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Synthesis of Some Antileprotic Drugs from Some Indigenous Flora

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In the present paper we have reported synthesis of some antileprotic drugs from some indigenous flora

INTRODUCTION

Leprosy is a communicable disease caused by *Mycobacterium leprae*, a ribosomal antigen having specific glycolipid and constitutes a serious public health problem. It has been estimated that approximately one-fourth of the total leprosy population (estimated 12 million) of the world is in India. It is considered that the human beings and particularly the patients suffering from leprosy are the only source of infection and that transmission of the disease takes place through various routes.

Leprosy is a curse to mankind due to its venomous contagious nature leading to social discard of *lepers*. National Hansen's Disease Centre, Carville, Lousiana has reported 5 types of leprosy but clinically leprosy manifests mainly as two main types—one in which the disease tends to be restricted and the other where there is a progressive spread of the disease over the body. The latter form of leprosy constitutes only 20 to 25% of the total leprosy population in India, but these are the cases that pose a serious health problem. These cases are known as multibacillary leprosy.

The social stigma based on ignorance and Biblical castigation of individuals with this disease must be replaced by the attitude that leprosy is a disease and can be cured with proper chemotherapy.

The patients with leprosy can be classified as "infectious" or "non-infectious" on the basis of type, duration and effects of therapy. The present endeavour in leprosy treatment is to make patients non-infectious.

Chemotherapy is the mainstay of leprosy control

Sulfones were found to cure leprosy. This was soon followed by successful clinical trials in human leprosy. Boiteau and Grimes[1], extracted a new glucoside from *Hydrocotyle asiatica* Syn. *Centella asiatica*[2–5] (fam. Umbelliferae) but it was not successful due to its high toxicity. Several workers isolated asiaticoside[6–10], a new glucoside which was not only active against leprosy but was also much less toxic, insoluble in water, slightly soluble in alcohol and very much soluble in pyridine. Later Boiteau[1] prepared suitable injections and Devanne and Razafimahery studied its chemical constitution.

The remarkable results of the injection were the following:

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(1) Leprosy nodules were broken down.

(2) Diffuse infiltration disappeared.

(3) Perforating ulcers and lesions on the fingers,were healed.

(4) All eye lesions were rapidly cured by treating the posterior chamber of the eye.

Present knowledge of bibliography

The treatment of leprosy is done by major synthetic drugs[1–3]. Dapsone is bacteriostatic. *Rifampin* being expensive is not used commonly. Other drugs recommended are *Clofazomine*, Propionamide and DDS. *Mycobacterium leprae* do not survive on artificial media, estimated sensitivity to the drug is 1 to 10 mg/mL for microorganisms recovered from untreated patients.

Our country is bestowed with indigenous medicinal plants from which effective drugs have been isolated, *e.g.*,

(i) *Centella asiatica*[2–5] *syn. Hydrocotyle asiatica Linn. (Fam. Umbelliferae):* It is a medicinal plant, A prostrate, faintly aromatic herb found throughout India and Ceylon up to an altitude of 2,000 ft. The leaves are orbiculoreniform, 0.5–1.5 inches in diameter, with short stalks[11] and used in leprosy.

In alcoholic extract[12], essential oil, fatty oil, sitosterol and an alkaloid, hydrocotylon from dried plant have been reported.[8]

A glycoside *Asiaticoside*[9] (active in the treatment of leprosy), a rhamnose-glucose derivative of asiatic acid (a triterpene acid), has been reported which contains centoic, centellic and centic acid[4–6]. On the basis of chemical properties *asiaticoside* is named *centelloside*, has the composition of centellic acid : glucose : fructose = 1:10:2 (mol) on the basis of periodate oxidation[9].

(ii) *Melia azedarach*[13] *Linn. (Fam. Meliaceae) PH and Bo-Bakain (Hindi, Bakain), Drek:* It is a moderate-sized deciduous tree, 9–12 m high with a cylindrical bole *ca.* 3.5 m long, 1–1.2 m girth, found growing wild in the sub-Himalayan tracts up to 18,000 m. Bark dark grey with shallow longitudinal furrows; leaves bi- or occasionally tripinnate; leaflets ovate or lanceolate, serrate, flowers lilac, fragrant, in axillary panicles, fruit an ellipsoid globose drupe with 4–5 seeds. It is a native of west Asia and is now naturalized throughout the warm countries. In India, it is often cultivated in plains as an ornamental tree. It bears a spreading crown and withstands a colder climate than neem. It is sometimes grown as a shade tree in coffee and tea plantations. Leaves and bark of the plant are used internally and externally in leprosy and scrofula. Fruit is also used in leprosy.

Fruits contain a poisonous constituent[14] alkaloid, *azaridine*, a resin, tannin, meliotannic acid and benzoic acid. The aqueous extract produces dyspnoea in rabbit, tremor, convulsions and death[12]. The fruit yields *bakayanin* (sterol). The species contains *bakalactone*, which reduces intensity of asthamatic attack. Leaves have significant anthelmintic activity due to vanillic acid and ±dl catechin.

(iii) *Ipomoea hispida (Roem and Schulz)*[11] *Syn. I. eriocarpa R.Br. (Fam. Convolvulaceae):* The plant is a herbaceous, slender, twining, villous annual, found almost throughout India ascending upto 4,000 ft in the Himalayas, It is common in open grasslands, hedges, fields, secondary forests and dry areas.

Leaves oblong, cordate, acute, hairy; flowers small, campanulate, pink or purple, axillary, solitary or in multiflowered cymes; capsules small, globose, hairy; seeds 4, glabrous.

The plant when boiled in oil is used as an application for headache, rheumatism, leprosy, epilepsy, ulcers and fevers. It is also applied to neck-sores of bulbs[15–16]

Glycosides phytosterin, epuranol, resin etc. are reported from the whole plant.

(iv) *Luffa acutangula (Fam. Cucurbitaceae)*[11] *(Hindi, Jinga Torai)*: It is cultivated throughout the greater part of India. The plant is large cirrhose juicy herb, climbing by tendrils; leaves cordate or palmately lobed with coarse hair; fruit fleshy; berry with exalbuminous seeds.

Its seeds are reported to be emetic purgative. The juice of leaves when dropped into eyes is reported to treat granular conjunctivitis. Its pounded leaves are applied locally to treat splenitis, haemorrhoids and leprosy.

A bitter substance *luffin*[19] has been reported which contains 20% of a saponin, along with enzyme and a fixed oil causing salivation, vomiting and purging in dogs[18].

The chemical constituents from different plants have been reported as follows:

S. No.	Name of the plant	Family	Plant part	Compounds isolated
1.	*Centella asiatica* (*Hydrocotyle asiatica*)	Umbelliferae	Fresh leaves and stems	asiaticoside, vellarine, pectic acid
2.	*Melia azedarach*	Meliaceae	Leaves, bark and fruits	azaridine, resin, tannin, meliotannic and benzoic acid bakayanin (sterol)
3.	*Ipomoea hispida* (*I. eriocarpa*)	Convolvulaceae	Whole plant	Phytosterin, epuranol, resin
4.	*Luffa acutangula*	Cucurbitaceae	Pounded leaves	Luffin

The above preamble clearly transpires that there is enough scope to warrant the attention of scientists to ponder over the problem in view of significant information available in literature. It is finally thought worth while to investigate phytochemically the following plants available and some other available plants with a view to isolate, purify or carry out its structural elucidations in order to develop a more potential or cheap therapeutic agent of plant origin to ameliorate human suffering:

(i) *Centella asiatica Syn. Hydrocotyle asiatica*
(ii) *Melia azedarach*
(iii) *Ipomoea eriocarpa Syn. I. hispida*
(iv) *Luffa acutangula*

Methodology and techniques and phased programme

(i) The selected plants may be collected from suppliers, dried, powdered and extracted (cold and hot) by various solvents and rectified spirit of different polarity.

(ii) The plant extract may be concentrated under reduced pressure to get a viscous mass which is subjected to successive extraction according to polarity

order and then undergoes TLC and paper chromatography to identify number of components and then column chromatographic techniques are applied.

(iii) Classical chemical degradation may be done and the structure may be established by UV, IR, ^{13}C-NMR and mass spectroscopic analysis.

Structure of *Mycoderma leprae*

Ribsomal antigens of Mycoderma bacterium leprae (Ridell, M., Inst. Med. Microbiol., Dep. Bacteriol., S-41346 Goeteborg, Swed.): Immunodiffusion of the ribosmal material from *M. leprae* with a monospecific anti-β-serum showed the presence of β-antigen. When the *M. leprae* material was tested with antiserums prepared against purified whole ribosomes from several mycobacteria (BCG and M. fortuitum), > 1 precipitinogen were detected, indicating that not only B but also additional ribosomal antigens are common to *M. leprae* and other mycobacteria.

Structure and antigenicity of the major specific glycolipid antigens of Mycobacterium leprae (Hunte, Shirley W., Fujiwara, Tsuyoshi, Brennan, Patrick J., Dep. Microbiol, Colorado State Univ., Fort Collins, Co, 80523 U.S.A., J. Biol. Chem., 1982, 257 (24), 15072–8 (Eng.)): The presence of specific phenolic glycolipid (Ph-I) in *M. leprae*, in injected armadillo tissues, was reported previously.

$$HO—C_6H_4—(CH_2)_{18}\cdot CH(OH)\cdot CH_2CH(OH)\cdot(CH_2)_4\cdot CHMeCHEtOMe$$

(I)

It had an inherent oligosaccharide, composed of 3-O-Me-rhamnose, 2,3-di-O-Me-rhamnose and 3,6-di-O-Me-glucose, glycosidically linked to the phenol substituent. The structure of the oligosaccharide has now been determined by partial acid hydrolysis permethylation, ^{1}H-NMR, ^{13}C-NMR as: 3,6-di-O-Me-glycp = (β1→4) 2,3-di-O-Me-rhap ($\alpha_1 \rightarrow 2$) 3-O-Me-Rhap (α1→2), assuming that the glucose substituent is in the d-enantiomeric configuration and the 2-methylated rhamnose are *l*). Acid hydrolysis of deacetylated phenolic glycolipid-1 yielded a phenolic phthiocerol core, and mass spectroscopy and proton NMR of the permethylated core suggested the following structure:

$$(OH—C_6H_4—CH_2—(CH_2)_{17}—CH(OH)—CH_2—CH(OH)—(CH_2)_4$$
$$—CH(CH_3)—CH(OCH_3)—C_2H_5)$$

Combined GLC, mass spectroscopy showed 3-tetra-Me branched mycoserosic acids, C_{30}, C_{32} and C_{34} with mol. wts. (as Me esters) of 466, 494 and 522 respectively. These are esterified to the hydroxyl functions of the branched glycolic chain. Evidence is also presented that the glycolipid is immunol. active, reacting with rabbit antisera to *M. leprae* and with sera from lepromatous leprosy patients.

The following is the recommended standard regime (drugs) for multibacillary leprosy:

Drug	Types of Cases	Doses
	No previous treatment or treatment with DDS for less than 6 months	Cases with suspicion of DDS resistance
RIMPIN	600 mg daily for the 1st 2–3 weeks followed by 600 mg once a month for a total of 2 years.	600 mg daily for at least 2 years.
Clofazimine	100 mg every other day for 2 years.	100 mg daily for at least 2 years.
DDS	100 mg daily for 2 years.	100 mg daily for at least 2 years.

REFERENCES

1. P. Boiteau and C. Grimes, *Nature*, **163**, 258 (1949).
2. S.C. Bhattacharya and B. Lythgoe, *Nature*, **163**, 259 (1949).
3. J.E. Bontems, *Bull. Sci. Pharmacol.*, **49**, 186 (1941).
4. E. Lederer *et al.*, *Nature*, **163**, 258 (1949); *J. Chem. Soc.*, 937 (1911) and 399, 1022 (1913).
5. The Wealth of India, A dictionary of Indian raw materials and industrial products, CSIR, New Delhi, Vol. II, p. 116 (1972).
6. (Asiaticoside), A.E. Meyer, *Chem. Abstr.*, **38**, 4094 (1944); John O. Hardesty, *Chem Abstr.*, **35**, 2223 (1941).
7. S.C. Bhattacharya, *Indian Chem. Soc.*, **33**(8), 579 (1956) and **33**(9), 630 (1956).
8. N.K. Basu and P.P. Lamsal, *J. Am. Pharma. Assoc.*, **35**, 275 (1946); *Quart. J. Pharma*, **20**, 135 (1947).
9. R.E. Reeves, *J. Am. Chem. Soc.*, **63**, 1476 (1941). S. Tripett, *Nature*, **163**, 280 (1949).
10. Ian Heilbron, H.M. Bunbury, A.H. Cook and T.G. Halsale, Dictionary of Organic Compounds, Vol. 1, 215 (1953).
11. R.N. Chopra, S.L. Nayar and I.C. Chopra, Glossary of Indian Medicinal Plants, CSIR, New Delhi, pp. 141, 156 (1956).
12. R.N. Chopra and B.S. Verma, Supplement to Glossary of Indian Medicinal Plants CSIR, New Delhi, p. 66 (1974).
13. The Wealth of India, A dictionary of Indian raw materials and industrial products, Vol. VI (L–M), CSIR, New Delhi, p. 323 (1962).
14. E.S.G. Barran and C.E. Schuidt , *Chem. Abstr.*, part 3, 6951 (1939).
15. K.N. Kritikar and B.D. Basu, Indian Medicinal Plants, Vol III, 1729, Rama Rao, 278, Bressers, 99, Fl. Delhi, 244.
16. The Wealth of India, A dictionary of Indian raw materials and industrial products, Vol. V (H–K), CSIR, New Delhi, p. 248 (1959).
17. Hodgson and Walker *J. Chem. Soc.*, 937 (1911); 399, 1022 (1913).
18. Khem S. Grewal and B.D. Kochhar, *Indian J. Med. Research*, **31**, 63 (1943).
19. A.E. Meyer, *Chem. Abstr.*, 5003 (1944).
20. E.F. Elslager, A.A. Phillips and D.F. Worth, *J. Med. Chemistry*, **12**, 363 (1969).

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