International Journal of Herbal Medicine
Available online at www.florajournal.com

IJHM International Journal of Herbal Medicine

E-ISSN: 2321-2187
P-ISSN: 2394-0514
IJHM 2018; 6(1): 40-46
Received: 08-11-2017
Accepted: 09-12-2017

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Filariasis: Role of medicinal plant in lymphatic filariasis

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Abstract
Lymphatic filariasis is a vector-borne disease and is one of the major public health problems in many parts of the tropics. About one-third of the global population at risk for this disease lives in India. Although large scale initiatives have been taken to eliminate this disease by WHO and countries where disease is endemic, strategies followed involve the use of synthetic drugs which have side effects, owing to which public support is not very promising in following the drug regimen required for the elimination of the disease. Filarial menace is further aggravated by the endosymbiont Wolbachia's association with the filariid. This further necessitates the use of safe, non-toxic alternatives for the eradication of filarial menace. Since times immemorial plants have always been considered as safe bet as alternative sources. This review aims to bring forth the role of medicinal plants in combating filariasis and worldwide research findings in the usage of plants in the field of filariasis.

Keywords: Lymphatic filariasis, medicinal plants, toxic, Wolbachia, filariid

1. Introduction
Tropical countries are endowed with a number of parasitic infections such as trypanosomiasis, leishmaniasis, schistosomiasis, lymphatic filariasis and onchocerciasis [1]. All of these represent major health problems in the tropical countries like central Africa, Nile Delta, South and Central America and the tropical regions of Asia including southern China and Pacific. Amongst these Lymphatic filariasis is one of the major health concern. Causative agents of Lymphatic filariasis are three nematode parasites i.e. *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori*, which invade the lymphatic system of humans creating pathological changes leading to filarial manifestations. These three filarial nematode parasites are transmitted by a number of species of mosquitoes namely Culex, Anopheles, Aedes and Mansonia species [2]. Further to aggravate the filarial menace, there is one obligate intracellular bacterium *Wolbachia pipientis* associated with them [3]. About one-third of the global population at risk for this disease lives in India. This facilitated initiation of national programs in endemic countries, including India. The program in India was made a part of the National Vector Borne Disease Control Programme (NVBDCP) in 2003 under the National Health Policy of 2002, and it set a target for elimination of LF by 2015 In this, India adopted a two pillars strategy for the elimination of lymphatic filariasis by interrupting transmission through mass drug administration (MDA) with diethylcarbamazine (DEC) and providing care for those who are already infected [4]. Ramaiah, (2009) [5] reported that India's filarial control programme was scaled up MDA over past several years and then albendazole (ABZ) was added for the treatment of 590 million Indians living at risk of infection. In India the coverage level of MDA programme varies from 55% to 90% and Odisha has reported the microfilaraemia (mf) rate of 0.43% in 2011 as compared to 2.54% in 2004 [6]. Although there is considerable improvement of reduction is micorfilarae rates still 100% coverage has not been reported from any of the affected countries.

Cure and control of Lymphatic filariasis is dependent on three factors which are as follows:
1. Vector control
2. Blocking of transmission(WHO Strategy)
3. Chemotherapy to reduce symptoms and killing of adult worms.

In the present review why there is still need for development of a safe nontoxic alternative of existing synthetic drugs has been discussed.

Results and Discussion
First of all we would discuss the standard drugs available for filariasis, their properties, usefulness and then their side effects if any.

Diethylcarbamazine (DEC): Diethylcarbamazine (DEC, *N*, *N*-diethyl-4-methyl-1-piperazine carboxamide) is a synthetic derivative of piperazine used as an anthelmintic drug for the treatment of filariasis in humans, dogs and cats. The antifilarial action of hetrazan was discovered by Hewitt [7] working with cotton rats infected with *Litomosaides carinii*, and later activity of DEC on human filariasis by *W. bancrofti* was also reported and it was found that DEC lowers the blood microfilaria levels significantly even in single annual doses of 6 mg/kg, and this effect was sustained even at the end of one year. Even though DEC kills the adult worms, this effect was seen in only 50% of patients [8]. DEC does not act directly on parasites and its action is mediated through the host immune system. DEC is an inhibitor of arachidonic acid metabolism in filarial microfilaria. This results in vasoconstriction and amplified endothelial adhesion leading to immobilization of microfilarial parasites, enhanced adherence and cytotoxic activity by host platelets and granulocytes. These events represent activation of the innate, non-specific immune system, independent of the adaptive, antigen-specific, immune response. This makes the microfilariae more susceptible to innate immune attack, but does not kill the parasites outrightly[9]. The successful use of iodized salt to eliminate iodine-deficiency disorders is encouraging; similarly, fortified salt could be used as a vehicle to eliminate lymphatic filariasis. Despite the potential programmatic advantage of fortifying salt with DEC instead of undertaking mass administration of tablets, DEC- fortified salt remains an underutilized intervention [10].

Side effects associated with Diethylcarbamazine citrate (DEC)

Adverse reaction in some of the patients was observed by a single dose of DEC. It was reported that nine Nigerians with severe Onchocerciasis treated with DEC developed clinical changes, ranging in severity from mild itching to distress, cough and syncope [11]. Physiological changes such as, fever, tachypnoea, tachycardia or hypertension were seen in eight patients. Circulating eosinophils decreased profoundly in all cases just before or during the clinical and physiological changes. The reaction coincides with the death of microfilariae and the accompanying physiological changes may be so severe, even in generally healthy patients. Adverse effects of DEC i.e., the Mazzotti reaction, a complex, acute inflammatory response characterized by fever, tachycardia, hypotension, adenitis, and an ocular inflammatory response, usually results from the death of microfilarial load was also reported by other researchers[12]. However, it is sometimes difficult to determine whether these reactions are due to the death of microfilariae or by DEC itself.

Albendazole

Albendazole, methyl 5(propylthio)-2-benzimidazolecarbamate is the next preferred broad spectrum anthelmintic agentIt is useful for giardiasis, trichuriasis, filariasis, neurocysticercosis, hydatid disease, pinworm disease and ascariasis. As an antihelminthic, albendazole causes degenerative alterations in the intestinal cells of the worm by binding to the colchicine-sensitive site of tubulin, thus inhibiting its polymerization into microtubules. The loss of the cytoplasmic microtubules leads to impaired uptake of glucose by the larval and adult stages of the susceptible parasites and depletes their glycogen storage [13]. Degenerative changes in the endoplasmic reticulum, the mitochondria of the germinal layer and the subsequent release of the lysosomes result in decreased production of ATP. Due to diminished energy production, the parasite is immobilized and eventually dies. The efficacy of Albendazole in treating filarial nematode-based diseases is attributable to dual targeting of nematode microtubules and their *Wolbachia* endosymbiont [14].

Side effects associated with Albendazole

Albendazole causes abdominal pain, dizziness, headache, fever, nausea, vomiting, or temporary hair loss in sensitive patients. In rare cases, it causes persistent sore throat, severe headache, seizures, vision problems, yellowing eyes or skin, dark urine, stomach pain, easy bruising, mental/mood changes, very stiff neck, or changes in amount of urine. Elevation of liver enzymes during treatment is a common side effect, but in rare cases, acute liver failure has been reported. Allergic reactions are also possible. Rarely, albendazole has been reported to cause marrow suppression, agranulocytosis, or aplastic anaemia. The risk of developing this side effect seems to be increased in patients with liver disease, including echinococcal cysts [15].

Ivermectin

Ivermectin is a broad-spectrum antiparasitic agent, traditionally against parasitic worms. It is mainly used in humans in the treatment of onchocerciasis (river blindness), but is also effective against other worm infestations. Nobel Prize in Physiology or Medicine was awarded jointly to Campbell and Ōmura[16] for discovering avermectin, "the derivatives of which have radically lowered the incidence of river blindness and lymphatic filariasis, as well as showing efficacy against an expanding number of other parasitic diseases.

Ivermectin acts on parasites and kills by interfering with nervous system and muscle function, in particular by enhancing inhibitory neurotransmission. The drug binds to glutamate-gated chloride channels (GluCls) in the membranes of invertebrate nerve and muscle cells, causing increased permeability to chloride ions, resulting in cellular hyper-polarization, followed by paralysis and death [17].

Side effects associated with the drug Ivermectin

Adverse effects which include fever, myalgia, headache, sore throat, and cough are usually more prevalent in individuals with higher microfilaremic levels. As the drug acts via nervous system neurotoxicity can also not be ruled out [18].

Kar *et al* [19] evaluated the side reactions following ivermectin treatment in sixty males with high density bancroftian microfilaraemia (GM 1388/ml). Following a single oral dose of ivermectin of different strengths (20, 50, 100 or 200µg/kg). Microfilaria levels significantly lowered after ivermectin administration in all dosage groups and 98% of pre-treatment microfilariae were cleared after 12 h of treatment. The rate of microfilaria (mf) clearance was slower with 20 µg/kg than with the highest dose (200µg/kg) administered. Forty-six patients (77%) became amicrofilaraemic within 2 weeks of treatment. Side reactions were noted in 97% of cases. The most common reactions were fever, headache, weakness, myalgia and cough which appeared by 12 h and subsided by 72 h following treatment. Unusual side reactions were noted in a few patients with high density microfilaraemia. These included intense cough, shortness of breath, blood tinged mucoid expectoration associated with patchy pneumonitis of the lung. Itchy rashes, lymphatic nodules and raised alkaline phosphatase level were also observed in some patients. The frequency and intensity of side reactions were related to pretreatment mf densities and were independent of the dose administered. These side reactions were transient, self

limiting and were not serious enough to warrant any treatment. These exaggerated unusual reactions were possibly due to allergic response of the susceptible host to rapid killing of large number of microfilarae.

Moreover these standard drugs used against the filarial parasitic round worms kill only the micorfilarae when used in mass drug administration programme proposed by World Health organization (WHO). These drugs do not have macrofilaricidal effect and possess side effects, which discourage the people in the endemic areas where disease compliance is more and this could be a possible reason for the unwillingness towards the MDA programme. So this is essential to investigate the alternate source of higher efficacy and lower toxic lead molecules which possibly would become a safer new drug and for this reason medicinal plants would be a valid alternative for searching new drugs.

Therapeutic potential of ethno-medicinal plants

Medicinal plants and its healing activities against various diseases has been a valuable ingredient in various therapeutic applications since centuries ago in Ayurvedic, Unani, Siddha and Chinese medicinal practices According to WHO 80% of population in different countries relies on traditional medicinal herbs for curing diseases like fever, cough, joint pain, nausea, hypertension, insomnia, cancer, diabetes, Alzheimer's disease etc

The potency of medicinal plants in the treatment of parasitic diseases has gained increasing importance among researchers to formulate new drug leads. This could be a possible alternative towards the current drug regime, as the current synthetic drugs are effective but possess various side effects. In the context of lymphatic filariasis, the current drugs available for MDA implementation by national programmes such as Ivermectin, ALB and DEC, which have been the drugs of choice for filariasis control, are effective in reducing microfilariae counts but not effective in killing adult worms[20] It also has been reported to cause side effects such as fever, gastrointestinal disturbance, headache, malaise and skin rash that reduce patient compliance. So, there is an urgent need of a cheap, non-toxic and novel antifilarial drug with macrofilaricidal activity.

The present antifilarial drug diethyicarbamazine (DEC), ivermectin and albendazole have only microfilaricidal activity and possesses less activity against adult worms. These drugs also show some side effects in patients, so there is a social stigma regarding the mass consumption of these drugs. This warrants the need for developing an effective and safe drug, which could kill or sterilize the adult worm.

A total of 25 family members so far were reported in filarial chemotherapy out of which Fabaceae, Asteraceae and Euphorbiaceae showed maximum number of genus reported for activity. As can be observed from the table, four models were used in the reports these were *Brugia malayi, Brugia phangi, Setaria digitata* and *Setaria cervi.* None of the study involved human *Wuchereria bancrofti* as it is very difficult to procure the same for experimental work. Some of the significant results are as follows:

Cassia occidentalis Linn, *Oldenlandia herbacea* L.Roxb, *Sida acuta* Burm.f, *Clitoria ternatea* Linn and *Euphorbia hirta* Linn were selected for macrofilaricidal study against *Setaria digitata*. Methanolic extracts were used for the study. Worm motility assay was performed and all the plant extracts showed complete immobilization of worms at 10 mg/ml at the end of 4 hours incubation period. MTT formazan colorimetric assay for viability of worms were carried out. *Cassia occidentalis, Oldenlandia herbacea* and *Sida acuta* exhibited > 50 % of formazan inhibition at 4 hours. *Clitoria ternatea* and *Euphorbia hirta* exhibited <50 % of inhibition at 4 hours. *Oldenlandia herbacea* exhibited 65.67, 78.6 and 85.66 % of inhibition for the concentration of 1, 5 and 10 mg/ml respectively. This study identified *Oldenlandia herbacea* as a potential macrofilaricidal agent [21].

Antifilarial activity of Methanol/Hexane-ethanol extracts of *Butea monosperma* L. (leaves) and Ciprofloxacin was explored against adult *Setaria cervi worm* after incubation for 24 hrs with concentration range of 0.25 to 20 mg/ml. Inhibitory concentrations (IC_{50}) for the plant extracts with significant antifilarial activity against *Setaria cervi* adult *in vitro* system for MTT assay have been derived to be 1.25, 3.6 and 7.5 mg/ml Methanol, Hexane-ethanol extracts and Ciprofloxacin respectively. Methanol and Hexane-ethanol extracts of *Butea monosperma* L. plant leaves showed significant antifilarial activity as compared to Ciprofloxacin [22].

In vitro efficacy of ethyl acetate extract of *Vitex negundo* was studied against adult *Setaria cervi* worm [23]. Extract concentration 0.03 to 1.00mg/ml was used for worm motility assay followed by MTT reduction assay. In motility assay complete inhibition of motility was observed and in MTT assay >50% inhibition was found for concentrations 0.2, 0.5 and 1.00mg/ml at dose dependent manner. IC_{50} was obtained to be 0.16mg/ml. *Vitex negundo* plant extract showed potency towards the discovery of a novel drug candidate for lymphatic filariasis.

Efficient plant source that can induce apoptosis of filarial parasites possibly can provide a new direction towards developing a new class of antifilarials. Mukherjee *et al*[24] evaluated the antifilarial efficacy of an optimized polyphenol rich ethanolic extract of *Azadirachta indica* leaves. Motility reduction, MTT assay and dye exclusion test have confirmed the micro and macrofilaricidal potential of extract. They had found cellular disturbances in extract treated parasites characterized by chromatin condensation, in situ DNA fragmentation and nucleosomal DNA laddering. Depletion in worm GSH level and elevation in parasite GST, SOD, catalase, GPx and superoxide anion indicated the generation of ROS. They also reported that ethanolic extract causes decreased expression of anti-apoptotic genes and increased pro-apoptotic genes at the level of both transcription and translation.

Bioassay guided isolation of ferulic acid from ethyl acetate fraction of *Hibiscus mutabilis* was obtained. The crude and ferulic acid the active molecule showed significant microfilaricidal as well as macrofilaricidal against the *Setaria cervi* by both the worm motility and MTT reduction assay[25]. By the consequences of ferulic acid treatment extreme cellular disturbances was recorded by chromatin condensation, *in situ* DNA fragmentation and nucleosomal DNA laddering. Ferulic acid exerts its antifilarial effect through induction of apoptosis and by down regulating and altering the level of some key antioxidants (GST, GSH and SOD) of the filarial nematode. Further antifilarial effect of Ursolic acid (UA) isolated from ethyl acetate fraction of *Nyctanthes arbortristis*[26] was reported. Same compound was isolated from leaves of *Eucalyptus tereticornis*. The crude extract and Ursolic acid showed significant micro as well as macrofilaricidal activities against the filarial parasite Brugia malayi using *in vitro* and *in vivo* assays, and in silico docking search on glutathione-s-transferase (GST) parasitic enzyme were carried out. The UA was lethal to microfilariae (mf; LC100: 50; IC50: 8.84 µM) and female adult worms (LC100: 100; IC50: 35.36 µM) as observed oocyte, microfilaria and adult of *Setaria cervi* (*S.*

cervi) by dye exclusion test and MTT reduction assay. Antifilarial activity of UA against the human lymphatic by motility assay; it exerted 86% inhibition in MTT reduction potential of the adult parasites [27].

The effect of aqueous and alcoholic extract of the leaves and seeds of *P. corylifolia* on the spontaneous movement of the whole worm and the nerve muscle preparation of *Setaria cervi* and the survival of microfilariae *in vitro* was investigated. Alcohol extracts of both leaves and seeds caused the inhibition of spontaneous movements of the whole worm and the nerve muscle preparation of *S. cervi* at doses 160, 30 and 150, 20µg/ml, respectively characterized by initial, short lasting small increase in tone of contraction followed by paralysis. LC_{50} and LC_{90} for the death of microfilariae was obtained to be 12 and 25ng/ml for alcoholic leaf extract and 12 & 18ng/ml for alcoholic extracts of seeds respectively[28] Details of other medicinal plants have been given in Table 1, which have been explored for antifilarial activity and have shown mild activity. Plant kingdom is vast and further exploration is still warranted for a suitable and safe macrofilaricidal agent in order to alleviate the menace of filariasis.

Table 1: Medicinal plants used for treating Filariasis

Family	Plant name	Parts used	Target parasite	Activity on filarial parasites
Acanthaceae	*Andrographis paniculata*	Leaves	*B. malayi*	Anti-filarial activity of aqueous extracts on adult parasites at doses 5 and 10mg/ml in terms of reduction in relative motility of worms i.e. 0% after 24hrs of treatment [29]
Apiaceae	*Trachyspermum ammi*	Fruit	*S. digitata*, *B. malayi*	*In vitro* and *in vivo* antifilarial efficacy of crude as well as active fractions atdoses 0.01 to 0.5mg/ml on adult worms were reported in terms of motility inhibition and MTT reduction assays [30]
Asteraceae	*Centratherum anthelminticum*	Seed	*S. cervi*	Ethylacetate, acetone and methanol extracts showed inhibition of spontaneous motility of the nerve-muscle preparation of *S. cervi* characterized by decreasedamplitude and frequency of contractions [31]
	Neurolaena lobata	Leaf	*B. phangi*	Ethanolic extract was reported to be effective on micro as well as macrofilariae of *B. phangi* [32].
	Sphaeranthus indicus	Whole plant	*S. digitata*	Methanolic extract showed macrofilaricidal activity at dose below 4mg/ml after incubation of 100min [33]
Betulaceae	*Alnus nepalensis*	Leaves	*B. malayi*	The diarylheptanoid compounds isolated from this plant showed both micro as well asmacrofilaricidal activity with IC_{50} value of 6.57-10.31µg/ml concentration [34]
Caesalpinaeceae	*Bauhinia racemosa*	Leaves	*B. malayi*	Galactolipids isolated from ethanolic extract showed better adulticidalactivity than ivermectin and DEC at doses 58.3 ± 8.33% [35].
	Caesalpinia bonducella	Leaves and seeds	*B. malayi*	The leaves and seed kernel extract showed effective micro-filaricidalas well as macrofilaricidal activity using animal models [36]
Combretaceae	*Terminalia chebula*	Leaf and fruit	*S. digitata*	Methanolic extract showed potent macrofilaricidal activity at concentrations 8 to10mg/ml in terms of worm motility and MTT reduction assays [33].
Convolvulaceae	*Argyreia speciosa*	Whole plant	*S. cervi*	Aqueous and alcoholic extracts showed inhibitory activity on the whole worm andnerve muscle preparation at 150 and 75µg/ml concentration respectively [37].
Euphorbiaceae	*Ricinus communis*	Seeds	*S. digitata & B. Malayi*	Methanolic extract of seeds exhibited antifilarial activity on the adult worms at concentration 1mg/ml with 72.39% formazan inhibition [38]
	Mallotus philippensis	Leaves	*S. cervi*	Aqueous and alcoholic extract of leaves showed potential antifilarial activity due to alteration of membrane permeability [39].
	Excoecaria agallocha	Leaves	*S. digitata*	Methanolic extract showed promising antifilarial activity at very lower doseof 10µg/ml on the developmental stages of parasite [40].
Fabaceae	*Acacia auriculiformis*	Funicles Roots	*S. cervi*	Triterpenoid saponnins acaciaside A and acaciaside B isolated from funicles showed micro as well as macrofilaricidal effect of 97% and 100% inhibition Respectively within 100min [41].
	Butea monosperma	Leaves & fruits	*S. cervi and B. malayi*	Methanol and hexane-ethanol extract showed IC_{50} value of 1.25 and 3.6mg/ml respectively on adult worms [22].
	Pongamia pinnata			Aqueous and alcoholic extract at concentrations 250and 120µg/ml exhibited inhibition of spontaneous movement of Setaria worm [42]
			S. cervi	The alcoholic extract of leaves and seeds at concentrations160 and 30µg/ml showedinhibitory effect on whole worm respectively [28]
	Psoralea corylifolia	Leaves & seeds	*S. cervi*	
Lamiaceae	*Leucas cephalotes*	Flower & stem	*S. cervi*	Alcoholic and aqueous extract of flower as well as stem showed inhibitory effects on spontaneous movement of Setaria worms [28]
	Leucas aspera	Whole plant	*S. digitata*	The plant extract of *L. aspera* showed antiparasitic effect on *S. digitata* [43]
Liliaceae	*Asparagus adscendens*	Whole plant	*S. cervi*	The alcoholic and aqueous extract showed microfilaricidal activity with LC_{50} value of 8 and 3ng/ml respectively[44]
Lythraceae	*Lawsonia inermis*	Leaf	*S. digitata*	The column fractions obtained from methanolic and aqueous extracts showed antifilarial activity atconcentrations 0.01 to 1mg/ml in terms of worm motility inhibition of adult Setaria

				worms [45]
Malvaceae	*Hibiscus mutabilis*	Leaf	*S. cervi*	Methanolic extract from leaves and ferulic acid isolated from ethyl acetatefraction showed micro as well as macrofilaricidal activity on Setaria worms [25]
	Hibiscus sabdariffa	Leaf	*B. malayi*	Butanol fraction showed100% microfilaricidal activity at dose 250µg/ml and the leaf/extract at dose 500mg/kg produced 30% macrofilaricidal activity *in vivo* on *B. malayi* [46]
Meliaceae	*Xylocarpus granatum*	Seed, Fruit	*B. malayi*	Gedunin and photogedunin isolated from fruit extract exhibited adulticidal activity *in vitro* and *in vivo* with IC_{50} value of 0.239 and 0.213µg/ml resulted in 70 to 80% inhibition of adult *B. malayi* [47]
	Azadirachta indica	Flowers & leaves	*S. cervi*	Alcohol and aqueous extract of flower showed inhibitory effects on spontaneous movement of microfilariae of *S. cervi* with LC_{50}value of 15 and 18ng/ml The ethanolic extract of leaves also put significant inhibitory effect on the reduction of microfilariae as well as on the viability of adult worms confirmed by upregulation of ROS [24]
Menispermiaceae	*Tinospora crispa*	Stem	*B. malayi*	Dried stem extract of the plant showed strong antifilarial effect on adult worms of subperiodic *B. malayi* [28].
Moraceae	*Streblus asper*	Bark	*S. cervi* & *B. malayi*	Aqueous and alcoholic extract exhibited microfilaricidal activity *in vitro* with LC_{50} and LC_{90} value of 90 and 33.5ng/ml [48].
	Ficus racemosa	Fruits	*S. cervi*	The aqueous extract of stem bark also put strong macrofilaricidal effect on *B. malayi* in rodents [49] Alcoholic and aqueous extract showed microfilaricidal effect *in vitro* with LC_{50} value of 21 and 27ng/ml respectively [50].
Moringaceae	*Moringa oleifera*	Gum	*B. malayi*	The gum extract significantly inhibited the microfilariae at 125mg/ml concentration and also showed macrofilaricidal effect with 56% MTT reduction potential on adult worms of *B. malayi* [51].
Pinaceae	*Cedrus deodara*	Plant wood	*S. digitata*	Methanolic extract showed macrofilaricidal activity in terms of worm motility and MTT reduction potential at concentration 1mg/ml exhibited 86.56% inhibition [52].
Piperaceae	*Piper betle*	Leaves	*B. malayi*	Crude methanolic extract (100 mg/kg) and the hexane fraction significantly raise the antibody production and exhibited a mixed type 1 and type 2 cytokine responses showing immune modulatory property in this plant against filarial *Brugia malayi* infection [53].
Plumbaginaceae	*Plumbago indica*	Root	*S. digitata*	The methanolic extract of the root showed 83.3% immobilization of worms after 6hrs and the isolated compound plumbagin exhibited >70% inhibition of formazan in MTT assay at 0.05mg/ml concentration [54]
Rutaceae	*Aegle marmelos*	Leaves	*B. malayi*	Methanolic extract of leaves showed microfilaricidal activity at concentration 100ng/mlexhibiting complete immobilization after 48hrs of incubation period [55].
Sapindaceae	*Cardiospermum halicacabum*	Whole plant	*B. pahangi*	The aqueous extract exhibited worm motility inhibition at concentration less than 500µg/ml after 24hrs of exposure where as the ethanolic extract showed little effect on worms detected by MTT assay [56]
Saxifragaceae	*Saxifraga stracheyion*	Root	*S. cervi*	Aqueous and alcoholic extract at doses 140 and 250µg/ml exhibited inhibitory effect on spontaneous movement of the worm [57]
Solanaceae	*Solanum khastanum*	Fruit	*S. cervi*	Solamargine, a steroidal alkaloid glycoside obtained from the fruit showed 100% inhibition of adult worms and microfilariae at 4mg/ml concentration in 60 and 88mins respectively [58]
	Withania somnifera	Whole plant	*B. malayi*	Withaferin A, isolated from *W. somnifera* exhibited *in vivo* larvicidal activity at 7.8µg/ml and also reported about 63.6% inhibition of microfilariae of *B. malayi* [59].
Verbenaceae	*Vitex negundo*	Leaves, Root Stem	*B. malayi* & *S. cervi*	The ethyl acetate extract of leaves from *V. negundo* showed significant worm motilityand MTT reduction activity of >50% at doses 0.2, 0.5 and 1mg/ml at 10, 6 and 2hrs incubationperiod respectively on *S. cervi* (Sahare and Singh, 2013). The root extract of *V. negundo* also exhibited *in vitro* microfilaricidal activity at 100ng/ml on *B. malayi* after 48hrs of incubation [37]
	Lantana camara		*B. malayi*	The crude extract prepared from stem of *L. camara* at 1 g/kg for five days by oral route killed43.05% of the adult *Brugia malayi* parasites in the rodent model *Mastomys coucha* [60]

Acknowledgement
Authors are thankful to Forest and Environment Department of Odisha for providing financial support during the entire research process.

References

1. Ottesen EA, Duke BO, Karam M, Behbehani K. Strategies and tools for the control/elimination of lymphatic filariasis. Bull World Health Org. 1997; 75:491–503.
2. Bennuru S, Nutman TB. Lymphatics in human lymphatic

filariasis: *in vitro* models of parasite-induced lymphatic remodeling. Lymphat Res Biol. 2009; 7:215-219.
3. Baldridge G, Higgins L, Witthuhn B, Markowski T, Baldridge A, Armien A *et al*. Proteomic analysis of a mosquito host cell response to persistent Wolbachia infection. Res Microbiol. 2017; 168(7):609-25.
4. Ottesen EA, Duke BOL, Karam M, Behbehani K. Strategies and tools for the control/elimination of lymphatic filariasis. Bulletin of the World Health Organization. 1997; 75:491-503.
5. Ramaiah KD. Lymphatic filariasis elimination programme in India: progress and challenges. Trends Parasitol. 2009; 25:7-8.
6. Lahariya C, Mishra A. Strengthening of mass drug administration implementation is required to eliminate lymphatic filariasis from India: an evaluation study. J Vector Borne Dis. 2008; 45:313-320.
7. Hewitt RI, Kushner S, Stewart HW, White E, Wallace WS, Subbarow Y. Experimental chemotherapy of filariasis III. Effect of 1-diethylcarbamyl-4-methylpiperazine hydro-chloride against naturally acquired filarial infections in cotton rats and dogs. J Lab Clin Med. 1947; 32:1314-1329.
8. Noroes J, Dreyer G, Santos A..Assessment of the efficacy of diethylcarbamazine on adult *Wuchereria bancrofti in vivo*. Trans. R. Soc. Trop. Med. Hyg. 1997; 91:78-81.
9. Maizels RM, Denham DA. Diethylcarbamazine (DEC): immunopharmacological interactions of an anti-filarial drug. Parasitology, 1992; 105:49-60.
10. Lammie P, Milner T, Houston R. Unfulfilled potential: using diethylcarbamazine-fortified salt to eliminate lymphatic filariasis. Bull World Health Organ. 2007; 85(7):545-9.
11. Bryceson AD, Warrell DA, Pope HM. Dangerous reactions to treatment of onchocerciasis with diethylcarbamazine. Br Med J. 1977; 6063:742-4.
12. Francis H, Awadzi K, Ottesen EA**.** The Mazzotti reaction following treatment of onchocerciasis with diethylcarbamazine: clinical severity as a function of infection intensity. Am J Trop Mws Hyg. 1985; 34(3):529-36.
13. Prichard RK. Markers for benzimidazole resistance in human parasitic nematodes. Parasitology. 2007; 134(8):1087-1092.
14. Serbus LR, Landmann F, Bray WM, White PM, Ruybal J, Lokey RS et al. A cell-based screen reveals that the albendazole metabolite, albendazole sulfone, targets Wolbachia. PLoS Pathog. 2012; 8(9):10-13.
15. Babu BV, Rath K, Kerketta AS. Adverse reactions following mass drug administration during the programme to eliminate lymphatic filariasis in Orissa state, India. Trans R Soc Trop Med Hyg. 2006; 100:464-67.
16. Crump A, Omura S. Ivermectin, 'wonder drug' from Japan: the human use perspective. Proc Jpn Acad Ser B Phys Biol Sci. 2011; 87(2):13-28.
17. Yates DM, Wolstenholme AJ. Dirofilaria immitis: identification of a novel ligand-gated ion channel-related polypeptide. Exp Parasitol. 2004; 108(3, 4):182-5.
18. Ménez C, Sutra JF, Prichard R, Lespine A. Relative neurotoxicity of ivermectin and moxidectin in Mdr1ab (-/-) mice and effects on mammalian GABA(A) channel activity. PLoS Negl Trop Dis. 2012; 6(11):e1883. doi:
19. 10.1371/journal.pntd.0001883.
20. Newman, DJ, Cragg GM. Natural products as sources of new drugs over the last 25 years. J. Nat. Prod. 2007; 70:461-477.
21. Ottesen EA. Efficacy of diethylcarbamazine in eradicating infection with lymphatic-dwelling filariae in humans. Rev Infect Dis. 1985; 7:341-356.
22. Radhika J, Sathya P. *In vitro* macrofilaricidal activity of traditional medicinal plants. World J. Phar. and Phar. Sci. 2014; 3(12):1034-42.
23. Deshmukh M, Sahare KN, Patidar RK, Mahajan B, Singh V. Antifilarial activity of *Butea monosperma* L. leaves extracts against *Setaria cervi*. Trends in Vector Research and Parasitology. 2014; 1:123-45.
24. Sahare KN, Singh V. Antifilarial activity of ethyl acetate extract of *Vitex negundo* leaves *in vitro*. Asian Pac J Trop Med. 2013; 6:689-69.
25. Mukherjee N, Mukherjee S, Saini P, Roy P, Babu S. Antifilarial effects of polyphenol rich ethanolic extract from the leaves of *Azadirachta indica* through molecular and biochemical approaches describing reactive oxygen species (ROS) mediated apoptosis of *Setaria cervi*. Exp Parasitol. 2013; 136:41-58.
26. Saini P, Gayen P, Nayak A. Effect of ferulic acid from *Hibiscus mutabilis* on filarial parasite *Setaria cervi*: molecular and biochemical approaches. Parasitology International. 2012; 61(4):520-531.
27. Saini P, Gayen P, Kumar D, Nayak A, Mukherjee N, Mukherjee S et al. Antifilarial effect of ursolic acid from Nyctanthes arbortristis: molecular and biochemical evidences. Parasitol Int. 2014; 63(5):717-28.
28. Kalani K, Kushwaha V, Sharma P, Verma R, Srivastava M, Khan F, Murthy PK et al. *In vitro*, in silico and *in vivo* studies of ursolic acid as an anti-filarial agent. PLoS One. 2014; 9(11):e111244.
doi: 10.1371/journal.pone.0111244.
29. Qamaruddin, Parveen N, Khan NU, Singhal KC. Potential antifilarial activity of the leaves and seeds extracts of *Psoralea corylifolia* on cattle filarial parasite *Setaria cervi*. J Ethnopharmacol. 2002; 82:23-8.
30. Zaridah MZ, Idid SZ, Omar AW, Khozirah S. "*In vitro* antifilarial effects of three plant species against adult worms of subperiodic *Brugia malayi*," Journal of Ethnopharmacology. 2001; 78(1):79-84.
31. Mathew N, Misra-Bhattacharya S, Perumal V, Muthuswamy K. Antifilarial lead molecules isolated from *Trachyspermum ammi*. Molecules. 2008; 13(9):2156-2168.
32. Singhal KC, Sharma S, Mehta BK. Antifilarial activity of *Centratherum anthelminticum* seed extracts on Setaria cervi. Indian J Exp Biol. 1992; 30(6):546-8.
33. Fujimaki Y, Kamachi T, Yanagi T, Caceres A, Maki J, Aoki Y. Macrofilaricidal and microfilaricidal effects of *Neurolaena lobata*, a Guatemalan medicinal plant, *on Brugia pahangi*. J Helminthol. 2005; 79:23-28.
34. Nisha M, Kalyanasundaram M, Paily KP, Abidha, Vanamail P, Balaraman K. *In vitro* screening of medicinal plant extracts for macrofilaricidal activity. Parasitol Res. 2007; 100:575-579.
35. Yadav D, Singh SC, Verma RK. Antifilarial diarylheptanoids from *Alnus nepalensis* leaves growing in high altitude areas of Uttarakhand, India. Biomedicine. 2013; 20:124-132.
36. Sashidhara KV, Singh SP, Misra S, Gupta J, Misra-Bhattacharya S. Galactolipids from *Bauhinia racemosa* as a new class of antifilarial agents against human lymphatic filarial parasite, *Brugia malayi*. European Journal of Medicinal Chemistry. 2012; 50:230-235.
37. Gaur RL, Sahoo MK, Dixit S, Fatma N, Rastogi S,

Kulshreshtha DK et al. Antifilarial activity of *Caesalpinia bonducella* against experimental filarial infections.Indian J Med Res. 2008; 128:65-70.
38. Parveen N. Antifilarial activity of *Vitex negundo* L. against Setaria cervi. Fitoterapia. 1991; 62:163-70.
39. Shanmugapriya R, Ramanathan T. Antifilarial activity of seed extracts of *Ricinus communis* against *Brugia malayi*. Journal of Pharmacy Research. 2012; 5(3):1448-1450.
40. Singh R, Singhal KC, Khan NU. Antifilarial activity of the leaves of *Mallotus philippensis* Lam. on *Setaria cervi* (Nematode Filarioidea) *in vitro*. Indian J Physiol Pharmacol. 1997; 41:397-403.
41. Patra JK, Mohapatra AD, Rath SK, Dhal NK, Thatoi H. Screening of antioxidant and antifilarial activity of leaf extracts of *Excoecaria agallocha* L. International Journal of Integrative Biology. 2009; 7(1):9-15.
42. Ghosh M, Shinhababu SP, Sukul NC. Antifilarial effect of two triterpenoid saponins isolated from *Acacia auriculiformis*. Ind. J Exp. Biol. 1993; 31:604-606.
43. Uddin Q, Parveen N, Khan NU, Singhal KC. Antifilarial potential of the fruits and leaves extracts of *Pongamia pinnata* on cattle filarial parasite *Setaria cervi*. Phytother. Res. 2003; 17:1104-1107.
44. Mathai A, Devi KS. Anti-parasitic activity of certain indigenous plants. Anc Sci Life. 1992; 12(1-2):271-273.
45. Comley JC. New Macrofilaricidal leads from plants. Trop Med Parasitol. 1990; 1:1-9
46. Comley JC, Titanji VP, Ayafor JF, Singh VK. *In vitro* antifilarial activity of some medicinal plants. Acta Leiden. 1990; 59(1-2):361-3.
47. Saxena K, Dube V, Kushwaha V. Antifilarial efficacy of *Hibiscus sabdariffa* on lymphatic filarial parasite *Brugiamalayi*. Medicinal Chemistry Research. 2011; 20(9):1594-1602.
48. Misra S, Verma M, Mishra SK, Srivastava S, Lakshmi V, Bhattacharya SM. Gedunin and photogedunin of *Xylocarpus granatum* possess antifilarial activity against human lymphatic filarial parasite *Brugia malayi* in experimental rodent host. Parasitol Res. 2011; 109(5):1351-60.
49. Nazneen P, Singhal KC, Khan NU, Singhal P. Potential antifilarial activity of *Streblus asper* against *Setaria cervi* (Nematoda: Filarioidea). Indian J Pharmacol. 1989; 21:16.
50. Chatterjee RK, Fatma N, Murthy PK. Macrofilaricidal activity of the stembark of *Streblus asper* and its major active constituents. Drug Dev Res. 1992; 26:67-78.
51. Mishra V, Khan NU, Singhal KC. Potential antifilarial activity of fruit extracts of *Ficus racemosa* Linn. Against *Setaria cervi in vitro*. Indian J Exp. Bio. 2005; 43(4):346-50.
52. Kushwaha V, Saxena K, Verma SK, Lakshmi V, Sharma RK. Antifilarial activity of gum from *Moringa oleifera* Lam. on human lymphatic filarial *Brugia malayi*. Chronicles of Young Scientists. 2011, 202-06.
53. Mathew N, Kalyanasundaram M, Paily KP, Abidha, Vanamail P, Balaraman K. *In vitro* screening of medicinal plant extracts for macrofilaricidal activity. Parasitol Res. 2007; 100:575-579.
54. Singh M, Shakya S, Soni VK, Dangi A, Kumar N, Bhattacharya SM. The n-hexane and chloroform fractions of *Piper betle* L. trigger different arms of immune responses in BALB/c mice and exhibit anti filarial activity against human lymphatic filarid *Brugia malayi*. International J Immune. 2009; (6):716-728.
55. Mathew N, Paily NKP, Vanamail AP, Kalyanasundaram M, and Balaraman K. Macrofilaricidal Activity of the Plant *Plumbago indica*/*rosea in vitro*. Drug Development Research. 2002; 56:33-39
56. Sahare KN, Anandhraman V, Meshram VG, Meshram SU, Reddy MVR, Tumane PM *et al*. Antimicrifilarial activity of methanolic extract of *Vitex negundo* and *Aegle marmelos* and their Phytochemical analysis. Indian J Exp Biol. 2008; 46:128-131.
57. Khunkitti W, Fujimaki Y, Aoki Y. *In vitro* antifilarial activity of extracts of the medicinal plant *Cardiospermum halicacabum* against *Brugia pahangi*. J Helminthol. 2000; 74:241-246.
58. Singh R, Singhal YC, Khan NU. Exploration of Antifilarial Potential and Possible Mechanism of Action of the Root Extracts of *Saxifraga stracheyion* on Cattle Filarial Parasite *Setaria cervi*. Phytother. Res. 2000; 14:63-66.
59. Ghosh M, Shinhababu SP, Sukul NC, Sahu NP, Mahato SB. Antifilarial effect of solamargine isolated from *Solanum Khastanum*. Int J Pharm. 1994; 32:1-7.
60. Kushwaha S**,** Soni VK**,** Singh PK**,** Bano N**,** Kumar A**,** Sangwan RS *et al*. *Withania somnifera* chemotypes NMITLI 101R, NMITLI 118R, NMITLI 128R and withaferin A protect *Mastomys coucha* from *Brugia malayi* infection. Parasite Immunol. 2012; 34(4):199-209.
61. Misra N, Sharma M, Raj K, Bhattacharya SM. Chemical constituents and antifilarial activity of *Lantana camara* against human lymphatic filariid *Brugia malayi* and rodent filariid *Acanthocheilonema viteae* maintained in rodent hosts. Parasitol Res. 2007; 100(3):439-48.