of a given community member providing observations about plant species might directly interfere with the reception and cultural acceptance of that information by other community members. As a consequence, the dissemination of some information might remain restricted due to of forces that hinder its circulation (*e.g.*, family secrets) or block its reception (*e.g.*, low prestige of the information source).

On this view, such plants might be rarely mentioned for reasons like: a, the plant might have recently entered the local medical system (recent introduction); b, the plant is being excluded from the local medical system; c, the plant is indicated for the treatment of diseases affecting specific social actors (*e.g.*, age- or gender-specific diseases) and thus, it is not known by the overall population; d, the popularity of the plant in the local medical system might have always been low (restricted to a few families or individuals); or e, the low availability or the difficulty in accessing the plant in the environment.

As a result, rarely mentioned plants might actually be highly valuable from the bioprospecting perspective because they bear the additional advantage of being less well-studied and could serve as the basis for further systematic quests for medicinal products. There is a necessity to test differences in the pharmacological activity between the most and least popular plants.

Problems related to data collection and recording therapeutic indications

At times, testing of the biological activity of medicinal plants based on ethnodirected data is hindered by the lack of detail of the information gathered from local communities. Superficial data collection and interpretation is a serious mistake that one finds reproduced in many published studies. The lack of attention usually paid to therapeutic indications is noteworthy because it has a negative impact on the success of approaches requiring accurate and precise information. Many studies do not distinguish among the plants that serve to cure a disease, the ones that relieve its symptoms, and the ones that are able to prevent its occurrence. That distinction, however, has paramount importance in bioprospecting and thus should receive more attention.

Some studies have demonstrated the relevance of investigating the concept of disease held by the community (Beiersmann et al., 2007; Reyes-García, 2010). The choice of therapies by human groups is related to how they recognize and classify diseases (Reyes-García, 2010), so an accurate understanding of those features is key for the planning of future bioprospecting strategies. One simple method to investigate the local perception of a given disease is to ask the informants how it is recognized. This strategy identifies the symptoms that are directly associated with the disease. For instance, the activity of a plant mentioned in the treatment of various diseases mainly associated with the symptom pain might reduce the release of chemical mediators related to the production of pain.

More than a few studies have merely recorded the medicinal properties of plants without investigating the local notions of disease, which might be widely divergent from Western ideas. This situation is illustrated by the study by Ferreira Júnior et al. (2011), which investigated the plants from the Brazilian Caatinga used to treat inflammation. Although inflammation is considered as uniform in the ethnobotanical literature, the authors recorded 37 different categories of that condition as perceived by the community, and characterized it as a result of 26 different symptoms. Interestingly, the plants used for the treatment of the various categories exhibited broad differences, thus showing that inflammation could not be considered a homogeneous "category" and that the studies might be strongly biased. Ferreira Júnior et al. (2011) also found that some conditions identified as "inflammation" by the investigated community were not thus understood in Western

conventional medicine. That finding makes the elucidation of local notions of disease even more relevant. Similarly, Oliveira et al. (2011) paid attention to local notions of disease. While investigating the plants used by Quilombola communities in the state of Pará (Northern Brazil) for the treatment of respiratory diseases, the authors found that tuberculosis was called "enfeeblement" and so the identification of the local notions had direct implications for ethnodirected studies.

Beiersmann et al. (2007) studied the plants used to treat malaria in seven villages in Burkina Faso and identified four variations of disease, each one having its particular treatment, including the use of plants and/or conventional Western therapies. This finding further showed that studies that do not include a thorough understanding of the diseases mentioned by a given human group are at risk of collecting biased data and of using the ethnodirected information incorrectly. In this case, the researcher took notice of these differences and as a result errors were minimized in the process of noting points of convergence and divergence between local and biomedical systems.

The procedures for collecting data on the medicinal plants at a given site might exert a strong influence on the success of pharmacological studies. The informants might apply several criteria to the indication or use of a given species for medicinal purposes, including a variable that is often omitted in studies, the local perception of the efficacy of treatment (Ferreira Júnior et al., 2011; 2012). The latter might supply valuable hints for bioprospecting purposes because certain species might be preferentially reported as a function of their perceived efficacy. Therefore, the investigations of these species increase the odds of success in future studies. In addition, it is also worth investigating the informants' notion of the efficacious use of a plant for a given purpose (Etkin, 1988).

It must be considered that the issues we pointed out regarding the misinterpretation of the concepts of illnesses in other cultures happen mostly on societies whose knowledge has not still been decoded. One of the reviewers of this article left us the following reflection:

"In some codified traditional medicine system like Ayurveda and Unani, many of the traditional disease terms have been mapped to western medicine concept. Concepts and symptomology associated with the Traditional Chinese Medicine have already been started incorporating in the WHO's ICD versions."

Final considerations

We sought to call the attention to some of the weak points in ethnodirected approaches that might be overcome in the design of studies and interpretation of data. As a rule, the collection of ethnobotanical and ethnopharmacological data demands appropriate training and sound knowledge of the international literature from investigators of theoretical and methodological contributions to this field. Although significant methodological manuals, including those by Martin (1995) Alexiades (1996) and more recently by Albuquerque et al. (2010; 2014), and some important critical reviews (*e.g.*, Gertsch, 2009; Heirinch et al., 2009), they do not appear to have exerted much influence on the quality of the published studies (Albuquerque, 2013) on recent years. Therefore, a major lesson to be learned from the discussion above is that researchers must reconsider projects aiming at a mere elaboration of lists of species and their therapeutic indications. Such lists, and the various sources of bias they include, are increasingly showing their lack of relevance for bioprospecting purposes. The limitations pointed out in this study are not inherent to ethnopharmacological research, but rather happen due to the lack of knowledge on the chosen tools. Every single scientific method has limitations, which leaves the researchers the responsibility for applying theoretical and practical knowledge to make the most appropriate choices, as well as to draw pertinent conclusions

Authors' contributions

UPA designed the study. All the authors contributed to critical reading and writing of the manuscript, and have read the final manuscript and approved the submission.

Conflicts of interest

The authors declare no conflicts of interest.

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