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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

(Albuquerque et al., 2007; Almeida et al., 2011; Cartaxo et al., 2010). Albuquerque (2010) suggested that the preferential use of perennial resources has been selected as a strategy to ensure continued access to resources, both because herbs and the leaves of deciduous woody plants are available for only a short time (usually 2–4 months) in habitats such as the Brazilian Caatinga and because supply is often unpredictable due to yearly variation in climate conditions. People in the Caatinga frequently use the stem bark of woody plants (a perennial structure; Ferreira Júnior et al., 2011) for different "therapeutic targets", even when other structures (leaves or herbs) are available for the same purpose. Monteiro et al. (2006a,b) found evidence that people typically use the stem bark of a medicinal plant rather than the leaves, even when the latter have a higher concentration of the active compounds likely responsible for the desired therapeutic activity. These findings have significant implications for bioprospecting studies because it is possible that in highly seasonal habitats, where deciduous plants are abundant, people have not necessarily selected the resources with the highest biological activity. This refutes one of the basic principles that guide bioprospecting studies based on local knowledge.

3.2. The relative investment of apparent and unapparent plants in qualitative defenses

The findings from studies in seasonal habitats do not fully support the prediction that unapparent plants (e.g., herbs) invest more heavily in qualitative defenses than do apparent plants (e.g., trees). In some studies, a higher occurrence of qualitative investment has been observed in apparent plants (Almeida et al., 2005, 2011, in press; Alencar et al., 2009). The major conclusion to be drawn from these studies is that plant apparency is not a good predictor of the presence of certain classes of chemical compounds. Nevertheless, the findings by Almeida et al. (2011) produced new insights. These authors tested whether the apparency hypothesis could explain the selection of medicinal plants by local populations in the Caatinga (dry forest) and Atlantic Forest (humid forest) habitats. Although these authors unequivocally rejected the apparency hypothesis, an interesting pattern emerged from the data: plants in the semi-arid region invested in quantitative defenses (based on phenolic compounds such as tannins) significantly more than did plants in the Atlantic Forest, where a high occurrence of qualitative compounds (e.g., alkaloids) was observed, especially in unapparent plants. Only flavonoids were notably frequent in plants from both regions. This is an interesting pattern because even though some species were observed in both sites, there was a trend toward phenotypic plasticity in secondary metabolism. Herms and Mattson (1992) argued that this plasticity may be adaptive. The optimal use of plants with such phenotypic plasticity requires a cost/benefit analysis under different habitat conditions. Based on experimental evidence, Herms and Mattson (1992) suggested that this variation in secondary metabolism results from "regulated changes in biosynthetic pathways in response to environmental cues rather than an incidental response to environmental variation". In other words, this biosynthetic pathway regulation may be influenced by ecogeographic variation (e.g., variation between ecosystems) in factors such as light intensity, water availability and the carbon–nitrogen.

The two predictions of the plant apparency hypothesis discussed here do not reliably explain the selection of medicinal plants in traditional pharmacopoeias of seasonal habitats, indicating that other factors also influence the selection of such plants. In the context of herbivory studies, however, the apparency hypothesis has gained wide acceptance and is supported by many empirical studies (Endara and Coley, 2010). Although the predictions of the hypothesis, when applied to ethnobotanical studies, are thus far rejected by the existing evidence, additional studies using different plants and conducted in different habitats are required.

3.3. The investment of fast-growing and slow-growing plants in chemical defenses

The resource availability hypothesis predicts that fast-growing plants do not invest heavily in chemical defenses. Alencar et al. (2010) found no differences in chemical diversity between woody (considered apparent in that study) and herbaceous (unapparent) medicinal plants used in a semi-arid region of Brazil. Moreover, studies conducted in the Caatinga have shown that regardless of plant growth habit, phenolic compounds, especially tannins, are more abundant and common than other compounds (Almeida et al., 2005, 2011; Alencar et al., 2009). However, in a comprehensive review, Endara and Coley (2010) observed that fast-growing plants do in fact invest less in chemical defenses than do slow-growing ones. Nevertheless, this prediction does not appear to hold for the components of local flora that are harvested for medical use.

Data from Alencar et al. (2010) provide interesting insight into a separate but related issue. These authors found a significant difference in chemical diversity between native and exotic species used for medicinal purposes. This finding supports the diversification hypothesis (Albuquerque, 2006), which predicts that local communities introduce exotic plants into their repertoire of native medicinal plants in order to diversify the chemicals available in their pharmacopoeias and, therefore, their therapeutic targets. This notion is also supported by the findings of Almeida et al. (2011, in press) that different habitats have different phytochemical profiles and that different biosynthetic pathways may be regulated by ecogeographic variation, as is illustrated by the production of high-molecular-weight compounds such as tannins in semi-arid and arid habitats (see Gottlieb et al., 1996).

Another prediction of the resource availability hypothesis is that species in resource-rich environments have faster growth rates than species in resource-poor environments (Endara and Coley, 2010). In the Caatinga habitats, which are characterized by high levels of light intensity and water stress, woody plants have slower growth rates than do herbs, which exhibit fast growth rates over a short period of time in association with the arrival of the rainy season. In such seasonal habitats, we might also expect to find lower levels of certain chemical compounds in the leaves of woody plants, which grow only in the rainy season, than in other, slow-growing perennial structures, such as stem bark. *Anadenanthera colubrina* (Vell.) Brenan (yopo, angico – Fabaceae) follows this pattern and exhibits a higher concentration of tannin in the stem bark than in the leaves, whereas *Myracrodruon urundeuva* Fr. All. (aroeira – Anacardiaceae), which grows in the same habitat, adopts a different strategy (Monteiro et al., 2006b).

3.4. Bioactivity in fast-growing and slow-growing plants

Coley et al. (2003), using an ecological approach in a bioprospecting study, found a weak correlation between plant growth rate and bioactivity (activity against three cancer cell lines, leishmaniasis, malaria and Chagas disease). In that study, extracts from shrubs and trees were the most active. Similarly, Donaldson and Cates (2004) observed higher toxicity against epithelial carcinoma cell lines in the extracts of perennial evergreen leaves than in perennial deciduous leaves or perennial herbs and lower toxicity in annual species. To the best of our knowledge, no studies have evaluated this prediction in an ethnobotanical context.

4. Patterns, trends and perspectives

Although the evidence presented here is limited in that it was produced by one research group for one habitat type (Caatinga, or Brazilian semi-arid habitat), it allows us to make some inferences.

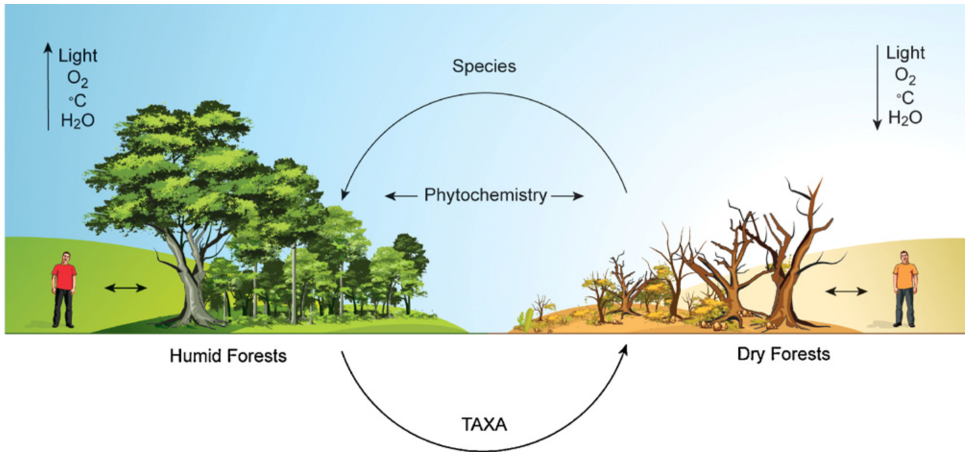

Fig. 1. Schematic illustration of the relationship between people and plants in dry and humid forests and the role of biotic and ecogeographic factors in trends in chemical and biological diversification.

Although the plant apparency and resource availability hypotheses offer plausible scenarios for hypothesis testing in ethnobotanical research, they do not appear to fully explain the choices of local communities in building their pharmacopoeias. This does not mean that these hypotheses should be discarded; rather, it indicates that further studies incorporating different predictions are required.

Fig. 1 summarizes the main trends in the studies analyzed, which represent insights into bioprospecting efforts, at least in the habitats studied. These trends are as follows: (1) ecogeographic variation appears to favor the production of high-molecular-weight compounds, such as polyphenols, in dry forests; (2) this has led to "metabolic specialization" in plants that naturally occur in these habitats, resulting in, for example, high concentrations of phenolic compounds in Caatinga plants at the expense of other compounds; (3) medicinal species in humid forests such as the Atlantic Forest appear to produce more highly toxic compounds such as alkaloids; and (4) because of this possible "metabolic specialization" in the plants of particular ecosystems, human populations have introduced species for the diversification of "therapeutic targets". One test of this last point would be to evaluate pharmacopoeia structure in terms of "therapeutic targets", taking into account both native and introduced plant species.

We can discuss some of the emerging patterns from an ecological, chemical and ethnobotanical standpoint with reference to Fig. 1, which is a reinterpretation of a scheme proposed by Gottlieb et al. (1996). Based on data from Brazil, Gottlieb and Borin (1999, p. 1639) note the following regarding the connection between metabolism and biogeography:

1. *Shikimic acid derived natural products, such as lignans, neolignans and benzylisoquinoline alkaloids are produced in great frequencies by species in forests, while acetic acid derived natural products, such as steroids, polyacetylenes and pyrrolizidine alkaloids, occur in great frequencies in cerrado species.*
2. *Chemistry of forests is characterized by stronger variations of shikimate derivatives, while chemistry of cerrados is characterized by stronger variations of acetate derivatives. Furthermore, forests are distinguished from cerrados by strikingly more feeble variations of total metabolic profiles.*
3. *The two types of vegetation are separated by ecological boundaries. Such ecotones, possessing creative potential, interrupt abruptly all chemical gradients.*

Gottlieb et al. (1998) argued that the phytochemical changes observed from one biome to another reflect sudden ecogeographic transitions (ecotones), rather than the gradual latitudinal variation that was previously believed to exist. These authors suggest that the highest levels of chemical complexity will be observed in the transition areas between biomes. In humid forests, oxidative levels are higher than in dry forests due to the higher availability of light and water, and more solar energy is used in the former (Fig. 1). In this context, the enhanced shikimate pathway found in humid forests results in greater production of lignified biomass (Gottlieb et al., 1996). In contrast, in dry forests (exemplified by the Cerrado biome), lignin precursor molecules can be replaced by polyphenols. This relationship is reversed, however, with regards to the diversity of higher taxa. This supports the ethnobotanical finding that high levels of phenolic compounds occur in the semi-arid region of northeastern Brazil. Moreover, human populations coexist with lower species diversity in dry forests than in humid forests. The following general scenario emerges when we evaluate all of the above data on dry forests: the diversity available to human communities in these forests is lower than that in humid forests and includes a predominance of phenolic compounds (with some variation in secondary metabolism according to ecogeography). Thus, the native plants used for medicinal purposes appear to have, in a sense, a "specialized metabolism" that restricts their potential (phenol-based) range of therapeutic activity. This situation, along with the range of chemical strategies developed by plants to reduce the impacts of herbivory, results in a complex scenario.

There is evidence of a correlation between the production of phenolic compounds and the attribution of therapeutic value to medicinal plants by people in the Caatinga. For example, Araújo et al. (2008) concluded that plants indicated for the treatment of inflammation have high levels of tannic compounds in comparison to plants indicated for other therapeutic uses. More recently, Siqueira et al. (2012) found the same to be true of plants popularly listed as antimicrobials. Across habitats, Almeida et al. (in press) found that medicinal plants harvested in the Caatinga exhibited higher antimicrobial activity than plants of the same species harvested in the Atlantic Forest. Moreover, plants harvested in the Caatinga usually exhibit greater versatility and stronger inhibition of sensitive microorganisms. Thus, the Caatinga may be a promising environment for bioprospecting research on antimicrobial compounds. 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.

Based on the scenario discussed here, we suggest the following strategies for research and bioprospecting:

1. Predictions of the resource availability hypothesis should be tested based on the use of plants by human communities. The available evidence, though scarce and thus far geographically limited, suggests that traditional human populations may adjust the use of resources in their medical practices according to the growth and defense strategies of plants.
2. Considering the metabolic specialization evident in Caatinga plants, bioprospecting research in this region should focus on the biological activity of phenolic compounds, especially polyphenols. Given the ability of tannins to interact with different proteins, these compounds are promising in terms of their potential for unpredicted, specialized activity. This would allow local communities in the Caatinga to adjust their medical systems according to this metabolic specialization. At the same time, this specialization may require that human communities introduce plants to fill gaps in their pharmacopoeias (as stated in the diversification hypothesis).
3. If chemical diversification and specialization prove to be highest in ecotones, as has been suggested, then chemical and ethnobotanical studies should be conducted in these areas not only to understand how human populations have adapted to such conditions but also to find clues for bioprospecting.

We believe that following these strategies to link ethnobotanical and chemical ecological approaches will increase the efficiency of bioprospecting studies in tropical forests.

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References

Albuquerque, U.P., Lucena, R.F.P., 2005. Can apparency affect the use of plants by local people in tropical forests? Interciencia 30, 506–511.

Albuquerque, U.P., 2006. Re-examining hypotheses concerning the use and knowledge of medicinal plants: a study in the Caatinga vegetation of NE Brazil. Journal of Ethnobiology and Ethnomedicine 2, 30.

Albuquerque, U.P., Hanazaki, N., 2006. As pesquisas etnodirigidas na descoberta de novos fármacos de interesse médico e farmacêutico: fragilidades e perspectivas. Revista Brasileira de Farmacognosia 16, 678–689.

Albuquerque, U.P., Medeiros, P.M., Almeida, A.L.S., Monteiro, J.M., Lins Neto, E.M.F., Melo, J.G., Santos, J.P., 2007. Medicinal plants of the Caatinga (semi-arid) vegetation of NE Brazil: a quantitative approach. Journal of Ethnopharmacology 114, 325–354.

Albuquerque, U.P., 2010. Implications of ethnobotanical studies on bioprospecting strategies of new drugs in semi-arid regions. The Open Complementary Medicine Journal 2, 21–23.

Alencar, N.L., Araújo, T.A.S., Amorim, E.L.C., Albuquerque, U.P., 2009. Can the apparency hypothesis explain the selection of medicinal plants in an area of Caatinga vegetation? A chemical perspective. Acta Botanica Brasilica 23, 910–911.

Alencar, N.L., Araújo, T.A.S., Amorim, E.L.C., Albuquerque, U.P., 2010. The inclusion and selection of medicinal plants in traditional pharmacopoeias – evidence in support of the diversification hypothesis. Economic Botany 64, 68–79.

Almeida, C.F.C.B.R., Silva, T.C.L., Amorim, E.L.C., Maia, M.B.S., Albuquerque, U.P., 2005. Life strategy and chemical composition as predictors of the selection of medicinal plants from the Caatinga (Northeast Brazil). Journal of Arid Environments 62, 127–142.

Almeida, C.F.C.B.R., Amorim, E.L.C., Albuquerque, U.P., 2011. Insights into the search for new drugs from traditional knowledge: an ethnobotanical and chemical-ecological perspective. Pharmaceutical Biology 49, 864–873.

Almeida, C.F.C.B.R., Cabral, D.L.V., Amorim, E.L.C., Araújo, J.M., Albuquerque, U.P. Comparative study of the antimicrobial activity of native and exotic plants from the Caatinga and Atlantic Forest selected through an ethnobotanical survey. Pharmaceutical Biology, doi:10.3109/13880209.2011.596205, in press.

Araújo, T.A.S., Alencar, N.L., Amorim, E.L.C., Albuquerque, U.P., 2008. A new approach to study medicinal plants with tannins and flavonoids contents from the local knowledge. Journal of Ethnopharmacology 120, 72–80.

Barone, J.A., Coley, P.D., 2002. Herbivorismo y las defensas de las plantas. In: Guariguata, M.R., Kattan, G.H. (Eds.), Ecologıa y Conservacion de Bosques Neotropicales. Libro Universitario Regional, Costa Rica, pp. 465–492.

Cartaxo, S.L., Souza, M.M.A., Albuquerque, U.P., 2010. Medicinal plants with bioprospecting potential used in semi-arid northeastern Brazil. Journal of Ethnopharmacology 131, 326–342.

Coley, P.D., Heller, M.V., Aizprua, R., Araúz, B., Flores, N., Correa, M., Gupta, M., Solis, P.N., Ortega-Barría, E., Romero, L.I., Gómez, B., Ramos, M., Cubilla-Rios, L., Capson, T.L., Kursar, T.A., 2003. Using ecological criteria to design plant collection strategies for drug discovery. Frontiers in Ecology and Environment 1, 421–428.

Donaldson, J.R., Cates, R.G., 2004. Screening for anticancer agents from Sonoran desert plants: a chemical ecological approach. Pharmaceutical Biology 42, 478–487.

Endara, M.-J., Coley, P.D., 2010. The resource availability hypothesis revisited: a meta-analysis. Functional Ecology, doi:10.1111/j. 1365-2435.2010.01803.x.

Feeny, P.P., 1976. Plant apparency and chemical defense. In: Wallace, J.W., Mansell, R.L. (Eds.), Recent Advances in Phytochemistry. Plenum Press, New York, pp. 1–40.

Ferreira Júnior, W.S., Ladio, A.H., Albuquerque, U.P., 2011. Resilience and adaptation in the use of medicinal plants with suspected anti-inflammatory activity in the Brazilian Northeast. Journal of Ethnopharmacology 138, 238–252.

Gertsch, J., 2009. How scientific is the science in ethnopharmacology? Historical perspectives and epistemological problems. Journal of Ethnopharmacology 122, 177–183.

Gottlieb, O.R., Kaplan, M.A.C., Borin, M.R.M., 1996. Biodiversidade – um enfoque químico-biológico. Editora UFRJ, Rio de Janeiro.

Gottlieb, O.R., Borin, M.R.M.B., 1999. Bioconnectivity: a blueprint for biodiversity? Pure and Applied Chemistry 71, 1635–1642.

Gottlieb, O.R., Borin, M.R.M.B., Pagorro, M.L.A.C., Zocher, D.H.T., 1998. Biodiversidade: o enfoque interdisciplinar brasileiro. Ciência & Saúde Coletiva 3, 97–102.

Herms, D.A., Mattson, W.J., 1992. The dilemma of plants: to grow or defend. The Quarterly Review of Biology 67, 283–335.

Houghton, P.J.M.-J., Howes, M.-J., Lee, C.C., Steventon, G., 2007. Uses and abuses of in vitro tests in ethnopharmacology: visualizing an elephant. Journal of Ethnopharmacology 110, 391–400.

Monteiro, J.M., Albuquerque, U.P., Lins Neto, E.M.F., Araújo, E.L., Amorim, E.L.C., 2006a. Use patterns and knowledge of medicinal species among to rural communities in Brazilĩs semi-arid northeastern region. Journal of Ethnopharmacology 105, 173–186.

Monteiro, J.M., Lins Neto, E.M.F., Albuquerque, U.P., Araújo, E.L., Amorim, E.L.C., 2006b. The effects of seasonal climate changes in the Caatinga on tannin levels in *Myracrodruon urundeuva* and *Anadenanthera colubrina*. Revista Brasileira de Farmacognosia 16, 338–344.

Siqueira, C.F., Cabral, D.L., Peixoto Sobrinho, T., Amorim, E.L.C., Melo, J.G., Araújo, T.A.S., Albuquerque, U.P., 2012. Levels of tannins and flavonoids in medicinal plants: evaluating bioprospecting strategies. Evidence-Based Complementary and Alternative Medicine 2012, 434782.

Stepp, J.R., 2004. The role of weeds as sources of pharmaceuticals. Journal of Ethnopharmacology 92, 163–166.

Stepp, J.R., Moerman, D.E., 2001. The importance of weeds in ethnopharmacology. Journal of Ethnopharmacology 75, 19–23.