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Review Article

NATURAL PRODUCTS AND THEIR ANTILEISHMANIAL ACTIVITY A CRITICAL REVIEW

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ABSTRACT
Ayurveda described certain diseases which mimics Indian Kala-azar namely Visamajwara (Satatajwara), Krimi (Raktaja) and Plihodara/Pliha roga are seems to be suitable correlation depending on their etiology, symptomatology, prognosis and treatment. Raktaja Krimi is also responsible for the manifestation Raktaja vyadhi, out of which Pliha roga is one. Plihodara is a syndrome characterized by splenomegally, debility, anorexia, indigestion, retention of stool and urine, thirst, bodyache, lassitude, cough, mild fever, emaciation, pain in belly, reddish or abnormal tinge or appearance of blue, green or yellow streaks on abdomen, severe anaemia etc.Visceral leishmaniasis patient presents at a late stage, with persistent but fluctuating low-grade fever, weight loss giving the appearance of severe starvation, spleno-or hepatosplenomegally. The skin is some times said to be muddy, pale or dark. Non-specific laboratory tests will show marked leucopenia (Pancytopenia, mainly neutropenia), anemia, and raised serum proteins, with reversal of albumin/globulin ratio. Morphology of subtypes of raktaja Krimi namely Jantumataraha mimics the leishmania donovani. Other than fever no other points supports the concept of Krimi with leishmaniasis. Besides this raktaja Krimi also manifests the diseases of blood, in which Pliha roga / Plihodara is one. Most of the clinical features mentioned for Plihodara / Pliha roga are similar with Indian Kala-azar. Besides this epidemiological incidence, etiology, pathogenesis and treatment support strongly to correlate the concept of Kala-azar vis-à-vis Plihodara / Pliha roga. So it may be summarized that Krimighna drugs as well as plihaghna and plihodara management principles are useful in the management of kala-azar. This article gives glimpses of natural products and their antileishmanial activity. It also provides the clue to select drugs from Ayurveda to develop antileishmanial drug. This article also provides the information pertaining to kala-azar research by using natural products. Many natural products exhibited antileishmanial activity in experimental models was collected.
KEYWORDS: antileishmanial activity, kala-azar, visamajwara, Ayurveda

INTRODUCTION

Visceral leishmaniasis patient presents at a late stage, with persistent but fluctuating low-grade fever, weight loss giving the appearance of severe starvation, spleno-or hepatosplenomegally. The skin is some times said to be muddy, pale or dark. Non-specific laboratory tests will show marked leucopenia (Pancytopenia, mainly neutropenia), anemia, and raised serum proteins, with reversal of albumin/globulin ratio. Ayurveda described certain diseases which mimics Indian Kala-azar namely Visamajwara (Satatajwara), Krimi (Raktaja) and Plihodara/Pliha roga are seems to be suitable correlation depending on their etiology, symptomatology, prognosis and treatment. Raktaja Krimi is also responsible for the manifestation Raktaja vyadhi, out of which Pliha roga is one. Plihodara is a syndrome characterized by splenomegally, debility, anorexia, indigestion, retention of stool and urine, thirst, bodyache, lassitude, cough, mild fever, emaciation, pain in belly, reddish or abnormal tinge or appearance of blue, green or yellow streaks on abdomen, severe anaemia etc[1].

Emergence of resistance to antileishmanial agents pose a growing challenge to medicine and it has played havoc with various ongoing national programmes related to control of infectious diseases like leishamnia, malaria etc. The problem is that a switch from normally less expensive first line drugs to second or third line involves a dramatic escalation in the price of treatment and presently available antileishmanial agents must be administered under medical supervision, require extensive hospitalization and are not affordable by individuals. New drugs for human diseases have also originated from alternative sources over the decade. The Chinese herb artemisine derivative ginghaosu, is widely available in South East Asia and Africa for malaria treatment. This prompted the researchers to invent a safe, cheap, effective oral antileishmanial agent from medicinal plants/Ayurvedic drugs. In this connection

many efforts are undergoing worldwide for the development of drug from traditional system of medicine. Many single and compound formulations were described in Ayurvedic texts for the management of Plihodara/Pliha roga, Udara and Krimi. Medicinal plants/drugs may be chosen depending on their therapeutic action on liver, spleen, abdominal disorders, parasites, and fevers for the experimental and clinical trials[2]. In this regard Dr.P.S.Byadgi collected a list of medicinal plants and compound preparations of Ayurveda. For more detail refer the book Kala-azar in Ayurveda written by Dr.P.S.Byadgi[3].

The list of the Natural products showed Antileishmanial activity are given below

Sapanins of the ivyplant, *Hedera helix* and their Leishmanicidal activity. Leishmanicidal activity of espintanol confirmed .A novel leishmanicidal labdane from polyathea macropoda. Evaluation of Plant extracts for Antileishmanial activity using a mechanism based radio respirometric microtechnique (RAM). Effect of some bisbenzylisoquinolone alkaloids on American Leishmania Sp. in BAL B/c mice. Antileishmanial activity of dehydrozaluzanin C, a sesquiterpene lactone isolated from Munnozia maronil. A process for the preparation of product having antileishmanial activity from the seeds of the plant *Nyctanthes arbortrystis*. Piperine : A potent inhibitor of leishmania donovani promastigates in vitro. In the pursuit of new leishmanicidal natural products, 5, 7, 4 trihydroxyflavan and the new product, 5,7-dihydroxy-4-methoxy and flavan, were isolated from the leaves of guianian medicinal plant F. guianensis. Antiprotozoal activity of quinolone alkaloids isolated from *Galipea longiflora*, a Bolivian plant used as a treatment for cuteneous leishmaniasis Synthesis of an antileishmanial alkaloid isolated from *Galipea longiflora* and of related compounds. An Antileishmanial chalcone from Chinese Licorice roots. Leishmanicidal activity of 2-benzoxazalinone from Acanthus illicifolius in vitro. Antileishminicidal activity of *Annona senegalensis* seeds. Isolation of Bis-indole alkaloids with antieishmanial activity from peshiera van heurkii. Chemical nature and antileishmanial activity of alkaloids, Terpenoids, Saponins, iridoid glycosides, quinones, chalcones and tetralones isolated from medicinal plants have been reviewed. Antileishmanial activity of neolignans from virola species and synthetic analogues. Moderate and weak antileishmanial activity of new trichothecenes isolated from *Holarrhena floribunda*. Antileishmanial activity of Minaquartynoic acid was isolated from Peruvian tree minquartia guianensis. Antileishmanial activity of ancistrocalaines A and B, two new bioactive napthylisoquinolones and related napthoic acids from *Ancistrocladus ealansis*. Leishmanicidal, antiplasmodial and cytotoxic activity of indole alkaloids from corynanthe pachyceras. Leishmanicidal activity of Oxoaprophine alkaloids and quinones from stephania dinklagei. Invitro and Invivo leishmanicidal activity of 2-hydroxy-3-(3 methyl-2-butenyl)-1, 4-napthoquinone (Lapachol). Leishminicidal, antiplasmodial and cytotoxic activity of novel diterpenoid 1, 2-quinones from perovskia abrotanoides. New source of tanshiones.Strong leishmanicidal activity of steroidal saponin isolated from *Yucca filamentosa*. In vitro leishmanical activity of Naturally occurring chalcones . Leishmanicidal activity of Trypanocidal withanolides and withanolide glycosides from Dunaila brachyacantha.Leishmaniasis Phytotherapy. Nature's leadership against an ancient disease. New Sesquiterpene lactones from elephantopus mollis and their leishmanical activities. Antileishmanial activity of hydrolyzable tannis and their modulatory effects on nitric oxide and tumor necrosis factor-alpha release in macrophges invitro. Invitro antileishmanial activity of three saponins isolated from ivy, alpha, hederin, beta-hederin and hederacolchiside A1, in association with pentamidine and amphoterich B. Leishmanicidal activity of pelargonium sidoides Synthesis of plumbagin derivatives and their inhibitory activities against ehrlich Ascites carcinoma invivo and leishmania donovani promastigotes invitro. Abietane diterpenoids and triterpenoic acids from salvia cilicica and their antileishmanicidal activities.Inhibitory activity of Diospyrin derivatives against leishmania major parasites invitro. Antileishmanial activity of Ancistrocongolines A-D, new naphthylisoquinoline alkaloids from *Ancistrocladus congolensis* established. Leishmanicidal activity of terpenoids from the oleoresin of the Peruvian Medicinal Plant *Copaifera pauper*. Efficacy of plant 4032 against experimental visceral leishmaniasis.

ANTILEISHMANIAL ACTIVITY OF NATURAL PRODUCTS

The plant *Nyctanthes arbortristisis* used in the Ayurvedic system of medicine for the treatment of various diseases such as fever, rheumatism, and intestinal worm infection. A decoction of the leaves is recommended as specific treatment for obstinate sciatica. The powdered seeds are used to cure scurvy infection of the scalp. A 50% ethanolic extract of the aerial part of the plant exhibited encouraging antileishmanilal activity of the order of 85.89% at a dose level of 1 g/kg/day x 5 on the 28the day post treatment against hamsters infected with amastigotes of the parasite. The ethanolic extract of the leaves also showed significant amoebicidal activity in

rats. Antileishmanial activity of ethanolic extract of seeds was mainly localized in n-butanol soluble fraction. Three new iridoid glycosides, arbortristoside-A (1) arbortristoside D and (78) arbortristoside E (79) along with nyctanthic acid, oleanolic acid, friedelin, β-sitosterol D-glucoside and 6β-dihydroxy loganin were isolated from the n-butanol soluble fraction. Arbortristosides A and B showed 79% and 78% inhibition of parasite, L. donovani, at 100 µg. ml conc. in vitro.

The antileishmanial activity of arbortristoside – A has been confirmed in hamsters. It showed significant protection in certain hepatic markers enzymes viz GOT, GPT, SDH, G-6-Pase along with MFO system in host. Arbortristoside A and C were given prophylactically (5, 2, 1 mg/kg) to mouse against C. albicans systemic infection. Former showed 44% protection at 5 mg/kg whereas latter protection at 2 mg/kg dose. Both compound also showed 92% inhibition of mast cells degranulation induced by compound 48/80 at dose at a dose of 10 mg/kg x 4 P.O. in rat. Two new iridoid glycosides Arbortristoside E (79) from seed and arbortristoside G (80) from the leaves alongwith three iridoids 7β-O-benzyl, 6β-O-benzolyloxy, 6β-hydroxy loganin besides cinnamic acid, oleanolic acid, 4-O-hydroxy-5, 7-dimethoxy flavone – 3-O-glucoside and three carotenoids were isolated from the leaves. Activity profile of different part of *Nyctanthes arbortristis* was studied. Leaves, seeds, flowers and roots showed antileishmial, (Puri, 1994) and antifungal activities. Leaves and seeds also showed hepatoprotectie activity and only leaves showed antimalarial activity. Arbortristosid A (1) and C (1a) showed significant antiviral activity against EMCV and SFV with an increase in average survival time of the infected animals.

Anitleishmanial activity of the crude extract of *Tephrosia purpurea* was localized in nhexane and n-butanol fractions. A fraction rich in active constituents was obtained from n-butanol fraction without using chromatographic separation technique. This fraction showed 80.72% inhibition at 50 mg/kg/p.o. x 5 dose where it showed 86, 82 and 90% inhibition respectively as compared to sodium stibogluconate which produced 95 and 99% inhibition at 20 and 10 mg/kg/p.o. x 5 respectively. ED_{50} and ED_{90} of this fraction determined using 3 days of old and 25-30 days old infection in hamsters. The ED_{50} and ED_{90} were 26.6 and 91.7 mg/kg x 5 p.o. in spleen. LD_{50} of active fraction in mice, was more than 2.15 g/kg p.o. i.p. There flavonoid glycosides, kaempferol-3-O-rhamnoglucoside, rutin and biochanin-A, a glucoside containing glucose and rhamnose were isolated from active fraction but these compounds were found to be inactive. The active fraction was also found to cause humoral immuno stimulation but it was devoid of nay antimoebic and antiviral activity. It however showed 63.74% activity against Giardia lamblia at a higher dose but inactive at a lower dose. *Alstania scholaris* not only could be confirmed for possessing the antileishmanial activity but also had very high order of activity (78-89% inhibition of multiplication of amastigites in spleen of treated animals). It was also evaluated for dose dependent efficacy of crude extract administered by oral rout for 5 consecutive days at log doses. It whosed ED_{50} value of 590. The crude extract of stem bark also showed hypotensive and anticancer activities. Picralinal, a new alkaloid of picralima group was also isolated and characterized from the leaves of *A. Scholaris*. A new pterocarpan, barbacarpan was isolated from the chloroform soluble fraction of an antileishmanila active ethanolic extract of the dried aerial parts of *Crotalaria barbata*. Its structure was established as 1, 2-dihydro-2-isopropenyl-3-hydroxy-furano (2,3-1) pterocarpan (81). Crude extract of *Amoora rohituka* showed antileishmanial activity in vivo. However, on further fractionation higher activity than crude extract could not be achieved as the fractions tended to polymerise on standing. Its ethanolic extractive also showed immunostimulant and antinflammatory effect. Roots of *Caesalpinia digyna* are recommended in phthisis, scrofulous affections and diabetes. *Swertia Chirata, Tibouchina semidecandra, Tinospora cordifolia* possed the antileishmanial activity (78-89% inhibition of multiplication of amstigites in spleen of treated animals). These plants were also evaluated for dose dependent efficacy of crude extracts administered by oral route for 5 consecutive days at log doses. *Swertia chirata* showed ED_{50} 398, where as the ED_{50} values in rest of the cases could not be calculated due to prolong plateau in the activity at different dose levels[5]. Author carried out experimental study to find out the antileishmanial activity of some medicinal plants and encouraging results were observed[6].

SUMMARY

It may be concluded that concept of Indian Kala-azar may be compared with Visamajwara, Krimi, Plihodara / Pliha roga. Depending on the clinical feature of Visamajawra (Sataja jwara), it may be correlated to Kala-azar. But except fever no other points supports this point. Based on clinical feature, the concept of Krimi may be correlated to Kala-azar, for example fever is characteristic feature in both cases. Besides this discoloration indicates the concept of post Kala-azar dermal leishmaniasis. Morphology of subtypes of raktaja Krimi namely Jantumataraha mimics the leishmania

donovani. Other than fever no other points supports the concept of Krimi with leishmaniasis. Besides this raktaja Krimi also manifests the diseases of blood, in which Pliha roga / Plihodara is one. Most of the clinical features mentioned for Plihodara / Pliha roga are similar with Indian Kala-azar. Besides this epidemiological incidence, etiology, pathogenesis and treatment support strongly to correlate the concept of Kala-azar vis-à-vis Plihodara / Pliha roga. So it may be summarized that Krimighna drugs as well as plihaghna and plihodara management principles are useful in the management of kala-azar. In this regard Dr.P.S.Byadgi collected exhaustive list of drugs from ayurvedic texts (please refer kala-azar in Ayurveda by Dr.P.S.Byadgi. This article also provides the information pertaining to kala-azar research by using natural products. Many natural products exhibited antileishmanial activity in experimental models was collected.

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