Chapter 60

Phytochemistry of Medicinal Plants of the Amazon

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ABSTRACT
The results of the phytochemical research involving medicinal plants of the Amazon traditionally used by the population are described in this chapter as *Pilocarpus microphyllus, Copaifera sp, Carapa guianensis,* and *Bauhinia sp,* as well as qualitative and quantitative analysis of the phenolic content of *Connarus perrottetti, Cecropia obtusa, Cecropia palmata,* and *Mansoa alliacea*. A method was developed and validated to characterize the presence of phenolic compounds in extracts of medicinal plants from the Amazon for different years of sampling. A complete evaluation of the different possible causes of ion suppression in the analysis of extracts of medicinal plants by UHPLC-MS / MS using electrospray ionization is shown. The mineral content of dry matter composition of *Cecropia palmata* and *Cecropia obtusa* at different seasons evaluated the nutritional properties of the tea produced by infusion of the leaves of these two species of *Cecropia*. In the phytochemical analysis carried out in some species, the presence of sugar, protein, amino acid reducers, foamy saponin, and tannins was revealed. All of these results are part of this chapter.

Keywords: Amazon, phytochemical analysis, phenolic compounds Cecropia sp, *Pilocarpus, Connarus, Mansoa.*

1 INTRODUCTION

From prehistory, man has sought to take advantage of the active principles in plants, though empirically or intuitively, based on random discoveries. This can still be observed among primitive peoples, isolated as some indigenous tribes of South America (BERG, 1991).

Besides the belief, in many cases, the full realization of popular wisdom is observed. Many drugs originated from this empirical use, the result of a long process of tentative discoveries, for example, digitalis, drugs derived from the foxglove (*Digitalis purpurea* and D. *lanata*), with the powerful specific

action on the heart muscle. Its active principles, cardiotonic glycosides, are now mandatory weapons in the fight against certain heart diseases (LAMEIRA and PINTO, 2008).

Identifying, evaluating, and determining the way of obtaining and concentration rate of the active principles in plant species is of fundamental importance for the validation of their use and recommendation. Consequently, the valuation of traditional knowledge will become more important in scientific studies.

In the Amazon region considered the most biodiverse region of the planet (Silva et al, 2007), numerous plant species have been the subject of phytochemical studies aimed at identifying their mineral composition, the concentration rate of primary and secondary metabolites, and their activities. In this context, several scientific articles have been published with these objectives (FACCIN et al, 2017; SILVEIRA et al, 2015; RAMOS et al, 2017).

To evaluate the different possible causes of ion suppression in the analysis of extracts of medicinal plants, to determine the mineral content of composition in the dry matter obtained at different times of the year from the evaluation of the nutritional properties in the different forms of use, as well as, the presence of certain primary and secondary metabolites are the main objectives of this chapter.

Phytochemical of *Pilocarpus microphyllus, Copaifera reticulata, Carapa guianensis, and Bauhinia sp,*

a) Pilocarpus microphyllus Stapf ex Wardleworth (jaborandi, Rutaceae) is one of the most important Brazilian medicinal species owing to its content of pilocarpine (PIL), an alkaloid used for treating glaucoma and xerostomia. This species contains another alkaloid, epiisopiloturine (EPI), which has demonstrated effectiveness against schistosomiasis. the objective of the work developed by LIMA et al, (2017) was to assess seasonal changes of PIL and EPI in three populations of cultivated *P. microphyllus* from northeastern Brazil over one year, including the dry and rainy seasons.

Alkaloid profiles were correlated to phenotypic and genetic patterns in the morphological and molecular characterizations. PIL was the primary alkaloid and its levels differed among populations in all months except September. The S01 population (green line) showed an especially high PIL content compared to populations S02 and S03 (traditional line), which had similar alkaloid contents. PIL content gradually decreased in the three populations in the rainy season.EPI content was significantly different between the green line (S01) and the traditional line (S02 and S03).S01 had a significantly lower EPI content in all months, demonstrating that it was not the best source for EPI extraction. Inter simple sequence repeat (ISSR) markers and morphological analyses separated S01 from S02 and S03, in agreement with the alkaloid results.

This study shows the first correlation between the chemical, morphological, and molecular markers of *P. microphyllus* and highlights the potential benefits of a multidisciplinary research approach aimed at supporting both industry and the conservation of natural resources.

b) The genus *Copaifera* belonging to Leguminosae, Caesalpinioideae, consists of 43 species. In the Brazilian Amazonian rain forest nine species occur: C. *multijuga* Hayne, C. *glycijcarpa* Ducke, C. *pubiflora* Bentham, C. *nuirtii* Hayne, C. *paupera* (Herzog) Dwyer, C. *reticulata* Ducke, C. *duckei* Dwyer, C. *piresii* Ducke and C. *gutjanenevs* Desf (Martins-da Silva, 2006). Oleoresins produced in the trunk wood of the *Copaifera* species, popularly known as copaiba oil, are widely used in Brazilian popular medicine and several medicinal uses for copaiba oil have been reported in the literature, mostly for anti-inflammatory, analgesic, and bactericidal purposes (LAMEIRA and PINTO, 2008).

The volatiles of the oleoresin of C. *reticulata* has been previously reported. The paper developed aimed to determine the variation in volatiles of the oleoresins obtained from C. *reticulata* harvested at different places in the States of Para and Amapá, Brazil. The work developed by Zoghbi et al, (2009) aimed to determine the variation in volatiles of the oleoresins obtained from C. *reticulata* harvested at different places in the States of Pará and Amapá, Brazil.

The oleoresins of 12 trees of *Copaifera reticulata* growing wild in the States of Pará and Amapá were examined by GC-FID and GC/MS. The majority of oleoresins from Pará possessed high amounts of β-bisabolene (18.4-42.4%) and trans-α-bergamotene (11.8-29.6%). The oleoresins from Amapá were rich in β-caryophyllene (27.8-68.0%),

β-selinene (0.2-20.6%), and β-bisabolene (3.7-17.8%). The results presented reveal a great compositional variation in the oleoresins of C. *reticulata* which agrees with a previous study on *Copaifera* where the oleoresin collected at different times was analyzed (CASCON and GIIBERT, 2000).

c) Species commercialized frequently in Amazon include *C. multyuga* Hayne, *C. reticulata* Ducke, and *C. officinalis* (Jacq.) L. Commercial copaiba oil is a mixture of oleoresins isolated from *Copaifera* species. Numerous studies have been carried out to identify the components and biological properties of this oleoresin. The objective of the study carried out by Zoghbi et al, (2007) was to investigate the variation of the oleoresin per harvest and chemical composition of the *C. martii* during one year of seasonal observation. The oleoresins from *Copaifera martii* were harvested from September 2003 at one-month intervals up to September 2004, from the same individual tree, and examined by GC/FID and CC/MS.

The highest oleoresin per harvest occurred in January 2004 in the dry Amazonian season. The major volatiles of the oleoresin, (α-copaene and δ-cadinene, change from 36.4% to 51.2% and 13.7% to 17.3%, respectively. No appreciable changes were observed in the percentage of the volatile compounds during the seasonal observation, but the percentage of essential oils in the oleoresins also changes considerably (1.3% -21.3%).

The amount of oleoresin harvested ranged from 0-100mL. In conclusion, for the specimen of *C. martii* studied, during the seasonal observation, oleoresin per harvested and the percentage of the essential oil changed considerably during seasonal observation, but the chemical composition was not affected to

any great extent. According to our knowledge, this is the first report of the volatiles and seasonal observation from *C. martii.*

d) In the study developed by Lameira et al, (2009) the oleoresins of three trees of *Copaifera duckei* Dwyer were harvested from September 2003 at one-month intervals up to September 2004, and the volatiles examined by GC-FID and GC/MS. The oleoresins of three trees of C. *duckei* (Sample A: 138 cm DBH, Sample B: 262 cm DBH and Sample C: 133 cm DBH) were harvested from the same individual trees, in the experiment-al campus of the Brazilian Agricultural Research Corporation (Embrapa), in the municipality of Moju, State of Para, Brazil.

The highest oleoresin harvested from Sample A occurred from October 2003 to May 2004 (in the later dry season to early rainy season); the highest oleoresin harvested from Sample B occurred in September and October 2003 (in the later dry season), and from Sample C in June (in the later rainy season).

The percentage of the major volatiles of the oleoresin of Samples A and C (Sample A: 03-caryophyllene, trans-a-bergamotene, 03-selinene, and 0-bisabolene; Sample C: 13-caryophyllene and P-bisabolene) changes in a minor extent during the seasons. However, appreciable changes were observed in the percentage of p-caryophyllene and 0-bisabolene in Sample B. In the same way, appreciable changes were observed in the amount of oleoresin harvested: Sample A: 10 mL to 500 mL, Sample B: zero to 3000 mL, and Sample C: zero to 70 mL.

In conclusion, for all samples of C. *duckei* studied here, we observed considerable changes in the amount of oleoresin harvested. Nevertheless, the percentage of the main components of Samples A and C was not affected to a great extent. Contrary, the Sample B, the percentage of the major compounds changes considerably during seasons.

e) A phytochemical approach carried out by Lameira et al (2004) through phytochemical screening with the species *Adenocalymna alliaceum,Cecropa obtusa*, *Eugenia uniflora*, and *Pellucida peperomia*, identifying the main groups of organic compounds. The results of the phytochemical analysis revealed the presence of reducing sugars, amino acids, foamy saponin, and tannins in all species analyzed.

f) The phytochemical prospection of derivatives for the species *Carapa guianensis* Aubl. carried out by the Ministry of Health and Anvisa (2015) in other sources of the researched literature report the presence of alkaloids, essential oils, saponins, and tannins in leaves EtOH extract, triterpenoids in hexane seed extract, and tannins in the aqueous, hexane, chloroform, ethyl acetate and peel EtOH extracts. For fixed seed oil the presence of triterpenes, tetraterpenes, alkaloids, and limonoids was reported.

Qualitative and quantitative analysis of the phenolic content of *Bauhinia variegata var. variegata, Bauhinia variegata var. alboflava, , Cecropia obtusa, Cecropia palmata, Connarus perrottetti and Mansoa alliacea.*

A considerable number of analytical methodologies have been developed for the identification and confirmation of bioactive compounds in a wide variety of matrices. Several studies have been reported on coumarins (Melo and Sawaya, 2015), terpenes (Bellumori et al, 2015), saponins (Cheok et al, 2014) (poly)phenolic compounds (Zaupa, et al, 2015), and other classes of substances. Phenolic compounds have received increasing attention in the literature thanks to their high antioxidant activities, as well as for their cardioprotective and antimicrobial activities, anti-osteoporosis, anti-inflammatory, and anti-carcinogenic actions (GULTEKIN-OZGUVEN, et al, 2015).

Polyphenols have been increasingly investigated and consumed in recent years due to their nutritional potential and therapeutic value (AJILA et al., 2011). However, numerous species of medicinal interest still need to be studied regarding this and other classes of compounds. Amongst them are *Connarus perrottetti* var.*angustifolius* Radlk., *Cecropia obtusa* Trécul, *Cecropia palmata* Willd., Urticaceae, and *Mansoa alliacea* (Lam.) A.H.Gentry, Bignoniaceae, all native species of the Amazon rainforest, where are extensively used by the locals with limited scientific information.

Bauhinia variegata is one of the medicinal species present in the Amazon biome. Traditionally, *B. variegata* is used for its hypoglycemic activity (COELHO-FERREIRA, 2009). Only very few reports in the literature confirm the antidiabetic activity of *B. variegata* and other species of the *Bauhinia* genus, which is probably due to the action of its flavonoids.

Cecropia palmata and *Cecropia obtusa* have been reported to present tranquilizing and antirheumatic properties, as well as action against coronary artery disease (GIORGETTI, et al, 2007).

Connarus perrottetii has been reported for the treatment of female genitourinary infections and uterus problems with bleeding, ovarian cysts, and vaginal discharge, for cytotoxic activity against the human adenocarcinoma colon cancer cell line KM-12, as well as for its use to attenuate influenza symptoms, such as cough, nasal congestion and headache (SUFFREDINI, et al, 2007).

Mansoa alliacea is traditionally used for the treatment of rheumatism, fever, and influenza. Studies also indicate that M. alliacea has anti-inflammatory, antifungal, antiviral, and antimicrobial actions (SANZ-BISET and CANIGUERAL, 2011).

a) A method for the separation, identification, and quantification of 24 phenolic compounds using ultra-high performance liquid chromatography coupled to tandem mass spectrometry (UHPLC-ESI-MS/MS) was developed and validated by (FACCIN, H. et al., 2017). Six species of traditional medicinal plants from the Brazilian Amazon region were studied (*Mansoa alliacea, Bauhinia variegata var. variegata, Bauhinia variegata var. alboflava, Connarus perrottetii var. angustifolius, Cecropia obtusa* and *Cecropia palmata*).

The analytes were separated by a reversed-phase SB-C18 column (2.1 _ 50 mm, 1.8 mm) using a gradient elution of 7 min composed of 0.1% acetic acid in water (v/v) and acetonitrile, at a constant flow rate of 0.8 mL min_1. The limit of detection for the analytes ranged between 0.5 and 130.3 mg L_1. Intra- and inter-day precision showed satisfactory results and the recoveries obtained for the 24 analytes varied between 91.7 and 111.9% for most of the evaluated matrices.

Quantifications were performed with the standard addition method ($r > 0.99$) using the data acquired in a multiple reaction monitoring (MRM) modes. Rutin, apigenin, vanillic acid, caffeic acid, ferulic acid, p-coumaric acid and trans-cinnamic acid were found in all the studied plants. However, we highlight the high contents of rutin in varieties of *Bauhinia variegate* (up to 2.52 mg g_1 of plant), chlorogenic acid in species of genus *Cecropia* (up to 0.57 mg g_1 of plant) and catechin in *Connarus perrottetii var. angustifolius* (1.77 mg g_1 of a plant).

b) The phenolic content of the medicinal species *Connarus perrottetti var. angustifolius* Radlk., Connaraceae, *Cecropia obtuse* Trécul, *Cecropia palmata* Willd., Urticaceae; and *Mansoa alliacea* (Lam.) A.H.Gentry, Bignoniaceae, collected in three different years was evaluated by Pires et al, (2017). Plant infusions and hydroalcoholic, butanol, and ethyl acetate extracts were analyzed by high-performance liquid chromatography with diode array detection. To endorse these results, analysis by electrospray mass spectrometry was also performed. Were identified: gallic acid, catechin, caffeic acid, ferulic acid, rutin, quercitrin and resveratrol. *C. perrottetti* showed a greater diversity of polyphenols. *M. alliacea* had the higher concentration of caffeicacid even though it was found in all species. Catechin was the major antioxidant, but was not detected in *M. alliacea*. However, we discuss the popular use of these species, as well as their phenolic constitution and the interannual distribution of phenolic compounds.

c) An analytical method using liquid chromatography-atmospheric pressure photoionization tandem mass spectrometry with toluene as a dopant was developed by Gobo et al., (2016) for the determination of triterpenes in medicinal plant extracts. The 12 compounds determined have been shown to exhibit biological activity, such as gastroprotective, hepatoprotective, anti-inflammatory, antiviral and anti-tumor effects. The parameters of the atmospheric pressure photoionization interface were optimized to obtain the highest possible sensitivity for all of the compounds. The limits of detection and quantification ranged from 0.4 to 157.9 μg l^{-1} and 1.3 to 526.4 μg l^{-1}, respectively.

The method was validated and applied to extracts of five medicinal plants species (*Mansoa alliacea* (Lam.) A.H.Gentry, *Bauhinia variegata var variegata*, *Bauhinia variegata var alboflava*, *Cecropia obtuse* Trécul and *Cecropia palmate* Willd) from the Amazonian region. The concentrations of the six triterpenes quantified in the samples ranged from0.424mg kg^{-1} for ursolic acid to 371.96mg kg^{-1} for β-amyrin, which were quantified by using the standard addition method (n=3).

d) A chromatographic RP-HPLC method with amperometric detection at a gold electrode has been developed to characterize the presence of phenolic compounds in extracts of medicinal plants from Amazonia (SILVEIRA, et al, 2015). The method allowed the identification and quantification of at least one of the 12 phenolic compounds studied in each of the different extracts of the medicinal plants. Pulsed amperometric detection at a gold electrode combined with HPLC separation with b-cyclodextrin as a mobile phase modifier was found to be a useful analytical tool to selectively characterize the phenolic compounds in samples with complex chemical compositions. Furthermore, the optimal detection potential (þ0.7 V) in PAD at the gold electrode was found to be in the potential range.

Among the studied phenolic compounds, quercetin, rutin, quercitrin, resveratrol, catechin, gallic acid, caffeic acid, ferulic acid, chlorogenic acid, and q-coumaric acid were identified and quantified in 6 species of Amazonia medicinal plants. Considering the investigated infusion extracts of the studied plants, the phenolic compounds found represented a total content (w/w) of whole plant material of 0.20% in *Mansoa alliacea* (Lam.) A.H.Gentry, 0.58% in *Connarus perrottetii var. angustifolius* (Radlk), 0.18% in *Bauhinia variegata var. variegata*, 0.10% in *Bauhinia variegata var. alboflava*, 0.27%in Cecropia palmata Willd, and 0.16% in *Cecropia obtusa* Trécul. Therefore, the proposed method permitted the identification of ten phenolic compounds that 445 represented, individually or as a group, at least 0.1% of the plant composition.

e) An analytical method using CZE with UV detection was developed, which enables the determination of selected phenolic compounds in *Connarus perrottetii* var *angustifolius*, (MULLER et al., 2015). The methodology allowed the detection of 3-acetylcoumarin, resveratrol, 6-hydroxycoumarin, catechin, rutin, ferulic acid, quercitrin, kaempferol, fisetin, myricetin, quercetin, caffeic acid, gallic acid and 4-hydroxycinnamic acid in the same run with relatively short analysis times. In the species studied, it was possible to identify and quantify the compounds catechin and rutin in aqueous extracts, crude ethanolic extract and butanolic extract.

Furthermore, it is the first work to document the phenolic antioxidants present in this plant species, which are often used for medicinal purposes in Amazonia region. The studied species presented good antioxidant activity against *in vitro*-generated oxygen free radicals. Performing a comparison between the obtained values in the plant and the fractions, it was noticed that they were able to concentrate polyphenolic compounds 21.7 times in ethanol fraction and 17.2 times in butanol fraction, which represents a more concentrated and pure bioactive product with potentially high pharmacological activity.

In general, the extracts exhibited good *in vitro* antioxidant activities against DPPH* and reactive oxygen species (ROS). It was noticed that *Connarus perrotteti* aqueous infusion has a higher activity for most of the tested free radicals.

Causas de supressão de íons na análise de extratos de plantas medicinais por UHPLC-MS / MS usando ionização por eletropray

a) A systematic study covering the various sources of ion suppression in analysis by HPLC-ESI–MS/MS was performed by Faccin et al, (2016). The developed separation method and the different plant extracts were evaluated by six experimental approaches, which were designed to identify different mechanisms of ion suppression. The study showed the influence of diverse variables on the ionization efficiencies of 24 analytes, including the mobile phase composition, co-elution of analytes, matrix effects, competition for charges in the ionization source and differential ionization of an IS. To the best of our knowledge, it is the first time that an evaluative study of several causes of ion suppression in the analysis of phenolic compounds by UHPLC-ESI–MS/MS is performed by comparing different species of plants and using the same sample pre-treatment procedure.

The different effects observed, even between very similar matrices, showed that ion suppression studies are essential during the development and validation of methods using UHPLC-ESI–MS/MS. It was also evidenced how far from reality may be the results of a quantification study of (poly) phenols in plant-based samples. Herein, some critical points were identified to reduce the LODs of the method, such as the choice of appropriate mobile and stationary phases so that ion suppression caused by additives and co-elution could be avoided.

The influence of matrix components, in turn, can be minimized by choosing an appropriate sample pre-treatment, such as the SPE used in this study. Moreover, obtaining false positive or false negative results deserves attention and is mainly affected by the choice of an appropriate dilution of the matrix as well as the use of a suitable IS. Lastly, to reduce the effects of ion suppression caused by the matrix or errors in the choice of an IS, the use of calibration by the standard addition method is highly recommended, even though it is laborious.

b) Samples of *Bauhinia variegata* L., *B. variegata var. candida* Voigt, Fabaceae, *Cecropia palmate* Willd. and *C. obtusa* Trécul, Urticaceae, collected in 2012, 2013 and 2014 from Amazon were treated with two different solvents (ethyl acetate and chloroform) and analyzed by the new analytical method described by Schmitd et al, (2018). This method has been developed for the simultaneous identification and quantification of triterpenes compounds using HPLC-UV and isocratic elution, to analyze these compounds in *Cecropia* and *Bauhinia* species. The HPLC-UV method is effective to separate and quantify medicinal plant extracts with good validation parameters, such as linearity, LOD, LOQ, recovery, accuracy, precision, robustness and repeatability.

Although triterpenoids contribute significantly to the bioactivity and pharmacology of *Bauhinia* and *Cecropia*, no study was reported so far for the quantitative determination of these compounds in these folk medicine plants. Triterpenes compounds such as maslinic acid, oleanolic acid, α-amirin, β-amirin and β-sitosterol were found as major compounds in chloroform and ethyl acetate extracts.

Furthermore, the presence of these triterpenic compounds in the extracts reinforces the pharmacological action, and the medical use of such plants in folk medicine. Overall, ethyl acetate showed better performance as the extractor solvent than chloroform. Based on the results, the species with the highest variety of compounds and concentrations were *B.variegata* and *C. obtusa*. The present method developed can be used in research of chemical markers in medicinal plants as well as in the quality control of herbal medicines widely used in Brazil and folk medicine.

The identified compounds in *Bauhinia* (lupeol, β-sitosterol, β-amirin and α-amirin), as well in *Cecropia* (β-amirin, lupeol and β-sitosterol) extracts were also observed and using the same sample by HPLC-APCI-MS/MS analysis, therefore, ratifying the importance of this work.

Mineral composition and nutritional properties in the dry matter of the seasonality of *Cecropia palmata* **and** *Cecropia obtuse*

a) Studies show that the concentration of minerals in plants may be associated with several factors, such as species, genetic variety, age, part of the plant tissue and the environment in which they are grown (ERNEST, E, 2002). There are several studies related to the phytochemical and pharmacological evaluation of Cecropia species (GOBO et al, 2016; SILVA et al, 2007).

In the study developed by Ramos et al, (2017) were evaluated the Ca, Cu, Fe, K, Mg, Mn, Na e Zn concentrations in leaf teas of Cecropia from different seasons. The samples were digested by microwave and analyzed by inductively coupled plasma optical emission spectrometry. The results showed that there was a reduced metal transfer from the dry matter to the teas, and mineral levels did not exceed the maximum tolerable. Chemometric studies showed that the species *Cecropia obtusa e Cecropia palmata* obtained during the rainy season has the highest similarity, concerning levels of nutrients Ca, Cu and Mn.

The PCA and HCA methods were useful to show the similarity between variables in the Cecropia species in the different collection periods, with the formation of groups with their concentrations. During the rainy season, Ca, Cu and Mn were similar for two species. Independently of the rainy season, some elements had their concentrations increased in the different species of Cecropia studied.

Among the limits considered safe for human consumption, the use of a cup of tea/day of the species of Cecropia can be used as a possible source of elements without risk of toxicity for the concentration of Ca, Cu, K, Na, Fe, Zn and Mg, since the levels found did not exceed the maximum tolerable limit (UL) established by the World Health Organization.

REFERENCES

AJILA, C.M., BRAR, S.K., VERMA, M., TYAGI, R.D., GODBOUT, S., VALÉRO, J.R. Analysis of polyphenols: recent trends. **Crit. Rev. Biotechnol**. v.31, p.227–249, 2011.

BELLUMORI, M.; MICHELOZZI, M.; INNOCENTI, M.; CONGIU, F.; CENCETTI, G.; MULINACCI, N. An innovative approach to the recovery of phenolic compounds and volatile terpenes from the same fresh foliar sample of Rosmarinus officinalis L. **Talanta**, v.131, p.81-87, 2015.

BERG, M.E.V.D. Plantas de origem africana de valor sócio-econômico atual na região amazônica e no meio-norte do Brasil. **Boletim Museu Emílio Goeldi**, Série Botânica. Belém, v.7, n.2, p.499-510, 1991.

CASCON, V.; GIIBERT, B. Characterization of the chemical composition of oleoresins of *Copaifera guianensis* Desf., *Copaifera duckei* Dwyer and *Copaifera muitijuga* Hayne. **Phytochemistry**, v.55, p.773-778, 2000.

CHEOK, C.Y.; SALMAN, H.A.K.; SULAIMAN, R. Optimization of total phenolic content extracted from Garcinia mangostana Linn. hull using response surface methodology versus artificial neural network. ***Food Research International,*** v.59, p.16–40. 2014.

COELHO-FERREIRA, M. Medicinal knowledge and plant utilization in an Amazonian coastal community of Marudá, Pará State. **Journal Ethnopharmacology**, v.126, n.1, p.159–175. 2009.

Ernest, E. Toxic heavy metals and undeclared drugs in Asian herbal medicines. **Trends Pharmacological Sciences,** v.*23*, n.3, p.136-139. 2002.

FACCIN, H.; LOOSE, R. F.; VIANA, C.; LAMEIRA, O. A.; CARVALHO, L. M. de. Determination of phenolic compounds in extracts of Amazonian medicinal plants by liquid chromatography-electrospray tandem mass spectrometry. **Analytical Methods**, v. 9, n. 7, p. 1141-1151, 2017.

FACCIN, H.; VIANA, C.; NASCIMENTO, P.C. do; BOHRER, D.; CARVALHO, L.M. Study of ion suppression for phenolic compounds in medicinal plant extracts using liquid chromatography–electrospray tandem mass spectrometry. **Journal of Chromatography A,** v.1427, p.111-124, 2016.

GOBO, L. A.; VIANA, C.; LAMEIRA, O. A.; CARVALHO, L. M. de. A liquid chromatography-atmospheric pressure photoionization tandem mass spectrometric (LC-APPI-MS/MS) method for the determination of triterpenoids in medicinal plant extracts. **Journal of Mass Spectrometry**, v.51, n.8, p.558-565, 2016.

GIORGETTI, M.; NEGRI, G.; RODRIGUES, E. Brazilian plants with possible action on the Central Nervous System - A study of historical sources from the 16th to 19th century. **Journal Ethnopharmacology**, v.109, p. 338–347, 2007.

GULTEKIN-OZGUVEN, M.; DAVARCI, F.; PASLI, A.A.; DEMIR, N.; OZÇELIK, B. Determination of phenolic compounds by ultra-high liquid chromatography-tandem mass spectrometry: applications in nuts *LWT*. ***Food Science Technolology****, v. 64, p.42–9*, 2015.

LAMEIRA, O.A.; PINTO, J.E.B.P. **Plantas medicinais**: do cultivo, manipulação e uso à recomendação popular. Belém, PA: Embrapa Amazônia Oriental, 2008. 264p.

LAMEIRA, O.A.; MARTINS-DA-SILVA, R.C.V.; ZOBHBI, M.G.B.; OLIVEIRA, E.C.P. Seasonal variation in the volatiles of *Copaifera duckei* Dwyer growing wild in the state of Pará – Brazil. **Journal of Essential Oil Research**, v.21, p.105-107, 2009.

LAMEIRA, O. A.; PAIVA, J. S.; OLIVEIRA, E. C. P. de; PINTO, J. E. B. Fenologia e análise fitoquímica de plantas medicinais de ocorrência na Amazônia. **Horticultura Brasileira**, v.22, n.2, jul. 2004. Suplemento CD-ROM.

LIMA, D. F.; LIMA, L. L.; ROCHA, J. A.; ANDRADE, I. M.; GRAZINA, L. G.; VILLA, C.; MEIRA, L.; VERAS, L. M. C.; AZEVEDO, L. F.S.; BIASE, A. G.; COSTA, J.; OLIVEIRA, M. B. P. P.; MAFRA, I.; SOUZA, J. R. Seasonal change in main alkaloids of jaborandi (*Pilocarpus microphyllus* Stapf ex Wardleworth), an economically important species from the Brazilian flora. **Article in PLoS ONE**, p.1-19, February. 2017.

MARTINS-DA-SILVA, R.C.V. Taxonomía das especies de Copaifera L.(Leguminosae-Caesalpinioideae) ocorrentes na Amazonia brasileira. DSc Thesis. Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil (2006).

MELO, L. V. de.; SAWAYA, A. C. H. F. UHPLC–MS quantification of coumarin and chlorogenic acid in extracts of the medicinal plants known as guaco (*Mikania glomerata* and *Mikania laevigata*). **Revista Brasileira Farmacognesia**, v.25, p.105–110, 2015.

MINITÉRIO DA SAÚDE E ANVISA. **Monografia da espécie** *Carapa guianensis* **Aubl. (Andiroba).** 2015. 66p.

MÜLLER, L. S.; SILVEIRA, G. D. da; PRÁ, V. D.; LAMEIRA, O.; VIANA, C.; CARVALHO, L. M. de. Investigation of phenolic antioxidants as chemical markers in extracts of Connarus perrottetii var. Angustifolius Radlk by capillary zone electrophoresis. **Journal of Liquid Chromatography & Related Technologies**, v. 39, n. 1, p. 13-20, 2016.

PIRES, F. B.; DOLWITSCH, C. B.; PRÁ, V. D.; FACCIN, H.; MONEGO, D.L.; CARVALHO, L. M. de; VIANA, C.; LAMEIRA, O. A.; LIMA, F. O.; BRESSAN, L.; ROSA, M. B. da. Qualitative and quantitative analysis of the phenolic content of *Connarus* var. *angustifolius*, *Cecropia obtusa*, *Cecropia palmata*, and *Mansoa alliacea* based on HPLC-DAD and UHPLC-ESI-MS/MS. **Brazilian Journal Pharmacognosy**, v.27, n. 4, p. 426-433, July/Aug. 2017.

SANZ-BISET, J.; CANIGUERAL, S. Plants as medicinal stressors, the case of depurative practices in Chazuta valley (Peruvian Amazonia). **Journal Ethnopharmacology**, v.137, p.271–288, 2011.

SILVA, E.M.; SOUZA, J.N.S.; ROGEZ, H.; REES, J.F.; LARONDELLE, Y. Antioxidant activities and polyphenolic contents of fifteen selected plant species from the Amazonian Region. ***Food Chemistry***, v.*101, p.1012-1018*, 2007.

SCHMIDT, M.E.P.; PIRESB, F.B.; BRESSANA, L.P.; SILVA Jr., F.V. da; LAMEIRA, O.A.; ROSA, M.B. da. Some triterpenic compounds in extracts of *Cecropia* and *Bauhinia* species for different sampling years. **Brazilian Journal of Pharmacognosy**, v.28, p.21-26, 2018.

SILVA, E. M.; SOUZA, J. N. S.; ROGEZ, H.; REES, J. F.; LARONDELLE, Y. Antioxidant activities and polyphenolic contents of fifteen selected plant species from the Amazonian region. **Food Chemistry** v.*101*, n.3, p.1012-1018, 2007.

SILVEIRA, G. D. da; MOTTA, M. J.; MÜLLER, L. S.; LAMEIRA, O.; ATHAYDE, M. L.; PIANA, M.; ROSA, M. B. da; VIANA, C.; CARVALHO, L. M. de. Determination of phenolic antioxidants in Amazonian medicinal plants by HPLC with pulsed amperometric detection. **Journal of Liquid Chromatography & Related Technologies**, v.38, n.13, p.1259-1266, 2015.

SUFFREDINI, I.B.; PACIENCIA, M.L.; VARELLA, A.D.; YOUNES, R.N. In vitro prostate cancer cell growth inhibition by Brazilian plant extracts. **Fitoterapia**, v.78, p. 223–226, 2007.

ZAUPA, M.; CALANI, L.; DEL RIO, D.; BRIGHENTI, F.; PELLEGRINI, N. Characterization of total antioxidant capacity and (poly)phenolic compounds of differently pigmented rice varieties and their changes during domestic cooking. **Food Chemistry**, v.187, p.338–347, 2015.

ZOBHBI, M.G.B.; ANDRADE, E.H.A.; MARTINS-DA-SILVA, R.C.V.; TRIGO, J.R. Chemical variation in the volatiles of *Copaifera reticulata* Ducke (Leguminosae) growing wild in the states of Pará and Amapá, Brazil. **Journal of Essential Oil Research**, v.21, p.501-503, 2009.

ZOBHBI, M.G.B.; LAMEIRA, O.A.; OLIVEIRA, E.C.P. Seasonal variation of oleoresin and olatiles from *Copaifera martii* Hayne growing wild in the state of Pará, Brazil. **Journal of Essential Oil Research**, v.19, p.504-506, 2007.