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Review

Treating leishmaniasis in Amazonia: A review of ethnomedicinal concepts and pharmaco-chemical analysis of traditional treatments to inspire modern phytotherapies

Guillaume Odonne[a,*], Emeline Houël[b], Geneviève Bourdy[c], Didier Stien[d]

[a] Laboratoire Ecologie, Evolution, Interactions des Systèmes Amazoniens (LEEISA), CNRS, Université de Guyane, IFREMER, 97300 Cayenne, France
[b] CNRS, UMR EcoFoG, AgroParisTech, Cirad, INRA, Université des Antilles, Université de Guyane, 97300 Cayenne, France
[c] UMR 152 Pharma Dev, Université de Toulouse, IRD, UPS, France
[d] Sorbonne Universités, UPMC Univ Paris 06, CNRS, Laboratoire de Biodiversité et Biotechnologies Microbiennes (LBBM), Observatoire Océanologique, Banyuls-sur-Mer, France

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ABSTRACT

Ethnopharmacological relevance: Cutaneous and mucocutaneous leishmaniasis are neglected tropical diseases that occur in all intertropical regions of the world. Amazonian populations have developed an abundant knowledge of the disease and its remedies. Therefore, we undertook to review traditional antileishmanial plants in Amazonia and have developed new tools to analyze this somewhat dispersed information.

Material and methods: A literature review of traditional remedies for cutaneous/mucocutaneous leishmaniasis in the Amazon was conducted and the data obtained was used to calculate distribution indexes designed to highlight the most relevant uses in Amazonia. The cultural distribution index represents the distribution rate of a given taxon among different cultural groups and was calculated as the ratio of the number of groups using the taxon to the total number of groups cited. The geographical distribution index allowed us to quantify spatial distribution of a taxon's uses in Amazonia and was calculated geometrically by measuring the average distance between the points where uses have been reported and the barycenter of those points. The general distribution index was defined as an arithmetic combination of the previous two and provides information on both cultural and spatial criteria.

Results: 475 use reports, concerning 291 botanical species belonging to 83 families have been gathered depicted from 29 sources. Uses concern 34 cultural groups. While the use of some taxa appears to be Pan-Amazonian, some others are clearly restricted to small geographical regions. Particular attention has been paid to the recipes and beliefs surrounding treatments. Topical application of the remedies dominated the other means of administration and this deserves particular attention as the main treatments against Neotropical leishmaniasis are painful systemic injections. The data set was analyzed using the previously defined distribution indexes and the most relevant taxa were further discussed from a phytochemical and pharmacological point of view.

Conclusions: The Amazonian biodiversity and cultural heritage host a fantastic amount of data whose systematic investigation should allow a better large-scale understanding of the dynamics of traditional therapies and the consequent discovery of therapeutic solutions for neglected diseases. Distribution indices are indeed powerful tools for emphasizing the most relevant treatments against a given disease and should be very useful in the meta-analysis of other regional pharmacopeia. This focus on renowned remedies that have not yet benefitted from extended laboratory studies, could stimulate future research on new treatments of natural origin for leishmaniasis.

1. Introduction

For years, ethnopharmacologists and ethnobotanists have tried to develop quantitative methods of understanding the use of biodiversity in traditional health systems, from field data collection to analysis. Quantitative analysis is mainly used in two ways; the first consisting of

* Corresponding author.
E-mail address: guillaume.odonne@gmail.com (G. Odonne).

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quantifying the importance of plant taxa among human groups, particularly by reaching a consensus amongst data from various informants (Alexiades and Sheldon, 1996; Hoffman and Gallaher, 2007; Tardio and Pardo-de-Santayana, 2008) and the second is understanding the complex relationship between peoples and their surrounding plant diversity (Bennett and Husby, 2008; Moerman, 1979, 2005; Moerman and Estabrook, 2003; Weckerle et al., 2011, 2012). Although the methods developed to establish plant use values, cultural importance indices or consensus analysis have led to the development of useful tools for ethnobotanical studies dealing with multiple use categories, these indices may also specifically refer to a single plant use, especially medicinal use (Heinrich et al., 1998; Moerman, 2007). The meta-analytic approach has also been considered to show that the selection of useful taxa is based on a logical process more than on a random selection, representing local biodiversity. In particular, Leonti et al. (2013) applied it in an evolutionary perspective to traditional uses and chemical data at pharmacopoeia level. However, from Milliken (1997) collecting information on antimalarial plants at Roraima scale, to Molander et al. (2012), focusing on snakebites and comparing anti-venom uses worldwide, works centered on single diseases are not so numerous. Among them, Andrade-Cetto et al. (2006) developed for example a Disease-Consensus Index (DCI) for specifically analyzing ethnopharmacological field data from a Yucatec Mayan community and selecting useful plant species to treat type 2 diabetes. Eventually, other types of indices, such as those illustrated by Willcox et al. (2011) with the development of an evaluation score including both ethnobotanical and pharmacological data, were designed to prioritize antimalarial traditional remedies for further pharmacological and possibly clinical investigations. In general, strengthening the use of these methods to forge consensus, systematically review information and select plant species for further evaluation is one of the major challenges for ethnopharmacology in the forthcoming years (Heinrich et al., 2009; Leonti, 2011).

The need for intercultural comparisons of plant uses and more particularly medicinal ones, as previously emphasized by Heinrich et al. (1998), is continually growing in order to understand the intimate relationship between people and plants. However, this has been poorly addressed apart from Scarpa (2009) who summarized 573 ethnobotanical data from various bibliographical sources concerning wild food plants used by 10 indigenous groups of the Gran Chaco or the remarkable work of Camara-Leret et al. (2014) to understand the complexity of regional knowledge sharing of the geographical qualification and quantification of patterns of medicinal use, allowing comparisons between numerous cultural groups. In our group, we undertook to understand and quantify the use of medicinal plants against a single disease in a large geographical area. Owing to our previous experience, we decided to focus our study on leishmaniasis in Amazonia.

Plant knowledge in Amazonia is a highly dynamic field and intercultural exchanges are numerous, even if lightly documented (Milliken and Albert, 1996; Milliken, 1997; Camara-Leret et al., 2014). As an example, Lewis and Elvin-Lewis (1991) precisely describe how a remedy against snakebite prepared from *Pentagonia gigantifolia* Ducke quickly transferred from the Candoshi to the Achuar in the Peruvian Amazon. These transfers are meaningful and we assume that a geographical and ethnomedical overview of the practices related to a given disease will help to precisely understand many aspects of this disease and its treatments and particularly its anthropologic rationales. Moreover, over the last few years, our team has studied traditional antimicrobials of natural origin in many parts of Amazonia, from Peru to French Guiana. These studies have led to hundreds of new records of traditional uses (Bourdy et al., 1998, 2000, 2004; Vigneron et al., 2005; Estevez et al. 2007; Valadeau et al., 2009, 2010; Odonne et al., 2013), a better understanding of Amazonian medicines both on ethnomedical (Vigneron et al., 2005; Valadeau et al. 2010; Odonne et al., 2011a, 2013) and pharmacological bases (Bertani et al., 2005; Estevez et al. 2007; Houël et al., 2009; Odonne et al., 2009) and to the discovery of dozens of active molecules, some of them new to science (Bertani et al., 2006; Castillo et al., 2007; Portet et al., 2007; Cachet et al., 2009; 2012; Acebey et al., 2010; Cabanillas et al., 2012; Odonne et al., 2011b). In addition, this extensive work also led to the gathering of a rich bibliography concerning natural medicines in Amazonia and to critical insight on the globalization of Amazonian cultures.

Leishmaniasis are vector borne diseases, caused by several species belonging to the *Leishmania* genus, among which 15 species are human pathogens in the Americas and are transmitted by phlebotomine sand flies belonging to the *Lutzomyia* genus (PAHO, 2016). They are considered neglected tropical diseases (Hotez et al., 2008) and occur in the neotropics in three main forms: a cutaneous, a mucocutaneous and a visceral form (WHO, 2016). This disease complex, even if rarely fatal, is responsible for severe conditions. In Amazonia, 3 *Leishmania* species are prevailing: *Leishmania amazonensis*, *L. braziliensis* and *L. guyanensis*, along with a handful of less common species (Dedet, 1999). Not all species are present everywhere and, in our opinion, their spatial distribution might be an important clue to understand the regional specificity of traditional remedies. Briefly, *L. amazonensis* is present in Bolivia, Colombia, Brazil, Ecuador, French Guiana, Peru and Venezuela and leads to the less serious clinical forms. *L. braziliensis* is the most widespread, occurring in the same countries as *L. amazonensis*, but responsible for more cases. This species is known to cause both cutaneous and mucocutaneous forms and is thus considered to be more detrimental. Lastly, *L. guianensis* is responsible for non-severe cutaneous forms. It is mainly present on the Guiana shield (North of Brazil, French Guiana, Suriname, Guyana and Venezuela) (Dedet, 1999). It is likely that *Leishmania* have been present in South America since the pre-Columbian era, as suggested by historical (Altamirano-Enciso et al., 2003), anatomical and histological evidence (Tuon et al., 2008). It has been suggested that the facial deformations observed on pre-Inca ceramics (Chimu, Moche) were representations of the invalidating mucocutaneous forms (Weiss, 1943; Altamirano-Enciso et al., 2003). These artistic representations illustrate the relevance of the ethnopharmacological approach in the field of leishmaniasis, more particularly concerning cutaneous and mucocutaneous forms, which has already been widely discussed in Odonne et al. (2011a). Briefly, they are generally well recognized diseases by local populations, with a high overlapping of local and biomedical definitions.

Based on ethnological and ecological considerations, Amazonia includes the Amazon basin, the Orinoco basin, the Guiana shield and the North of the Brazilian shield (Mato Grosso) (Erikson, 2001). It is constituted of a patchwork of environments, from altitude cloud forests to mangroves, including lowland inundated forests (varzea) and savannahs. Politically, it is divided into nine countries: Bolivia, Brazil, Columbia, Ecuador, French Guiana, Guyana, Peru, Suriname and Venezuela (Fig. 1). Cultural groups present in this geographical area are numerous. For example, in 2001 Erikson counted more than 60 Amerindian groups in Peru, around 30 in Bolivia and more than 200 in Brazil. Amazonian inhabitants are commonly classified into 3 groups: Amerindian (or native South Americans), Maroons (i.e. people from African origin, escaped from slavery in the 18th century: Aluku, N'djuka, Saramaka...) and Mixed groups (Creoles, Mestizos, Caboclos and the rural populations of lowland Amazonia in general). Whereas the last groups mix European, Amerindian and African descents, they still have very singular cultures. In general, these different origins also notably influence the ethnopharmacopeias (van Andel et al., 2012; Vossen et al., 2014; Torres-Avilez et al., 2015). The patchwork of environments mentioned above might thus be compared to the patchwork of cultures and in both cases, they share constant factors. From the ecological point of view, a few hundred species among the more or less 16,000 tree species of the Amazon are widespread throughout the area and account for more than half of the individuals encountered (Ter Steege et al., 2013). Also numerous species are shared in the home gardens from the Amazon delta to the Andean slopes, supported by a