Boletim Informativo Geum
InformativeGeumBulletin

Boletim Informativo Geum, v. 5, n. 2, p. 71-77, abr./jun., 2014
ISSN 2237-7387 (Impresso)

Development of Phyto-therapeutic Medicines from Native Species from the Brazilian Atlantic Forest

Desenvolvimento de Medicamentos Fitoterápicos a Partir de Espécies Nativas da Mata Atlântica Brasileira

André Mesquita Marques[1] and Davyson de Lima Moreira[2*]

[1]*Instituto de Pesquisas de Produtos Naturais, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil.*
[2]*Instituto de Tecnologia em Fármacos, Farmanguinhos, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil.*

* Correspondência:
Endereço:Av. Sizenando Nabuco, 100, Manguinhos, Rio de Janeiro, CEP. 21041-250.
E-mail: davysonmoreira@hotmail.com

RESUMO

Plantas medicinais foram os primeiros recursos terapêuticos disponíveis para o tratamento de enfermidades. Com o avançar da síntese orgânica, os medicamentos chamados de naturais deram lugar aos de origem sintética. Ainda assim, a população de países com grande biodiversidade vegetal, como o Brasil, continua a fazer uso de recursos terapêuticos naturais, principalmente, os obtidos de plantas. Na maioria dos casos o conhecimento tradicional está associado às comunidades restritas, como indígenas. Ainda que o Brasil concentre uma mega diversidade vegetal e populações que conhecem e usam recursos naturais, estima-se que apenas 1% da biodiversidade tenha sido devidamente explorada para gerar benefícios terapêuticos. A ação humana tem colocado em risco valiosos ecossistemas, como a Mata Atlântica, que possui apenas 1% de sua área nativa original. Dessa forma, é urgente a pesquisa para aproveitamento racional dos recursos biomoleculares disponíveis na Mata Atlântica. A pesquisa por novos fitoterápicos com metodologia científica adequada pode trazer enormes benefícios para a população brasileira e mundial. Incluir na pesquisa plantas ainda inexploradas dos pontos de vista químico e farmacológico, de ecossistemas com grande diversidade biológica, como a Mata Atlântica, pode levar ao descobrimento de novos agentes terapêuticos. Esse é o grande desafio brasileiro na pesquisa por novos agentes terapêuticos de origem natural. Esse artigo discute os principais tópicos relacionados à pesquisa de novos fitoterápicos e apresenta alguns resultados de mais de 15 anos de pesquisa com espécies de Piperaceae nativas da Mata Atlântica.

Palavras-chave: plantas medicinais, fitoterapia, medicamento tradicional, ecossistema.

ABSTRACT

Medicinal plants were the first therapeutic resources available for the treatment of human diseases. Advances in organic synthesis led to those medicines from synthetic origin. The population of countries with high plant biodiversity, such as Brazil, continues to make use of natural therapeutic resources, especially those obtained from plants. In most cases, traditional knowledge is associated with restricted communities such as indigenous. Although Brazil concentrates a plant megabiodiversity and populations who know and use natural resources, it is estimated that only 1% of biodiversity has been duly exploited to generate therapeutic benefits. Human action has put into risk valuable ecosystems, such as the Atlantic Forest, which has only 1% of its original native range. Thus, it is urgent the research to rational use of biomolecular resources available in the Atlantic Forest. The search for new phyto-therapeutic medicines with appropriate scientific methodology can bring huge benefits to the Brazilian and world population. Include in search unexplored plants from the chemical and pharmacological point of view, from ecosystems with high biodiversity, such as the Atlantic Forest, may lead to the discovery of new therapeutic agents. This is the main Brazilian challenge in searching for new therapeutic agents of natural origin. This article discusses the main research problems of new herbal topics and presents some results of more than 15 years of research with native Piperaceae species from the Atlantic Forest.

Keywords: medicinal plants, phyto-therapeutic medicines, traditional medicines, ecosystem.

INTRODUÇÃO:

Natural products were the only therapeutic option available and even today continue to provide models for synthesis or semi-synthesis of new drugs. Brazil, a country of continental proportions and that concentrates biological and chemical megabiodiversity, emerges as one of the leading nations in the world scenario to afford new molecules with biodynamic activity (MARINO et al., 2008; MONT´ALVERNE & ANDRADE, 2011).It is believed that most Brazilian plant species have some medicinal property, due to this complexity of natural resources, however, from the chemical and pharmacological point of view it is estimated that only about 1% of the native species have been adequately studied (PEIXOTO& CALICO, 2003; MONT´ALVERNE & ANDRADE, 2011).

The research for new phyto-terapeutic medicines starts with choosing the plant. This choice can be made by ethnopharmacological, random or chemotaxonomical approach. Special attention must be given to authorization to collect the plant material (SISBIO) as well as to the licenseto access the genetic resources (CEGEN). After choosing the plant material, extracts are prepared with different solvents. The extracts are then subjected to separation procedures that can afford semi-pure fractions and/ or pure compounds. Extracts, fractions and pure compounds undergo rapid *in vitro* biological tests (screening) and if any relevant activity is found, those extract, fraction, substance or mixture of substances will undergo pharmaceutical formulation. The preclinical toxicological testing and quality control of extracts and fractions with specific chemical markers begin still in laboratorytesting stage. The *in vivo* tests are started once that is achieved any significant *in vitro* biological activity. After the initial tests *in vivo* and *in vitro*as well no relevant toxicological effects are observed, the clinical tests begin. This is the traditional routine for the developing of new drugs that also applies to phyto-therapeutic medicines, according to current legislation (ANVISA, 2010). The chain of development of a new phyto-therapeutic medicine can take up to 20 years and millions of dollars are spent (SEIDL, 2003; SOUZA-MOREIRA, 2010).

The regulation published by the Brazilian National Health Surveillance (ANVISA) in 2010 (RDC 14/2010) puts in the same category phyto-therapeutic medicines and synthetic medicines for registration purposes. This regulation is still in force and represents a breakthrough in the control of phyto-therapeutic medicines. However, a recently regulation defines two categories of herbal drugs for registration: "**phyto-therapeutic medicines**" and "**traditional phyto-therapeutic products**" (ANVISA, 2014). Considering this new regulation some herbal products are regarded as "acceptably safe, although not having a recognized level of efficacy" and can fit into this new special category of drugs "traditional herbal medicine products". The requirements for non-clinical and clinical studies are less rigorous for these products. By this mean, the new regulation published by ANVISA (2014) is more lenient regarding proof of efficacy and consider longstanding folk use as evidence of safety and a waiver of a thorough toxicological evaluation (MOREIRA et al., 2014). We can stand out some herbal product that fit in the category Traditional Phyot-therapeutic product: *Arnica montana* L., *Calendula officinalis* L. and *Matricaria recutita* L. (ANVISA, 2014)

Among different Brazilian ecosystems, special interest in Atlantic Forest, considered a biodiversity hotspot, which has been highly threatened by humanaction since the arrival of the colonizers. The Atlantic Forest concentrates a huge endemic vegetal diversity and it is estimated that 80% of its area focuses in forest patches comprise by less than 50 hectares. Only 1% of the Atlantic Forest remains as native area and only 9% are protected in conservation areas (CARNAVAL et al., 2009; RIBEIRO et al., 2009.). These numbers are quite alarming and, considering the large amount of native and endemic plant species of the Atlantic Forest,it is an urgent need to understand and rationally exploit the natural resources of this valuable ecosystem.

Among the many different plant species from different plant families identified and cataloged in the Brazilian Atlantic Forest, we highlighted Piperaceae species. In recent years it has been found that species of this family have showed valuable active substances that can act in many biological systems and only recently the chemistry of Piperaceae has been addressed successfully (PARMAR et al., 1997;MOREIRA 1999a; GRAHAN et al., 2000; SUNILA&KUTTAN, 2004).

The Piperaceae family is predominantly tropical with great occurrence in Central and South America, being found mainly in Mexico, Panama, Peru, Costa Rica and North to South of Brazil, until the Southeast Argentina (Figure

1).

Species of Piperaceae have herbaceous habit (herbs, vines and shrubs), with record of the occurrence of small trees (Figure 2). *Piper* is large genus of the Piperaceae family, comprising over 1,000 species, of which about 170 grow natively in Brazil. *Piper nigrum* L. (black or white pepper) is the species of greatest economic value because since antiquity its fruits are used as a condiment (YUNKER, 1972; JOLY, 1985;GUIMARÂES et al., 1992; TEBBS, 1993;JARAMILLO& MANOS, 2001; SOUZA& LORENZI, 2005).Recently, the taxonomy of the family was revised (APGIII, 2009) and according to the new taxonomic classification, Piperaceae comprises five genera: *Piper*, *Peperomia*, *Manekia*, *Zippelia* and *Verhuellia*. However, since several studies conducted by our group took into consideration previous taxonomic classifications, this paper also distinguishes the genera *Ottonia* and *Pothomorphe* which is at the present the same of *Piper* (APGIII, 2009).

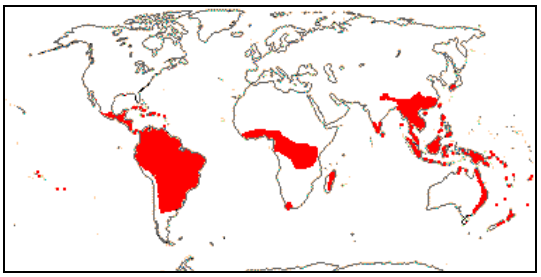


Figure 1 – Piperaceae geographic distribution worldwide (APGIII, 2009).

Figure 2 – Piper aduncum L., Piperaceae. Emphasis on the inflorescences. Photo: Gisele Lopes.

The chemistry of Piperaceae is based mainly in substances isolated from species of the genus *Piper* (amides, lignans, neolignans, C6-C3 derivatives, arylpropanoids, flavonoids and chromenes), however, the literature reports the occurrence of special species metabolites in *Peperomia* (benzoic acid derivatives and seconeolignans),*Ottonia* (aliphatic amides, aristolactams and C6-C4 derivatives) and *Pothomorphe* (cathecol derivatives) (PARMAR et al., 1997; MOREIRA, 1999; VELOZO, 2004). Phytochemical investigations of *Piperaceae species* conducted by our group led to the isolation of hundreds of known compounds and some novel, such as kaplanin, lhotzchromene and blandachromenos I and II (MOREIRA et al., 1998; MOREIRA et al., 2000; SANTOS et al., 2001; VELOZO et al., 2006; VELOZO et al., 2009; MESQUITA et al., 2011).

The biological activities obtained from extracts, semi-purified fractions and pure compounds isolated of Piperaceae species from the Brazilian Atlantic Forest shows a fantastic wealth, mainly regarding to stimulating and depressant on the central nervous system, anti-leishmania, cytotoxicity in mammalian cells, antimicrobial, anti-inflammatory and analgesic effects (MOREIRA et al., 2001a; GUADALUPE-ROJAS et al., 1999; TORRES-SANTOS et al., 1999a; VELOZO, 2004).

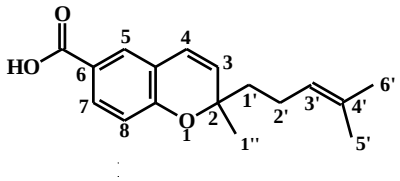
RESULTS:

We highlightedin this paper some important results archived in more than 15 years of research with Piperaceae species from the Atlantic Forest. We have focused in the isolation and chemical characterization of substances with biological activity:

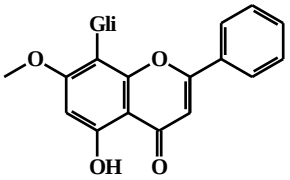
(1) *Ottonia anisum* Spreng. –Plant collected in Paraty, near the border of the States of Rio de Janeiro and São Paulo. The essential oil from the leaves of this species was found to be rich (> 95%) on C6-C4 derivative 3,4-methylenedioxy-butylbenzene (MOREIRA et al., 1997). This compound can be used as a precursor for synthesis of substances with biological activity. From the extract of the roots of *O. anisum* collected in the Atlantic Forest fragment in Duque de Caxias, Rio de Janeiro State, six aristolactams were isolated(MESQUITA et al., 2011).

(2) *Piper gaudichaudianum* Kunth –Species collected in the Tijuca Forest, city of Rio de Janeiro and near of city of Teresopolis. It was possible to isolate flavonoids from the leaves. The main flavonoid content was characterized as 2',4'-dimethoxy-6'-hidroxichalcona. The leaf extract and its partitions showed*in vivo* anti-inflammatory and analgesic effect (MOREIRA et al., 2001b).

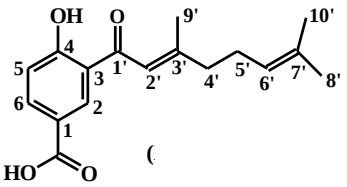
(3) *Piper lhotzkyanum* Kunth – Plant collected in Teresopolis. Extracts of low and medium polarity yielded two new substances, one chromene (lhotzchromeno, I) and a flavonoid naemdkaplanin (II), in honor of Professor. Dr. Maria Auxiliadora Coelho Kaplan who started the project with Piperaceae species at Núcleo de Pesquisas de Produtos Naturais, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil. This flavonoid was the first C-glycoside flavone with unsubstituted B ring isolated on the Plant Kingdom. In addition to these novel substances, other known were isolated as sakuranetin, ferulic acid derivatives, two chromenes - (*E*) and (*Z*) - 4- hydroxy - 3 - (3,7 - dimethyl - 1 - oxo) - 20, 6 octadienylbenzoic acid (III) and oxygenated sesquiterpenes (MOREIRA et al., 1998a & 2000).



(I) - lhotzchromene



(II) - kaplanin



(III) – (*E*)-4-hydroxy-3-(3,7-dimethyl-1-oxo)-20,6 octadienylbenzoic acid

(4) *Piper aduncum L.* - Species collected in forest fragments near the towns of Volta Redonda and Carmo, State of Rio de Janeiro. The extracts of the leaves and stems afforded many known flavonoids (flavones, flavanones, and chalcones), a novel chromene (2,2-dimethyl-8-(3-methyl-2-butenyl)-2H-chromeno-6 methylcarboxylate) and a known chromene (eupatoriochromeno). The chalcone 2',6'-dihydroxy- 4'-methoxy isolated from the extract of the leaves showed excellent leishmanicidal activity against amastigotes and promastigotes of *Leishmania amazonensis* (TORRES-SANTOS et al., 1999a & 1999b). The essential oil from the leaves of *P. aduncum* revealed the presence of monoterpenes, sesquiterpenes and arylpropanoids, especially dilaiol and apiol (MOREIRA et al., 1998b).

(5) *Piper solmsianum* C.DC. –The botanical material was collected in Teresopolis. The *n*-hexane extract of this species provided the neolignaneupomatenoid-6 and the sesquiterpene calamenene. The essential oil from the leaves, after purification on silica column, yielded the pure substances Δ3-carene and sarisan. These substances showed significant stimulant and depressant effect on the central nervous system (MORIERA et al. 2001a & 1995).

(6) *Piper cabralanum* C.DC. – Plant collected in Teresopolis. From the polar fraction of the methanol extract of the leaves was possible the isolation and identification of steroids (sitosterol, stigmasterol and campesterol), sesquiterpenes, aliphatic hydrocarbons and esters of fatty acids (MOREIRA et al., 2010). In lesser amounts were also isolated and identified cinnamic acid derivatives (3,4-dimethoxy-dihydrocinamic acid and 3,4-dimethoxy-dihydrocinnamic methyl ester) and a mixture of glucosylsitosterol and stigmasterol. *In vitro* assays on promastigotes of *Leishmania amazonensis* showed great activity for crude methanol extract of the leaves and its partition in*n*-hexane (MOREIRA et al., 2010). Tests with leukemic cells strains K-562 and K-562 Lucena-1 demonstrated excellent antitumor activity for the non-polar fraction of the methanolic extract of the leaves. This fraction was formulated in nanoparticles

using polymethylmethacrylate (PMMA). The nano-formulation proved to be efficient in increasing the activity of the *n*-hexane fraction (unpublished data). The active fraction has been characterized by LC-MS.

Essential Oils

Studies on volatile components of Piperaceae species from the Atlantic Forest have revealed rich fractions of several components, especially monoterpenes and sesquiterpenes. It is worth to note the presence of arylpropanoids. Essential oils have shown excellent biological activities. For example, the essential oil from the leaves of *Piperclaussenianum* (Miq.) C.DC. revealed to be rich in nerolidol (ca. 80%) and inflorescences essential oilshowed great amounts of linalool (ca. 50%) and nerolidol (ca. 20%). The essential oil from the leavesof*P. claussenianum* was very active against promastigotes of *L. amazonensis* (MESQUITA et al., 2010). The study of the volatile components of 10 Piperaceae species from the Atlantic Forest fragment near the city of Paraty, performed by Santos and co-workers (2001) revealed rich and diverse fractions in monoterpenes and sesquiterpenes. The majority of the identified sesquiterpenes were biosynthesized prior from the precursor *E,E*-farnesyl pyrophosphate. This study pointed out the absence of arylpropanoids that are very common in essential oils from species of Piperaceae. The low occurrence of arylpropanoids in Piperaceae species from the Atlantic Forest may be due to an adaptive function, since these substances are very common in Piperaceae species from the Amazon Rainforest.

CONCLUSION

The development of new phyto-therapeutic medicine from native plants from Atlantic Forest can led the isolation of many bioactive compounds.

Isolated compounds from Piperaceae, as well as mixtures and fractions, have shown great potential for the development of new phyto-therapeutic medicines. Considering that even 10% of Piperaceae species native of Atlantic Forest were studied successfully, our efforts aim to search precisely these species, in order to contribute to the knowledge of the Piperaceae chemistry; for the improvement of routine isolation, purification and structural elucidation; training of human resources; and obtaining new natural pharmaceuticals.

ACKNOWLEDGMENTS:

Authors thank to financial support provided for CNPq, CAPES, FAPERJ and Farmanguinhos; to Professor Elsie Franklin Guimarães for their valuable partnership and taxonomic identification and to Professor Maria Auxiliadora Coelho Kaplan who teaches with dedication and who started the research with Piperaceae species in Brazil.

REFERENCES:

BRASIL. **Ministério da Saúde**. Agência Nacional de Vigilância Sanitária. Resolução de Diretoria Colegiada (RDC) nº14, de 31 de março de 2010. Dispõe sobre o registro de medicamentos fitoterápicos;

BRASIL. **Ministério da Saúde**. Agência Nacional de Vigilância Sanitária. Agência Nacional de Vigilância Sanitária. Instrução Normativa nº2, de 13 de maio de 2014. “Lista de medicamentos fitoterápicos de registro simplificado” e a “Lista de produtos tradicionais fitoterápicos de registro simplificado;

APGIII - STEVENS, P.F. September 28, 2013 - University of Missouri, St Louis, and Missouri Botanical Garden. http://www.mobot.org/MOBOT/research/APweb

CARNAVAL, A.C.; HICKERSON, M.J.; HADDAD, C.F.B.; RODRIGUES, M.T.; MORITZ, C. **Science,** v.323,n.5915,p.785-789, 2009;

CEGEN – Conselho de Gestão do Patrimônio Genético – Disonível em http://www.mma.gov.br/patrimonio - genetico/conselho - de - gestao - do -patrimonio - genetico. Acesso em 26/06/2014;

GUADALUPE-ROJAS, M.; MOREIRA, D.L.; PEREIRA, N.A.; KAPLAN, M.A.C. Atividade antiinflamatória de extratos de *Piper aduncum* L. (Piperaceae). **Revista Brasileira de Farmácia,**v.80,p.5-6, 1999;

GUIMARÃES, E.F.; MAUTONE, L.; MAGALHÃES, H.G.; GUIMARÃES, L.A. Estudos Taxonômico e farmacoquímico e

bioensaios de *Piper lhotzkyanum* Kunth (Piperaceae), uma espécie ocorrente em Minas Gerais. **Daphne**,v.2,n.3,p.10-13, 1992;

GRAHAN, J.G.; QUINN, M.L.; FABRICANT, D.S.; FARNSWORTH, N.R. Plants used against cancer - an extension of the work of Jonathan Hartwell.**J. Ethnopharmacol.,**v.73,p.347–377, 2000;

JARAMILLO, M.A. & MANOS, P.S. Phylogeny and patterns of floral diversity in the genus *Piper* (Piperaceae). **American Journal of Botany**,v.88,n.4,p.706-716, 2001;

JOLY, A.B. **Introdução à Taxonomia Vegetal.** 7ª ed. São Paulo: Ed. Nacional, 777p, 1985;

MARINHO, V.M.C.; SEIDL, P.R.; LONGO, W.P. O papel governamental como ator essencial para a P&D de medicamentos – um estudo de caso. **Quim. Nova**,v.31,n.7,p.1912-1917, 2008;

MESQUITA, A.M.; VELOZO, L.S.M.; BARRETO, A.L.; BATISTA, E.M.; CURVELO, J.A.; MOREIRA, D.L.; GUIMARÃES, E.F.; SOARES, R.M.; KAPLAN, M.A.C. Chemistry and Biological Activity of Essential Oils from Piper claussenianum (Miq.) C.DC. (Piperaceae). **Natural Product Communications**, v.5,p.1837-1840, 2010;

MESQUITA, A.M.; VELOZO, L.S.M.; MOREIRA, D.L.; GUIMARÃES, E.F.; KAPLAN, M.A.C. Aristolactams from roots of *Ottoniaanisum* Spreng. (Piperaceae). **Natural Product Communications,** v.6, p.939-942, 2011;

MONT'ALVERNE, T.F. & ANDRADE, D.A. O acesso justo e equitativo à biodiversidade brasileira como direito fundamental à saúde. **Constituição e garantia de direitos**, v.4,n.1,p.1-14, 2011;

MOREIRA, D.L.; GUIMARÃES, E.F.; KAPLAN, M.A.C. Constituintes Químicos de *Piper solmsianum* C.DC. (Piperaceae). **Revista Brasileira de Farmácia**, v.76,n.4,p.106-109, 1995;

MOREIRA, D.L.; GUIMARÃES, E.F.; KAPLAN, M.A.C. Butyl-3,4-methylenedioxybenzene as the Major Constituent of the Essencial Oil from *Ottoniaanisum*. **The Journal of Essential Oil Research**,v.9, n.5, p. 175-178, 1997;

MOREIRA, D.L.; GUIMARÃES, E.F.; KAPLAN, M.A.C. Non-Polar Constituents from *Piper lhotzkyanum*. **Phytochemistry**,v.49, n.5, p.1054-1057, 1998a;

MOREIRA, D.L.; GUIMARÃES, E.F.; KAPLAN, M.A.C. A chromene from *Piper aduncum*. **Phytochemistry**,v.48,n.3,p.1075-1077, 1998b;

MOREIRA, D.L. 1999. Aspectos químicos e farmacológicos de Piperaceae. Tese (Doutorado em Química de Produtos Naturais) - Núcleo de Pesquisa de Produtos Naturais, Universidade Federal do Rio de Janeiro, Rio de Janeiro, 147p;

MOREIRA, D.L.; GUIMARÃES, E.F.; KAPLAN, M.A.C. A C-glucosylflavone from Leaves of *Piper lhotzkyanum*. **Phytochemistry**,v.55,n.7,p. 783-786, 2000;

MOREIRA, D.L.; CARDOSO, G.L.; SOUZA, P.O.; GUIMARÃES, E.F.; PEREIRA, N.A.; KAPALNA, M.A.C. Effect of Leaf Essential Oil from *P. solmsianum* C.DC. in Mice Behaviour. **An. Acad. Bras. Ciênc.**, v.73,n.1,p.33-37, 2001a;

MOREIRA, D.L.; SOUZA, P.O.; CARDOSO, G.L.; PEREIRA, N.A. ; KAPLAN, M.A.C. Estudos Fitoquímico e Farmacológico de *Piper gaudichaudianum* Kunth (Piperaceae). **Revista Brasileira de Farmácia**,v.82,n.1/2,p. 29-32, 2001b;

MOREIRA, D.L.; FONSECA, V.M.; BHERING, C.A.; VASCONCELOS, F.G.; TORRES-SANTOS, E.C.; KAPLAN, M.A.C. Estudo Químico e da Atividade leishmanicida de frações de *Piper cabralanum* C.DC. (Piperaceae). **Revista Fitos (ALANAC)**, v.5,p.92-98,2010;

PARMAR, V.S.; JAIN, S.C.; BISHT, K.S.; JAIN, R.; TANEJA, P.; JHA, A.; TYAGI, O.D.; PRASAD, A.K.; WENGEL, J.; OLSEN, C.E.; BOLL, P.M. Phytochemistry of the genus *Piper*. **Phytochemistry**,v.46,n.4,p.597-673, 1997;

PEIXOTO, A.L.; MORIM, M.P. Coleções botânicas: documentação da biodiversidade brasileira. **Cienc. Cult.**,v.55,n.3,p. 21-24, 2003;

RIBEIRO, M.C.; METZGERA, J.P.; MARTENSENA, A.C.; PONZONIB, F.J.; HIROTA; M.M. The Brazilian Atlantic Forest: How much is left, and how is the remaining

forest distributed? Implications for conservation. **Biological Conservation**. v.142,n.6,p.1141–1153, 2009;

SANTOS, P.R.D.; MOREIRA, D.L.; GUIMARÃES, E.F.; KAPLAN, M.A.C. Essential Oil Analysis of 10 Piperaceae species from the Brazilian Atlantic Forest. **Phytochemistry**, v.58,n.4,p.547-551, 2001;

SEIDL, P.R. 2003. Pharmaceuticals from natural products: current trends. **An. Acad. Bras. Ciênc.**, 74(1); 145-150;

SISBIO - Autorizações para coleta de material biológico e para a realização de pesquisa em unidades de conservação federais e cavernas. Disponível em http://www.icmbio.gov.br/sisbio/. Acesso em 25/06/2014;

SOUZA, V.C. & LORENZI, H. **Botânica Sistemática: guia ilustrado para identificação das famílias de Angiospermas da flora brasileira, baseado em APG II.** Nova Odessa, São Paulo, Instituto Plantarum, 639p, 2005;

SOUZA-MORIERA, T.M.; SALGADO, H.R.N.; PIETRO, R.C.L.R. O Brasil no contexto de controle de qualidade de plantas medicinais. **Rev. Bras. Farmacogn.**,v.20,n.3,p.435-440, 2010;

SUNILA, E.S.; KUTTAN, G. Immunomodulatory and antitumor activity of *Piper longum* Linn. and piperine. **J. Ethnopharmacol.**, v.90,n.2-3,p.339-346, 2004;

TEBBS, M.C. Piperaceae. Pp. 516-520. In: K. Kubitzki; J. G. Rohwer; V. Bittrich. **Flowering Plants Dicotyledons - The Families and Genera of Vascular Plants**.vol. 2. Springer Berlin Heidelberg, 1993;

TORRES-SANTOS, E.C. ; MOREIRA, D.L.; KAPLAN, M.A.C.; BERGMANN, B.R.; MEIRELLES, M.N. Selective Effect of 2',6'-Dihydroxy-4'-methoxychalcone Isolated from *Piper aduncum* on *Leishmania amazonensis*. **Antimicrobial Agents and Chemotherapy**, v.43,n.1234-1241, 1999a;

TORRES-SANTOS, E.C.; MOREIRA, D.L.; RODRIGUES, J.M.; KAPLAN, M.A.C.; BERGMANN, B.R. Improvement of in vitro and *in vivo* Antileishmanial Activity of 2',6'-dihydroxy-4'-methoxychalcone in Poly(D,L-Lactide) Nanoparticles. **Antimicrobial Agents and Chemotherapy**,v.43,n.7,p.1776-1778, 1999b;

VELOZO, L.S.M. 2004. **Química e Atividade Biológica de Piperacea Brasileiras**, Tese (Doutorado em Química de Produtos Naturais) - Núcleo de Pesquisa de Produtos Naturais, Universidade Federal do Rio de Janeiro, Rio de Janeiro, 150p;

VELOZO, L.S.M.; FERREIRO, M.J.P.; SANTOS, M.I.S.; MOREIRA, D.L.; EMERECIANO, V.P.; KAPLAN, M.A.C. Unusual chromenes from *Peperomia blanda*. **Phytochemistry**, v.67,n.492-496, 2006;

VELOZO, L.S.M.; FERREIRA, M.J.P.; SANTOS, M.I.S.; MORIERA, D.L.; GUIMARÃES, E.F.; EMERECIANO, V.P.; KAPLAN, M.A.C. C-glycosyl flavones from *Peperomia blanda*. **Fitoterapia**,v.80,p.119-122, 2009;

YUNKER, T.G. **The Piperaceae of Brazil. Hoehnea**,v.2,n.19,p.19-366, 1972.