Received 05/20/06. Accepted 11/17/06

Revista Brasileira de Farmacognosia
Brazilian Journal of Pharmacognosy
17(1): 141-148, Jan./Mar. 2007

Revisão

Natural products with antileprotic activity

José M. Barbosa-Filho*, Francisco A. do Nascimento Júnior, Anna Cláudia de Andrade Tomaz, Petrônio F. de Athayde-Filho, Marcelo S. da Silva, Emídio V. Leitão da Cunha, Maria de F. Vanderlei de Souza, Leônia M. Batista, Margareth F.F. Melo Diniz

Laboratório de Tecnologia Farmacêutica "Delby Fernandes de Medeiros", Universidade Federal da Paraíba, Caixa Postal 5009, 58051-970, João Pessoa, Paraíba, Brazil

RESUMO: "Produtos naturais com atividade antileprótica". A hanseníase é uma doença crônica infecciosa ocasionada pelo *Mycobacterium leprae*. Foi considerada incurável por muitos anos. Atualmente a lepra é uma doença em desaparecimento, apesar de podermos encontrá-la principalmente nos países da zona tropical. O Brasil é o país que tem o segundo maior número de casos de lepra ao redor do mundo com quase 30.000 novos casos diagnosticados em 2005. Este trabalho teve como objetivo revisar a literatura dos vegetais e substâncias de origem natural com atividade antileprótica. Foram encontradas 11 plantas e 17 substâncias isoladas de plantas e microrganismos que foram classificados em grupos químicos adequados. Alguns aspectos de pesquisa recente com produtos naturais direcionados à produção de drogas contra a lepra também são discutidos. Foram consultadas 63 referências.

Unitermos: *Mycobacterium leprae*, lepra, hanseníase, doença de Hansen, produtos naturais, plantas medicinais, revisão.

ABSTRACTS: Leprosy is a chronic infectious disease caused by *Mycobacterium leprae* bacillus. It was considered to be an incurable disease for ages. Nowadays leprosy is a vanishing disease although we can meet it principally in the tropical zone countries. Brazil has the second greatest number of leprosy cases around the world with almost 30,000 new cases diagnosed in 2005. The present work constitutes a literature review on plant extracts and chemically defined molecules of natural origin showing antileprotic activity. The review refers to 11 plants, their families, and geographical distribution, the utilized parts, the type of extract and the tested organism. It also includes 17 compounds isolated from higher plants and microorganisms, classified into appropriate chemical groups. Some aspects of recent antileprotic-activity-directed research on natural products are discussed. For this purpose 63 references were consulted.

Keywords: *Mycobacterium leprae*, lepra, leprosy, Hansen's disease, natural products, medicinal plants, revision.

INTRODUCTION

The Norwegian doctor Gerhard Hansen identified the etiologic agent, *Mycobacterium leprae*, which causes the infectious disease leprosy or Hansen's disease that affect mainly the peripheral nerves and human being skin. The terms *lepra* and *leprous* will probably disappear as a result of the diminishing number of cases and because of the pejorative connotation given to people who suffered from this illness in the past (Hansen, 2007).

Bible contents passages that refer to lepra, however it is unknown if it is really Hansen's disease. This term was used to name various dermatologic diseases of variable origin and gravity. During much time lepra was incurable and much mutilator, forcing the isolation of patients in leprosaries, mainly in Europe Middle Age, where they were obliged to take bells with them to announce their presence (Eidt, 2004).

Over than 5 million people around the world are infected with *Mycobacterium leprae*. Hansen's disease is more frequently in Asia, Africa, Latin America, and Pacific Islands. Many Hansen cases in developed countries affect people who have emigrated from developing countries. Brazil has the second greatest number of leprosy cases around the world with almost 30,000 new cases diagnosed in December 2005 (WHO, 2006; Deps et al., 2006).

Over the last 20 years, a series of health policy reforms have been implemented in Brazil with the objective of decentralizing preventive health measures and basic services to the primary care network. One of the most important changes has been the introduction of the Community Health Agent-*Programa de Agentes Comunitários de Saúde* (PACS) and Family Health Programmes-*Programa de Saúde da Família* (PSF). During this period, Hansen's disease control has been integrated into the restructured Brazilian basic health system, a strategy that is considered effective and efficient

* *E-mail: jbarbosa@ltf.ufpb.br, Tel./Fax +55-83-32167364*

in all national contexts (Ramos Jr et al., 2006).

In order to 'eliminate' leprosy from all countries, the Worth Health Organisation formulated 'the final push', a strategy based on the early case detection and treatment with multi-drug therapy (Who, 2000).

Plants represent an important source of drugs, considering the wide diversity of molecules with medicinal potential, and can make an effective contribution to the search of new bioactive products, semi-synthetic medicines or lead compounds for the synthesis of medicines (Cowan, 1999; Yunes; Calixto, 2001; Pinto et al., 2002; Anthony et al., 2005; Gilani; Rahman, 2005). The exploitation of this potential medicine source requires the bringing together of ethnobotanical, ethnopharmacological, chemical, biological, pharmacological and toxicological studies (Gilani; Rahman, 2005; Gurib-Fakim, 2006).

In a previous paper this research group has reviewed crude plant extracts and chemically defined molecules with potential antitumor activity for mammary (Moura et al., 2001), cervical (Moura et al., 2002) and ovarian neoplasias (Silva et al., 2003), as inhibitors of HMG CoA reductase (Gonçalves et al., 2000), central analgesic activity (Almeida et al., 2001), employed in prevention of osteoporosis (Pereira et al., 2002), for the treatment of Parkinson's disease (Morais et al., 2003), with antileishmanial (Rocha et al., 2005), hypoglycemic (Barbosa-Filho et al., 2005), antiinflammatory activity (Falcão et al., 2005, Barbosa-Filho et al., 2006a), inhibitors of the enzyme acetylcholinesterase (Barbosa-Filho et al., 2006b), inhibitors of the angiotensin converting enzymes (Barbosa-Filho et al., 2006c) and giardicidal activity (Amaral et al., 2006).

In this work we present such natural products, in other words, plant extracts, chemically defined molecules isolated from plants and metabolites from fungi and bacteria that act specifically inhibiting the microorganism *Mycobacterium leprae* development, so that discussion and new research on the area can be done.

MATERIAL AND METHODS

The keywords for this review were: leprosy x natural products x plants, from which a research was performed in the data bank from University of Illinois, Chicago, USA, named NAPRALERT (registered trade name, acrostic of "NAtural PRoducts ALERT''), updated to July 2005. The scientific specialized references cited on the abstracts were later consulted. Various periodical publications available on CAPES electronic site (www.periodicos.capes.gov.br), the periodical portal, were research sources, as well as books from the authors' personal collection.

RESULTS AND DISCUSSION

Plants used in the treatment of leprosy

During the 18th and 19th centuries, intending to minimize the leprosy people suffering, European seek the most diversified treatments, even before the discovering of specific medicines. In Spain, Gordônio, cited by Faes (1966), registered the use of bleeding, warm baths, ingestion of snake broth, and even nodules extirpation. In relation to the treatment discharge, 90% were because of death; however, true lepras were not discharged. The other ones were given by cure confirmed by the doctor when he visited the leprosaries.

In Brazil, the therapeutic employed for all the existent diseases, since the colonization time, was based on medicinal plants, with hard influence of indian medicine. After that, the influences of the medicine used by the Jesuit and African, who utilized native plants in large-scale, were added. The Portuguese, and in a general way, the European, introduced a little number of imported medicines that compound the "caixa de botica", however the quantity was extremely limited and the lack of medicines became a great obstacle to the European medicine practice in colonial lands (Santos Filho, 1960).

In the 19th century, the indian from Amazonas employed, in the treatment of lepra and other skin diseases, the oil extracted from many plants of the Flacourtiaceae family, like *Carpotroche brasiliensis, Lindackeria maynensis* and *Mayna odorata* which were studied by various doctors who considered them to be a true nature miracle in that time (Pupo, 1926; Gonçalves, 1941).

There are reports that, in Pará, patients were submitted to treatments with laxative herbs as an infusion made with assacú (*Hura brasiliensis*, Euphorbiaceae) leaves which promoted hard evacuations; but this practice was condemned by the region indians who considered this plant dangerous because it promoted skin spots and gastroenteritis (Sousa-Araújo, 1956).

The application of cajueiro (*Anacardium occidentale*, Anacardiaceae) resin was another attempt made by Brazilian doctors, intending to minimize the symptoms presented by leprosy people. After the extraction, the resin was applied as a patch, directly on the nodules, maintained close for 24 hours. The resin acted as a vesicant, promoting a burn that should be treated like itself, making the nodules disappear (Sousa-Araújo, 1956).

Consultation of various types of literature sources resulted in the elaboration of a list of 11 plants (Table 1) evaluated specifically for *Mycobacterium leprae* inhibition. For details on the models or mechanism-based bioassays utilized for selecting plant extracts against *Mycobacterium leprae*, the original references should be consulted. The plants are listed in alphabetical order of scientific name, family, country, used part, dose, tested organism, result and references.

Antileprotic activity of chemically defined molecules

We founded 17 chemically defined natural molecules reported in the literature which have been identified as antileprotic activity (Table 2); but only four, viz., chaulmoogric acid, fusidic acid, rifampicin, and clarithromycin, are currently clinically used in the chemotherapeutic treatment of the leprosy. The principal compounds which have been isolated and identified belong to the class of lipids (5), triterpenes (4), macrolides (2), alkaloid (1), benzenoid (1), flavonoid (1), matansinoid (1), proteid (1), and sulfur compound (1).

Chaulmoogric acid

From *Chaulmoogra odorata* seeds, a Flacortiaceae family plant, it is extracted an oil whose 90% chemical composition is constituted by chaulmoogric acid and hydinocarpico (Pupo, 1926). The antileprotic medicine first industrialized was Antileprol®, made by Bayer laboratory, in Cairo in 1907 (Possolo, 1941).

Chaulmoogra oil probably reached its height of popularity as a treatment of leprosy in the 1920s and 1930s. The oil, or perhaps more commonly the esters of its acids (p. ex. Chaulmoogric acid), had become the treatment of choice at facilities such as the Public Health Service leprosy hospital in Carville, LA, which had taken over the Louisiana Leper Home in 1921. Stanley Stein, who had entered the Carville hospital as a patient in 1931, recalled taking the oil for years without being cured of the disease, although he believed that it had once cleared up a cluster of nodules on his temple (Stein, 1963).

The downfall of Chaulmoogra came about through the introduction of the sulfones to treat leprosy in the 1940s. Public Health Service Officer Guy Faget, Medical Director of the Carville hospital, was able to demonstrate through clinical trials the effectiveness of sulfone drugs against the disease. In 1947, Chaulmoogra oil therapy was officially abandoned at Carville, and the sulfones became the treatment of choice. As for Chaulmoogra oil, by the 1950s it had essentially become just a colorful relic of pharmacy's past (McCoy, 1942; Parascandola).

Fusidic acid

Fusidic acid is a triterpene isolated for the first time from the microorganism *Fusidium coccineum* in 1960. It is used in Europe and Asia primarily for the treatment of methicillin-resistant *Staphylococcus aureus* infections (Greenwood, 1988). It is active against *Mycobacterium leprae* both in axenic medium and in macrophage culture as determined in the BACTEC 460 system (50% inhibition at 1.25 to 2.5 ,ug/ml) (Franzblau et al., 1992). Fusidic acid was assessed for antileprosy activity in nine lepromatous leprosy patients. Patients received fusidic acid at either 500 mg/day for 12 weeks or 750 mg/day for 4 weeks followed by 500 mg/day for 8 weeks. All patients showed time-dependent clinical improvement and decreases in bacillary morphological index, radiorespirometric activity and PCR signal, and in serum phenolic glycolipid I. Fusidic acid appears to be a weakly bactericidal antileprosy agent which may have a role in the multidrug treatment of leprosy pending an evaluation of lepra-reaction-suppressive activity (Scott et al., 1994).

Rifampicin

Rifampicin is a semi-synthetic macrolide isolated from *Nocardia mediterranei.* It is one of the most efficient antibiotics against *Mycobacterium leprae.* Its activity is greater than any drug by itself or antileprotic medicinal combination, (Ji et. al., 1996) fact that ensures the fundamental role of this medicine in Hansen's disease current therapy.

Over 100 patients with lepromatous leprosy were treated with rifampicin in a series of pilot, uncontrolled, and controlled trials in 1968-1977. The rapid bactericidal effect of rifampicin on *Mycobacterium leprae* was confirmed. Clinical improvement became apparent sometimes as early as 14 days after the start of treatment. Nevertheless, a few persisting viable *M. leprae* were detected as long as five years after the start of treatment with rifampicin either by itself or in combination with the bacteriostatic drug thiambutosine. Treatment with rifampicin and dapsone for six months reduced the number of persisting leprosy bacteria more than treatment with dapsone alone. Although rifampicin proved more effective than dapsone, it is unlikely that used by itself if can significantly shorten the length of treatment in lepromatous leprosy. Therefore initial intensive combined treatment with two or more bactericidal drugs (including rifampicin) warrants further investigation in both untreated leprosy and lepromatous leprosy resistant to dapsone (Waters et al., 1978).

Clarithromycin

Clarithromycin is a semi-synthetic macrolide isolated from *Streptomyces erythreus* with activity, pharmacokinetics, and gastric tolerance superior to those of erythromycin. It has demonstrated exceptional activity against *Mycobacterium leprae* both in vitro and in vivo; its activity surpasses that of other macrolides and approximates that of rifampicin (Gertrude et al., 1994).

Clarithromycin was administered to nine previously untreated lepromatous leprosy patients. Patients received two 1,500-mg doses on the first day, followed by 7 days of no treatment, in order to evaluate the potential efficacy of intermittent therapy. Patients then received 1,000 mg daily for 2 weeks followed by 500 mg daily for 9 weeks. The therapy efficacy was monitored clinically, by changes in morphological index, mouse footpad infectivity, and radiorespirometric activity of *Mycobacterium leprae* obtained from serial biopsies and

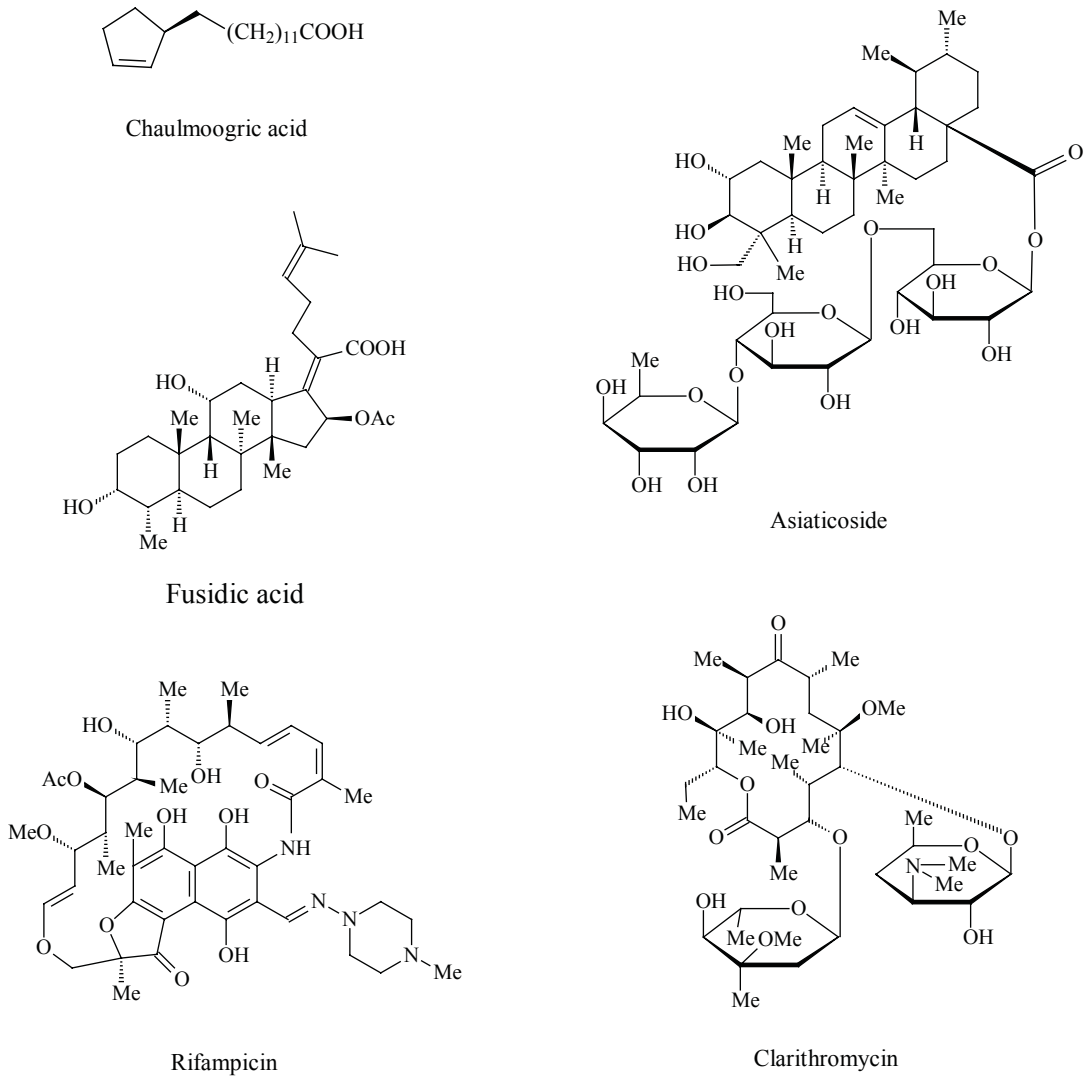

Figure 1. Chemical structures of the natural products used in clinical treatment of leprosy.

by serum levels of phenolic glycolipid I. Clarithromycin was well tolerated, with only minor side effects noted in two patients. Most patients showed reductions in morphological index and radiorespirometry 1 week after the first two doses. Within 3 weeks of starting treatment (total of 17 g of clarithromycin), biopsy-derived *M. leprae* specimens from all patients had a morphological index of zero, were noninfectious for mice, and had less than 1% of the radiorespirometric activity of pretreatment specimens. Reductions in serum phenolic glycolipid I levels were observed for most patients in 3 weeks. Significant clinical improvement was evident after 4 weeks of treatment. All analyses indicate that clarithromycin is rapidly bactericidal for *M. leprae* in humans (Gertrude et al., 1994).

CONCLUSION

This work aimed at searching for literature available data about plants and natural products that present antileprotic activity. It could be observed that they played an important role as efficient therapeutic path against leprosy centuries ago. This fact is not so different from nowadays because it is necessary the use of natural origin drugs to which no similar synthetic compound has been found in the main polychemotherapeutic regimens proposed by modern medicine for the confirmed disease cases.

REFERENCES

Almeida RN, Navarro DS, Barbosa-Filho JM 2001. Plants with central analgesic activity *Phytomedicine 8*: 310-322.

Amaral FMM, Ribeiro MNS, Barbosa-Filho JM, Reis AS, Nascimento FRF, Macedo RO 2006. Plants and chemical constituents with giardicidal activity. *Rev Bras Farmacogn 16(Supl.)*: 696-720.

Anthony JP, Fyfe L, Smith H 2005. Plant active components

Table 1. Plant with antileprotic activity.

Botanical name (Family)	Origin	Used part (Extract)	Dose or Concent.	Tested organism	Result	References
Acacia catechu (Leguminosae)	India	Entire plant (Hot H_2O ext)	Dose not stated*	Human adult	Active	Ojha et al., 1969
Achyranthes aspera (Amaranthaceae)	India	Entire plant (Hot H_2O ext)	30.0 mL / person	Human adult	Active	Ojha; Singh,1968
Albizzia lebbeck (Leguminosae)	Senegal	Seed (Oil)	Dose not stated*	Human adult	Active	Miralles; Pares, 1980
Centella asiatica (Apiaceae)	India	Entire plant (Powder)	1.0 g / person	Human adult	Active	Chaudhuri et al., 1978
Hemidesmus indicus (Asclepiadaceae)	India	Dried root (H_2O ext)	2.0 % of diet	Mouse	Active	Gupta, 1981
Lasiosiphon kraussianus (Thymelaeaceae)	West Africa	Dried root (EtOH 95%)	0.1 mg / kg	Human adult	Active	Tubery, 1969
Leucaena glauca (Leguminosae)	Senegal	Seed (Oil)	Dose not stated*	Human adult	Active	Miralles; Pares, 1980
Melia azedarach (Meliaceae)	India	Not stated*	Dose not stated*	Human adult	Active	Kataria, 1994
Semecarpus anacardium (Anacardiaceae)	India	Cotyledon (H_2O ext)	10.0 g / person	Human adult	Active	Murty, 1974
Smilax ornata (Liliaceae)	Marocco	Dried root (Hot H_2O ext)	15.0 g / person	Human adult	Active	Rotlier, 1951
Tripterygium wilfordii (Celastraceae)	China	Multiglycoside of the radix	Dose not stated*	Human adult	Active	Xu et al., 2005

* Data incomplete - derived from an abstract.

Rev. Bras. Farmacogn.
Braz. J. Pharmacogn.
17(1): Jan./Mar. 2007

Table 2. Chemically defined natural compounds showing antileprotic activity.

Chemical substance	Class	Source	Dose/Concentr.	Organism	Result	References
Allicin	Sulfur compound	*Allium sativum*	Dose not stated*	Species not stated*	Active	Holzhey et. al. 1984
Ansamycin	Matansinoid	*Nocardia mediterranei*	0.001 %	Species not stated*	Active	Hastings et. al., 1984
Asiaticoside	Triterpene	*Centella asiatica*	Dose not stated*	Human adult	Active	Boiteau et. al., 1956
Asiaticoside, Oxy	Triterpene	*Centella asiatica*	4.0 mg/animal	Mouse	Active	Boiteau et. al., 1956
Boswellin acid	Triterpene	Boswelia serrata	Dose not stated*	Not stated*	Active	Nowak; Surylo, et al., 2006
Chaulmoogric acid	Lipid	*Chaulmoogra odorata*	Dose not stated*	Mouse	Active	Levy, 1975
Chaulmoogric acid, dihydro	Lipid	*Chaulmoogra odorata*	Dose not stated*	Species not stated*	Weak activity	Levy, 1975
Clarithromycin	Macrolide	*Streptomyces erythreus*	Dose variable	Human adult	Active	Gertrude et al., 1994
Curcumin	Benzenoid	*Curcuma longa*	15.0 Micromols	Cell culture	Inactive	Han et al., 1999
Dalibotrin	Flavonoid	*Dalbergia latifolia*	Dose not stated*	Not stated*	Active	Saxena et al., 1993
Desoxyfructo-serotonin	Alkaloid	Not stated*	20.0 mg/kg	Mouse	Active	Mester de Parajd et al., 1982
Fusidic Acid	Triterpene	*Fusidium coccineum*	500.0 mg/person	Human adult	Active	Scott et al., 1994
Glucose mycolate	Lipid	*Nocardia rubra*	30.0 mcg/animal	Mouse	Active	Natsuhara et al., 1990
Hydnocarpic acid	Lipid	*Hydnocarpus wightiana*	50.0 mg/day	Human adult	Active	Chaudhuri et al., 1978
Palmitic acid	Lipid	*Chaulmoogra odorata*	Dose not stated*	Mouse	Inactive	Levy, 1975
Proteoglycan-G009	Proteid	*Ganoderma lucidum*	Dose not stated*	Species not stated*	Active	Lee et al., 1992
Rifampicin	Macrolide	*Nocardia mediterranei*	600.0 mg	Human adult	Active	Shepard et al., 1974

* Data incomplete - derived from an abstract.

- a resource for antiparasitic agents? *Trends Parasitol 21*: 462-468.

Barbosa-Filho JM, Vasconcelos THC, Alencar AA, Batista LM, Oliveira RAG, Guedes DN, Falcão HS, Moura MD, Diniz MFFM, Modesto-Filho J 2005. Plants and their active constituents from South, Central, and North America with hypoglycemic activity. *Rev Bras Farmacogn 15*: 392-413.

Barbosa-Filho JM, Piuvezam MR, Moura MD, Silva MS, Lima KVB, Cunha EVL, Fechine IM, Takemura OS 2006a. Anti-inflammatory activity of alkaloids: A twenty century review. *Rev Bras Farmacogn 16*: 109-139.

Barbosa-Filho JM, Medeiros KCP, Diniz MFFM, Batista LM, Athayde-Filho PF, Silva MS, Cunha EVL, Almeida JRGS, Quintans-Júnior LJ 2006b. Natural products inhibitors of the enzyme acetylcholinesterase. *Rev Bras Farmacogn 16*: 258-285.

Barbosa-Filho JM, Martins VKM, Rabelo LA, Moura MD, Silva MS, Cunha EVL, Souza MFV, Almeida RN, Medeiros IA 2006c. Natural products inhibitors of the angiotensin converting enzyme (ACE). A review between 1980-2000. *Rev Bras Farmacogn 16*: 421-446.

Boiteau P, Batsimamanga AR 1956. Asiaticoside extracted from *Centella asiatica,* it's therapeutic uses in healing of experimental refractory wounds, leprosy, skin tuberculosis and lupus. *Therapie 11*: 125-149.

Chaudhuri S, Ghosh S, Chakraborty T, Kundu S, Hazra SK 1978. Use of a common indian herb "Mandukaparni" in the treatment of leprosy. *J Indian Med Ass 70*: 177-180.

Cowan MM 1999. Plants products as antimicrobial agents. *Clin Microbiol Rev 12*: 564-582.

Deps PD, Guedes BVS, Bucker Filho J, Andreatta MK, Marcari RS, Rodrigues LC 2006. Characteristics of known leprosy contact in a high endemic area in Brazil. *Lepr Rev 77*: 34-40.

Eidt LM 2004. Breve história da hanseníase: sua expansão do mundo para as Américas, o Brasil e o Rio Grande do Sul e sua trajetória na saúde pública brasileira. *Saúde e Sociedade 13*: 76-88.

Faes JT 1966. *Hospitales de leprosos en Asturias durante las edades media y moderna*. Oviedo, [s.n.].

Falcão HS, Lima IO, Santos VL, Dantas HF, Diniz MFFM, Barbosa-Filho JM, Batista LM 2005. Review of the plants with anti-inflammatory activity studied in Brazil. *Rev Bras Farmacogn 15*: 381-391.

Franzblau SG, Biswas AN, Harris EB 1992. Fusidic acid is highly active against extracellular and intracellular *Mycobacterium leprae*. *Antimicrob Agents Chemoth 36*: 92-94.

Gertrude PC, Bernadette YGI, Virgínia EC, Jocelyn BL, Claribel LJ, Manuela LRP 1994. Clinical trial of clarithromycin for lepromatous leprosy. *Antimicrob Agents Ch 38*: 515-517.

Gilani AH, Rahman A 2005. Trends in ethnopharmacology. *J Ethnopharmacol 100*: 43-49.

Gonçalves JG 1941. *A introdução e a aclimação de plantas contra a lepra*. São Paulo - Brasil.

Gonçalves MCR, Moura LSA, Rabelo LA, Barbosa-Filho JM, Cruz HMM, Cruz J 2000. Produtos naturais inibidores da enzima HMG CoA redutase. *Rev Bras Farm 81*: 63-71.

Greenwood D 1988. Fusidic acid. In P. K. Peterson and J. Verhoef (ed.), *Antimicrobial agents annual 3*. Elsevier Science Publishers BV, Amsterdam.

Gupta PN 1981. Antileprotic action of an extract from "Anantamul" (*Hemidesmus indicus*) *Leprosy in India 53*: 354-359.

Gurib-Fakim A 2006. Medicinal plants: traditions of yesterday and drugs of tomorrow. *Mol Aspects Med 27*: 1-93.

Han SS, Chung ST, Robertson DA, Ranjan D, Bondada S 1999. Curcumim causes the growth arrest and apoptosis of B cell lymphoma by downregulation of EGR-1, C-MYC, BCL-XL, NF-KB, and P53. *Clin Immunol 93*: 152-161.

Hansen GHA 2007. Who named it? www.whonamedit.com/doctor.cfm/596.html. Accessed in January 28th, 2006.

Hastings RC, Richard VR, Jacobson RR 1984. Ansamycin activity against rifampicin-resistant *Mycobacterium leprae***.** *Lancet. 8386*: 1130.

Holzhey M, Roth HH, Hoepfner V 1992. Use of Allicin-urotopin as internal drug for the treatment of infections and cancer. Patent-Ger Offen-4,024,155.

Ji B, Perani EG, Petinom C, Grosset JH 1996. Bactericidal activities of combinations of new drugs against *Mycobacterium leprae* in nude mice. *Antimicrob Agents Chemoth 40*: 393-399.

Kataria HC 1994. Medicinal plant *Melia azedarach* used in leprosy control. *Orient J Chem 10*: 178-180.

Lee KH, Chung H, Lee CW, Chung CH 1992. Antitumor and immunostimulating proteoglycan G009 manufacture with ganoderma. *Patent-Pct Int Appl-92***,***10,562*.

Lepra 2004. Manual Merck de saúde para a família. www.manualmerck.net/artigos/imprime.asp?id=208&cn=1715. Accessed in January 28th, 2006.

Levy L 1975. The activity of chaulmoogra acids against *Mycobacterium leprae. Amer Rev Respir Dis 111*: 703.

McCoy GW 1942. Chaulmoogra oil in the treatment of leprosy. *Pub Health Rep 57*: 1727-1733.

Mester de Parajd L, Balakrishnan S, Saint-Andre P, Mester de Parajd M 1982. Deoxyfructo-serotonin: A new drug with anti-leprosy activity. *Ann Microbiol 133B*: 427-432.

Miralles J, Pares Y 1980. Fatty acid composition of some oils from Senegalese seeds. *Revue Francaise des Corps Gras 27*: 393-396.

Morais LCSL, Barbosa-Filho JM, Almeida RN 2003. Plants and bioactives compounds for the treatment of Parkinson's desease. *Arquivo de Fitomedicina 1*: 127-132.

Moura MD, Torres AR, Oliveira RAG, Diniz MFFM, Barbosa-Filho JM 2001. Natural products inhibitors of models of mammary neoplasia. *Brit J Phytotherapy 5*: 124-145.

Moura MD, Silva JS, Oliveira RAG, Diniz MFFM, Barbosa-Filho JM 2002. Natural products reported as potential inhibitors of uterine cervical neoplasia. *Acta Farm Bonaerense 21*: 67-74.

Murty GK 1974. Clinical toxicity study of *Semecarpus anacardium*. *Indian J Exp Biol 12*: 444-446.

Natsuhara Y, Oka S, Kaneda K, Kato Y, Yano I 1990. Parallel antitumor, granuloma-forming and tumor-necrosis-factor-priming activities of mycoloyl glycolipids from *Nocardia rubra* that differ in carbohydrate moiety:

structure-activity relationships. *Cancer Immunol Immunother 31*: 99-106.

Nowak K, Surylo P 2006. Antileprosy drugs. *Wiadomosci Chemiczne 60*: 257-278.

Ojha D, Singh G 1968. Apamarga (*Achyranthes aspera*) in the treatment of lepromatous lepra. *Lepr Rev. 39*: 23.

Ojha D, Singh G, Upadhyaya YN 1969. Clinical evaluation of *Acacia catechu*, Willd. (Khadira) in the treatment of lepromatous leprosy. *Int J Lepr Other Mycobact Dis 37*: 302-307.

Parascandola J 1998. Miracle at Carville: The introduction of the sulfones for the treatment of leprosy. *Pharm Hist 40*: 59-66.

Pereira JV, Modesto-Filho J, Agra MF, Barbosa-Filho JM 2002. Plant and plant-derived compounds employed in prevention of the osteoporosis. *Acta Farm Bonaerense 21*: 223-234.

Pinto AC, Silva DHS, Bolzani VS, Lopes NP, Epifanio RA 2002. Current status challenges and trends on natural products in Brazil. *Quim Nova 25*: 45-61.

Possolo H 1941. *As flaucortiáceas antilepróticas*. Monografia do Laboratório Químico-Farmacêutico do Instituto "Conde de Lara".Rio de Janeiro.

Pupo JA 1926. *Tratamento específico da lepra pelo óleo de chaulmoogra e seus derivados – estudo das flacourtiaceas do Brasil*. Publicação do Brasil-Médico, Sodré Ed., Rio de Janeiro.

Ramos Jr AN, Heukelbach J, Gomide M, Hinders DC, Schreuder PAM 2006. Health systems research training as a tool for more effective Hansen's disease control programmes in Brazil. *Lepr Rev 77*: 175-188.

Rocha LG, Almeida JRGS, Macedo RO, Barbosa-Filho JM 2005. A review of natural products with antileishmanial activity. *Phytomedicine 12*: 514-535.

Rotlier R 1951. Treatment of leprosy by a *Smilax* species. *Maroc Med 30*: 776-780.

Santos Filho L 1960. Medicina colonial. In H Sérgio Buarque (org.) *História da civilização brasileira*. DIFEL, São Paulo.

Saxena VK 1993. Novel 4-phenyl coumarin glycoside: a potential antileprotic drug from *Dalbergia latifolia* seeds. *Journal of the Institution of Chemists 65*: 161-162.

Scott GF, Diana LW, Thomas PG, Rally FC, Gertrude PC, Bernadette YGI, Virgínia EC, Jocelyn BL, Claribel LJ, Manuela LRP 1994. Clinical trial of fusidic acid for lepromatous leprosy**.** *Antimicrobial Agents Chemoth 38*: 1651-1654.

Shepard CC, Levy L, Fasal P 1974. Further experience with the rapid bactericidal effects of rifampin on *Mycobacterium leprae*. *Amer J Trop Med Hyg 23*: 1120-1124.

Silva JS, Moura MD, Oliveira RAG, Diniz MFFM, Barbosa-Filho JM 2003. Natural products inhibitors of ovarian neoplasia. *Phytomedicine 10*: 221-232.

Sousa-Araújo HC 1956. *História da lepra no Brasil; 1500-1952*. Departamento da Imprensa Nacional, Rio de Janeiro.

Stein S 1963. *Alone No Longer: The Story of a Man who Refused to Be One of the Living Dead*. New York: Funk and Wagnalls, pp. 38-39.

Tubery PR 1969. Glycosidic extract of *Lasiosiphon kraussianus* useful as an antileprous medicament. *Patent-Fr M-7333*.

Waters MF, Rees RJ, Pearson JM, Laing AB, Helmy HS, Gelber RH 1978. Rifampicin for lepromatous leprosy: nine years' experience. *Brit Med J 1(6106)*:133-136.

WHO 2000. The final push towards elimination of leprosy: strategic plan, 2000-2005. www.paho.org/common/Display.asp?Lang=E&RecID=7211. Accessed in January 28th, 2006.

WHO 2006. Leprosy situation in the WHO Region of the Americas. www.who.int/lep/situation/americas/en/print.html. Accessed in January 28th, 2006.

Xu R, Fidler JM, Musser JH 2005. Bioactive compounds from *Tripterygium wilfordii***.** In *Studies in natural products chemistry*. v. 32, Bioactive natural products (Part L) Publisher, Elsevier.

Yunes RA, Calixto JB 2001. *Plantas medicinais sob a ótica da química medicinal moderna*. Chapecó: Argos, 500p.