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1 **Treating leishmaniasis in Amazonia: a review of ethnomedicinal concepts and pharmaco-chemical**
2 **analysis of traditional treatments to inspire modern phytotherapies.**

3

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18 **Abstract:**

19 **Ethnopharmacological relevance:**

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

24 **Material and Methods:**

25 A literature review of traditional remedies for cutaneous/mucocutaneous leishmaniasis in the
26 Amazon was conducted and the data obtained was used to calculate distribution indexes designed to
27 highlight the most relevant uses in Amazonia. The cultural distribution index represents the
28 distribution rate of a given taxon among different cultural groups and was calculated as the ratio of
29 the number of groups using the taxon to the total number of groups cited. The geographical

30 distribution index allowed us to quantify spatial distribution of a taxon's uses in Amazonia and was
31 calculated geometrically by measuring the average distance between the points where uses have
32 been reported and the barycenter of those points. The general distribution index was defined as an
33 arithmetic combination of the previous two and provides information on both cultural and spatial
34 criteria.

35 **Results:**

36 475 use reports, concerning 291 botanical species belonging to 83 families have been gathered
37 depicted from 29 sources. Uses concern 34 cultural groups. While the use of some taxa appears to be
38 Pan-Amazonian, some others are clearly restricted to small geographical regions. Particular attention
39 has been paid to the recipes and beliefs surrounding treatments. Topical application of the remedies
40 dominated the other means of administration and this deserves particular attention as the main
41 treatments against Neotropical leishmaniasis are painful systemic injections. The data set was
42 analyzed using the previously defined distribution indexes and the most relevant taxa were further
43 discussed from a phytochemical and pharmacological point of view.

44 **Conclusions:**

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

52

53 Keywords: Ethnomedecine, medicinal plants, distribution indices, interculturality, leishmaniasis,
54 traditional medicine, Amazonia

55

56 **1. Introduction**

57 For years, ethnopharmacologists and ethnobotanists have tried to develop quantitative methods of
58 understanding the use of biodiversity in traditional health systems, from field data collection to
59 analysis. Quantitative analysis is mainly used in two ways; the first consisting of quantifying the
60 importance of plant taxa among human groups, particularly by reaching a consensus amongst data
61 from various informants (Alexiades & Sheldon, 1996; Hoffmann and Gallaher, 2007; Tardio & Pardo-

62 de-Santayana, 2008) and the second is understanding the complex relationship between peoples and
63 their surrounding plant diversity (Bennett & Husby, 2008; Moerman, 1979; 2005; Moerman &
64 Estabrook, 2003; Weckerle et al., 2011; 2012). Although the methods developed to establish plant
65 use values, cultural importance indices or consensus analysis have led to the development of useful
66 tools for ethnobotanical studies dealing with multiple use categories, these indices may also
67 specifically refer to a single plant use, especially medicinal use (Heinrich et al., 1998; Moerman,
68 2007). The meta-analytic approach has also been considered to show that the selection of useful taxa
69 is based on a logical process more than on a random selection, representing local biodiversity. In
70 particular, Leonti et al. (2013) applied it in an evolutionary perspective to traditional uses and
71 chemical data at pharmacopoeia level. However, from Milliken (1997) collecting information on
72 antimalarial plants at Roraima scale, to Molander et al., (2012), focusing on snakebites and
73 comparing anti-venom uses worldwide, works centered on single diseases are not so numerous.
74 Among them, Andrade-Cetto et al. (2006) developed for example a Disease-Consensus Index (DCI) for
75 specifically analyzing ethnopharmacological field data from a Yucatec Mayan community and
76 selecting useful plant species to treat type 2 diabetes. Eventually, other types of indices, such as
77 those illustrated by Willcox et al. (2011) with the development of an evaluation score including both
78 ethnobotanical and pharmacological data, were designed to prioritize antimalarial traditional
79 remedies for further pharmacological and possibly clinical investigations. In general, strengthening
80 the use of these methods to forge consensus, systematically review information and select plant
81 species for further evaluation is one of the major challenges for ethnopharmacology in the
82 forthcoming years (Heinrich et al., 2009; Leonti, 2011).

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

93 Plant knowledge in Amazonia is a highly dynamic field and intercultural exchanges are numerous,
94 even if lightly documented (Milliken & Albert, 1996; Milliken, 1997; Camara-Leret et al., 2014). As an
95 example, Lewis & Elvin-Lewis (1991) precisely describe how a remedy against snakebite prepared

96 from *Pentagonia gigantifolia* Ducke quickly transferred from the Candoshi to the Achuar in the
97 Peruvian Amazon. These transfers are meaningful and we assume that a geographical and
98 ethnomedical overview of the practices related to a given disease will help to precisely understand
99 many aspects of this disease and its treatments and particularly its anthropologic rationales.
100 Moreover, over the last few years, our team has studied traditional antimicrobials of natural origin in
101 many parts of Amazonia, from Peru to French Guiana. These studies have led to hundreds of new
102 records of traditional uses (Bourdy et al., 1998; 2000; 2004; Vigneron et al., 2005; Estevez et al. 2007;
103 Valadeau et al., 2009; 2010; Odonne et al. 2013), a better understanding of Amazonian medicines
104 both on ethnomedical (Vigneron et al., 2005; Valadeau et al, 2010; Odonne et al., 2011a; 2013) and
105 pharmacological bases (Bertani et al., 2005; Estevez et al, 2007; Houël et al., 2009; Odonne et al.,
106 2009) and to the discovery of dozens of active molecules, some of them new to science (Bertani et
107 al., 2006; Castillo et al., 2007; Portet et al., 2007; Cachet et al., 2009; 2012; Acebey et al., 2010;
108 Cabanillas et al., 2012; Odonne et al., 2011b). In addition, this extensive work also led to the
109 gathering of a rich bibliography concerning natural medicines in Amazonia and to critical insight on
110 the globalization of Amazonian cultures.

111 Leishmaniasis are vector borne diseases, caused by several species belonging to the *Leishmania*
112 genus, among which 15 species are human pathogens in the Americas and are transmitted by
113 phlebotomine sand flies belonging to the *Lutzomyia* genus (PAHO, 2016). They are considered
114 neglected tropical diseases (Hotez et al., 2008) and occur in the neotropics in three main forms: a
115 cutaneous, a mucocutaneous and a visceral form (WHO, 2016). This disease complex, even if rarely
116 fatal, is responsible for severe conditions. In Amazonia, 3 *Leishmania* species are prevailing:
117 *Leishmania amazonensis*, *L. braziliensis* and *L. guyanensis*, along with a handful of less common
118 species (Dedet, 1999). Not all species are present everywhere and, in our opinion, their spatial
119 distribution might be an important clue to understand the regional specificity of traditional remedies.
120 Briefly, *L. amazonensis* is present in Bolivia, Colombia, Brazil, Ecuador, French Guiana, Peru and
121 Venezuela and leads to the less serious clinical forms. *L. braziliensis* is the most widespread,
122 occurring in the same countries as *L. amazonensis*, but responsible for more cases. This species is
123 known to cause both cutaneous and mucocutaneous forms and is thus considered to be more
124 detrimental. Lastly, *L. guyanensis* is responsible for non-severe cutaneous forms. It is mainly present
125 on the Guiana shield (North of Brazil, French Guiana, Suriname, Guyana and Venezuela) (Dedet,
126 1999). It is likely that *Leishmania* have been present in South America since the pre-Columbian era,
127 as suggested by historical (Altamirano-Enciso et al., 2003), anatomical and histological evidence
128 (Tuon et al., 2008). It has been suggested that the facial deformations observed on pre-Inca ceramics
129 (Chimu, Moche) were representations of the invalidating mucocutaneous forms (Weiss, 1943;

130 Altamirano-Enciso et al., 2003). These artistic representations illustrate the relevance of the
131 ethnopharmacological approach in the field of leishmaniasis, more particularly concerning cutaneous
132 and mucocutaneous forms, which has already been widely discussed in Odonne et al. (2011a).
133 Briefly, they are generally well recognized diseases by local populations, with a high overlapping of
134 local and biomedical definitions.

135 Based on ethnological and ecological considerations, Amazonia includes the Amazon basin, the
136 Orinoco basin, the Guiana shield and the North of the Brazilian shield (Mato Grosso) (Erikson, 2001).
137 It is constituted of a patchwork of environments, from altitude cloud forests to mangroves, including
138 lowland inundated forests (varzea) and savannahs. Politically, it is divided into nine countries: Bolivia,
139 Brazil, Columbia, Ecuador, French Guiana, Guyana, Peru, Suriname and Venezuela (figure 1). Cultural
140 groups present in this geographical area are numerous. For example, in 2001 Erikson counted more
141 than 60 Amerindian groups in Peru, around 30 in Bolivia and more than 200 in Brazil. Amazonian
142 inhabitants are commonly classified into 3 groups: Amerindian (or native South Americans), Maroons
143 (i.e. people from African origin, escaped from slavery in the 18th century: Aluku, N'djuka, Saramaka...)
144 and Mixed groups (Creoles, Mestizos, Caboclos and the rural populations of lowland Amazonia in
145 general). Whereas the last groups mix European, Amerindian and African descents, they still have
146 very singular cultures. In general, these different origins also notably influence the
147 ethnopharmacopeias (van Andel et al., 2012; Vossen et al., 2014; Torres-Aviles et al., 2015). The
148 patchwork of environments mentioned above might thus be compared to the patchwork of cultures
149 and in both cases, they share constant factors. From the ecological point of view, a few hundred
150 species among the more or less 16 000 tree species of the Amazon are widespread throughout the
151 area and account for more than half of the individuals encountered (Ter Steege et al., 2013). Also
152 numerous species are shared in the home gardens from the Amazon delta to the Andean slopes,
153 supported by a long history of plant exchanges throughout the region (Clement et al., 2015). On the
154 other hand, from the socio-cultural point of view, there is a common base in remedies used (see
155 Schultes & Raffauf (1990) or Duke & Vasquez (1994) for overviews and overlapping of
156 ethnopharmacopeias) or in general cultural concepts (see for example Erikson (2001) or Levi-Strauss
157 (1964)).

158 Antileishmanial traditional phytotherapies are numerous and of frequent use, notably in Amazonia.
159 For many of them, pharmacological evidence of bioactivity no longer needs to be proven
160 (Akendengue et al., 1999; Davies & Kedzierski, 2005; Fournet & Munoz, 2002; Ioset, 2008; Kaiser et
161 al., 2003; Mishra et al., 2009; Rocha et al., 2005). However, although many traditional remedies are
162 effectively shared by thousands of people across Amazonia (Cámara-Iret et al., 2014; Roersch,

163 2010), the precise reason for each use, whether it be emic or etic efficacy, is not always understood
164 by researchers.

165 Cultural considerations may indeed be underpinning diffusion process. According to a study realized
166 in four Basque regions (Menendez-Baceta et al., 2015), cultural factors such as language, cultural
167 meaning of plants, cultural identity or social network may indeed account for the structuration of
168 local ethnofloras, even if some preparations were also highlighted to be widely used among the
169 different regions of the study area. In the latter case, it can be hypothesized that ecological
170 availability and chemical composition of the plants may explain the persistence of these widely
171 spread remedies. This is consistent with the work of Moerman (2007), who studied information on
172 219 Native American groups and concluded that a consensus of use between different cultural
173 groups tends to correlate with pharmacological activity. In fact, Saslis-Lagoudakis et al. (2012)
174 proposed after analyzing phylogenetic patterns of representative floras that the: *“use of the same or*
175 *related plants by people from different regions and cultures provides indirect evidence for bioactivity,*
176 *if the similarities in medicinal floras are the result of independent discoveries rather than cultural*
177 *transmissions”*. This competition between cultural transmission and clinical objectivity has been
178 studied by Tanaka et al. (2009), calculating through modelisation that the most active remedies are
179 not always the most widespread. Nevertheless, his modeling lacks the geographical dimension.
180 Eventually, assuming that on a large scale, the “cultural bias” might be less important than the
181 pharmacological activity is controversial.

182 Cultural distribution in Amazonia is an intermediate between a cultural continuum and a mosaic. The
183 novelty of our proposition is to question if cultural exchanges necessarily balance biological activity,
184 in a comparison involving more than 30 cultural groups. Quantifying the geographical distribution of
185 a plant's use for a specific disease had never been realized and our objectives are double. On the one
186 hand, the mechanisms underlying medicinal plant selection by local people are still poorly
187 understood and such a study might help to define patterns of use at a regional scale, a first step
188 before further investigation of this complex mix of culture, ecology and pharmacology. On the other
189 hand, we aim to propose a practical tool to help pharmacologists and phytochemists in the selection
190 of plants to be explored for antileishmanial nature-based solutions. Agreeing here again with Leonti
191 (2011) when he argues that phytochemical/pharmacological exploration of ethnopharmacopeias is
192 often done *“indiscriminately and overoptimistically”*; we suppose that having an inside view will lead
193 to better detection of the pharmacological potential of a given species, allowing better assessment
194 between the emic and etic perceptions of efficacy of antileishmanial remedies.

195

196 2. Material and methods

197 2.1 Literature review

198 Bibliographic sources dealing with Amazonian ethnobotany were carefully revised between 2006 and
199 2014. We consulted books and journals from best sellers to old documents in libraries, as well as Ph.
200 D. or Master's theses available on the web or in Peruvian, French and Brazilian libraries. Scopus,
201 Google Scholar, Pubmed, Science Direct and SciELO databases were consulted using as many
202 keywords related to Amazonian ethnobotany and leishmaniasis as possible. Unfortunately, many
203 sources were useless for this study because our main criterion was a reliable correlation of described
204 symptoms with cases of leishmaniasis. Classification in medicinal ethnobotany is a recurrent problem
205 (Gruca et al., 2014; Staub et al., 2015) and clustering is often based on subjective organ or symptom
206 defined criteria. Thus, many sources describing imprecise use-categories such as "wounds" or
207 "dermatological affections" were rejected. Botanical names were updated according to APG3
208 nomenclature according to the Missouri botanical garden (Tropicos, 2016).

209 2.2 Setting up of distribution indices

210 To measure distribution of the antileishmanial use of each species on both a cultural and
211 geographical level, three indices were defined: a geographical distribution index, a cultural
212 distribution index and, lastly, a general distribution index combining both previously defined indices.
213 Ecologists already model species diversity on a spatial scale, but their tools and the way they use
214 them, are too complex for researchers that are not very close to statistical ecology. Here, we tried to
215 set the simplest and most user-friendly index possible. To calculate these indices, a Use Record UR
216 was defined as a combination of one species, used in one cultural group, cited in one reference. The
217 same species used in the same group but cited by 2 references are then considered as 2 URs
218 (although only occurring very few times).

219 2.2.1 Geographical distribution index (I_g)

220 The geographical distribution index (I_g) aims to measure, for each species, the extent of the spatial
221 distribution of its antileishmanial use reports. Each use report for a given species was located on a
222 map of Amazonia (considered as an orthonormal system) in order to obtain a scatter plot. A pair of
223 coordinates (x_i, y_i) was attributed to each locality by placing the mouse cursor on the map with the
224 Gimp 2.0 software. The coordinates (x_b, y_b) of the barycenter of the scatter plot were calculated using
225 Excel software. We measured the distance (D_i , without units) between each locality and the
226 barycenter: $D_i = \sqrt{(x_i - x_b)^2 + (y_i - y_b)^2}$, and calculated the average of the distances D_i (aD_i). The
227 maximal theoretical distance (D_{max}) that can be observed between a dot and a barycenter is
228 calculated as half of the distance between the two most distant use-reports for any plant species (the

229 Embera in Columbia and the rural population of Maranhão in Brazil) and is 512.7. Then we calculated
 230 the ratio D_i/D_{\max} in order to obtain a value ranging between 0 and 1, normalized by dividing by the
 231 maximal value of D_i obtained ($D_{i\max}$): $I_g = \frac{D_i - D_{\min}}{D_{i\max} - D_{\min}}$. The closer to 0 the I_g value for a given species is,
 232 the more the use reports are restricted to a small area in Amazonia. The closer to 1 the I_g value is, the
 233 more the use reports are widespread over the region.

234 2.2.2 Cultural distribution index (I_c)

235 The cultural distribution index (I_c) aims to measure, for a given species, the ratio of cultural groups
 236 using that species as antileishmanial. Assuming that two use reports in two different groups was
 237 more significant than two use reports in only one group, we decided to count not the total number of
 238 use reports but the total number of groups using a plant species. Then, this number is divided by the
 239 maximum number of Amazonian groups using a same species (i.e. 10 groups, for *Spondias mombin*,
 240 Anacardiaceae). The value obtained ranges from 0 to 1 with 0 corresponding to a species with no use-
 241 reports and 1 corresponding to the species with the highest number of groups using it.

242 For some large groups, such as the Peruvian Mestizos cited by Kvist et al. (2006), only one group was
 243 counted in the I_c calculation despite the 4 different places of study but the geographical localization
 244 was selected depending on the sub-group using the most the plant species.

245 2.2.3 General distribution index (I_d)

246 The general distribution index (I_d) is calculated as following for a given species, as the mean of the
 247 two former indices: $I_d = (I_c + I_g)/2$

248

249 3. Results

250 3.1 Inventory of cultural groups and geographic distribution

251 Twenty-nine references have been selected after analysis and revision of the bibliography (table 1,
 252 also including anthropological references). They document leishmaniasis knowledge and therapeutic
 253 practices of 34 cultural groups (table 1). The groups are localized on figure 1. One of these groups,
 254 the H'mong present in French Guiana since the 1970's, arrived from Laos and are thus of recent
 255 Asiatic origin. The Teribe from Panama and the rural population of San Jose in Costa-Rica are not
 256 considered in the calculation of the indexes (as they are far from Amazonia) but as their remedies
 257 and perceptions are very similar to Amazonian ones, they were only included in the discussion.

258 **Insert Table 1 synthesis of the results/groups**

ID	Cultural group	Country	local name	Use reports	References (ethno. & bota.)
----	----------------	---------	------------	-------------	-----------------------------

1	Aluku	French Guiana	<i>azo</i>	21	Agelas, 1999
2	Arawak	Guyana		34	Van Andel, 2000
3	Bora	Peru		1	Denevan & Padoch, 1988
4	Brazilian	French Guiana		10	Agelas, 1999; Odonne et al., 2011a
5	Campa-Ashaninca	Peru		3	Reynel et al., 1990
6	Carib	Guyana		11	Van Andel, 2000
7	Chayahuita	Peru	<i>ta'ta', huayani</i>	60	Kvist et al., 2006; Estevez et al., 2007; Odonne et al., 2009
8	Chimane	Bolivia		4	Fournet et al., 1994a; Fournet et al., 1994b
9	Chinese	French Guiana		1	Agelas, 1999
10	Cocama	Peru		13	Kvist et al., 2006
11	costlanders	Guyana		9	Van Andel, 2000
12	Créoles	French Guiana	<i>pian bois</i>	56	Agelas, 1999; Grenand et al., 2004
13	Embera	Colombia	<i>aidá</i>	4	Morales, 1995
14	H'mong	French Guiana	<i>txhab qawj</i>	1	Agelas, 1999
15	Kali'na	French Guiana	<i>aleko</i>	11	Agelas, 1999
16	Karipuna	French Guiana		2	Agelas, 1999
17	Kechua	Bolivia		5	Fournet et al., 1994b
18	Matsigenka	Peru	<i>tsirivaito</i>	1	Shepard, 1999
19	N'djuka	French Guiana	<i>busi yasi</i>		Agelas, 1999
20	Palikur	French Guiana	<i>yatuwe, yatuwa</i>	25	Agelas, 1999; Grenand et al., 2004; Odonne et al., 2011a
21	Quichua (Napó)	Peru		1	Benett & Prance, 2000
22	rural pop.	Bolivia	<i>espundia</i>	5	Fournet et al., 1994b
23	rural pop.	Brazil	<i>lésh, boba, ferida brava</i>	17	França et al., 1996; Moreira et al., 2002
24	rural pop.	Colombia	<i>bejuco, yatevi</i>		Isaza et al., 1999
25	rural pop.	Costa Rica	<i>papalomoyo</i>	12	Dobles-Ulloa & Perriard, 1994
26	rural pop.	Ecuador	<i>sarna brava, charra brava, marca de Santo Domingo, la colombiana</i>	34	Weigel et al., 1994

27	rural pop. (Mestizo)	Peru	<i>uta</i>	38	Weiss, 1943; Hermoso et al., 2003; Kvist et al., 2006; Castillo et al., 2007; González-Coloma et al., 2012
28	Saramaka	French Guiana	<i>busi yasi</i>	8	Sauvain, 1989; Agelas, 1999
29	Shipibo-Konibo	Peru		7	Tournon, 2006
30	Tacana	Bolivia		11	Bourdy, 1998; Bourdy et al., 2000
31	Teko	French Guiana	<i>kalasapa</i>	10	Odonne et al. 2011a
32	Teribe	Panama		4	Gupta et al., 2005
33	Ticuna	Peru		4	Kvist et al., 2006
34	Warao	Guyana		5	Van Anandel, 2000
35	Wayãpi	French Guiana	<i>kalasapau</i>	33	Grenand et al., 2004
36	Yanesha	Peru	<i>mareñets</i>	12	Valadeau et al., 2009

Table 1: Synthesis of the results by group. The 473 URs (different from the 470 counted in the article) are due to 3 redundant use reports (same plant/same group/different source)

259

260 **Insert figure 1 (Distribution map of groups cited in the study)**



Figure 1: Repartition map of the groups cited in the study (in orange, extra-Amazonian groups).

261

262 3.2 Designation and emic etiology of leishmaniasis across Amazonia

263 In spite of the evidence of *Leishmania* presence in South America since ancient times, only few

264 documents describe leishmaniasis and their causes from an emic perspective. In **table 1** the names of

265 leishmaniasis in different Amazonian cultures are summarized.

266 Among the Matsigenka (Peru) two forms of leishmaniasis (*tsirivaito*) are recognized (Shepard, 2004).
267 They are strictly cutaneous and two insects are perceived as responsible. In one case a pathogenic
268 agent is thought to be transmitted by the pulsating glow of the lightning bug (*Lampyridae* order) and
269 in the other, the gnawing pincers of the click beetle (*Elateridae* order) is involved. Even if these
270 insects are different from the biomedical vector, it is interesting to see how close these etiologies are
271 to the biomedical one. In rural communities of the Choco region (Columbia), cutaneous leishmaniasis
272 is called *bejuco* and *yatevi* (Isaza et al., 1999). Two etiologies prevail in local perception: disease may
273 come either from a worm (*guzano*) living in mud or under tree leaves or from a liana (*bejuco*). A
274 mosquito transmitting the disease is finally evoked at a lower frequency. Still in the Choco but in
275 Embera groups, cutaneous ulcers linked to leishmaniasis (*aidá*) were brought to earth by the mythical
276 twins *Tutruika* and *Karagabi* (Morales, 1995). One can be affected by the disease after a social
277 transgression and particularly during female puberty and periods of mourning. In addition, *aidá*
278 appears here as a social sanction. In Costa-Rica (geographically far from our study area, but culturally
279 close enough to be discussed here) Dobles-Ulloa & Perriard (1994) have collected information about
280 knowledge and practices in the rural area of San Jose. They highlight a good knowledge of the disease
281 called *papalomoyo* and its variations: *papalomoyo seco*, *llorando*, *con hijitos*; respectively dry, crying
282 (wet), or with children (disseminated). These names may refer to the different clinical forms
283 (granulomatous, ulcerate or diffuse). This study also highlights the knowledge of the population
284 regarding the biomedical etiology, including the role of a fly vector. Still, the nature of the agent
285 transmitted is vague and it is sometimes said that the vector only transmits a poison picked up from a
286 poisonous animal (snake, toad). In Brazilian rural communities from Maranhão, Moreira et al. (2002)
287 report a good knowledge of the disease, even if the etiology is poorly known. It is named *lésh*, *boba*,
288 or *ferida brava*. Among the Yaneshá (Peru), cutaneous leishmaniasis is called *mareñets* (Valadeau et
289 al., 2009). It is a spirit from the non visible world, pictured as a short legged man, carrying a heavy
290 bag, biting men or women, in order to make them die and live after their death a matrimonial union.
291 Also, Alexiades (1999) reports from the Ese-eja that leishmaniasis is caused by the spirit (the *eshawa*)
292 of a small undetermined fish.

293 We have previously shown that the Chayahuita (Peru) have a good knowledge of the disease and
294 consider *ta'ta* (cutaneous leishmaniasis) to be mainly transmitted by a leach, or to a lesser extent by
295 a mosquito (Odonne et al., 2009). The watery aspect of the disease is of a cultural importance. The
296 Teko and the Wayãpi from French Guiana also know leishmaniasis very well (*kalasapa* and *kalasapau*
297 respectively) and insects (everything but sandflies) are said to be the vector. The sign associated to
298 the *kalasapau* is the growth rate of the ulcer (Odonne et al., 2011a).

299 From all of these perceptions of leishmaniasis, 3 classes of etiologies arise: the transgression of social
300 rules, the action (physical or symbolic) of an animal or a spirit and contact with a plant. The first class
301 is very representative of Amazonian Amerindian logic (Grenand & Grenand, 1981) and it is likely that
302 this etiology was probably more represented before the arrival of Europeans. Some aspects deriving
303 from the biomedical definition seem to be at least partially integrated into traditional concepts,
304 mainly in non-Amerindians populations, in a form of cultural hybridization.

305 3.3. Medicinal attitudes among Amazonian cultures

306 As everywhere, disease is part of general systems of thought that structure knowledge. Here we aim
307 to link the emic perception of leishmaniasis to the nature of the remedies. For the Chayahuita, the
308 watery aspect of the disease, as previously mentioned, is seen as important. Thus, the consumption
309 of chilies and salt is prohibited due to the nasal and ocular discharge associated with chili eating and
310 to the hydrophilic properties of salt. The leishmaniasis is a cutaneous ulcer and the depth of the
311 wounds is a sign of seriousness. Chayahuita avoid eating the meat from animals that dig (armadillos
312 or tortoises for example) because the wound would enlarge immediately. This must be related to
313 Shepard's statement (Shepard, 2004): "(...) illnesses are treated by ingesting or applying plants with
314 strong, noxious sensory properties (bitter, astringent, pungent, caustic, and sour). Such properties are
315 manifestations of the plant's soul (osure), a holistic healing force that infuses (okitsitingakero) the
316 herbal decoction and the body of the patient. Pathogenic agents react to noxious properties much like
317 humans, suffering pain and discomfort, retreating, and at high enough doses, perishing". Amongst
318 the Yanésha, the skin ulcer is considered to be a sure indication of the attraction of Mareñets for
319 someone. Part of the cure is based upon the the necessity for the person to refrain any expression of
320 pain or feeling of discomfort when treated with medicinal plants poultices applied topically, as it
321 could be interpreted as the manifestation of a pain resulting from the separation with this spirit. In
322 the contrary, it is said that the treatment will not be efficient (Valadeau et al., 2009).

323 Amongst the Wayãpi Amerindians, the most important character of the disease is the speed of ulcer's
324 growth. Thus, the selected plants are of two kinds: fast growing species, often encountered in second
325 growth vegetation and species whose bark scars quickly after cutting. Alexiades (1999), discussing
326 cutaneous ulcers of the Ese-eja, relates a symbolic association concerning the disease and its
327 treatment: "*Certain types of chihi, skin ulcers, are believed to be caused by (the eshawa of) minute*
328 *fish who 'eat' away the flesh of their human hosts. The effect of certain plants applied over chihi is*
329 *likened to that of fish poisons: indeed, shaka [Tephrosia sinapou (Buc'hoz) A. Chevalier, Fabaceae] is*
330 *used both as a fish poison and as a cure for a number of skin infections". It appears clearly from the*
331 *last examples that the way the disease is perceived induces different therapeutical consequences,*
332 *both in the practices and in the choice of the plant remedies and particularly towards painful plants.*

333 Nonetheless, it is almost impossible not to discuss one of the most widespread aspects, although not
334 linked with medicinal plants. The title of Ramdas (2012) article: "*Cruel disease, cruel medicine...*" is
335 evocative and perfectly reflects what has been observed throughout Amazonia. Household products
336 (e.g. bleach), non-biomedical chemicals (e.g. battery acid, fuel), veterinary insecticides for example,
337 are in common use in Colombia, Ecuador and Suriname (Isaza et al., 1999; Ramdas, 2012; Velez et al.,
338 2001; Weigel & Armijos, 2001; Weigel et al., 1994). These practices have also been observed by the
339 authors in French Guiana, Bolivia and Peru. Even if Ramdas (2012) claims that low income,
340 remoteness and low levels of education might explain the use of these types of products, she also
341 highlights a gender ideology, where masculinity is associated with toughness and courage,
342 particularly amongst the Maroons that represent half of her sample. The use of many irritant plants
343 throughout Amazonia should be related to this behavior.

344 3.4. Analysis of botanical traditional remedies

345 3.4.1 Galenic

346 Amongst the 475 URs of Table 1, precision concerning the method of application are only presented
347 211 times. Thus, 93.8 % (198/211) of the URs are strictly external and 6.1 % (7/211) strictly internal.
348 Mixed applications occur for only 2.8 % (6/211). As far as external use is concerned, topical
349 application (89.4 %; 177/198) is by far the most common, followed by washes (5.6 %; 10/198),
350 washes and topical application together (4.5 %; 9/198) and fumigation (1.0 %; 2/198). In Odonne et
351 al. (2013) we observed in the general Chayahuita pharmacopoeia, a balance between internal and
352 external treatments. Lacking a global database of Amazonian remedies, and as these results seemed
353 to be representative of Amazonian phytotherapy, we used them to compare practices concerning all
354 diseases in general to leishmaniasis in particular. Here, the difference observed (Chi^2 , 1 df,
355 $p < 0.00001$) clearly illustrates that the topical form is favoured for cutaneous leishmaniasis. This form
356 of application is interesting when compared to its marginal status in chemotherapy (Blum et al.,
357 2012). In fact, external administration is rarely employed in biomedicine and one of the major
358 recommendations inspired by traditional use might be to reconsider it.

359 3.3.2 Plant parts

360 Out of 475 plants, our database only includes 359 URs with detailed plant parts (75.6 %). By order of
361 decreasing importance, chlorophyllous parts (leaves, meristems and aerial parts of herbaceous taxa)
362 occur for 33.1 % (119/359) of use reports, barks for 29 % (104/359), exudates (latex, resins and saps)
363 for 17.8 % (64/359), roots and underground organs for 11.1 % (40/359), fruits and seeds for 9.5 %
364 (34/359) and wood and stems for 4.5 % (16/359, total over 100 % due to multiple uses). The
365 distribution of plant parts used against leishmaniasis versus all types of diseases (from Odonne et al.,

366 2013) is once again clearly independent (χ^2 , 5 df, $p < 0.001$), which we assume to be influenced by
367 the nature of the disease treated, at least at least at an Amazonian scale.

368 3.3.3 Families, genera most used

369 Amongst the 83 plant families in table 1, the most cited are respectively Fabaceae (63 URs)
370 Euphorbiaceae (38 URs), Solanaceae (26 URs), Araceae (23 URs), Anacardiaceae (22 URs), Asteraceae
371 and Bignoniaceae (20 URs), Hypericaceae (18 URs), Rutaceae (16 URs) and Apocynaceae, Meliaceae
372 and Rubiaceae (13 URs). Concerning the 201 genera cited, the most frequent are *Inga* (Fabaceae, 19
373 URs), *Vismia* (Hypericaceae, 18 URs), *Citrus* (Rutaceae, 13 URs), *Piper* (Piperaceae, 11 URs), *Jatropha*
374 (Euphorbiaceae, 10 URs), *Spondias* (Anacardiaceae, 10 URs), *Manihot* (Euphorbiaceae, 8 URs),
375 *Anacardium* (Anacardiaceae, 7 URs), *Carapa* (Meliaceae, 7 URs) and *Solanum* (Solanaceae, 7 URs).
376 Many of these families and genera are notably known to produce bioactive secondary metabolites
377 (Zhu et al., 2011) and it would thus be interesting to search for a phylogenetic signal. However, we
378 lack both a global Amazonian phylogeny, and to define the interesting chemical patterns to be
379 correlated to these traditional uses.

380 3.3.4 Ecology of species used

381 Are cultivated plants more used than wild plants and does this depend on the population's degree of
382 proximity to the forest? Furthermore, are introduced plants more commonly used than local ones?
383 These are some of the questions that need to be answered. At first glance, with 218 species (324
384 URs) of strictly wild plants, 48 species (107 URs) of strictly cultivated plants and 25 species (44 URs)
385 of both wild and cultivated plants, wild plants appear to be highly valued as antileishmanials.
386 Although cultivated plants might be more easily accessed in daily use, the clear tendency to select
387 wild plants is interesting and their ecological status, be they weeds or mature forest plants, would
388 have been a valuable variable to explore (Stepp & Moerman, 2001), but difficult to implement in this
389 study.

390 Following the work of Bennet & Prance (2000), occasionally completed by general botanical
391 bibliography and localizations given by GBIF.org (GBIF, 2016), we propose a rough "Amazonian native
392 vs Amazonian exotic plants dichotomy". Plants with debatable status are few and do not significantly
393 affect the analysis. Native plants account for 256 species (88%; 411 URs) whilst exotics account for 35
394 species (64 URs). In addition, results are very different in this field although Molares & Ladio (2009)
395 observed a less contrasted proportion, with 39% of exotic species generally used as medicinal by the
396 Mapuche in south American Patagonia which is similar to the 55% native vs. 45% exotics observed in
397 Bahia state (Brazil) by de Santana et al. (2016), in the Atlantic Brazilian forest Alencar et al. (2014)
398 observed a neat dominance of native plants (13 spp. vs 3 spp.) used for wound healing, the closest

399 indication we found to antileishmanials. Pedrollo et al. (2016) observed a similar proportion of 80%
 400 of native plants used in a wide array of indications among riverine communities along the Rio Negro
 401 (Amazonian Brasil). In our opinion, as exotic plants are mainly cultivated (as food crops or as
 402 ornamentals) or weeds, they are more prone to be found around houses. A global reflection
 403 associating ecology (wild, cultivated, weeds) to geography is necessary and still needs to be
 404 undertaken in order to disentangle medicinal flora use patterns throughout Amazonia. Nevertheless,
 405 this predominant use of native species might be of interest to help define conservation policy in the
 406 region.

407 The present study also highlights the profound influence of humans on Amazonia. Pre-Columbian
 408 evidence of Amerindian-mediated floristic modifications are now numerous (Clement et al., 2015;
 409 Lins et al., 2015; Shepard & Ramirez, 2011), but this review shows that this could extend to present
 410 day and to less salient taxa. Medicinal use of many non-Amazonian cultivated plants, as well as of
 411 some exotic weeds, such as *Plantago major*, for example, is a good illustration.

412 3.4 Classification by distribution indexes

413 We restricted the calculation of the distribution indices to the plants with at least 3 URs (31 spp.,
 414 **table 2**)

415 **Insert table 2: Distribution indices for the most used plants.**

Scientific name	I _g	I _c	I _d	Agr.	Or.
<i>Spondias mombin</i> L.	0,73	1	0,86	W/C	Na
<i>Nicotiana tabacum</i> L.	1	0,5	0,75	C	Na
<i>Citrus aurantifolia</i> (Christm.) Swingle	0,84	0,6	0,72	C	Ex
<i>Jatropha curcas</i> L.	0,66	0,7	0,68	C	Ex
<i>Musa x paradisiaca</i> L.	0,79	0,5	0,65	C	Ex
<i>Carica papaya</i> L.	0,84	0,4	0,62	C	Na
<i>Anacardium occidentale</i> L.	0,52	0,7	0,61	C	Na
<i>Chelonanthus alatus</i> (Aubl.) Pulle	0,72	0,5	0,61	W	Na
<i>Manihot esculenta</i> Crantz	0,40	0,8	0,60	C	Na
<i>Plantago major</i> L.	0,89	0,3	0,60	W/C	Ex
<i>Cedrela odorata</i> L.	0,63	0,5	0,57	W	Na
<i>Citrus limon</i> (L.) Burm. F.	0,78	0,3	0,54	C	Ex
<i>Jacaranda copaia</i> (Aubl.) D. Don	0,74	0,3	0,52	W	Na
<i>Bixa orellana</i> L.	0,63	0,4	0,51	C	Na
<i>Carapa guianensis</i> Aubl.	0,22	0,7	0,46	W	Na

<i>Mangifera indica</i> L.	0,61	0,3	0,46	C	Ex
<i>Scoparia dulcis</i> L.	0,50	0,4	0,45	W	Na
<i>Brunfelsia grandiflora</i> D. Don	0,24	0,6	0,42	W	Na
<i>Jatropha gossypifolia</i> L.	0,50	0,3	0,40	C	Ex
<i>Inga alba</i> (Sw.) Willd.	0,07	0,7	0,39	W	Na
<i>Hura crepitans</i> L.	0,26	0,5	0,38	W	Na
<i>Vismia guianensis</i> (Aubl.) Pers.	0,21	0,4	0,31	W	Na
<i>Senna alata</i> (L.) Roxb.	0,15	0,4	0,28	W	Na
<i>Croton lechleri</i> Muell. Arg.	0,20	0,3	0,25	W	Na
<i>Aloe vera</i> (L.) Burm. F.	0,19	0,3	0,24	C	Ex
<i>Curarea tecunarium</i> Barneby & Krukoff	0,08	0,3	0,19	W	Na
<i>Calycophyllum spruceanum</i> (Benth.) Hook. f. ex K. Schum.	0,08	0,3	0,19	W	Na
<i>Momordica charantia</i> L.	0,05	0,3	0,18	W/C	Ex
<i>Chromolaena odorata</i> (L.) King & Robinson	0,05	0,3	0,18	W	Na
<i>Gossypium barbadense</i> L.	0,05	0,3	0,18	C	Na
<i>Pentaclethra macroloba</i> (Willd.) Kuntze	0,05	0,3	0,17	W	Na

Table 2: Distribution indices for the most used plants.

Agr.: agricultural status; W: wild; C: cultivated. Or.: origin of the species; Na.: native from Amazonia; Ex.: exotic.

416

417 3.4.1 Taxa with the highest distribution values

418 In this subchapter, we aim to briefly discuss how these patterns might testify to different aspects of
419 ethnobotanical use and how they can be used both to select interesting candidates for further
420 evaluation, or to understand use patterns in Amazonian societies, bridging ethnology and
421 pharmacology. **Figure 2** is a graphical representation of the species depending on their I_g and I_c ,
422 allowing clusters to be visually determined. These clusters are not representative of any
423 mathematical formula, but might reflect some different patterns.

424 **Insert figure 2: graphical representation of the species depending on their I_g and I_c**

443 interesting for pharmacological development. Interestingly, wild plants such as *Chelonanthus alatus*,
444 *Plantago major* or *Jacaranda copaia* are more numerous in this cluster.

445 3.4.1.3 High I_c , low I_g (yellow)

446 Three plants belong to this cluster: *Inga alba*, *Carapa guianensis* and *Brunfelsia grandiflora*. They
447 reflect highly localised and therefore highly locally shared uses. The first two species are actually very
448 widespread, but the third one, although present in all the Amazon, is much more frequent in the
449 Western part of the area. From our sources, *C. guianensis* is used throughout the Guiana shield
450 (French Guiana, Guyana) while *I. alba* is only used in French Guiana. Conversely, *B. grandiflora* is only
451 used in Peru. Two types of hypotheses might there be formulated: a cultural one, with a highly
452 culture-dependent perception of these plants, where neighbouring groups, more prone to sharing
453 cosmological concepts, also share plants. This might be the case for *C. guianensis*, which provides
454 *Andiroba* oil, the main preventive/protective oil used throughout the Guiana shield. The other
455 hypothesis relies on biologic variability: these patterns might either reflect chemical variations
456 between eastern or western chemotypes, or a different pathosphere, i.e. different species or sub-
457 species of *Leishmania* with different responses to allelochemicals, appearing as a kind of regional
458 pharmacological match between plants used and parasites. As the Guiana shield is mainly affected by
459 *Leishmania guianensis*, this hypothesis potentially explains the uses of *I. alba* or *C. guianensis* in this
460 area. Lastly, the case of *B. grandiflora* is certainly explained by its restricted distribution, nevertheless
461 making it an interesting candidate for evaluation.

462 3.4.2 Phytochemical and pharmacological review

463 A bibliographical survey was undertaken for the 10 species with the highest I_g . Major metabolites are
464 presented hereafter, along with some activities of extracts and pure molecules when available. The
465 review was limited to the plant part used as recorded in **table 3 in supplementary data**. We
466 concentrated on antileishmanial activities, and antitrypanosomal activities were treated as they are
467 closely related to Leishmaniasis. Antibacterial activities are also reported due to frequent co-
468 infections, the reduction of a bacterial co-infection leads to a perceived improvement by traditional
469 societies. Antifungal activities are also reported due to the taxonomic proximity between yeasts and
470 *Leishmania*, leading to a therapeutic translation where antifungals achieve good results against
471 *Leishmania* (Houël et al., 2015). Lastly, due to the intramacrophagic location of the parasites,
472 inflammatory processes subtending the pathogenesis and immunity in general, are key targets in
473 leishmaniasis healing (Alexander & Russel, 1992; Sher & Coffman, 1992; Soong et al., 1997; Matte &
474 Olivier, 2002).

475 1. *Spondias mombin* (leaves and bark)

476 To our knowledge, few data are available concerning *S. mombin* leaves and bark chemistry. This
477 species is characterized by the presence of flavonol-3-*O*-glycosides, with quercetin-3-*O*-rutinoside
478 being identified as the major phenolic compound in a methanolic leaf extract (Pereira et al., 2015).
479 Quercetin, isoquercetin, ellagic acid and chlorogenic acid were also identified in hydromethanolic or
480 hydroethanolic leaves extracts (Cabral et al., 2016; da Silva et al., 2012), and ellagitannins (geraniin
481 and galoilgeraniin) and phenolic acids (6-alkenyl-salicylic acids) from *S. mombin* leaves and stems
482 hydroethanolic extract (figure 3) (Corthout et al., 1991; Corthout et al., 1994). Moreover, 3 β -olean-
483 12-en-3-yl (9Z)-hexadec-9-enoate was isolated from methanolic leaf extract (Fred-Jaiyesimi et al.,
484 2009).

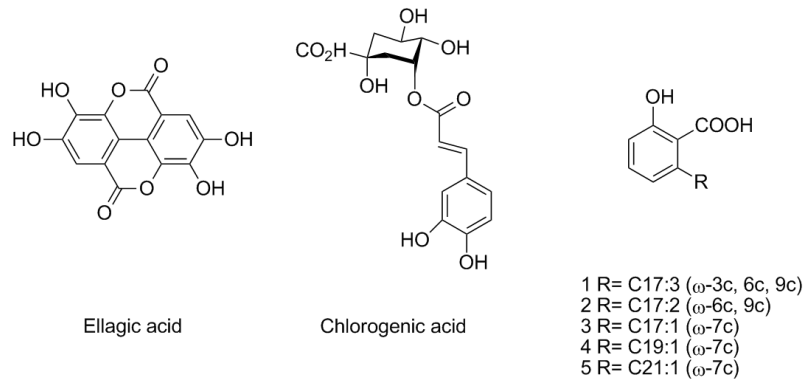
485 Using carrageenan-induced peritonitis model in mice, a significant anti-inflammatory effect was
486 demonstrated for hydroethanolic leaf extract at 300 and 500 mg/kg, by inhibiting leukocyte
487 migration to the peritoneal cavity and without cytotoxicity *in vitro* on 3T3 fibroblast cells. The same
488 activity was observed for ellagic acid and chlorogenic acid pure compounds at doses of 2.5, 5 and 10
489 mg/kg (Cabral et al., 2016). Similar results concerning anti-inflammatory activity have also been
490 obtained by Nworu et al. (2011) on methanolic leaf extract, which reduced the production of LPS-
491 induces TNF- α and NO in a dose-dependent manner and inhibited carrageenan-induced paw edema
492 at doses of 100, 200, and 400 mg/kg per os.

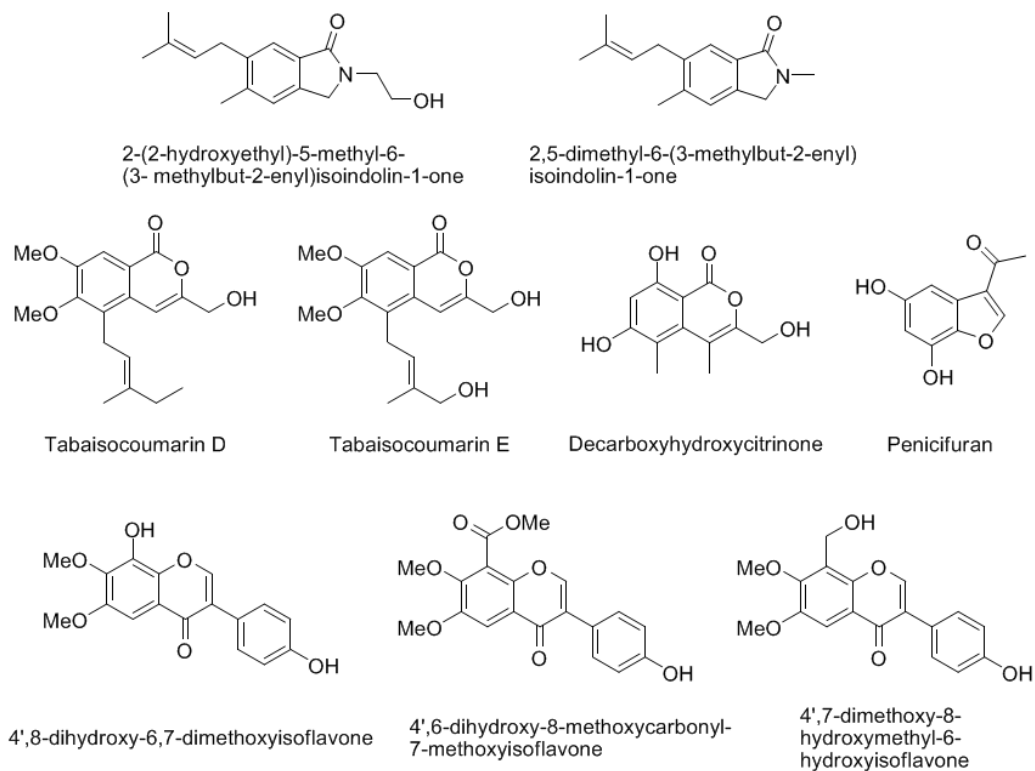
493 A moderate antibacterial activity was demonstrated for a hydromethanolic leaf extract, with MIC
494 values of 125 μ g/ml against *Serratia marcescens*, *Proteus mirabilis* and *Enterobacter cloacae* (da Silva
495 et al., 2012). Phenolic acids isolated from leaves and stems also exhibited strong antibacterial activity
496 (MIC in the 3-25 μ g/ml range) against *Bacillus cereus*, *Streptococcus pyogenes* and *Mycobacterium*
497 *fortuitum* (Corthout et al., 1994). Anticandidal activity was demonstrated for a crude methanolic
498 extract of *S. mombin* bark and leaves (Okwuosa et al., 2012).

499 No antileishmanial activity was detected for *S. mombin* ethanolic bark extract on *L. major*
500 promastigotes (Kvist et al., 2006) or *L. amazonensis* axenic amastigotes (Estevez et al., 2007). Bark
501 aqueous decoction was also inactive on *L. guyanensis*, *L. major* and *L. donovani* promastigotes as well
502 as on *L. donovani* amastigotes, with IC₅₀ > 500 μ g/ml in all cases (Mans et al., 2016). *S. mombin* bark
503 extracts were also inactive against *L. infantum* but exhibited strong antitrypanosomal activity (IC₅₀ in
504 the 2.3-12.2 μ g/ml range) against *T. brucei brucei* (Traore et al., 2014). Interestingly, two fractions
505 obtained from a methanolic extract of *S. mombin* leaves and consistent with galloylquinic acids, were
506 inactive against *L. chagasi* promastigotes (IC₅₀ > 200 μ g/ml) but exhibited IC₅₀ of 0.6 and 17.1 μ g/ml
507 respectively against the amastigote stage. A third fraction, presenting chemical characteristics of
508 galloyl-glucose, exhibited an IC₅₀ of 0.3 μ g/ml against *L. chagasi* amastigotes (Accioly et al., 2012).

509 Eventually, biological evaluation of *S. mombin* extract did not display any cicatrizant activity (Villegas
510 et al., 1997).

511

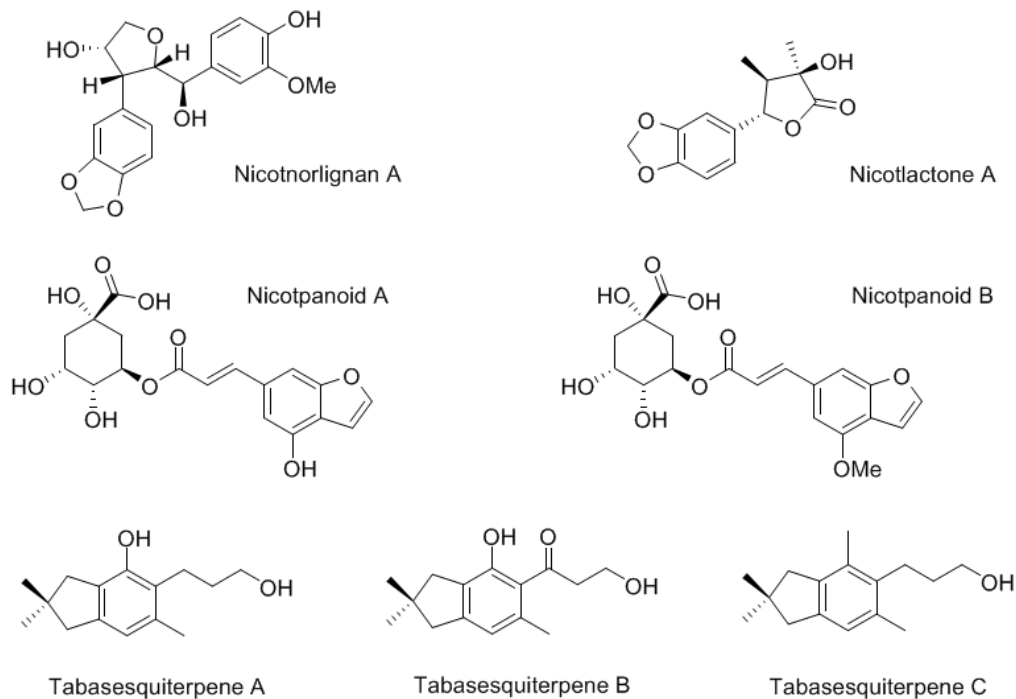




528
529

Figure 4a: Recently isolated constituents of *N. tabacum* leaves

530



531

532 Figure 4b: Recently isolated constituents of *N. tabacum* leaves

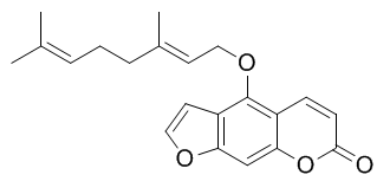
533 3. *Citrus aurantifolia* (fruit, bark)

534 Numerous flavonoids such as isorhamnetin derivatives, luteolin and luteolin derivatives, apigenin and
535 apigenin derivatives, narigin, rutin, quercetin and quercetin derivatives, kaempferol, nobiletin,
536 hesperidin and eriocitrin were identified from methanol and ethyl acetate extracts of peel and juices
537 of *C. aurantifolia* (Brito et al., 2014; Costa et al., 2014; Loizzo et al., 2012). Coumarins and
538 furocoumarins, such as bergamotin, 5-geranyloxypsoralen or 5,7-dimethoxycoumarin were also
539 identified in *C. aurantifolia* peel and juice (figure 5) (Costa et al., 2014; Sandoval-Montemayor et al.,
540 2012). Limonoids (limonexic acid, isolimonexic acid, and limonin) are present in *C. aurantifolia* juice
541 (Patil et al., 2009). *C. aurantifolia* fruits are also characterized by the presence of essential oil, the
542 major compound being limonene, alongside with α -terpineol, γ -terpinene, β -pinene, neral, geranial
543 and coumarins (Amorim et al., 2016; Craske et al., 2005).

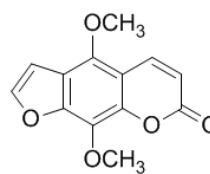
544 No evaluation of antileishmanial properties of *C. aurantifolia* was found in literature. Weak activity
545 has been measured for *C. limon* root extract against *L. major* promastigotes and *C. paradisi* root
546 extract was shown as inactive against *L. major* promastigotes (Kvist et al., 2006). Interestingly
547 however, limonene and derivatives show activity *in vitro* against *L. braziliensis* promastigotes
548 (Graebin et al., 2010) and pure limonene applied topically led to a significant reduction of lesion sizes
549 and a notable decrease in the parasite burden in *L. amazonensis*-infected mice (Arruda et al., 2009).

550 Immunomodulatory properties of concentrated lime juice extract were demonstrated on PHA
551 activated human mononuclear cells (Gharagozloo & Ghaderi, 2001). Anti-inflammatory properties
552 were also demonstrated, measuring the effect of *C. aurantifolia* essential oil on inflammation models
553 in mice. Inhibition of cytokines and NO production was also observed for the essential oil and pure
554 limonene. However, *C. aurantifolia* induced myelotoxicity in mice, which could be due to the
555 presence of citral (Amorim et al., 2016).

556 As far as antimicrobial activity was concerned, 5,8-dimethoxypsoralen, 5-geranyloxypsoralen,
557 palmitic acid, linoleic acid, oleic acid, 4-hexen-3-one and citral, isolated or identified from a hexane
558 extract of *C. aurantifolia* peels, were active against *Mycobacterium tuberculosis*, with MIC values in
559 the 25-100 $\mu\text{g/ml}$ range (Sandoval-Montemayor et al., 2012). Antibacterial activity against the same
560 microorganism has also been demonstrated for a hexane peel extract (Camacho-Corona et al., 2008).
561 Methanolic extract of *C. aurantifolia* fruit also exhibited antimicrobial activity against various Gram-
562 negative and Gram-positive micro-organisms (Melendez & Capriles, 2006).



5-geranyloxypsoralen



5,8-dimethoxypsoralen

563

564 **Figure 5:** Antibacterial furanocoumarins isolated from *C. aurantifolia* peel extract

565 4. *Jatropha curcas* (latex, leaves, bark, fruit, roots)

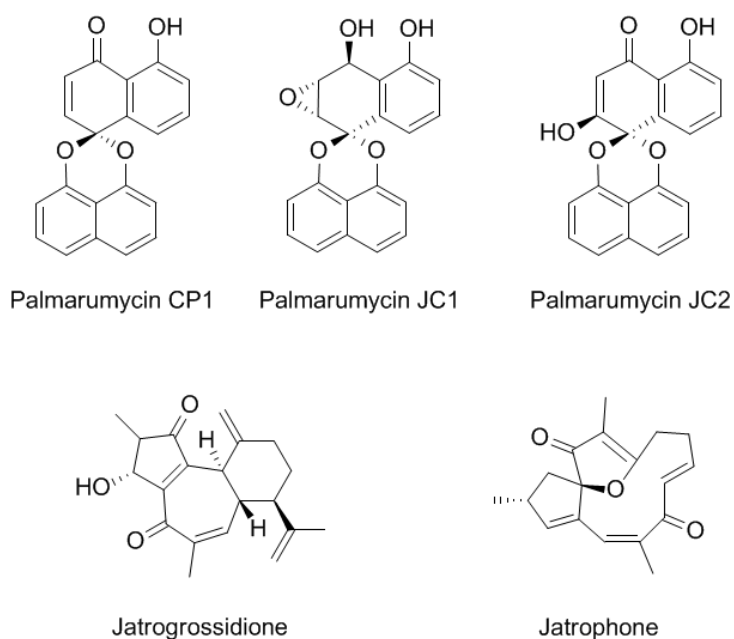
566 *Jatropha curcas* phytochemistry has been extensively studied and constituents isolated from various
567 organs were specifically reviewed by Zhang et al. (2009). Diterpenes and diterpenoids represent an
568 important class of compounds isolated from diverse *J. curcas* plant parts, e.g. jatrophalactone,
569 jatrophalone and jatrophadiketone (Liu et al., 2012) curcusones A, B and spirocurcasone (Chianese et
570 al., 2011; Li et al., 2014) isolated from roots, jatrophodione from aerial parts methanolic extract (Xu
571 et al., 2011), or jatrocucadiones A and B from twig ethanolic extract (Bao et al., 2015). Most of these
572 compounds have been tested for cytotoxic activity (Li et al., 2014; Liu et al., 2012; Xu et al., 2011).
573 Lignans and coumarins are also a representative class of *J. curcas* compounds (Zhang et al., 2009). In
574 particular, the lignans jatrophasins A, C and D were isolated from dried seed ethanolic extract (Li et
575 al., 2014). Lignans, such as curcaslignan A-D, are also present in aerial plant parts (Xu et al., 2012).
576 Phytosterols are mostly found in leaves (e.g. campesterol, stigmasterol and β -sitosterol) (Ribeiro et al.,
577 2012), whereas seeds are characterized by the presence of phorbol esters (*Jatropha* factors C1-C6)
578 (Haas et al., 2002). Cyclic peptides (curacycline A and B) were isolated from *J. curcas* latex, alongside
579 with the protease curcain (Auvin et al., 1997; Van den Berg et al., 1995; Nath & Dutta 1991).

580 An aqueous decoction of *J. curcas* root bark was tested for antiprotozoal activity against
581 *Trypanosoma b. brucei*, *T. cruzi*, *Leishmania infantum*. An IC_{50} of 30.3 μ g/ml was measured against *T.*
582 *b. brucei*, but the extract was shown to be inactive in the other bioassays (Musuyu Muganza et al.,
583 2012). Interestingly, jatrogrossidione isolated from *J. grossidentata* roots, and jatrophone isolated
584 from *J. isabellii* roots exhibited notable antileishmanial activities *in vitro* against *L. braziliensis*, *L.*
585 *amazonensis* and *L. chagasi* (promastigote forms, and amastigote forms infecting macrophages).
586 Jatrophone, also identified in *J. gossypifolia*, was also active *in vivo* against *L. amazonensis*, but
587 exhibited significant toxicity (Schmeda-Hirschmann et al., 1996).

588 Noticeable anti-inflammatory activity of *J. curcas* acetone leaf extract was measured using nitric
589 oxide (NO) production measurement and 12-lipoxygenase (LOX) inhibitory bioassay. The extract had
590 a significant effect on LOX inhibition at 100 μ g/ml, and inhibited 92.7 to 85.0 % of NO production at

591 concentrations ranging from 50 to 6.25 µg/ml in a dose-dependant manner (Dzoyem & Eloff, 2015). A
592 strong inhibition of NO production was also demonstrated for a root extract, which however also
593 showed high cytotoxicity. According to the authors, the anti-inflammatory activity of the root extract
594 could be due to the presence of hexadecanoic acid methyl ester, octadecanoic acid methyl ester and
595 octadecanoic acid (Othman et al., 2015). *Jatropha curcas* root powder applied topically in paste form
596 in distilled water significantly reduced ear inflammation in mice at the dose of 1.0 mg per ear and
597 this anti-inflammatory activity was also observed for the methanol extract in various induced
598 oedema models (Mujumdar & Misar, 2004). *J. curcas* crude latex (Villegas et al., 1997) and bark
599 extract (Shetty et al., 2006) exhibited significant wound healing activity *in vivo*. Lastly, curacycline A
600 was shown to exhibit anti-inflammatory properties by inhibiting the classical pathway complement
601 activity and human T-cell proliferation in a moderate dose-dependant manner (Van den Berg et al.,
602 1995).

603 Antimicrobial activity of *J. curcas* leaf methanolic extract was also studied against various strains of
604 fungi and bacteria (Villaseñor & Cariño, 2011). Palmarumycins CP1, JC1 and JC2, three
605 deoxypreussomerins isolated from *J. curcas* stems, were active against *Staphylococcus aureus*
606 (Ravindranath et al., 2004).



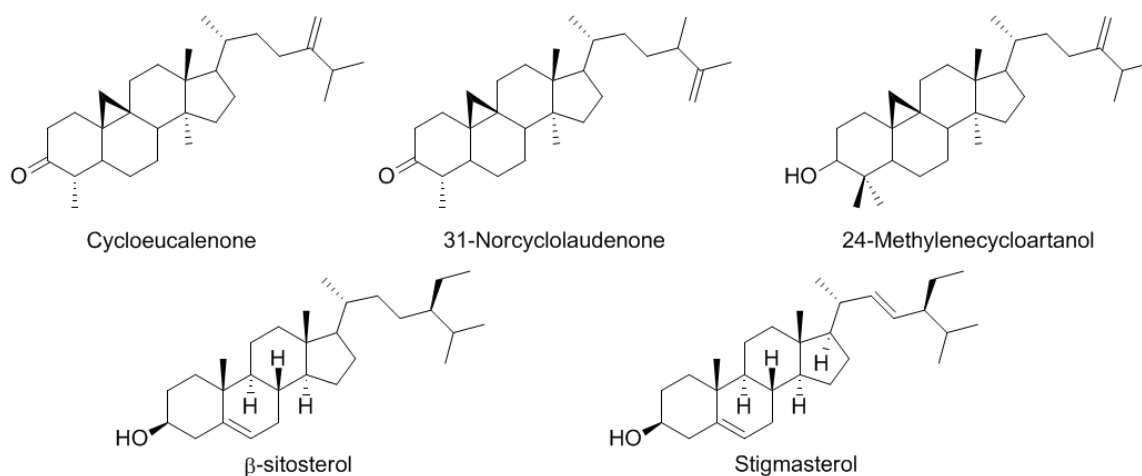
607
608 **Figure 6:** Antimicrobial compounds (palmarumycins) isolated from *Jatropha curcas* stems and
609 antileishmanial compounds (jatrogrossidione and jatrophone) isolated from *J. grossidentata* and *J.*
610 *isabellii* roots

611 5. *Musa x paradisiaca* (leaves, fruit peels)

612 Tannins and steroids of a methanolic extract obtained from *M. paradisiaca* leaves were identified
613 using colorimetric and spectroscopic detection (Accioly et al., 2012). Fruit peel methanol extracts led
614 to the isolation of the acyl steryl glycosides sitoindoside-I, sitoindoside-II, sitoindoside-III and
615 sitoindoside-IV, and of the glycoside sitosterol gentobioside and sitosterol *myo*-inosityl- β -D-
616 glucoside. Some of these compounds were responsible for the anti-ulcerogenic activity of the
617 extracts (Ghosal, 1985; Ghosal & Saini, 1984).

618 Similar compounds, *i.e.*, triterpenes and sterols isolated from *M. paradisiaca* fruit peels, were tested
619 for antileishmanial activity against *L. infantum chagasi* promastigotes and amastigotes. 31-
620 Norcycloclaudenone, 24-methylene-cicloartanol and a mixture of β -sitosterol and stigmasterol
621 exhibited activities similar to pentamidine against promastigotes, with EC₅₀ values of 39.3, 14.3 and
622 16.5 μ g/ml, respectively, and cycloeucaenone, 24-methylene-cicloartanol, and the mixture of β -
623 sitosterol and stigmasterol (figure 7) exhibited statistically similar activity to amphotericin B against
624 amastigotes, yet with large confidence intervals (Silva et al., 2014).

625

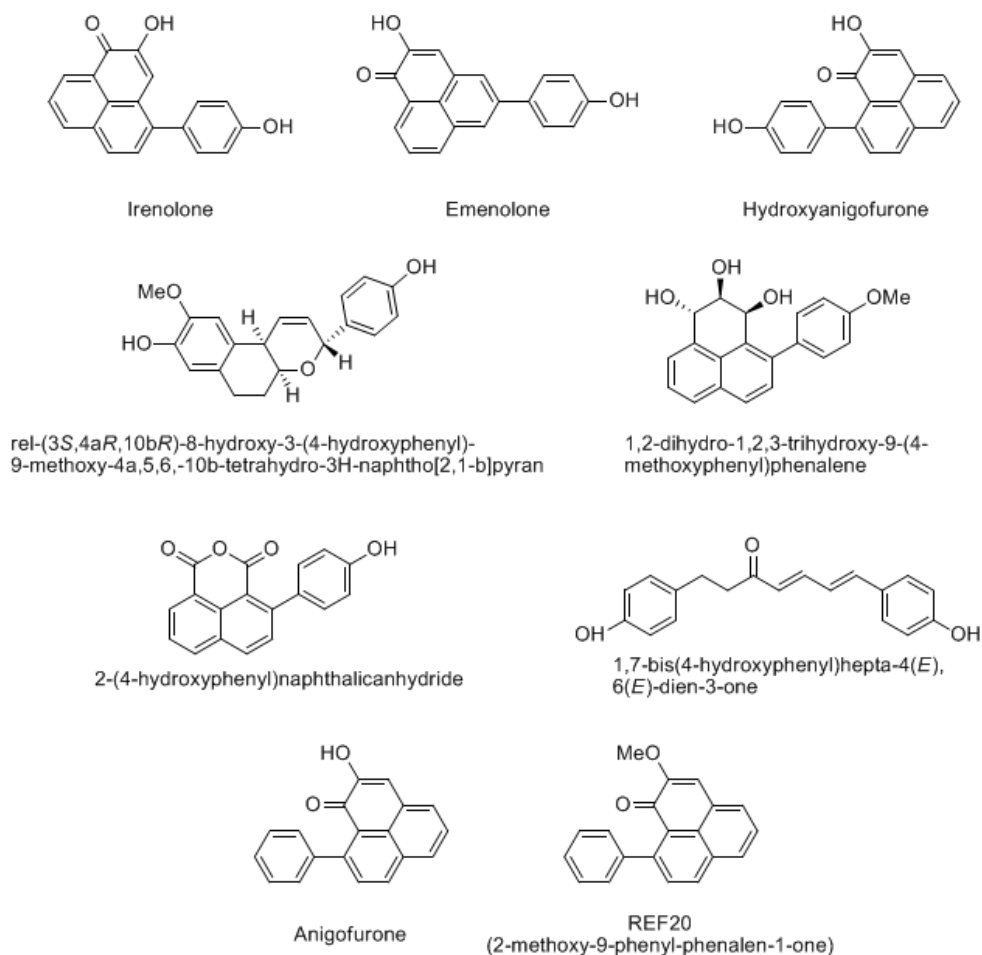


626

627 **Figure 7:** Leishmanicidal triterpenes and sterols isolated from *Musa x paradisiaca*

628 In addition, five compounds were isolated from a methanol extract of the fruits of *Musa x*
629 *paradisiaca*: hydroxyanigorufone, rel-(3*S*,4*aR*,10*bR*)-8-hydroxy-3-(4-hydroxyphenyl)-9-methoxy-
630 4*a*,5,6,10*b*-tetrahydro-3*H*-naphtho[2,1-*b*]pyran, 1,2-dihydro-1,2,3-trihydroxy-9-(4-
631 methoxyphenyl)phenalene, 2-(4-hydroxyphenyl)naphthalic anhydride and 1,7-bis(4-
632 hydroxyphenyl)hepta-4(*E*),6(*E*)-dien-3-one (figure 8) (Jang et al., 2002). Previously, two phenalene
633 phytoalexins, irenolone and emenolone, had also been isolated from an ethyl acetate extract of
634 *Musa x paradisiaca* leaves and green fruits treated with kanamycin as inducer (figure 8) (Luis et al.,

635 1993). It is of notable interest that antifungal phenyl-phenalenone phytoalexins (anigorufone as well
 636 as precursors and derivatives, particularly 2-methoxy-9-phenyl-phenalen-1-one, **figure 8**) isolated
 637 from *M. acuminata* plants submitted to fungal stress exhibited moderate leishmanicidal activities
 638 against *L. infantum* axenic amastigotes (LC₅₀ in the 10.5-23.9 µg/ml range) and *L. donovani*
 639 promastigotes (LC₅₀ in the 10.3-68.7 µg/ml range) (Luque-Ortega et al., 2004).



640

641 **Figure 8:** Compounds isolated from fruits and leaves of *Musa x paradisiaca*, alongside two
 642 antileishmanial phytoalexins (anigorufone and 2-methoxy-9-phenyl-phenalen-1-one) isolated from
 643 *Musa acuminata*.

644

645 Moreover, fractions obtained from a methanolic extract of *M. x paradisiaca* leaves were subjected to
 646 antileishmanial activity evaluation against *L. chagasi* promastigotes and amastigotes. Two of them
 647 exhibited IC₅₀ values < 2 µg/ml against promastigotes. Against the amastigote stage, their respective
 648 IC₅₀ were of 14.2 and 16.5 µg/ml. In terms of chemical composition, the data concerning these
 649 fractions indicated the presence of condensed tannins (Accioly et al., 2012).

650 Anti-inflammatory properties of *M. x paradisiaca* extracts were also evaluated. A decoction of fresh
651 leaves topically applied on *Croton* oil-induced ear oedema in mice significantly reduced the lesion
652 (Brito Alvarez et al., 2014). Likewise, stem juice methanol extract at a dose of 200 and 400 mg/kg
653 orally exhibited significant anti-inflammatory activity in a dose-dependent manner in various oedema
654 models in rats (Biswas et al., 2012). Interestingly, wound healing activity was also demonstrated for
655 *M. sapientum* var. *paradisiaca* aqueous and methanolic extracts at 100 mg/kg in rats, decreasing
656 wound area, scar area and lipid peroxidation in particular (Agarwal et al., 2009).

657 An alcoholic extract of *M. x paradisiaca* stems tested for antimicrobial activity did not inhibit the
658 growth of various pathogens (*Staphylococcus aureus*, *Salmonella paratyphi*, *Shigella dysenteriae*,
659 *Escherichia coli*, *Bacillus subtilis*, *Candida albicans*) (Ahmad & Beg, 2004), whereas organic leaves
660 extracts, and ethanolic and water fruit peel extracts, exhibited moderate antibacterial and antifungal
661 activity respectively with agar diffusion method (Karuppiah & Mustaffa, 2013; Okechukwu, 2012).

662 6. *Carica papaya* (latex, fruit)

663 A characteristic of *C. papaya* is the abundant presence of latex in several organs, including leaves and
664 stems. This latex is known to contain four main cysteine endopeptidases: papain, chymopapain, glycil
665 endopeptidase and caricain, alongside with minor enzymatic constituents (Azarkan et al., 2003;
666 Brocklehurst et al., 1985). The presence of lipids in the lipophilic fraction of *C. papaya* latex was also
667 investigated and revealed the presence of polar lipids composed of free fatty acids, sterols and
668 triterpenic alcohols. Among fatty acids oleic acid and linoleic acid (Barouh et al., 2010) were
669 specifically identified. Phytochemical studies were also conducted on leaves, for example on
670 methanolic leaf extract (Canini et al., 2007) and chromatographic analyses revealed the presence of
671 numerous classes of compounds: alkaloids represented by carpaine, the major alkaloid of *C. papaya*
672 leaves, phenolic compounds including tocopherol, ascorbic acid, caffeic acid, coumarin and
673 derivatives, flavonoids (kaempferol, quercetin and derivatives) and aminoacids.

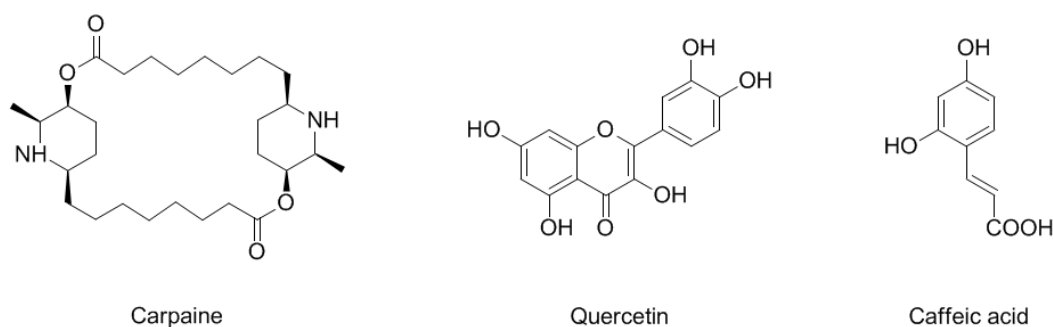
674 Carpain has demonstrated moderate *in vitro* activity against *Trypanosoma brucei rhodesiense*
675 trypomastigotes and *T. cruzi* amastigotes (IC₅₀ of 12.7 and 16.3 µM) but was inactive against
676 *Leishmania donovani* amastigotes (IC₅₀ > 200 µM) (Julianti et al., 2014), and it was recently
677 demonstrated that pure caffeic acid and quercetin (figure 9) exhibited interesting antileishmanial
678 activities against various stages of *L. amazonensis* (promastigotes, amastigotes, infected
679 macrophages) (Montrieux et al. 2014).

680 The medicinal properties of *Carica papaya* L. (Caricaceae) were reviewed by Mbosso Teinkela et al.
681 (2016). Notably, significant anti-inflammatory activity of an ethanolic extract of air-dried leaves was
682 demonstrated *in vivo* using carrageenan induced paw oedema model in rats as well as formaldehyde

683 arthritis model (Owoyele et al., 2008). Anti-inflammatory activity was also demonstrated *in vitro* for
684 an ethanol fresh aerial parts extract which, in a dose dependent manner, inhibited the TNF- α
685 production induced by LPS or IPP by immature dendritic cells (Sagnia et al., 2014). However, it should
686 be noted that papaya latex is commonly used to induce oedema in inflammation models (Gupta et
687 al., 1992).

688 As far as wound healing is concerned, papaya latex prepared in gel form was shown to be effective in
689 the treatment of burns in a mouse model (Gurung & Skalko-Basnet, 2009).

690 Lastly, antimicrobial activity of the methanol extract of *C. papaya* latex was studied against various
691 bacteria and pathogenous fungi (*Enterococcus faecalis*, *Staphylococcus aureus*, *S. saprophyticus*, *S.*
692 *epidermididis*, *Escherichia coli*, *Klebsiella pneumonia*, *Salmonella typhimurium*, *Candida albicans*, and
693 *Trichophyton rubrum*). The extract exhibited weak antimicrobial activity, with MIC values from 125 to
694 500 $\mu\text{g}/\text{mL}$ (Mbosso Teinkela et al., 2016). Fungistatic effect of the latex against *Candida albicans* was
695 also demonstrated and attributed by the authors to the presence of cysteine proteases present in
696 the latex and causing cell wall degradation (Giordani et al., 1996). To our knowledge, no evaluation of
697 antileishmanial activity of *C. papaya* latex or leaves has been performed to date.



698

699 **Figure 9:** Antiparasitic compounds isolated from *Carica papaya* leaves

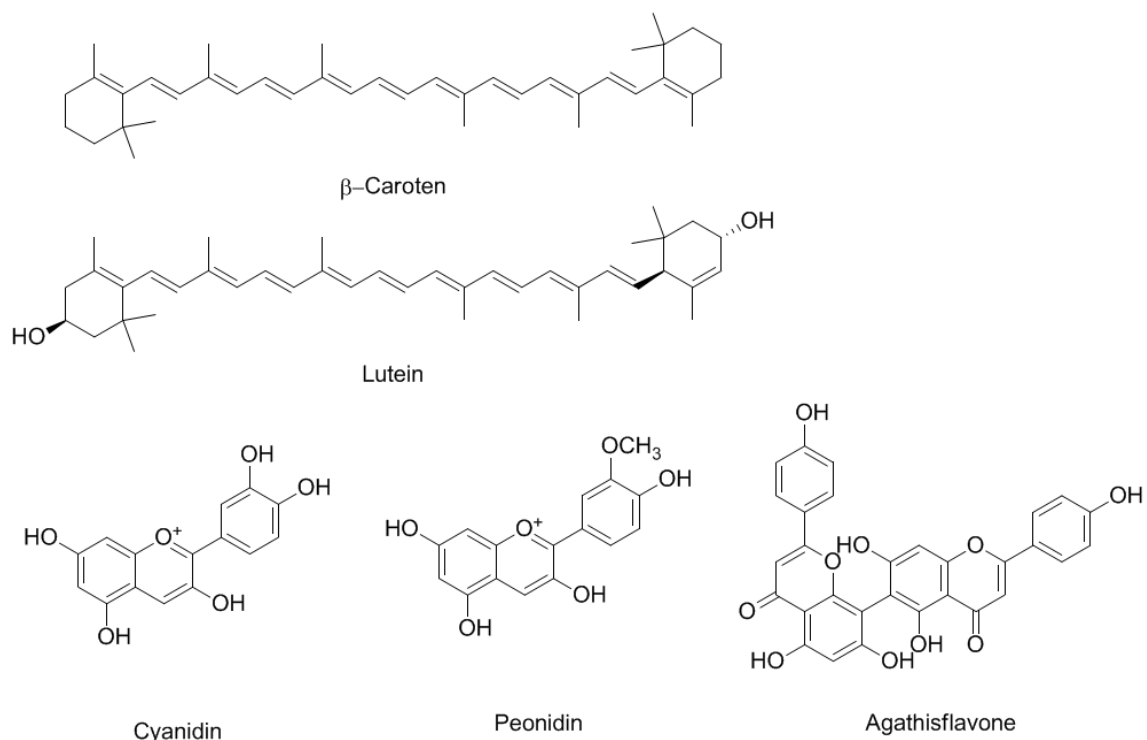
700

701 7. *Anacardium occidentale* (leaves, bark)

702 Several parts of this tree native to North-East Brazil are used in traditional medicine, particularly
703 against leishmaniasis. Bark contains a yellowish resin containing a polysaccharide named bassorin
704 (Oliver-Beyer, 1986). Anacardic acids, aromatic phenols such as cardol, anacardol and ginkgol, tanins,
705 flavones and sigmat-4-en-3-one (figure 10a & b) were also isolated from the bark (Huok, 2014;
706 Sankara Subramanian et al., 1969; Roth & Lindorf, 2002; Alexander-Lindo et al., 2007). Essential oils
707 were identified from leaves containing as major compounds mostly sesquiterpenes (among which β -
708 phellandrene, germacrene B and D, *trans*- α -bergamotene, α - and β -copaene, (*E*)-caryophyllene) and

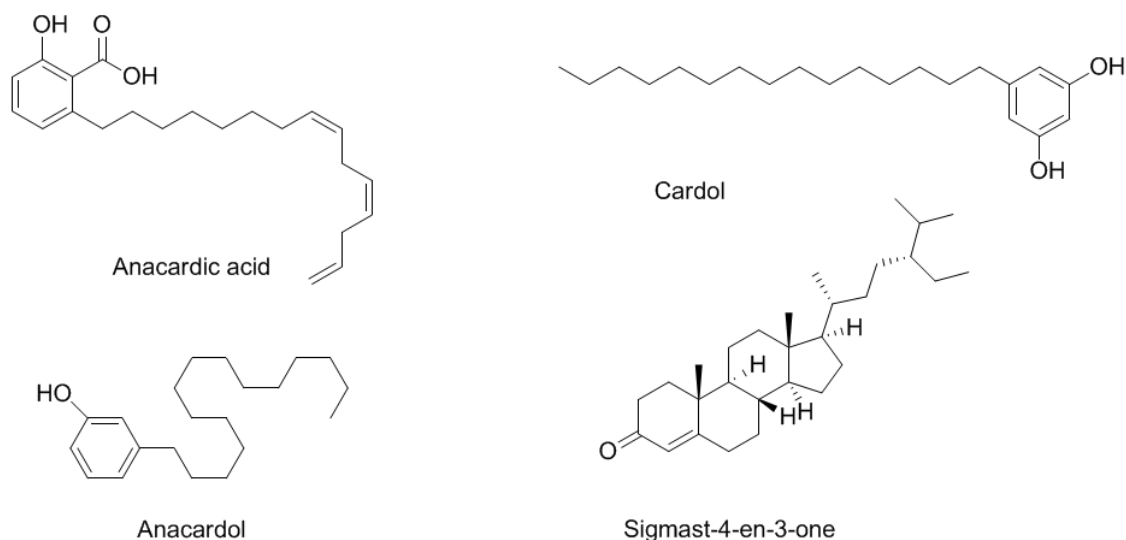
709 some monoterpenes (limonene, methyl-chavicol, and linalool) (Kossouoh et al., 2006; Montanari et
 710 al., 2012). A high content of phenolic compounds was also measured in leaves, including the
 711 presence of cyanidin and peonidin alongside β -carotene and lutein, (Konan and Bacchi, 2007;
 712 Kongkachuichai et al., 2015). The biflavonoid agasthisflavone was also isolated (Konan et al., 2012).
 713 *A. occidentale* stem bark methanolic extract was shown to be inactive against *L. amazonensis* and *L.*
 714 *chagasi* promastigotes (Braga et al., 2007).
 715 Significant anti-inflammatory activity was observed *in vivo* (carrageenan induced rat paw oedema)
 716 for crude leaf ethanolic extract and a butanone fraction (Patil et al., 2003). *In vivo* and *in vitro* anti-
 717 inflammatory effects were also observed for bark extracts (Olajide et al., 2009; Olajide et al., 2013;
 718 Mota et al., 1985).
 719 Weak antifungal activity was observed for this extract against *Cryptococcus neoformans* (Braga et al.,
 720 2007). Antimicrobial activity was also demonstrated *in vitro*, particularly against *Staphylococcus*
 721 *aureus*, *Bacillus stearothermophilus* and *Shigella dysenteriae* (Akinpelu, 2001).
 722 Cytotoxicity and toxicity of pure compounds or leaf extracts was also studied (Konan et al., 2007;
 723 Konan et al., 2012).

724



725

726 **Figure 10a:** Carotenoid and flavonoid compounds identified in *Anacardium occidentale* leaves and
 727 bark.



729

730 **Figure 10b:** Phenolic and sterol compounds identified in *Anacardium occidentale* leaves and bark.

731

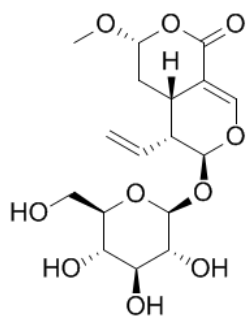
732 8. *Chelonanthus alatus* (whole plant)

733 This herbaceous plant from the Gentianaceae family is characterized by the presence of secoiridoids,
 734 which are acknowledged as chemotaxonomic markers of this botanical family. Sweroside, vogeloside
 735 and chelonanthoside were isolated from leaves of *C. alatus* (Sanchez et al., 2012; Shiobara et al.,
 736 1994) (Figure 11). Phenolic compounds and flavonoids were also described in the leaves (Lizcano et
 737 al., 2010), as well as bisphosphocholine irlbacholine (Bierer et al., 1995).

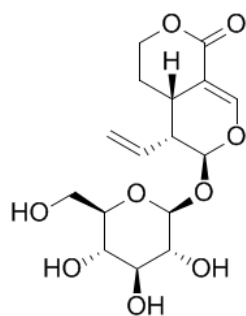
738 An ethanolic leaf extract exhibited moderate activity (CI_{50} 37,4 $\mu\text{g/ml}$) on *L. amazonensis* axenic
 739 amastigotes (Valadeau et al., 2009).

740 Interestingly, irlbacholine, isolated from *C. alatus* roots showed a strong antifungal activity against
 741 *Candida albicans*, *Cryptococcus neoformans* and *Aspergillus fumigatus* (Lu et al., 1999). Notably, it
 742 can be considered as a dimer of miltefosine, also demonstrated as antifungal (Lu et al., 1999) but
 743 more particularly used as a promising antileishmanial compound in the neotropics (Soto et al., 2004;
 744 Croft et al., 2006).

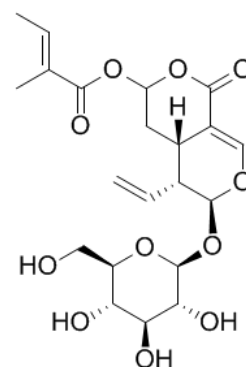
745 Sweroside demonstrated antibacterial (Dinda et al., 2007) and wound healing properties *in vitro*
 746 (Oztürk et al., 2006).



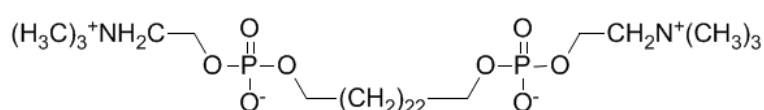
Vogeloside



Sweroside



Chelonanthoside



Irlbacholine

747

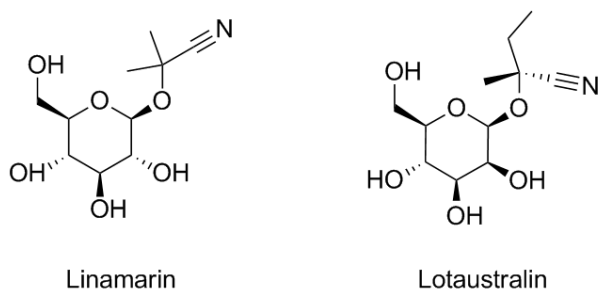
748 **Figure 11:** Secoiridoids and bisphosphocholine irlbacholine isolated from *Chelonanthus alatus*.

749

750 9. *Manihot esculenta* (leaves, roots)

751 Chemicals studies concerning *Manihot esculenta* (Euphorbiaceae) reveal the presence of two major
 752 classes of compounds: lipids and glycosides. Notably, phospholipids, glycolipids, free sterols and
 753 triacylglycerol were isolated from fresh roots, representing 0.25% of roots fresh weight (Lalaguna &
 754 Agudo, 1988). Cyanogenic glycosides are known to accumulate in all parts of *M. esculenta*, the two
 755 major compounds being linamarin which accounts for around 90% of the total glycosides, and
 756 lotaustralin (Burns et al., 2012; Du et al., 1995) (**Figure 12**). These compounds were, for example,
 757 isolated from an ethanolic extract of the fresh root cortex, alongside other cyanogenic and non-
 758 cyanogenic glycosides, and were also identified in a methanolic extract of fresh leaves (Prawat et al.,
 759 1995). The presence of flavonoids, including rutin, correlated to the antioxidant effect of an aqueous
 760 extract of young leaves (Tsumbu et al., 2012). Two flavonoid glycosides, kaempferol-3-*O*-rutinoside
 761 and quercetin-3-*O*-rutinoside, were also isolated from leaves (Prawat et al., 1995). Terpenoids such
 762 as the two acid triterpenes esculentoic acid A and B, alongside with taraxerol, 3-*epi*-taraxerol, β -
 763 amyrin, taraxerone, lupenone, β -amyrinone and sigmasterol, were identified from an ethyl acetate
 764 extract of aerial parts (leaves, stems and twigs) in the context of the search for novel anticancer
 765 compounds (Chaturvedula et al., 2003). Other terpenoids were also isolated from stems (Zeng et al.,
 766 2015; Pan et al., 2015; Li et al., 2011).

767 To our knowledge, no evaluation of this species' biological activity against *Leishmania* has been
768 undertaken.
769 Based on the use of *M. esculenta* in traditional African medicine against inflammation and pain, the
770 anti-inflammatory and analgesic effects of an aqueous leaf extract were evaluated *in vivo*, and the
771 results obtained were significant in carrageenan-induced paw oedema in rats as well as against
772 xylene-induced ear oedema in mice models (Adeyemi et al., 2008). Taraxerol is also known as an anti-
773 inflammatory compound (Yao et al., 2013).
774 Antibacterial activity was also demonstrated *in vitro* for the chloroform leaf extract against *Listeria*
775 *monocytogenes*, *Vibrio cholerae*, *Shigella flexneri* and *Salmonella typhi* and for the ethanol leaf
776 extracts against *Pseudomonas aeruginosa*, *Corynebacterium diphtheria* and *Vibrio cholerae* (Zakaria
777 et al., 2006). β -Amyrin has been reported as antibacterial (Abdel-Raouf et al., 2015).
778



779
780 **Figure 12:** Major cyanogenic glycosides isolated from roots and leaves of *Manihot esculenta*.

781
782 *10. Plantago major* (leaves)

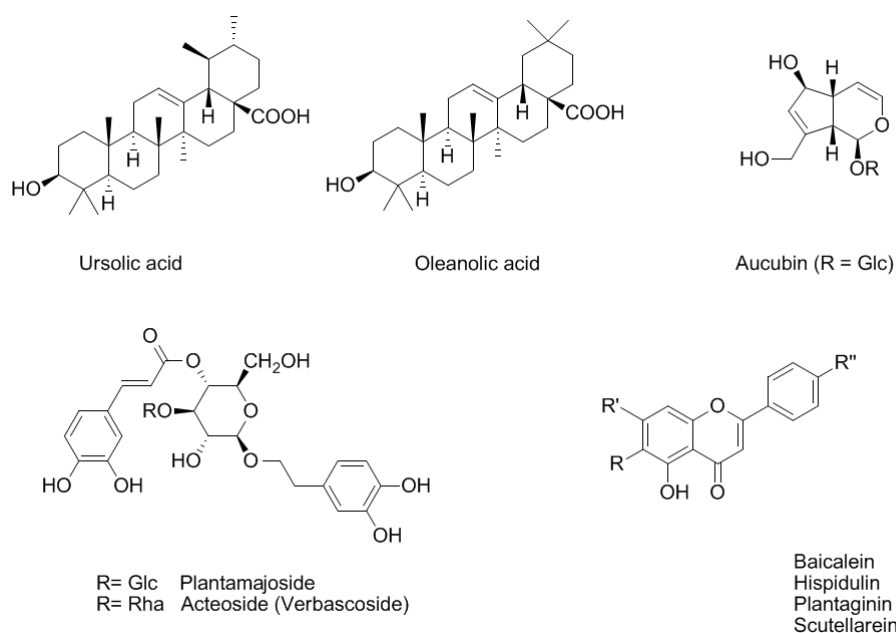
783 Chemical constituents and biological activities of *Plantago major* are well described and have been
784 extensively reviewed by Samuelsen (2000). Numerous chemical compounds from various classes
785 have been isolated from leaves, such as polysaccharides presenting anti-inflammatory and
786 immunostimulatory properties *in vitro* and *in vivo* (Hetland et al., 2000; Samuelsen et al. 1995;
787 Samuelsen et al., 1998). Leaves also contain fatty acids and are characterized by the presence of leaf
788 wax rich in triterpenic acids, notably oleanolic acid and ursolic acid, which are also anti-inflammatory
789 (Samuelsen, 2000). Caffeic acid derivatives, including plantamajoside and acteoside were also
790 isolated from *P. major*. Plantamajoside has anti-inflammatory, inhibitory of lipoxygenases,
791 antioxidant and antibacterial activities amongst others. Acteoside is a known antioxidant,
792 antibacterial and immunosuppressant (Jimenez & Riguera, 1994; Ravn and Brimer, 1988; Samuelsen,
793 2000). Flavonoids are well represented in *P. major* extracts. Plantaginidin, scutellarein, baicalein and

794 hispidulin are antioxidant compounds and the last three compounds have been described as anti-
 795 inflammatory and antiallergic (Bellik et al., 2013; Clavin et al., 2007; Toyoda et al., 1997; Wang et al.,
 796 2011). Finally, iridoid glycosides represent the last major class of compounds isolated from *P. major*.
 797 These include aucubin, particularly known for its topical anti-inflammatory properties *in vivo* (Recio
 798 et al., 1994). Structures of the major biologically active compounds isolated from *P. major* are
 799 represented in **figure 13**.

800 To our knowledge, no *in vivo* or *in vitro* evaluation of *P. major* extract on *Leishmania* has been
 801 performed.

802 Biological activities of crude leaf extracts are nonetheless numerous. Anti-inflammatory properties
 803 have been demonstrated *in vivo* (Samuelsen, 2000). In addition, the influence of *P. major* leaf
 804 methanol extract on NO and TNF- α production by rat peritoneal macrophages has been studied by
 805 Gomez-Flores et al. (2000) and strong immunoenhancing properties have been highlighted. Anti-
 806 inflammatory properties and enhancement of innate antioxidant activity of *P. major* extracts were
 807 also shown in the case of liver injury caused by acetaminophen (Hussan et al., 2015). Wound healing
 808 properties of water and ethanol-based leaf extract have been demonstrated in the case of oral
 809 epithelial cells in a scratch assay (Zubair et al., 2012) using an *ex-vivo* porcine wound-healing model
 810 (Zubair et al., 2016).

811 Lastly, *P. major* extracts presented antibacterial and antifungal activities. The 50% aqueous ethanol
 812 extract was active against *Staphylococcus aureus*, *Bacillus subtilis*, *Shigella dysenteriae* and
 813 *Escherichia coli* and the methanol extract was effective against *Fusarium tricinctum*, *Saccharomyces*
 814 *cerevisiae*, *Microsporium gypseum* and *Candida albicans* (Samuelsen, 2000).



816 **Figure 13:** Examples of biologically active compounds isolated from *Plantago major*

817

818 **3. Conclusion**

819 This review of Amazonian people's perceptions of cutaneous leishmaniasis and its treatments shows
820 that many practices are shared throughout the region although questions regarding the selection of
821 plants are raised. Nevertheless, this type of review of traditional antileishmanials in Amazonia is
822 indubitably biased. Firstly, in terms of bibliography, as it is clear that ethnobotanical publications are
823 not equally available for all countries: French Guiana accounts for 178 URs, while Brazil only accounts
824 for 17. This probably reflects a combination of field accessibility (both logistic and administrative), of
825 the dynamics of both local and international research, and of the publication strategies of public
826 researchers in the countries. On this basis, the use of the most current statistical tests is impossible,
827 as the basic sampling needs to be balanced. Nevertheless, this work has enabled us to highlight some
828 patterns of use: plants are still used throughout the region and the compromise between clinical
829 efficiency, resource availability, and cultural relevance of the remedy plays an important role, leading
830 to an over representation of cultivated species some of which are exotic to Amazonia.

831 One criticism that could be made of these indices is that they are compare uses taken at different
832 times, in a synchronic study. However, it is impossible to overcome the problem of different dates.
833 As local knowledge is dynamic, a diachronic approach would better fit to the study of ethnobotanical
834 knowledge evolution, but is beyond the realms of the current state of research.

835 Analysing the botanical species level instead of the genus level is explained by the high variations of
836 phytochemical patterns between species of a same genus, although traditional uses are sometimes
837 more coherent at genus level. Nevertheless, a genus analysis can be provided if necessary. Examples
838 of genera that suffer from this choice are *Piper* (Piperaceae) and *Vismia* (Hypericaceae). The first
839 genus, including 11 URs, barely includes 2 URs for the two most highly cited species, *P. elongatum*
840 and *P. marginatum*. The *Vismia* genus includes 18 URs while the most highly cited species, *V.*
841 *guianensis*, includes 4 URs in the area.

842 In addition, the more localised the plant use is, the more difficult it is to discriminate a regional
843 pharmacological match from cultural dissemination. In the case of *B. grandiflora*, with a high I_c and a
844 low I_g , its high level of activity on *L. major*, *L. guyanensis* and *L. panamensis* promastigotes was
845 described ($< 10 \mu\text{g/mL}$ for each) (Fuchino et al., 2008) and tips the balance in favour of
846 pharmacological activity.

847 It might be easier to detect pharmacological potential in the Low I_c high I_g cluster as a convergence of
848 use due to independent discoveries seems highly probable. In this category, *Chelonanthus alatus* is

849 astonishing as it produces a unique dimer of miltefosine, a synthetic molecule now being trialed
850 against cutaneous leishmaniasis in the Neotropics. This compound would need to be tested in order
851 to better evaluate its therapeutic potential.

852 An important factor is the high predominance of topical application of these remedies, with nearly
853 90 % of recipes collected being applied directly on the wound. Until now, the main antileishmanials
854 are given by injection. A topical formulation would be a revolution in the field and traditional
855 practices advocate for such a paradigm shift. A convergence has also been observed between the use
856 of irritating/burning plants and the use of household chemicals highlighted by Ramdas (2012).
857 Species such as *Jatropha curcas* or *Anacardium occidentale* could easily enter in this category.
858 Another lesson from this review is that very few of the traditional antileishmanial plants have
859 undergone *in vivo* assays. Promastigote tests are still the norm despite years of discussion for a
860 model closer to reality. It also appears that many of the high I_d plants have anti-inflammatory
861 activities and sometimes anticandidal activities. The example of *Jatropha* should be cited as a
862 potential synergy: a protease (curcain) might ease the penetration of leishmanicidal diterpenes, all
863 supported by anti-inflammatory metabolites calming down the pro-inflammatory cytokine response
864 leading to tissue necrosis. Lastly, all these remarks support the need for more integration in
865 ethnopharmacology ... for antileishmanials as for everything else.

866

867 **4. Acknowledgments**

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870

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