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New strategies for drug discovery in tropical forests based on ethnobotanical and chemical ecological studies

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ABSTRACT

Ethnopharmacological relevance: Hypotheses from ethnobotany and chemical ecology can increase our ability to predict the pharmaceutical potential of tropical flora. In order to illustrate how bioprospecting studies can benefit from the incorporation of these hypotheses, especially in tropical dry forests, we discuss evidence from ethnobotanical studies that examine hypotheses about the ecology of plant defense against herbivory.
Materials and methods: We focus on two hypotheses regarding defense patterns in plants—the plant apparency hypothesis and the resource availability hypothesis—and analyze how these can help us understand the use of medicinal plants by traditional communities.
Results: The evidence suggests that medicinal plants in the dry forest are a rich source of drugs in which phenolic compounds, especially tannins, are directly responsible for the therapeutic activity. Phenolic compounds and their potential therapeutic activity are likely good candidates for bioprospecting efforts.
Conclusion: We believe that following strategies to link ethnobotanical and chemical ecological approaches will increase the efficiency of bioprospecting studies in tropical forests.

1. Introduction

The rapid conversion of tropical forests for human use threatens not only biodiversity itself but also local human communities, endangering traditional lifestyles and, by extension, the accumulated knowledge of the uses of tropical organisms. Addressing this problem requires urgent efforts towards increasing our understanding of tropical biodiversity. However, we believe that it is important not only to increase the number of bioprospecting studies but also, above all, to increase our ability to predict the factors that make a particular organism (plant, microorganism or animal) a promising candidate for further investigation.

Over the past few years, scientists have pursued a variety of phytochemical and pharmacological approaches to investigating the pharmaceutical potential of tropical organisms, but few studies have actually resulted in the development of new drugs (see Gertsch, 2009). This lack of success may be due to multiple causes, from the absence of systematic, continuous studies (which increases research costs and effort) to inappropriate experimental designs and premature conclusions regarding the potential of particular plant extracts (Houghton et al., 2007; Gertsch, 2009). The great challenge is not to advance such approaches, but rather to coordinate efforts and develop studies that are conducted and interpreted based on available theories in order to increase our predictive power regarding the biological phenomena of interest.

Interestingly, although the number of flora bioprospecting studies has increased, we still understand very little about the factors that can increase the efficiency of such studies. Such factors have the potential to optimize scientific research in terms of time, money and human resources. The role of ethnodirected (ethnobotanical and ethnopharmacological) studies in this context is undisputed, as the search for new drugs based on traditional knowledge has been shown to be effective by several authors (see studies in Albuquerque and Hanazaki, 2006). Some studies focus on the process of introducing a plant into a pharmacopoeia and the selection criteria adopted from a cultural perspective. However, if we acknowledge that traditional botanical knowledge may be adaptive, it is reasonable to assume that variables other than culture might explain the development of a local pharmacopoeia. Stepp and Moerman (2001) and Stepp (2004) made an effort in this direction by observing that herbaceous plants are the most common ingredients of traditional pharmacopoeias. This realization lead scientists to propose that hypotheses such as the plant apparency hypothesis (usually appraised in chemical ecological studies) might explain the predominance of herbs used for medicinal purposes over plants with other growth habits.

Another relatively recent approach is that of chemical ecology, which seeks to advance the discovery of new drugs based on predictions of the distribution of plant secondary metabolites. These predictions are in turn based on widely accepted theories in

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ecology, especially those that attempt to understand the investment of plants in anti-herbivore defense (see examples in Donaldson and Cates, 2004). Coley et al. (2003) concluded that ecological theories of plant defense can aid in the discover of the compounds with biological activity against human disease targets. For example, these authors found that young leaves showed higher activity than mature leaves in some bioassays. Nevertheless, comparative studies are required to confirm whether this approach is in fact more successful than ethnodirected, ethological, random or chemosystematic studies.

In this review, we aim to illustrate how bioprospecting studies can benefit from the increase in our ability to predict the pharmaceutical potential of tropical plants, especially in tropical dry forests, with the incorporation of theoretical hypotheses from ethnobotany and chemical ecology. We focus on two hypotheses regarding defense patterns in plants—the plant apparency hypothesis and the resource availability hypothesis—and analyze how these can help us understand the use of medicinal plants by traditional communities.

2. Plant defense hypotheses

The plant apparency hypothesis, presented by Feeny (1976), revolutionized the field of ecology with the proposal of a basis for the prediction of how chemical defenses are distributed in plants (Endara and Coley, 2010). Feeny (1976) proposed that plants can be categorized as either apparent or unapparent. Apparent plants, such as long-lived trees, are expected to invest "quantitatively" in chemical compounds of high molecular weight, such as tannins. In contrast, unapparent plants, such as short-lived ephemeral herbs, are expected to invest "qualitatively" in potent defenses that occur in low concentration in plant tissues, such as alkaloids (Albuquerque and Lucena, 2005). Stepp (2004) argued that this investment in qualitative defenses would explain the large representation of herbs in the pharmacopoeias of traditional communities around the world. According to this notion, as most herbs are short-lived and ephemeral (unapparent), they accumulate highly bioactive compounds that are useful for treating human diseases. Based on this principle, we should focus our bioprospecting efforts on herbaceous plants used by traditional communities.

Another hypothesis concerning the distribution of plant defenses is the resource availability hypothesis. This hypothesis is based on the cost/benefit ratio of defenses (Endara and Coley, 2010). According to this hypothesis, the variation in the growth rates across species, which is affected by resource availability, is partly responsible for the differential investment in anti-herbivore defense. Simply put, the level of investment in defense depends on whether the plant is fast-growing or slow-growing and thus on resource availability in the habitat. Plants in resource-rich habitats usually have fast growth rates, and for such plants, it is expected that investment in growth is more cost-effective than investment in defense. In habitats with low resource availability, plants are expected to invest more in anti-herbivore defense than in growth.

Four predictions of the resource availability hypothesis are the following: "(i) species adapted to resource-rich environments have intrinsically faster growth rates than species adapted to resource-poor environments; (ii) fast-growing species have shorter lifetimes than slow-growing species; (iii) fast-growing species have lower amounts of constitutive defenses than slow-growing species; and (iv) fast-growing species support higher herbivory rates than slow-growing species" (Endara and Coley, 2010, p. 4). Applied to the relationship between people and plants, especially considering prediction (iii), this hypothesis suggests that the medical potential of a plant species, which depends on its chemical composition, is associated with its growth rate and, therefore, with the availability of resources in its habitat.

Table 1
Predicted characteristics of the pharmacopoeias of local communities based on the plant apparency hypothesis (PAH) and the resource availability hypothesis (RAH).

Pharmacopoeia characteristic	Apparent plants (PAH)/slow-growing species (RAH)	Unapparent plants (PAH)/fast-growing species (RAH)
Cultural importance for local communities	Low	High
Bioactivity of plants	Low	High
Occurrence of secondary metabolites of high molecular weight, e.g., tannins	High	Low
Occurrence of secondary metabolites of low molecular weight, e.g., alkaloids	Low	High
Variety of chemical defenses	High	Low

Thus, to summarize: ". . .*what a plant invests in defense, especially chemical defenses, varies from one habitat to another, and within habitats. The apparency hypothesis proposes that this investment reflects how abundant a plant is, according to season and area. The resource availability hypothesis postulates that plant defenses are largely determined by the availability of nutrients, water and light, and that the investment level will be higher where resources are more limiting*" (Barone and Coley, 2002, p. 481).

3. Application of ecological theories of plant defense to the relationship between people and plants

In order to analyze the extent to which ecological theories of plant defense can explain the compositions of pharmacopoeias of local communities in the tropics, we next examine whether these theories accurately predict the characteristics of these pharmacopoeias (Table 1).

To the extent that the presence of plants in a particular pharmacopoeia is related to their ecological traits, we would expect unapparent plants to predominate in these local medical systems because of their predicted propensity to produce toxic compounds, especially alkaloids and terpenes. Such plants are expected to exhibit a wide range of biological activity of medical and pharmaceutical interest. The lower quantities of chemical defenses in these plant groups are explained by different factors in the plant apparency hypothesis and the resource availability hypothesis. Here, we review the currently available evidence that ecological traits predict pharmacopoeia characteristics, generated by ethnobotanical studies conducted in rural communities of northeastern Brazil, particularly in semi-arid habitats marked by strong climate seasonality.

3.1. Relative cultural importance of apparent and unapparent plants

Comparative studies of the native species used for medicinal purposes by local communities in the Caatinga biome (tropical dry forest) of northeastern Brazil do not support the prediction that unapparent plants have greater cultural importance to such communities (Almeida et al., 2005, 2011). In general, growth habit is not a good predictor of the relative importance of a plant for medicinal use by traditional communities either in the Caatinga or in the Atlantic Forest (Almeida et al., 2011), and woody plants are usually more important for communities living in seasonal habitats (Albuquerque, 2006; Alencar et al., 2010; Almeida et al., 2011). Several studies conducted in the semi-arid region of Brazil support the finding that woody plants are important for local communities