Natural products with antileprotic activity

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

In order to ‘eliminate’ leprosy from all countries, the World 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., 2001), 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), anti-inflammatory activity (Falcão et al., 2005; Barbosa-Filho et al., 2006), inhibitors of the enzyme acetylcholinesterase (Barbosa-Filho et al., 2005; Barbosa-Filho et al., 2006), inhibitors of the angiotensin converting enzymes (Barbosa-Filho et al., 2006) 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 lepers 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 Flacourtia 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 cajeiro (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), matansinoi (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 sulphones 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 sulphones 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 \( \mu \text{g/ml} \)) (Franzbblau 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 macroclide 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

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- *Chaulmoogra odorata* seeds
- *Fusidium coccineum*
- *Staphylococcus aureus*
- *Mycobacterium leprae*
- *Nocardia mediterranei*
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

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Table 1. Plant with antileprotic activity.

<table>
<thead>
<tr>
<th>Botanical name (Family)</th>
<th>Origin</th>
<th>Used part (Extract)</th>
<th>Dose or Concent.</th>
<th>Tested organism</th>
<th>Result</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Acacia catechu</em> (Leguminosae)</td>
<td>India</td>
<td>Entire plant (Hot H2O ext)</td>
<td>Dose not stated*</td>
<td>Human adult</td>
<td>Active</td>
<td>Ojha et al., 1969</td>
</tr>
<tr>
<td><em>Achyranthes aspera</em> (Amaranthaceae)</td>
<td>India</td>
<td>Entire plant (Hot H2O ext)</td>
<td>30.0 mL / person</td>
<td>Human adult</td>
<td>Active</td>
<td>Ojha; Singh, 1968</td>
</tr>
<tr>
<td><em>Albizia lebbeck</em> (Leguminosae)</td>
<td>Senegal</td>
<td>Seed (Oil)</td>
<td>Dose not stated*</td>
<td>Human adult</td>
<td>Active</td>
<td>Miralles; Pares, 1980</td>
</tr>
<tr>
<td><em>Centella asiatica</em> (Amaranthaceae)</td>
<td>India</td>
<td>Entire plant (Powder)</td>
<td>1.0 g / person</td>
<td>Human adult</td>
<td>Active</td>
<td>Chaudhuri et al., 1978</td>
</tr>
<tr>
<td><em>Hemidesmus indicus</em> (Amaranthaceae)</td>
<td>India</td>
<td>Dried root (H2O ext)</td>
<td>2.0 % of diet</td>
<td>Mouse</td>
<td>Active</td>
<td>Gupta, 1981</td>
</tr>
<tr>
<td><em>Lasiosiphon kraussianus</em> (Thymelaeaceae)</td>
<td>West Africa</td>
<td>Dried root (EtOH 95%)</td>
<td>0.1 mg / kg</td>
<td>Human adult</td>
<td>Active</td>
<td>Tubery, 1969</td>
</tr>
<tr>
<td><em>Leucaena glauca</em> (Leguminosae)</td>
<td>Senegal</td>
<td>Seed (Oil)</td>
<td>Dose not stated*</td>
<td>Human adult</td>
<td>Active</td>
<td>Miralles; Pares, 1980</td>
</tr>
<tr>
<td><em>Melia azedarach</em> (Melaceae)</td>
<td>India</td>
<td>Not stated*</td>
<td>Dose not stated*</td>
<td>Human adult</td>
<td>Active</td>
<td>Kataria, 1994</td>
</tr>
<tr>
<td><em>Semecarpus anacardium</em> (Anacardiaceae)</td>
<td>India</td>
<td>Cotyledon (H2O ext)</td>
<td>10.0 g / person</td>
<td>Human adult</td>
<td>Active</td>
<td>Murty, 1974</td>
</tr>
<tr>
<td><em>Smilax ornata</em> (Liliaceae)</td>
<td>Marocco</td>
<td>Dried root (Hot H2O ext)</td>
<td>15.0 g / person</td>
<td>Human adult</td>
<td>Active</td>
<td>Rotlier, 1951</td>
</tr>
<tr>
<td><em>Tripterygium wilfordii</em> (Celastraceae)</td>
<td>China</td>
<td>Multiglycoside of the radix</td>
<td>Dose not stated*</td>
<td>Human adult</td>
<td>Active</td>
<td>Xu et al., 2005</td>
</tr>
</tbody>
</table>

* Data incomplete - derived from an abstract.
### Table 2. Chemically defined natural compounds showing antileprotic activity.

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

* Data incomplete - derived from an abstract.
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