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Pharmacology and Medicobotany of Anti Leprotic Plants: A Review

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Abstract: Background: Leprosy, an infectious disease, caused by bacteria *Mycobacterium leprae* and *Mycobacterium lepromatosis* has been known since biblical times. The disease is associated with damage of the skin, nerve, limbs and eyes. It has a long incubation period and children are more susceptible. Common forms of leprosy are tuberculoid and lepromatous and a few intermediates. It is not very contagious and tentative mode of transmission is respiratory droplets. The disease is widespread throughout the tropical, subtropical and temperate regions of the world but is prevalent among the underprivileged of the third world countries. **Results:** The present review deals with the literature covering the use of antileprotic plants, their pharmacological investigations and ethnobotanical remedy of the disease. The authors have tried to bridge between the folklore use of the herbs and their pharmacological investigations for antileprotic properties. **Conclusions:** Although different antileprotic drugs are available in the market, herbs and herbal constituents have been neglected as a possible remedy. Most of the present treatments are difficult, time consuming, expensive and with adverse side effects. Development of drug resistance in the bacteria is another major concern worldwide. Considering the facts, herbal remedy can be an exciting aspect in the treatment of the disease with less side effects and at a reasonable cost. The vast ethnic knowledge inherited by the local medical practitioners can be exploited scientifically to find out novel antileprotic compounds.

Key words: Leprosy, pharmacology, traditional, chemotherapy

INTRODUCTION

Leprosy (Hansen's disease) is an ancient disease which may be associated with organ deformity and social rejection. The causal organism is *Mycobacterium leprae*, an aerobic and rod-shaped intracellular acid-fast bacterium. The disease has two polar clinical forms: the "paucibacillary" tuberculoid leprosy and disseminated form known as the "multibacillary" or lepromatous leprosy with other intermediate forms (Kustner *et al*., 2006). If untreated, the later form may lead to anesthesia, ulceration and loss of distal parts of extremities (Gelber, 1994). A series of cytokine mediated inflammatory responses are associated with tissue damage (Yamamura *et al*., 1992). There might be a possible role for interferon-gamma and interleukin-12 in cytokine mRNA expression in leprosy (Moraes *et al*., 1999). The bacterium shows metabolic activity in cell free (Murohashi and Yoshida, 1969, 1972) and macrophage (Veliath *et al*., 1979) tissue culture. Being an absolute parasite, it has been difficult to grow the bacteria *in vitro*. Dhople-Hanks (DH) medium with different manipulations has been used for *in vitro* growth of *M. leprae* (Dhople, 1998; Dhople and Lamoureux, 1991a, b). Lack of multiplication of the bacterium under the cell-free condition might be due to fragile nature of the cell wall (Nakamura, 2001). The mouse foot-pad technique is a widely used and reproducible model for cultivation of *M. leprae* and to assay and quantify antimycobacterial agents (Pattyn, 1983; Levy and Ji, 2006). Other animal models namely congenitally athymic mice (nude mice) and nine-banded armadillo are also used for the purpose (Colston and Hilson, 1976; Job, 2003).A second bacterium named *Mycobacterium lepromatosis* has been recently discovered associated with Diffuse Lepromatous Leprosy (DLL) mainly occurs in Mexico and the Caribbean (Han *et al*., 2008).

CHEMOTHERAPY

The downfall of Chaulmoogra oil, the natural remedy against leprosy during 1920s and 1930s came about due to the introduction of the sulfones (Barbosa-Filho *et al*., 2007). Promine was introduced as an antileprotic drug in the 1940s (Sloan, 1947). It was

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substituted by dapsone in 1950s (Garrett and Corcos, 1952) and due to indefinite use and antibiotic resistance it became useless by the 1960s. Clofazimine and rifampicin in were popular in the 1960s and 1970s against the disease. Multidrug therapy (MDT) combining three drugs were introduced by WHO in 1981, using any of the one alone may develop drug resistance. Chemotherapy of leprosy has been a popular area of research for the last few decades (Parikh *et al*., 1985; Ellard, 1990; Sansarricq, 1986; Winsley *et al*., 1983). Combination drug therapy (Terencio, 1983; Ellard, 1980) and multidrug therapy (MDT) (Ramu, 1985; Noordeen, 1990) have been the two modern aspects of antileprotic treatments. Tetracyclines (minocycline), macrolides (clarithromycin), fluoroquinolones (pefloxacin, ofloxacin and sparfloxacin), isoniazide and thioamides (ethionamide and prothionamide) have been tried as antileprotic drugs (Van Saane and Timmerman, 1989; Waters, 1993; Franzblau and Hastings, 1988; Gelber *et al*., 1991; Ji *et al*., 1998). Some recommended multidrug therapy and rationally based therapy to combat drug resistance and bacterial persistence (Gelber, 1994). Drug resistance of *M. leprae* has been a severe problem globally (Pattyn, 1986; Ji, 1985; Gupta and Katoch, 1999; Roche *et al*., 2000). Problems of multidrug therapy and relapses have been reported though (De Carsalade *et al*., 1997; Becx-Bleumink, 1992a, b). Immuno-allergic side-effects of rifampicin (Flageul *et al*., 2001), Dapsone Hypersensitivity Syndrome (DHS) (Jaswal *et al*., 1998; Ng and Goh, 1998; Pandey *et al*., 2007; Rao and Lakshmi, 2001; Bucaretchi *et al*., 2004; Alves-Rodrigues *et al*., 2005a, b; Sapkota *et al*., 2008), red and dark skin pigmentation and abdominal complications due to clofazimine therapy (Ramu and Iyer, 1976; Pais *et al*., 2004), hepatitis due to thioamide along with dapsone and rifampin (Cartel *et al*., 1983) are the adverse effects of chemotherapy.

ANTI LEPROTIC HERBS

Chaulmoogric acid (from the seeds of the members of Flacortiaceae family), triterpene fusidic acid (from *Fusidium coccineum*), semi-synthetic macrolides rifampicin (from *Nocardia mediterranei*) and Clarithromycin (from *Streptomyces erythreus*) have been among the antimycobacterial natural products (Barbosa-Filho *et al*., 2007). Plants and plant derived natural products as antimycobacterial agents have been reported (Newton *et al*., 2000; Gautam *et al*., 2007). Antileprotic herbal drugs in combination with dapsone were evaluated (Asthana *et al*., 2001). *Tinospora cordifolia* was found to one of the ingradients against leprosy (Singh *et al*., 2003; Upadhyay *et al*., 2010). Geranylgeraniol and geranylgeranyl acetate, the terpenoids were found to be the potent inhibitors of the bacterium *in vitro* assayed by microplate alamar blue technique. Treatment of leprosy by Unani medicine (Zafarullah *et al*., 1980) and Ayurveda (Gaikwad and Gaikwad, 2010) has been reported. Usefulness of Nimbadi-lepa in leprosy treatment was reported (Ojha, 1966). Ayurvedic Samshodhan-karm was reported to be effective against leprosy (Ojha and Singh, 1967). Hepato-protective function of Liv. 52, an indigenous drug in lepromatous leprosy has been discussed (Nigam *et al*., 1982). Multiplication of *M. leprae* in mouse foot-pads was treated with some ayurvedic preparations (Bhatia *et al*., 1984).

Chaulmoogra oil, isolated from different species of *Hydnocarpus* (Flacourtiaceae) has been an age old treatment of leprosy in India and surrounding countries before the advent of modern chemotherapy. It was used to cure leprosy from the late nineteenth century until the 1940s (Dos Santos *et al*., 2008). Origin and introduction of chaulmoogra were discussed (Zhao, 1986). Beneficial effects of chaulmoogra in the treatment of leprous neuritis were reported (Schujman, 1957). Use of the oil in the treatment of leprosy has been reported by many authors (Cottle, 1879; McCoy, 1942; Parascandola, 2003). Chaulmoogra oil expressed from the seeds of *Gynocardia odorata* was reported to be used in two specific cases of Leprosy in England (Cottle, 1879). Antileprotic activity of a hydrogenated chaulmoogra oil derivative was recorded (Gate, 1952). Spaced injections of diaminodiphenylsulfone in ethyl chaulmoograte were given in the treatment of leprosy (Laviron *et al*., 1954). To treat leprosy, thioacetazone was injected weekly in chaulmoogra suspensions (Laviron *et al*., 1957). Chaulmoogra, extracted from *Hydnocarpus* seeds in Hawaii is a traditional medicine against leprosy (Norton, 1998). Fatty acid configuration in the activity of chaulmoogra in leprosy was reported (Jardin, 1953; Sengupta *et al*., 1973). Sodium salts of chaulmoogra oil, hydnocarpic and chaulmoogric acids were found to be effective in *Mycobacterium leprae* infected mouse footpad when administered intraperitoneally and subcutaneously 3 times per week. Dihydrochaulmoogric acid was also effective but palmitic acid was not (Levy, 1975). *Hydnocarpus* oil has been employed in wound healing in male Wistar rats based on its leprotic wound healing claims (Oommen *et al*., 1999). 5'-methoxyhydnocarpin, a multidrug pump inhibitor, previously reported from chaulmoogra oil potentiates antimicrobial action of berberine (Stermitz *et al*., 2000). *Carpotroche brasiliensis*, a native Brazilian tree

belonging to the family Flacourtiaceae contains cyclopentenyl fatty acids (hydnocarpic, chaulmoogric and gorlic acids) found in the well known chaulmoogra oil prepared from the *Hydnocarpus* seeds (Cole and Cardoso, 1938; Lima *et al*., 2005; Oliveira *et al*., 2009). These are potent antimycobacterial compounds (Jacobsen *et al*., 1973; Levy, 1975).

Centella asiatica contains Asiaticoside, a glucoside (Das and Mallick, 1991). The compound has been therapeutically used in the healing of leprosy (Bailey, 1945; Boiteau *et al*., 1949; Boiteau and Ratsimamanga, 1956; Viala *et al*., 1977). The waxy covering of *Bacillus leproe* was dissolved by the active principle resulted into destruction of the causal organism (Bailey, 1945). Liposomal delivered asiaticoside had better Mycobacterial property against *M. leprae* and *M. tuberculosis* than that of free asiaticoside. Liposomes containing asiaticoside and corchorusin D showed equal or more activity when compared to liposomal asiaticoside alone (Medda *et al*., 1995). The plant commonly known as "Mandukaparni" in India is reported to be used in the treatment of leprosy (Chaudhuri and Ghosh, 1977; Chaudhuri *et al*., 1978; 1979). *C. asiatica* powder was investigated against *M. tuberculosis* also (Herbert *et al*., 1994). Wound healing activity of *C. asiatic*a has been reported by Sunilkumar and Shivakumar (1998) and Shetty *et al*. (2006).

A variety of sarsaparilla has been tried in leprosy treatment (Rollier *et al*., 1951). A Combination of red sarsaparilla and 4,4'-diaminodiphenylsulfone (DDS) was tried in the treatment of lepromatous leprosy (Rollier, 1957).The same was treated by a combination of DDS and sarsaparilla (*Smilax ornata*) (Rollier, 1959). The saponosides of two sarsaparilla plants (*Smilax ornata* and *Smilax japicanga*) have been reported to be used against leprosy (Paris *et al*., 1952). Leprosy treatment by *Smilax ornata* has been reported (Rollier, 1951).

Achyranthes aspera (Apamarga) is being reported to be used in leprosy (Tripathi *et al*., 1963). Preliminary observations of using the plant in leprosy management were recorded (Ojha *et al*., 1966). The plant has been used in the treatment of lepromatous leprosy (Ojha and Singh, 1968).

Alectra parasitica var. *chitrakutensis* has been reported in the treatment of leprosy in Bihar, India (Ghosh and Chakraborty, 1964; Prasad, 1964). *Acacia catechu* (Khadira) was evaluated clinically in the treatment of lepromatous leprosy (Ojha *et al*., 1969). *Semecarpus anacardium* was found to be therapeutically active against leprosy (Murty, 1974). Flowers of *Ochrocarpus longifolia* (Nagkesar), used against leprosy were chemically investigated and Nuclear Magnetic Resonance (NMR) data has been produced (Khan *et al*., 1978). *Albizzia lebbeck* and *Leucaena glauca* seed oil were reported to be effective against leprosy in human (Miralles and Pares, 1980). In the antileprotic treatment of mouse foot-pads, extract from *Hemidesmus Indicus* had produced encouraging results (Gupta, 1981). A novel 4-phenyl coumarin glycoside isolated from *Dalbergia latifolia* seeds was reported as a potential antileprotic agent (Saxena, 1993). *Melia azedarach* has also been used in leprosy control (Kataria, 1994). *Calotropis procera*, another medicinal plant has been a popular use in the treatment of leprosy (Behl and Luthra, 2002). *Kigelia africana* is being used against leprosy as an alternative medicine especially in developing nations (Gabriel and Olubunmi, 2009).

Fifteen Rwandese medicinal plants prescribed by traditional healers were tested for antimycobacterial activities of which the leaves of *Bidens pilosa*, roots of *Pentas longiflora* and leaves of *Tetradenia riparia* have been effective (Van Puyvelde *et al*., 1994). Forty five plant species have been selected on the basis of traditional reports against TB and/or leprosy and the plant species were assayed *in vitro* for antimycobacterial activities using *M. aurum* and *M. smegmatis*, two model species of Mycobacteria. *Psoralea corylifolia* and *Sanguinaria canadensis* were found to be significantly active against *M. aurum*. Chelerythrine, a benzophenanthridine alkaloid from the roots *S. canadensis* was the most effective against *M. aurum* and *M. smegmatis*. These data supported their ethnic antileprotic use (Newton *et al*., 2002). *Ficus citrifolia* and *Pisonia borinquena* from the flora of Puerto Rico had shown activity against Mycobacteria, *M. tuberculosis* (Antoun *et al*., 2001). Certain Peruvial plants were also assayed against the same (Graham *et al*., 2003).

TRADITIONAL MEDICINE

Antileprotic use of ethnobotanicals has been compiled (Gupta *et al*., 2010). Some antileprotic plants of ethnomedicinal importance have been reported from Northeast India (Begum and Nath, 2000). The potential of South African plants against *Mycobacterium* infections has been tested (McGaw *et al*., 2008; Mmushi *et al*., 2010). The genus *Symplocos* is used as antileprotic in traditional medicine (Badoni *et al*., 2010). The seeds of *Melilotus indica* are antileprotic (Yadava and Jain, 2005). *Datura metel* (Dey and De, 2010), *Calotropis gigantea* (Rahmatullah *et al*, 2010), *Calotropis procera, Acacia catechu* (Singh *et al*, 2010), *Melia azedarach* (Malla and Chhetri, 2009), *Anagallis arvensis*, *Cyperus rotundus* (Panhwar and Abro, 2007), *Achyranthes aspera*

(Qureshi and Bhatti, 2009), *Centella asiatica* (Guleria and Vasishth, 2009; Pant and Samant, 2010), *Coix gigantea, Artemisia dubia* (Anisuzzaman *et al*., 2007). *Bidens pilosa* (Pant and Samant, 2010) etc. are among the other antileprotic herbs reported by the different ethnic groups indicating a strong correlation between pharmacology and ethnobotany of the medicinal herbs as possible antileprotic remedy.

CONCLUSION

The present treatment of leprosy is difficult, time consuming, expensive and with adverse side effects (Kustner *et al*., 2006). The emergence of drug-resistant bacteria and relapses are common concerns associated with the disease. To overcome the problems, some alternative treatment may be encouraged backed by pharmacological evidences and clinical trials. The herbs could be an exciting alternative. Traditional knowledge of the ethnic people can be exploited in order to achieve a natural remedy against the disease associated with trauma, social rejection and isolation. Although, herbs are no longer in use in the modern therapy of leprosy, some authors have been doubtful regarding the rejection of herbal treatment of the disease (Van Saane and Timmerman, 1989). Positive ethnopharmacological correlation with the traditional knowledge may have some answers in store.

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