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Uncaria tomentosa and *Uncaria guianensis* an agronomic history to be written

Uncaria tomentosa e *Uncaria guianensis* uma história agrônômica a ser escrita

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— REVIEW —

ABSTRACT

The *Uncaria tomentosa* and *Uncaria guianensis* species, which are endemic plants in the Amazonian region, are highlighted as medicinal plants mainly because of their anti-inflammatory activity. The vegetal drug and various types of extracts have been commercialized by pharmaceutical industries and distributed in several countries, thus configuring the economic potential of both species. The objective of the present research was to collect agronomical data published in PubMed, SciELO, and Scopus databases and analyze the main subjects that were either investigated or not investigated to enable the production chain of these species. The conclusion is that *U. guianensis* has been less studied than *U. tomentosa* under all aspects evaluated. Both species have been exploited in an extractivistic way. However, no report was found on either sustainable management or conservation or domestication strategies or yet large scale production that can continuously attend the global demand of the pharmaceutical industry. Furthermore, the amount currently produced is insufficient to supply the program of the Ministry of Health, which intends to provide herbal drugs from *Uncaria* to all Brazilian cities.

Key words: *Uncaria*, cat's claw, medicinal plants, extractivism.

RESUMO

As espécies *Uncaria tomentosa* e *Uncaria guianensis*, plantas endêmicas da Amazônia, destacam-se como plantas medicinais por apresentarem principalmente atividade anti-inflamatória. A droga vegetal e diversos tipos de extratos são comercializadas por indústrias farmacêuticas distribuídas em vários países, configurando o potencial econômico de ambas as espécies. O objetivo deste trabalho foi reunir dados agrônômicos publicados nas bases de dados PubMed, SciELO e Scopus para analisar os principais temas que já foram investigados ou que ainda precisam ser abordados

para viabilizar a cadeia produtiva dessas espécies. A conclusão é que *U. guianensis* é menos estudada do que *U. tomentosa* sob todos os aspectos avaliados. Ambas as espécies são exploradas de forma extrativista. Entretanto, não foram encontrados relatos de manejo sustentável, nem estratégias de conservação ou domesticação, ou ainda plantios em larga escala que possam atender de modo contínuo a demanda mundial da indústria farmacêutica. Além disso, não há quantidade suficiente para abastecer o programa nacional do Ministério da Saúde, que pretende disponibilizar fitoterápicos produzidos a partir de *Uncaria* a todos os municípios brasileiros.

Palavras-chave: *Uncaria*, unha de gato, plantas medicinais, extrativismo.

INTRODUCTION

Mankind has always found solutions to its health problems in nature. The use of plants in the treatment and cure of diseases is as old as the human species. For millennia, medicinal plants corresponded to about 90% of the medications used to the relief and healing of diseases (CUNHA et al., 2003).

Data from the World Health Organization (WHO) showed that at some point of life about 80% of the world population has used a medicinal plant in the search for relief from some unpleasant symptom, and at least 30% of them were prescribed by physicians (MARTINS et al., 2003). In the early 1990s, the WHO reported that 65-80% of the population in developing countries depends on medicinal plants as the only way to access for basic healthcare (VOLPATO, 2005). In

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addition, the WHO also recognizes that traditional knowledge on biodiversity products is an important tool to develop new drugs. They are expected to be useful in fighting diseases that afflict populations who live in developing countries (WORLD HEALTH ORGANIZATION, 2003).

Tropical forests, which are located in developing countries such as Brazil, are the major sources of biodiversity. These forests represent about one third of the world flora. However, countries such as USA, Japan, and some in Europe were those that most profited from the trade of natural products from these forests (KLEIN et al., 2009). Tropical forests have half of about 500,000 species of plants estimated to exist in the world, and less than 1% of them were researched for pharmacological activity (MARTINS et al., 2003).

Species from the genus *Uncaria*, which are among plants with a significant therapeutic and economic potential, occur in tropical forests, especially in Amazonia. This genus includes the tribe *Coptosapelteae* (LAUS, 2004), specifically subtribe *Mitragyninae* (KEPLINGER et al., 1999), subfamily *Cinchonoidae* (MUR et al., 2002), and family *Rubiaceae*.

Among botanists, there is not yet consensus regarding the number of species that compose the genus *Uncaria*. However, DWYER (1980), SHULTES et al., (1990), and SOUKUP (1987) mention that there are 60, and GENTRY (1993) reports that 50 species.

The genus *Uncaria* includes species with an expressive medicinal potential, e.g., *U. formosana*, *U. guianensis*, *U. macrophylla*, *U. rhynchophylla*, *U. sinensis* and *U. tomentosa* (FALKIEWICZ & LUKASIAK, 2001). *U. guianensis* e *U. tomentosa* are among the most commercialized species worldwide.

The species *U. guianensis* is found in areas between the 08°04'00"N-17°32'00"S and 44°56'00"E - 78°25'42"W coordinates (altitudes: 7-1010m), in Bolivia, Brazil, Colombia, Ecuador, Guyana, French Guyana, Peru, Suriname, and Venezuela. Whereas *U. tomentosa* is distributed between the 15°30'00"N-13°36'00"S and 51°58'00"E - 89°00'00"W coordinates (altitudes: 5-750m), in areas including Belize, Bolivia, Brazil, Colombia, Costa Rica, Ecuador, Guatemala, Guyana, French Guyana, Honduras, Nicaragua, Panama, Peru and Venezuela (ZEVALLOS-POLLITO & TOMAZELLO FILHO, 2010). In Brazil, the species *U. guianensis* is found in the States of Acre, Amazonas, Amapá, Maranhão, Mato Grosso,

Pará, Rondônia, Roraima, and Tocantins; whereas, *U. tomentosa* is mainly distributed in the States of Acre, Amapá, Amazonas, and Pará (PEREIRA & LOPES, 2006).

These species are typical of tropical and subtropical humid climates, needing favorable weather conditions (temperatures: 17.0-25.7°C; rainfalls: 1200-6000mm) during the year for their development (ZEVALLA & ZEVALLOS, 1996). They develop in soils of alluvial origin and sandy loam or open clay texture (SHUNKE, 1998), with pH values ranging from strongly acidic to slightly alkaline, abundant organic matter in poorly drained or flooded areas (ZEVALLOS et al., 2000).

They grow in various geo environments, and the mean number of individuals per hectare is variable in floodplain (33), secondary forest (10.7) and mainland (1.7) (MIRANDA et al., 2001). The species *U. tomentosa* occurs in soils rich in organic matter, areas of primary forests, salt marshes and banks of watercourses; whereas, *U. guianensis* grows in secondary forests, riverbanks and roads. This species has a high capacity to colonize anthropized and degraded areas, being considered invader in abandoned pasture areas. In Brazilian regions where *U. guianensis* occurs naturally, it is found more abundantly and frequently than the species *U. tomentosa* (GUEVARA, 1995; MIRANDA et al., 2001).

Both species are used by traditional people in Amazonia in the treatment of various diseases such as asthma, arthritis, dermatitis, diabetes, gastritis, gonorrhea, inflammation of the genito-urinary tract, irregularity in the menstrual cycle, viral processes, tumors (benign and malignant), and ulcers (VILCHES, 1997).

Although they are widely mentioned in ethnopharmacological surveys, data collected in the *PubMed* showed that the species *U. tomentosa* has been studied for a longer period (1974-2014) and the numbers of studies published are greater (164) and researches have been led by the USA (34) and followed by Brazil (21). Articles published with *U. guianensis* are more recent (1983-2014) and a smaller number (14) as compared to *U. tomentosa*, and the United States (3) and Brazil (3) are also the countries that most published on this species (PUBMED, 2014). According to the SciELO database, 40 studies were published on *U. tomentosa* (29) and *U. guianensis* (11). These numbers are also reported in the Scopus database.

Pharmacological studies conducted with extracts from *U. guianensis* and *U. tomentosa*

confirmed their antioxidant, anti-diabetic, anti-microbial, anti-inflammatory, immunostimulant, anticancer, and anti-Parkinson's disease effects (ZHANG et al., 2015).

Alkaloids are the most important group of secondary metabolites reported in the species *U. guianensis* and *U. tomentosa*. They are divided into indole tetracyclic alkaloids (corynanthein, dihydrocorynanthein, hirsutheine, and hirsutine) oxindole alkaloids (rhynchophylline, isorhynchophylline, corynoxine, isocorynoxine, rotundifolin, and isorotundifolin) indole pentacyclic alkaloids (akuamigine, augustine, augustolin, isoamalicin, and tetrahydroalstonin) and oxindole alkaloids (speciophylline, mitraphylline, isomitraphylline, pteropodin, isopteropodin, and uncarin F), and glycoindole alkaloids (3 α -dihydrocadambine and dolichantosin) (LAUS et al., 1997; FALKIEWICZ & LUKASIAK, 2001; LUNA-PALENCIA et al., 2013). Besides the alkaloids, the triterpenic heterosides (derived from the quinovic acid) and polyphenols (especially tannin) are also highlighted (PAVEI et al., 2012; SHENG et al., 2005).

In *U. tomentosa*, the alkaloids are distributed in flowers (2.10%), leaves (1.59%), stem bark (0.50%), branches with thorns (0.32%) (QUIROZ et al., 2004), and root (1.00-2.00%) (REINHARD, 1999). PEÑALOZA et al. (2015) conducted a study with access of *U. tomentosa* collected *in situ* in Peru and showed that the content of oxindole alkaloids varied significantly among individuals, in both stem bark (0.328-2.591%), sheets (0.360-4.792%) and branches (0.347-1.431%).

The fact that individuals, that produce much more alkaloids in the leaves than in the stem bark, have been found in environments of natural occurrence of the species, can make collection of leaves more viable whether obtaining alkaloid-rich extracts is the purpose of the pharmaceutical industry. The production of herbal drugs from leaves will facilitate the management of the species, since a 10-year interval, which is required to withdrawn bark from the stems, is a considerably long time. In addition, withdrawal of leaves causes less damage to the plant phytosanitary status and preservation.

Regarding the presence and absence of pentacyclic and tetracyclic alkaloids, both species have chemotypes that also vary according to the time of year in which the plant is collected (PEÑALOZA et al., 2015; REINHARD, 1999). Although the secondary metabolites present in *U. tomentosa* and *U. guianensis* are similar, some

substances are produced by one but not by the other, e.g., the flavonoid kaempferitrin, which is present in the leaves and branches of *U. guianensis*, which has been considered a chemical marker able to distinguish these species (VALENTE et al., 2009). Another important cytogenetic difference between them is that *U. guianensis* has larger chromosomes and more heterochromatin in the cell nucleus (TEPPNER et al., 1984).

In addition to the taxonomic, chemical, and cytogenetic differences, there is also a clear distinction regarding the economic value assigned to these species. *U. tomentosa* is more commercialized and; therefore, has a higher value in the market than *U. guianensis*. Despite this difference, extracts of both species are widely produced by various industries. Thirteen patents involving these species are registered in the United States Patent and Trademark Office (USPTO, 2015).

Whereas Peru and the USA started commercialization, pharmacological studies, and patent development with these species in the 80's, Brazil began to consider the importance of these genetic resources (which are abundant in the Brazilian Amazon forest) only in 2000. Then the extractive exploitation was initiated and these species were included in lists of priority plants in the herbal medicine programs of the Ministry of Health.

The importance of knowing the production chain of medicinal plants is described in the guidelines of the National Policy of Medicinal Plants and Herbal Drugs (BRASIL, 2013). However, development of this subject for the species *U. guianensis* and *U. tomentosa* could be higher. BLAS (1999) described, in part, the production chain of *U. tomentosa* in a 10-ha area in the native community of Bajo Naranjillo (Peru). The study included a forest inventory and a management plan based on the regrowth capacity of the species. A withdrawal of 740kg of bark per ha was estimated for a natural forest with a ten-year pruning cycle.

The bark of *Uncaria* has been commercialized with widely varying prices. In Peru (1996-1998), about 300ton of dry bark were purchased from the local communities by US\$0.90 and exported to the USA by US\$3.90 (prices per kg). According to the Ministry of Agriculture of Peru, about 135ton of cat's claw were exported in 2000 (SPIEGELFELD, 2005; MIRANDA, 2005). In Brazil (State of Acre), the export of *U. tomentosa* was intensified since 2000 and the plant crop was estimated to be 20ton per year (LIMA, 2005).

In general, the profit from commercializing forest products, which were collected extractivistically

by traditional communities, did not reach the hands of these ethnic groups. It remains concentrated in the hands of agents who send the raw material to the industry and/or large distribution centers.

Thus, the objective of this review was to gather information about *U. tomentosa* and *U. guianensis* dispersed in the literature, and suggest priority research areas that should be a funding target to make possible crop and preserve these species.

DEVELOPMENT

Uncaria tomentosa (WILLD.) DC

Some authors considered that the species *Uncaria tomentosa* was originated in Peru and Colombia (MAC BRIDE, 1936). It was described for the first time as *Nauclea aculeata* HBK, and only in 1830 it was named *Uncaria tomentosa*, as it is currently known. The term “*tomentosa*” comes from the observation of prominent ribs, with the appearance of fine veins in the abaxial surface of the leaves (VILCHES, 1997).

It is popularly known as cat's nail (DESMARCHELIER et al., 1997), a designation related to plant morphology. It has thorns on the stem, which are similar to nails (CHENG et al., 2007); although, it also has other popular names such as gabarato (DE FEO, 1992) vilcacora, samento (FALKIEWICZ & LUKASIAK, 2001), saventário (REINHARD, 1999), “jupindá” and “espera-ai” (PEREIRA & LOPES, 2006).

Figure 1 shows that leaves are perennial, flowers are yellow-white, and the thorns are sharp and of woody consistency, which facilitate their adherence to tree bark and branches (KEPLINGER et al., 1999; GANZERA et al., 2001). It is a giant climbing plant, whose height may reach 10-30m in the adult plant (MIRANDA et al., 2001).

The diameter at the base of the liana varies in the range 5-40cm in adult plants that have already flourished (GUEVARA, 1995). Individuals with diameter at breast height (DAP) 5-8cm provide on average 0.3-0.5kg of dry bark. Plants with such diameters usually have 20 to 25-m length, and yield 8-10kg of dry bark (MIRANDA et al., 2001; SILVA, 2008). The liana's bark is used for at least 2000 years in the traditional medicine of some Peruvian tribes, especially the *Asháninka* (PILARSKI et al., 2006), a people to whom the name Kampa is also assigned (PIMENTA, 2005).

A survey for the occurrence of *U. tomentosa* was performed in the micro-region of the Jurua river valley (Acre), which includes the High

Pentecost (in the city of Cruzeiro do Sul), Seringal São Salvador (in Mâncio Lima), and *Asháninka* Indian Reservation (in Marechal Traumaturgo) communities. In these areas, the production of dry bark (13kg ha^{-1}) was estimated. A mean diameter (5.4cm) was calculated for plants, and different numbers of individuals per hectare were observed in floodplain (17), secondary forest (44), and mainland (1) (MIRANDA et al., 2003).

The initial development of plants are affected by shading levels. Conditions of 55-60% shade favor the development in height and biomass accumulation (LUNZ et al., 2014). *U. tomentosa* has a positive phototropism, and luminosity required for the development of younger individuals located in areas of natural regeneration (CANALES-SPRINGETT et al., 2013a).

Plant growth (in height) is not influenced by rainfall levels and altitude. However, it is influenced mainly by fertility of the soil, which should be rich in organic matter, specific elements (N, P, K, Ca, and Mg), and pH in the range 5.3-6.1 (TOREJÓN & QUILIANO, 2007; MECHAN et al., 2007).

Different periods were observed for flowering (around September), fruiting and maturation of fruits (Oct-Nov), and seed dispersal (Jan-Feb). Insects are the main pollinating agents, and fruit development (until the maturity stage) occurs within 6-8 weeks after pollination. The species is evergreen, and the seed production cycle is annual (FLORES, 1995; MIRANDA et al., 2001).

The seedling production by seeds is viable. However, plants produced by sexual propagation show a significant chemical variability. Seeds have a variable size (2-4mm), and they are photoblastic positive. They may be preserved in cold room (10°C) when stored in paper bags and dry and dark conditions. The viability is lost after 10 (65-84%) and 120 (47-58%) days of storage in temperatures lower than 25°C (GUEVARA, 1995; INDACOCHEA & POLLITO, 1999).

In addition to seed propagation, multiplication can also be obtained by the micropropagation technique, which is seen as promising to obtain large-scale plants with industrial interest. In this context, various descriptions of *in vitro* insertion of *U. tomentosa* are available. However, a micropropagation protocol showing the production viability on a commercial scale, e.g., using a temporary immersion system was not yet published (FERIA-ROMERO et al., 2005; PEREIRA et al., 2006; LUNA-PALENCIA et al., 2013).

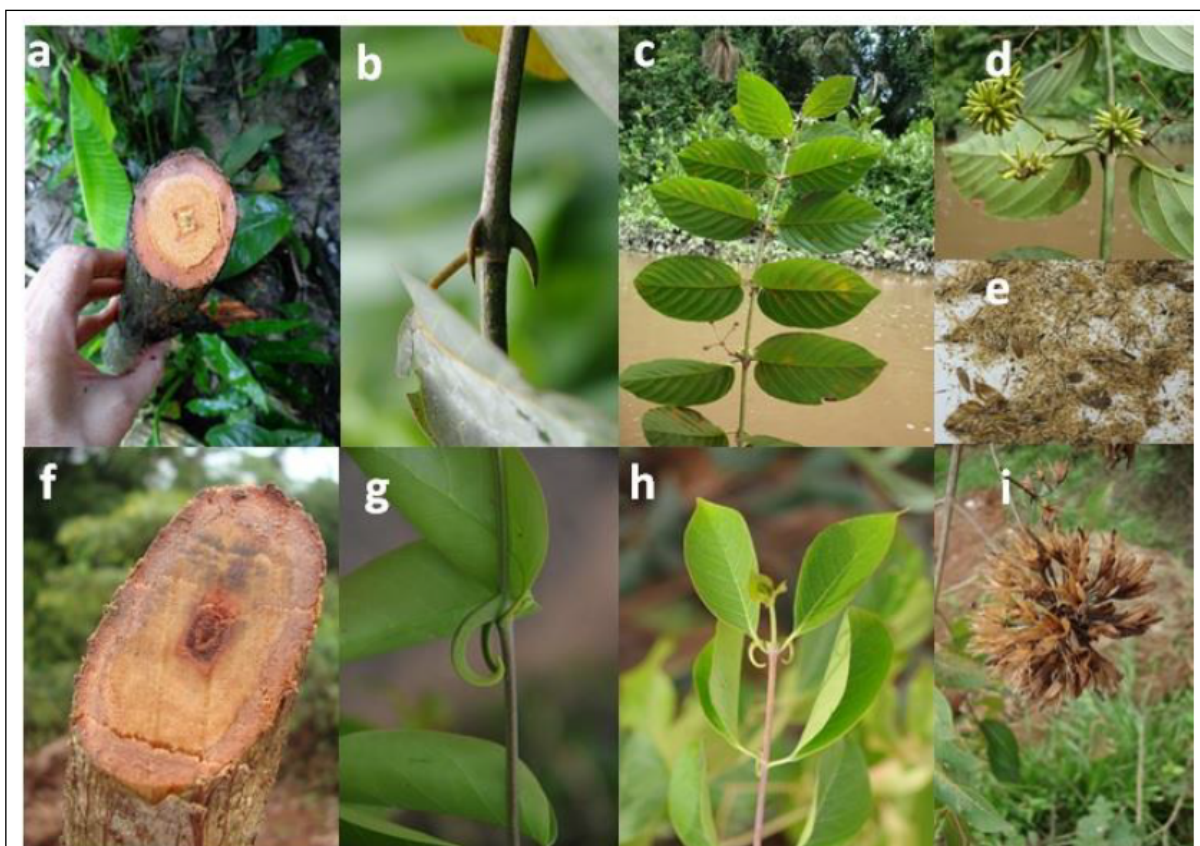


Figure 1 - *Uncaria tomentosa*: a) Stem, b) Thorns, c) Abaxial face of leaves, (showing the ribs that seem “fine veins”) d) Inflorescence, and e) Seeds. *Uncaria guianensis*: f) Stem, g) Thorns, h) Sheets, and i) Fruit.

Total alkaloid content in micropropagated plants after acclimatization varies according to age, and plants aged six months produce more than seedlings aged 2 months or 2 years. The content of tetracyclic alkaloids is higher in younger seedlings, whereas the pentacyclic alkaloids accumulate more in older plants (LUNA-PALENCIA et al., 2013).

Clone production by biotechnological techniques is certainly the most viable alternative to ensure standardization of raw material from the *Uncaria* species. In addition to the chemical variability found between individuals, there is a report that three varieties of *U. tomentosa* were found to be different from each other only by color of their freshly-cut cortex and root. Thus, colors are classified as liber whitish gray, yellowish brown, and dark red (KEPLINGER, 1982). Although this description is important, it is not included in the monographs of the American (AMERICAN HERBAL

PHARMACOPEIA, 1997) and British (BRITISH HERBAL PHARMACOPEIA, 1989) Pharmacopeia, and the *Hages Handbuch der Pharmazeutischen Praxis* (STRUM et al., 1999).

Ethnopharmacological studies performed with the species showed that it is popularly used in the treatment of abscesses, asthma, arthritis, skin and infectious diseases, deep wounds, gastritis, general inflammation, rheumatism, malignant tumors, gastric ulcers, postpartum recovery, prevention of general diseases, kidney cleansing, and menstrual cycle irregularities (AQUINO et al., 1991; DE FEO, 1992; AQUINO et al., 1997; SHENG et al., 1998; KEPLINGER et al., 1999; CUNHA et al., 2003; GARCIA PRADO et al., 2007; LORENZI & MATOS, 2008).

In addition to the ethnopharmacological data, various pharmacological tests performed *in vitro* and *in vivo* confirmed its antioxidant

(DREIFUSS et al., 2013), anticancer (PILARSKI et al., 2010), anti inflammatory (ROJAS-DURAN et al., 2012), antimicrobial (CCAHUANA-VASQUEZ et al., 2007), antiherpetic (CAON et al., 2014), contraceptive (NOGUEIRA NETO et al., 2011), neuroprotective (SHI et al., 2013), and antidiabetic (DOMINGUES et al., 2011) activities.

There is a consensus that a single substance or a single class of secondary metabolite being responsible for all pharmacological activities assigned to the species is unlikely. However, the pentacyclic oxindole alkaloids are considered chemical markers. Among them, uncarin, pteropodin, mitraphylline, speciophylline, isopteropodin, and isomitraphylline are highlighted (LAUS et al., 1997).

Due to the traditional use, pharmacological research confirming therapeutic efficacy, as well as phytochemical and analytical studies that enable the control over the quality of medicines produced from *U. tomentosa*, which has been stimulated by Brazilian government programs aiming primary health care. Thus, *U. tomentosa* was included in the list of plants described in the monographs on medicinal plants as published by the World Health Organization (WHO, 1997) and in the List of Essential Medicines published by the Brazilian government (RENAME) (BRAZIL, 2013).

Uncaria guianensis (Aubl.) J.F. Gmel

The species was described for the first time in the Guyanas (1775) as *Oourouparia guianensis* (Aublet). Two decades later, this nomenclature was changed to *Uncaria guianensis*, which remains unchanged so far (VILCHES, 1997). It is popularly known as uña de gato, uña de gavilán, gabarato colorado, gabarato casha (ARELLANO, 1994), unganangui (RUTTER, 1990), tambor huasca, ancaayacu (GENTRY, 1993), Paraguay, and ancajsillo (VILCHES, 1997). It is a climbing plant (height: 5-10m; base diameter: 4-15cm). Its liana is more creeping than climbing (Figure 1) because its thorns (with tip bent inward) impair its adherence to other plants (GUEVARA, 1995).

Different time periods were observed in the Peruvian forest for flowering (Feb-May) and fruiting (Apr-Jun) (FLORES, 1995; QUEVEDO, 1995), and in the Juruá river valley (Acre) for flowering (Feb-Apr), fruiting (May-Jun), and fruit maturation and seed dispersion (May-Aug) (MIRANDA et al., 2001). *U. guianensis* can propagate by seeds. Their germination are variable (25-85%) (GUEVARA, 1995; PEREIRA & LOPES, 2006) and can reach 90% when

the seeds are introduced *in vitro* (PEREIRA et al., 2006). According to a study, plants that grew from seeds presented great variability regarding morphology and content of secondary metabolites (TORREJÓN, 1997).

The alkaloid content in *Uncaria* varies between both individuals and different plant parts. This could be explained by the fact that the extracts were produced from plant samples collected in regions that are the center of origin of the species and; therefore, they have a considerable genetic diversity and chemical variability. Production of extracts from too much diversified herbal drugs hampers established quality standards for herbal drugs by the industry. In this context, the use of biotechnological techniques such as micropropagation are indicated for scaled production of elite clones, which are highly productive in terms of biomass and content of metabolites of interest.

A study on the occurrence of *U. guianensis* was conducted in the micro-region of the Juruá river valley and showed an estimated dry bark production of 199kg ha⁻¹, which is 15 times greater than that estimated for *U. tomentosa*. The average diameter (2.8cm) of plants and the number of individuals per hectare in floodplain (62), secondary forest (97), and mainland (4.8) were calculated (MIRANDA et al., 2003).

The natural regeneration of *U. guianensis* in anthropized areas are influenced by the amount of light that arrives at the under storey or ground vegetation. This factor is especially significant for higher plants, but the amount of light does not need to be abundant (CANALES-SPRINGETT et al., 2013b). As can be seen, the number of studies available in the scientific literature on the species *U. guianensis* is much smaller than that on *U. tomentosa*.

CONCLUSION

In Brazil, as in other countries, the use of and interest in *Uncaria tomentosa* is greater than those in *Uncaria guianensis*. However, the species *U. tomentosa* has a more restricted geographical distribution and occurs in more limited geo environments. It is important to investigate from the pharmacological point of view whether both species can be used for the same therapeutic purpose. If this assumption is confirmed, then cultivation of *U. guianensis* should be a priority, since its characteristics are more favorable to cultivation and management, e.g., non-sharp thorns and adaptation to environments with more drained and less fertile soils.

The Brazilian Ministry of Health and global pharmaceutical industry have a growing demand for raw material from *U. tomentosa* and *U. guianensis*. Although a reasonable number of phytochemical and pharmacological studies on these species can be reported, there is a lag regarding the agronomic researches, which are still preliminary, few and rather inconsistent. This scenario indicates that from this point of view almost everything has to be done.

Reports on areas cultivated with *U. tomentosa* and *U. guianensis* do not exist, and all raw materials for drug production are obtained in the extractivist mode, which impairs the genetic diversity and survival in natural environments. Thus, research in the genetic (conservation and diversity) and phytotechny (management, propagation, and cultivation) areas, should be a priority to enable large-scale production of both species.

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