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Lymphatic Filariasis: Drug targets and Nematicidal Plants.

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Abstract

Lymphatic filariasis (LF), a mosquito-borne disease, is caused by the parasitic filarial nematodes (roundworms) *Wuchereria bancrofti (W. bancrofti), Brugia malayi (B. malayi),* or *Brugia timori* (*B. timori*) puts more than 120 million suffering from this disease , When lymphatic filariasis develops into chronic conditions, it leads to lymphoedema (tissue swelling) or elephantiasis (skin/tissue thickening) of limbs and hydrocele (scrotal swelling). Involvement of breasts and genital organs is common. Such body deformities lead to social stigma, as well as financial hardship from loss of income and increased medical expenses. The current drugs available in the market are not effective against the adult worms and indiscriminate use of them has also resulted increase in drug resistance cases. Presently, work is going on various therapeutic targets like Aspargynyl t-RNA synthase, Glutathione peroxidase ,Transglutaminase and DNA vaccines. New research efforts will be required to screen various phytochemicals from plant and marine sources that would help in targeting important protein targets in adult worms with least side effects.

Key Words: Lymphatic filariasis, Filarial enzymes as drug targets, Nematicidal plants, *in silico* drug designing.

INTRODUCTION

Lymphatic filariasis(LF) also known as elephantiasis is a mosquito borne disease transmitted by species like culex , *Aedes aegyptii , Anopheles* Which inject the filarial worms like *Wuchereria bancrofti (W. bancrofti), Brugia malayi (B. malayi)*, or *Brugia timori* (*B. timori*) WHO Report 2005(1).More than 120 million people are affected by this disease with one third of the people infected with LF live in India; one-third are in Africa and one-third are in South Asia, the Pacific, and the Americas. Sabesan S l(2)Elephantiasis is a crippling condition in which limbs or other parts of the body are grotesquely swollen or enlarged. In addition, people with the disease suffer from hidden internal damage to the kidneys and lymphatic system caused by the filariae. Charles Morehead 2009 (3).

Filariasis elimination aims at transmission control through mass drug administration and at disease control through individual patient management Annual single dose coadministration of two drugs ivermectin + diethylcarbamazine) or albendazole reduces blood microfilariae by 99% for full year while a single dose of one drug (ivermectin or DEC) administered annually can result in 90% reduction. (4) Balakrishnan N 1992 Until recently, diagnosis of filarial infection depended on direct demonstration of the parasite in blood or skin specimens which was cumbersome. Circulating filarial antigen (CFA) detection should now be regarded as the 'gold standard' for diagnosing *Wuchereria bancrofti* infections. Ap Shah 2007. (5) The specificity of these assays is excellent, and the sensitivity is greater than that achievable by the earlier parasite detection assays.The latest developments in the diagnosis of lymphatic Filariasis are Membrane Filtration method[6], Ultrasonography [7], Immunographic test ICT [8] Membrane filtration method for microfilaria detection: usually seen in the early stages of the disease before clinical manifestations develop. Though this can be performed quickly, it is no more sensitive than examination of the conventional blood smear. Ultrasonography using a 7.5 or 10 MHz probe has helped to locate and visualise the movements of living adult filarial worms of W. bancrofti in the scrotal lymphatics of asymptomatic males with microfilaraemia. Ultrasonography is not useful in patients with filarial lymphoedema because living adult worms are generally not present at this stage of the disease. Immunochromatographic test (ICT): Highly sensitive and specific filarial antigen detection assays, both as card test and in ELISA based format are now available for the diagnosis of W. bancrofti infection. The card test has the advantage that it can be performed on blood sample drawn by finger prick at any time of the day.

LIFE CYCLE OF THE PARASITE

Development and replication of *B. malayi* occurs in two discrete phases: in the mosquito vector and in the human. Both stages are essential to the life cycle of the parasite.

Mosquito: The mosquito serves as a biological vector and intermediate host – it is required for the developmental cycle and Transmission of Brugiya malayi (4) The mosquito takes a human blood meal and ingests microfilariae (worm-like sheathed eggs)

That circulate in the blood stream 5-7.In the mosquito, the microfilariae shed sheaths, penetrate the midgut, and migrate to the thoracic muscles were the microfilariae increase in

size, molt, and develop into infective larvae (L1 and L3) over a span of 7–21 days. No multiplication or sexual reproduction of microfilariae occurs in the mosquioto 8-1 The infective larvae (L3) migrate to the salivary glands, enter the proboscis and escape onto human skin when the mosquito takes another blood meal.

Human: B. malayi undergoes further development in the human as well as sexual reproduction and egg production.1-2 The infective larvae (L3) actively penetrate the skin through the bite hole and develop into adults in the lymphatic system over a span of 6 months. Adult worms can survive in the lymphatic system for 5–15 years 3. The male and female adult worms mate and the females produce an average of 10,000 sheathed eggs (microfilaria) daily The microfilariae enter the blood stream and exhibit the classic nocturnal Periodicity and super periodicity 4. Another mosquito takes a blood meal and ingests the microfilariae. Infection depends on the mosquito taking a blood meal during a periodic episode – when microfilariae are present in the bloodstream.

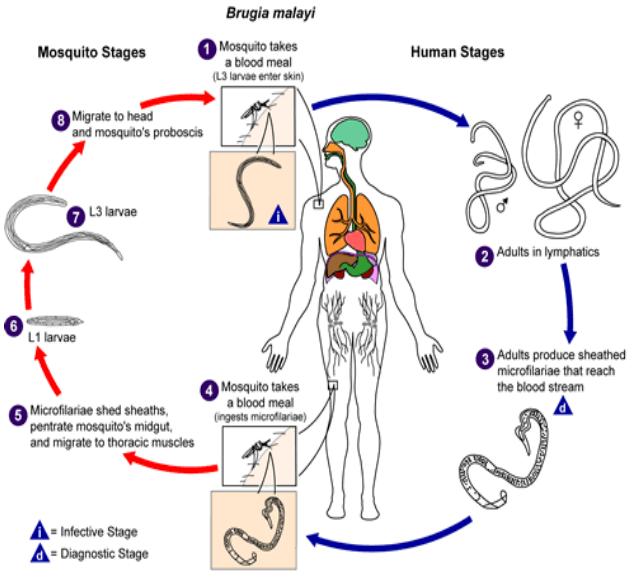

Fig 1 Life cycle of the parasite

Table 1. Antifilarial drugs available in the market.

S.no	Antifilarial Agent	Brandname	Mechanism of action	Reference
1	Diethycarbamazine	Hetrazan	Cyclo-oxygenase pathway and COX-1	Annielanham,2013
2	Ivermectin	Mectizan	Glutamate-gated chloride ion channels in invertebrate muscle and nerve cells of the microfilaria	Wilma 2005
3	levimazole	Lepuron	L-subtype nicotinic acetylcholine receptors in nematode muscles	Temu SE 1981
4	Albendazole	albenz	Tubulin polymerization	Achim Hoerauf 2008

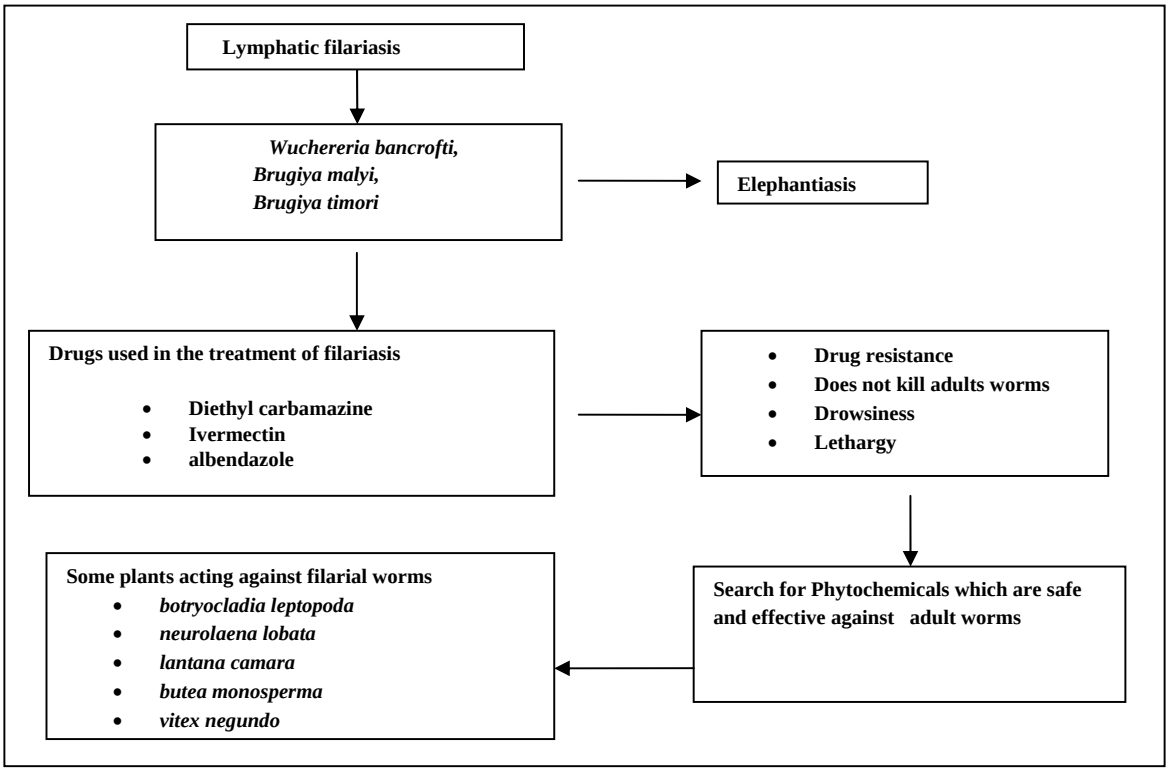

Fig 2. Over view of our drug target discovery approach.

Table 2 . Filarial parasite target enzymes and their mechanism of action.

Sno	Filarialparasite target enzyme	Mechanism of action	References
1	N-myristoyltransferase	It plays crucial role in the fatty acid metabolism	Brendan D 2014 (10)
2	Fatty acid retinol binding protein (FAR PROTEIN)	It is a structurally novel small helix-rich fatty acid and retinol binding protein. It's havinga potential role in the generation of pathology, and parasite development	Manish mishra 2013(11)
3	Aminoacyl-tRNA synthetase	It catalyzes the esterification of a specific amino acid or its precursor to one of all itscompatible cognate tRNAs to form an aminoacyl-tRNA	James s 2014(12)
4	Trehalose-6 Phosphate Phosphatase	It plays several physiological functions such as energy reserve, glucose uptake and egg hatching.	Jeremiaha D 2014(13)
5	Cystathionine-β - synthase	This enzyme acts in a chemical pathway and is responsible for using vitamin B6 to convertbuilding block of proteins (amino acid) called homocysteine and serine to a molecule called cystathionine	Saralustigman 2014(14)
6	Glutathione S-transferase	GSTs are one of the major detoxification systems ubiquitous among eukaryotes and havebeen found in a wide range of parasitic helminthes	Yadav.M. 2010 (15)
7	Phosphoglycerate mutase (iPGM)	It catalyzes the interconversion of 2- and 3-phosphoglycerate in the glycolytic andgluconeogenic pathways.	PRASHANT KUMAR SINGH 2013 (16)
8	Glutathione reductase	It is an important part of the antioxidant system of many living cells. It maintains the correct intracellular redox balance	Sharma OP 2013 (17)
9	Filarial chitin	Chitin metabolism has also been proposed to be a parasite unique target, as the vertebrate host does not contain chitin	Sapna gupta 2005(18)
10	Myristoyl-transferase	It plays crucial role in the fatty acid metabolism	Sharma OP 2013(19)
11	Prolyl-4-hydroxylase	It can alter protein conformation and protein-protein interactions	Nutman 2007(20)
12	Transglutaminase	Role in the growth, development and maturation of nematodes	Kapil mehta 1992 (21)
13	Glutathion peroxidase	GPXs protect the filarial worms from oxidative damage, and are thus important targets for novel chemotherapy.	Cookson.e 1992 (22)
14	Eicosanoid	It may act locally in the host and modify host-parasite interactions. The production ofthese lipid mediators may be one of the strategies for evading host immune responses	Belley A 1995 (23)
15	Aspargynyl t-RNA synthase	It catalyzes the esterification of a specific amino acid or its precursor to one of all itscompatible cognate tRNAs to form an aminoacyl-tRNA	Crepen T 2011 (24)
16	Farnesyl-transferase	It catalyzes the transfer of a farnesyl residue from farnesyl-pyrophosphate (FPP) to thethiol of a cysteine side chain of proteins, which carry at the C-terminal the so-calledCAAX-sequence	Sharma OP 2013 (25)
17	S-adenosyl-methionine decarboxylase	It is a key enzyme in polyamine metabolism and antioxidation.	Sharma OP 2013 (26)
18	DNA-Topoisomerase II	It has an important role in DNA replication, repair and transcription	Mohammed Ali 2007 (27)
19	Translationally controlled tumor protein	It has been implicated in important cellular processes, such as cell growth, cell cycle progression, and malignant transformation and in the protection of cells against various stress conditions and apoptosis.	Sharma OP 2013 (28)

Table 3. Some plants used in the treatment of Filariasis

S.No	Plant Name	Phytoconstituents	Reference
1.	*Adenia gummifera*	Tetraphyllin B (barterin), Epitetraphyllin B (volkenin), Gummiferol and Proanthocyanidins	Heirdi 1964 (37)
2.	*Alstonia boonei*	Echitamine, Echitamidine, Akuammidine, N-α -formylechitamidine	John prosper 2012 (38)
3.	*Alstonia congensis*	Echitamine, Nor-echitamine, 17-Acetoxy-nor-echitamine, kuammicine, 12-methoxy-N(4)-methylakuammicine, Tubotaiwine	Catherine caron 1989(39)
4.	*Boerhavia diffusa*	β-Sitosterol, α-2-sitosterol, Palmitic acid, Archidic acid, Boeravinone A, B	Bidyut kanthi1990 (40)
5.	*Cymbopogon Martinii Roxb*	Geraniol, Sabinene, Limonene ,Geranyl acetate	Katiki (41)
6.	Corallocarpus epigaeus	Ketodiol, carpenoyl ester	Shri Vijaya Kirubha(42)
7.	*Carapa procera*	Carapolide A, Mexicanolide, methylangolensate	Titanji VP 1990 (43)
8.	*Butea monosperma*	Glucoside,medicarpin,miroestrol.	Sahare KN 2012 (44)
9.	*Melia azidirachta*	Azadirachtin, Nimbin, Nimbidin, Nimbolin B	Misra V.2005 (45)
10.	*Plumbago indica*	Isoshinanolone, Isoshinanolone, Beta-sitosterol	Nisha Mathew 2002(46)
11.	*Ricinus communis*	Stearic acid, Ricinoleic acid, Isoricinoleic acid.	K.N.Sahare may 2008(47)
12.	*Streblus asper*	β-sitosterol, α-amyrin, Strebloside, Mansonin	Shubha rastogi 2006(48)
13.	*Bauhinia racemosa*	lupeol , bitasterol, kaempherol	Shashidar KV 2012(49)
14.	*Vitexnegundo*	Negundoside, Agnuside, and Vitegnoside	Reddy.MV 2008 (50)
15.	*Plumbago zeylanicum*	Isoshinanalone,beta sitasterol,plumbagin	Kumarganeshan 2013(51)
16.	*Barleria cristata*	Barlerin,luteolin	Hemalatha 2012(52)

Role of Phytochemicals of plants in the treatment of Filariasis acting against various proteins of nematode parasites.

Filarial parasites are responsible for various diseases like Elephantiasis, tropical Pulmonary Eosinophilia and River blindness. The present drugs that are available in the market like Ivermectin ,Levimazole, Diethylcarbamazine and Albendazole shown in table(2) are acting and effective against only larval stages of the parasite but are not able to kill the adult filarial worms, apart from this side effects shown in various patients requires the development of novel drugs which are safe and cheap.Some of the Phytochemicals obtained various medicinal plants which has antifilarial activity shown in table (4) which may be effective against various targets proteins of the parasite shown in table (1)

CONCLUSION:

In this review article, it has been discussed on how Lymphatic filariasis is causing great burden to the poor people in Africa and various south Asian countries, the drugs which are available in the market are not able to kill the adult worms and drug resistance cases are increasing Various drug targets of the parasite important in metabolism of parasite and phytochemicals of plants has been discussed in the manuscript which can be studied by using bioinformatic software like Protein data bank, zinc database. The protein ligand interactions studies can be performed by using software like Schrodinger.

Our focus to work on the targets like UDP- galactopyranose mutase, Trehalose -6 phosphate phosphatase and Chitinase which are present in the filarial parasite but its absence in humans makes it a promising drug target for the filarial parasites. Studies should be performed on various protein targets and finding activity of these Phytochemicals on these targets should be checked and understand the disease and design Antifilarial drugs.

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