

Lymphatic Filariasis and Chemotherapeutic Targets

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Lymphatic filariasis (LF) is one of the four important tropical diseases (LF, Oncocerciasis, Chagas disease and leprocy) as identified by WHO. It is an infectious disease caused by lymph dwelling nematode parasites and transmitted by mosquitoes. It is one of the oldest and most debilitating of all the neglected tropical diseases. Elimination of LF as public health problems is urgently required as it causes morbidity resulting into economic loss of developing countries. According to the WHO report, LF is commonly known as elephantiasis occurring in over 140 million people are currently infected, with about 40 million disfigured and incapacitated by the disease. About 17.7 million people are infected in 37 tropical countries of Africa and Latin America. LF causes alterations in the lymphatic system and the abnormal enlargement of body parts, causing pain and severe disability [1]. The acute episodes of local inflammation involving skin, lymph nodes and lymphatic vessels often accompany chronic lymphoedema.

Filariasis also occurs in the domestic animals such as cattle (*Parafilaria bovicola* causing Verminous haemorrhagic dermatitis; *Onchocerca dermati*, *O. ochengi*, and *O. dukei*. *O. ochengi* causing intradermal onchocercosis which resembles with that of human LF parasite, *O. volvulus* causing river blindness; *Stenofilaria assamensis* and others causing different diseases), horses (*Parafilaria multipapillosa* causing summer bleeding) and dogs (*Dirofilaria immitis* causing heart filariasis).

LF is caused by thread-like nematodes (roundworms) belonging to the superfamily Filarioidea also known as "filariae". These are transmitted from host to host by blood-feeding arthropods such as black flies and mosquitoes. Human as a host harbours eight known filarial nematodes which are placed into three different groups: (1) *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori* worms causing LF as they reside into lymphatic system resulting into elephantiasis, (2) Subcutaneous filariasis is caused by *Loa loa* (known as the eye worm), *Mansonella streptocerca*, and *Onchocerca volvulus* (causing river blindness) occupying the subcutaneous layer of the skin, in the fat layer and (3) Serous cavity filariasis caused by *Mansonella perstans* and *Mansonella ozzardi* occupying the abdominal serous cavity. The adult worms residing in a tissue release microfilariae into the host's bloodstream. The blood circulating microfilariae (Mf) are taken up by an arthropod vector through bite. Mf develop into infective larvae into the vector which are transmitted to a new healthy host. The life cycle of a filarial worm is shown in Figure 1.

Individuals infected by filarial worms may be described as either "microfilaraemic" or "amicrofilaraemic", depending on whether or not microfilariae can be found in their peripheral blood. Filariasis is diagnosed in microfilaraemic cases primarily through direct observation of microfilariae in the peripheral blood. Occult filariasis is diagnosed in amicrofilaraemic cases based on clinical observations and, in some cases, by finding a circulating antigen in the blood. The signs and symptoms of LF include edema with thickening of the skin and underlying tissues (elephantiasis) due to parasite's dwelling into lymphatics.

Different species of filarial worms tend to affect different parts of the body: *Wuchereria bancrofti* can affect the legs, arms, vulva, breasts, and scrotum (causing hydrocele formation), while *Brugia*

timori rarely affects the genitals. Those who develop the chronic stages of elephantiasis are usually amicrofilaraemic, and often have adverse immunological reactions to the microfilariae, as well as the adult worms. The diagnosis of LF is done by identifying microfilariae in blood using staining of thin and thick blood film smears using Giemsa stain or by Polymerase chain reaction (PCR) and antigenic assays.

LF treatment includes a combination of two medicines such as albendazole and ivermectin (in Sub-Sahara Africa) or albendazole with diethylcitrate (DEC) with an idea to sharply kill and clear Mf from the blood so as to disrupt the filarial cycle. The imidazole derivatives such as albendazole exert their antiparasitic effects by binding tubulin. The mechanisms of actions of Levamisole and the avermectins are to agonize the nicotinic acetylcholine receptor and glutamate-gated chloride channels, respectively [3]. In addition, doxycycline an antibiotic has also been introduced in medication as it kills symbiotic bacteria from genus *Wolbachia* residing inside the filarial worms and involved in its reproduction and disease development [4-6].

The existing challenges in the control and treatment of LF include unavailability of specific tools for early diagnosis of filarial worm's infection, insecticide resistance which limit the vector control programmes, lack of effective therapy due to limited number of existing repertoire of potential antifilarial drugs, lack of vaccine and drugs induced toxicity in the patients [7]. The current drugs can effectively eliminate the worm's larval stages (Mf), but their long term application increases the risk of emergence of drug resistance and toxicity. None of the drugs as mentioned above is effective in killing the long-lived adult worms (macrofilariae). The treatments are therefore aimed at reducing transmission and pathology. Therefore some new and more potential drugs designed and developed for new molecular targets are required for combating the filarial scourge by improving the treatment and control of LF by killing macrofilariae, and also to eradicate antifilarial drugs resistance.

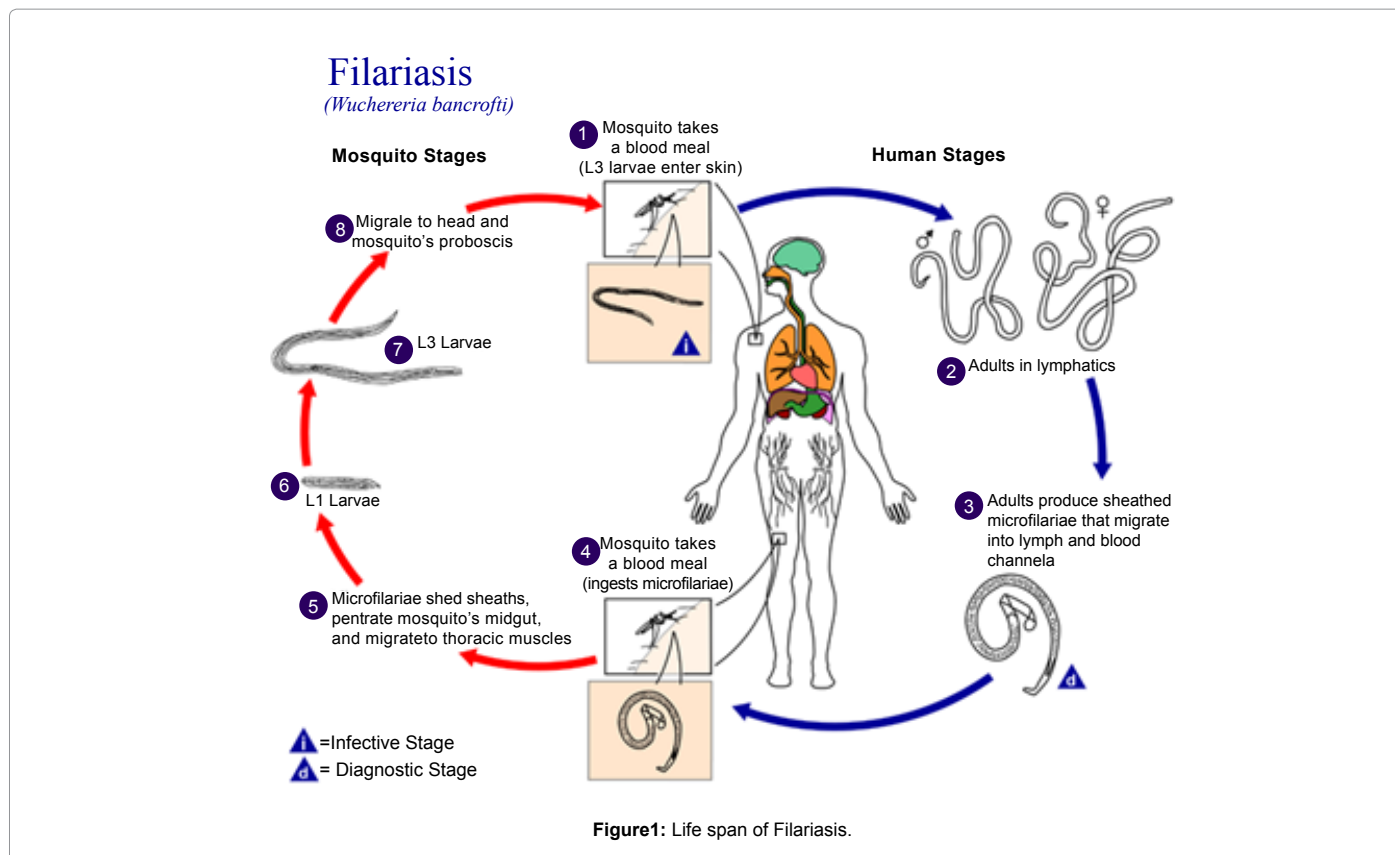
Some filarial metabolic pathways and their key regulatory enzymes have been characterized by many workers with a view to exploit them as the putative chemotherapeutic targets against LF. For example, the enzymes from carbohydrate metabolism (mainly glycolytic pathway and partially from tricarboxylic acid cycle) [8-17], respiratory metabolism [18], Isoprenoid metabolism [19], amino acid and protein metabolism [20,21], nucleic acids metabolism [20,22-24],

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polyamine metabolism [25], neurotransmitter metabolism [26-30] and glutathione metabolism [31-33] etc. The differences in the molecular / biochemical properties of these key metabolic enzymes from filarial worms as compared to that of the host may be exploited for design and development of relatively more effective and safer antifilarials.

Recently, the information of genome sequence of *Brugia malayi* and *Onchocerca volvulus* and their computational analyses have been shown to be essential for identification and validation of candidate drugs target [34]; development of RNA interference (RNAi) method to investigate gene function in model nematodes such as *Caenorhabditis elegans* as well as filarial worm, *B. malayi*. The criteria for selecting suitable antifilarial drug targets include (1) selectivity (specific to parasites), (2) validation with the evidence (such as RNAi, knockouts, inhibitors etc.) that the target is essential for growth, survival and fertility, (3) druggability i.e. molecules with a small ligand binding pocket, for example channels, receptors, transporters and enzymes etc., (4) structure: amino acid sequence of the target known, (5) assayability: existing biochemistry/enzymology, cell based assays etc., and (6) potential for development of resistance: absence of isoforms of the target with varying susceptibility within a species or absence of biochemical 'bypass' reactions to circumvent function of the target.

The quest for investigating a specific and viable tool for early detection and appropriate chemotherapy of filarial infection is still on but more emphasis is needed to be given in this direction. Since to get a vaccine to eradicate the disease is still far from reach, chemotherapy is the only option left for LF patients. There is a need to look forward for investigating some alternative medicines extracted from traditional Indian medicinal plants which could be relatively more cost effective and laced with no toxicity.

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