



Looking Forward to the Promising Anti-Filarial Plant Resources and Futuristic Drug Discovery Approaches

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ABSTRACT

In tropical and subtropical nations, lymphatic filariasis (LF) is considered a significant public health issue. Adult worms may survive in an infected person for many years, generating microfilariae (mf) and aiding disease transmission via vector mosquitoes. Elephantiasis, river blindness, and tropical pulmonary eosinophilia are among the illnesses caused by filarial worms. The medication of choice for treating filariasis has a slew of negative side effects. Current filariasis control methods aren't considered to be entirely safe or effective. This necessitates the development of an effective and safe medication to combat the adult filarial worm. Researchers have looked at the impact of a variety of medicinal herbs on filarial worms, and several of them have been shown to have anti-filarial action. The profiles of the plants as anti-filarial drugs are presented in this review, which should not only impact the target but also have very few or no adverse effects.

Key Words: Filariasis, Microfilariae, Anti-filarial, Worms, Extract, Natural, Herbal

INTRODUCTION

A number of parasite illnesses that are linked to morbidity and death have gotten less attention throughout the globe. Filariasis, one of the most devastating neglected tropical illnesses, is one of them. Filariasis is a socially stigmatizing vector-borne illness spread by an arthropod vector that is endemic in the tropics and subtropics. It is a category of human and animal infectious illnesses caused by nematode parasitic worms known as “filariae,” which comprise hundreds of species of thin and elongated worms that parasitize the tissues of different vertebrate hosts. Human infections are caused by parasites from the genera *Wuchereria*, *Brugia*,

Onchocerca, *Dipetalonema*, *Mansonella*, and *Loa*. They live in vertebrate hosts' lymphatics, muscles, connective tissues, bodily cavities, and so forth. Based on the adult worm's environment, they may be divided into three groups: the cutaneous group, the lymphatic group, and the body cavity group. Table 1 lists a few filarial species that infect humans and the illness they produce with their intermediate hosts, based on the adult worm's environment. The infection is spread by intermediate hosts, which are invariably blood-sucking Diptera arthropods. Human lymphatic filariasis (LF) is caused mostly by two genera: *Wuchereria* and *Brugia*. *Setariadigitata* and *S. cervi* (bovine), *Dirofilariaimmitis* (dog), *D. uniformis* (rabbit), *Litomosoidescarinii* and

Table 1. Pathogenic filarial worms.

Filarial worms	Diseases	Hosts	Habitats
<i>Brugiamalayi</i>	Malayan filariasis	Mosquito sp.	Lymphatics
<i>Brugia timori</i>	Timor fever	Mosquito sp.	Lymphatics
<i>Loa loa</i>	Loaiasis	<i>Chrysops</i> sp. (<i>C. dimidiata</i>)—Horse flies	Connective tissue
<i>Mansonella ozzardi</i>	Ozzard's filaria	<i>Culicoides</i> sp. (<i>C. furens</i>)—biting midges	Serous membranes
<i>Onchocerca volvulus</i>	Onchocerciasis	<i>Simulium</i> sp. (<i>S. damnosum</i>)—black flies	Skin
<i>Wuchereria bancrofti</i>	Elephantiasis	Mosquito sp.	Lymphatics

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Dipetalonema vitae (gerbils), *Brugiapahangi* (cat), and *Acanthocheilonemaviteae* (cat) are the most frequent animal parasites (jird) [1].

DEMOGRAPHY

According to current studies, this illness has affected 120 million individuals in 81 countries across the globe, with 1.34 billion people living in endemic regions at high risk of contracting it. Research programs are required to develop effective medicines and therapeutic targets, new vector management methods, and diagnostic procedures in order to eliminate filariasis worldwide. At the same time, in order to eliminate filariasis, disease-specific clinical care and patient education with counseling are required. Furthermore, statistical analysis and bioinformatics techniques should be used to analyze the mass drug administration (MDA) monitoring data, which may offer fresh insights into the proteins or genes that may contribute to the inhibition process. According to the latest World Health Organization (WHO) surveillance report, LF is prevalent in five WHO areas (LF). Preventive chemotherapy is required by 1.39 billion individuals worldwide. In Southeast Asia, 877 million people from nine countries are afflicted by the illness, while 432 million individuals from 39 nations in Africa are affected and need treatment. Nearly 40 million individuals in the Western Pacific Region, which encompasses the Mekong Plus region and the Pacific region, are at risk of LF. [2].

HISTORY OF FILARIASIS

The earliest recorded evidence of filariasis was described in India by the renowned physician Sushruta in the *Sushruta Samhita* (about 600 BC). The earliest credible recording of filariasis was recorded in the late fifteenth and early sixteenth centuries, according to certain sources. In 1849, William Prout described the pathological condition of chyluria, which is characterized by the transit of lymph in the urine and is linked to LF. The first person to notice microfilariae (mf) in the hydrocele fluid was French surgeon Jean Nicolas in 1863. Timothy Lewis discovered mf in human blood for the first time in India in 1872. Joseph Bancroft discovered female filarial worms in 1876 and called them *Filariabancrofti*, which eventually became part of the *Wuchereria* genus. By examining the parasitic growth of mf in the mosquito stomach that was fed on the blood of an infected gardener in 1877, Sir Patrick Manson identified the primary mechanism of filariasis transmission and revealed that filariasis is spread by the mosquito. Two additional filarial worm species, *B.malayi* and *B. timori*, were discovered and described in 1960 and 1977, respectively[3].

FILARIASIS

Lymphocytic filariasis is the most severe filariasis that causes impairment in people. The primary causes of LF are *W.bancrofti* and *B.malayi* or *B. timori*, both of which are transmitted by the bite of a particular insect vector. The vectors that cause LF are from the *Anopheles*, *Culex*, *Aedes*, and *Mansonia* genera. According to the WHO, high transmission rates of filariasis in a given region are caused by an increase in microfilariae density in affected people and the feeding rate of vector populations. The filarial worms like *O. volvulus* and *Loa loa* live in the cutaneous and subcutaneous tissues of the host, causing onchocerciasis and loiasis, respectively. The filarial worms *W. bancrofti* and *O. volvulus* do not need an animal host as a reservoir. The survey's findings painted a picture of a person suffering from the depressive disorder as a result of LF, with an estimated 5.09 million disability-adjusted life years (DALYs). Microfilaremia develops in children at the age of five following infection, although the symptoms of filariasis (including hydroceles) emerge after puberty. According to previous survey findings, the odds of a person being cured after contracting an illness are very slim.

Filarial worms in the lymphatic system may survive for up to eight years and discharge millions of mf into the circulation. In 2000, the WHO launched the Global Alliance to Eliminate LF (GPELF), with the aim of eliminating the disease by 2020 using MDA. GPELF is the most rapidly growing global health initiative in the history of public health. Fifty-three of the 81 endemic nations have begun widespread medication administration to stop filariasis transmission. To accomplish the goal of eradicating filariasis, two methods have been devised. To prevent the illness, the first approach involves giving single yearly doses of diethylcarbamazine or ivermectin with albendazole to the whole endemic region. The second approach is to decrease handicap rates by teaching lymphedema patients how to maintain cleanliness and skincare, as well as conducting surgery on hydrocele patients. During the years 2015-2020, an estimated US\$ 105-208 million will be spent on chemotherapy to manage this illness. "70 percent of endemic countries requesting MDA will have to begin post-intervention monitoring by 2016," according to the WHO, and "all remaining endemic countries must finish post-intervention surveillance by 2020," according to the WHO. The anti-filarial medicines described above are only effective against mf and have no impact on adult worms, thus they only offer a partial therapy to afflicted people. Drug resistance developed as a consequence of repeated usage of certain medicines. There have been no vaccinations produced to date, and the sole treatment option is anti-filarial medication. To combat this illness, researchers are working on a variety of novel anti-filarials and combination treatments[4].

LIFE CYCLE OF FILARIAL WORM

The mature filarial worms live in the lymphatic system of man, who is the ultimate host of the filarial worm. Mfs (290 μ m) are living embryos released by adult females. Mf circulates in the bloodstream and may live for a long time without metamorphosing until they are picked up by the intermediate host, the culicine mosquitoes, during their blood meal[5]. After reaching the mosquitoes, mf undergo development and become infective-stage larvae as described in Figure 1.

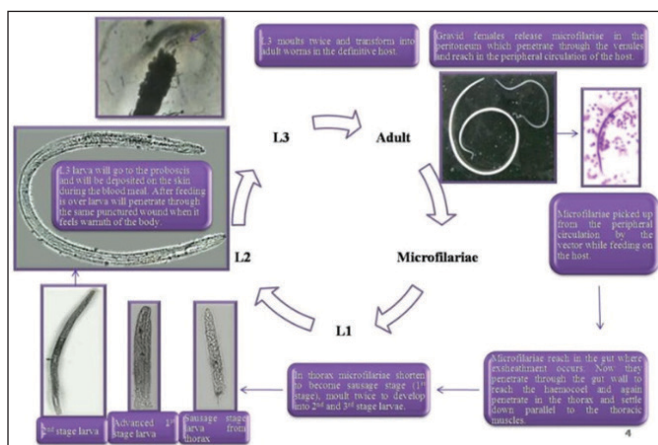


Figure 1: Structure of an Emulsome.

DIAGNOSIS OF LF

LF is diagnosed mainly via antigen detection techniques utilizing an immunochromatographic card test kit (which also detects latent infections). Microscopy is used to identify circulating mf in the conventional diagnosis of LF. Other diagnostic methods presently utilized include molecular xenomonitoring of parasites in mosquitoes, serological testing, ultrasonography, PCR tests, lymphoscintigraphy, identification of transmission exposure in children through antibody detection, and the newly developed filariasis test strip (FTS)[6].

DESIGNING NEW DRUGS AGAINST FILARIASIS

To discover therapeutic targets and understand the mechanism of action of anti-filarial drugs, a thorough understanding of parasite physiology is required. Compounds are sometimes examined without knowledge of the goal. Hits are compounds that are efficient against the whole parasite, while leads are compounds that are active in vivo. To improve their effectiveness, lead compounds must be standardized. Once a molecule has been refined, it may be tested in patients and classified as a "drug candidate." A medication should be developed and tailored to fight the

illness based on the physiological processes and symptoms. To combat filariasis, a variety of pharmacological targets should be studied for the development of novel anti-filarials, including macrofilaricidal and microfilaricidal medicines, drugs that inhibit mf exsheathment, and drugs that impede mf mobility. On the other hand, vaccine development and mosquito repellent practices such as the use of insecticide nets, body lotions, insecticide spray, coils, and other mosquito repellents, as well as a good understanding of sanitization, can help prevent vector development and thus help communities combat filarial worm infection. The pathology associated with LF, such as elephantiasis, hydrocoele, and lymphedema, is caused by the host immune system's D4+ T cells' hyporesponsiveness. As a result, immunological research is becoming more essential in the area of medication development. Drugs for the treatment of LF (drugs effective against adenolymphadenitis, funiculitis, epididymo-orchitis, lymphedema, hydrocele, chyluria, chylocele, lymph scrotum) and other manifestations like asymptomatic microfilaremia, occult filariasis, onchocerciasis, and loai) are also available[7].

ROLE OF BIOINFORMATICS IN DRUG DISCOVERY

Bioinformatics is a branch of computer science that focuses on computer-based analysis of biological information, with biology and computer science collaborating and influencing each other. Bioinformatics has improved our knowledge of the molecular mechanisms underlying a wide range of biological activities. Bioinformatics now encompasses a wide range of biological sciences and drug development to solve biological issues[8].

Genomic approach in filarial research

In bioinformatics, genomic research is a helpful method for understanding the structure and function of all the genes in an organism. Genomics aids in the discovery of a specific gene and other biological features in an organism's complete genome sequence. The genomics method may also be used to screen pharmacological targets. Casiraghi et al. used bioinformatics to do phylogenetic analysis on 11 filarial and Spirurida nematodes and discovered the mitochondrial cytochrome oxidase-I sequence (COI). Hoerauf et al. discovered a reciprocal interaction between internal bacteria (endobacteria) and filarial worms, which is now being exploited as a therapeutic target for anti-filarial drugs. Phylogenetic analysis parsimony tool (PAUP) was used by Nuchprayoon et al. to identify genetic diversity between the DNA sequences of two strains of Wb discovered in Myanmar and Thailand. The nuclear genome draft of Bm (95-Mb) was published by Ghedin et al., and it includes 88,363,057 bp sequences, with 17.84 percent protein-coding sequence. The

whole-genome sequences may be found in the NEMBASE4 database. The researchers discovered a number of filarial parasite genes and their new roles in miRNA regulation and processing[9].

Proteomic approach in filarial research

The proteomics technique included extremely effective protein separation methods such as two-dimensional polyacrylamide gel electrophoresis (2DPAGE) and detection, as well as contemporary bioinformatics tools. Using reverse-phase liquid chromatography-tandem mass spectrometry, a proteomic study of the different phases of Bm revealed 557 Bm proteins and 11,508 protein-coding genes, assisting in the definition of various proteins. Following that, Bennuru et al. identified the excretory/secretory (ES) and somatic proteins of adult, mf, and infective stages of B.malayi larvae. Some researchers used 3D structures to collect molecular information on a specific protein of interest, which is important in medication discovery and vaccine development for LF. In 2005, Bhargavi et al. investigated the 3D GST models of W.bancrofti and B.malayi to improve medication development. Novel drug targets are modeled utilizing a bioinformatics method that includes either ligand-based drug designing (LBDD) or structure-based drug designing for the creation of new medicines (SBDD). LBDD offers important information regarding the interaction between the drug target and the ligand molecule, as well as information on physiologically active compounds. Small compounds are now being studied using 3D-quantitative structural activity relationships (3D-QSAR) and pharmacophore modeling to determine the minimal structural features required to inhibit the target. These protein 3D structure studies were created using experimental methods such as X-ray crystallography, NMR, electron microscopy, and others. If experimental data for the target proteins are not available, homology modeling is used to construct the 3D structure using the target protein sequence. Potential inhibitors may be developed based on their binding sites or discovered using small-molecule databases including the Cambridge Structural Database, ChemBank, DrugBank, PubChem, and ZINC database, as well as databases accessible at Ligand [10].

Web-based available resources for LF

Bioinformatics, which analyses biological data for huge amounts of nucleotide sequences, amino acid sequences, and 2D or 3D structures for a wide variety of species and their therapeutic targets, relies heavily on web-based biological data. Only a few databases for LF are now accessible (Table 2), but the required database for LF is not available, which is an urgent requirement in the area of drug research and to combat developing drug resistance[11].

NEMBASE: It includes databases with information on filarial worms, including filarial biology and pathology,

Table 2. List of online databases for LF [11].

Database	Description
DBEMFDD diseases database	It is an annotated bibliography for filariasis, malaria, dengue, and diarrhea. It also contains the findings of the literature survey
FilaDB	Database on filaria detection, clinico-immuno monitoring, and management has been developed for Kasturba Hospital and private practitioners to screen the filarial infection
NEMBASE2	Contains the EST sequence for Brugia malayi and other nematodes
Filaria Journal	Full and freely access journal of filariasis
Wormbase	It is an online database for the biology and genome of the C. elegans and related nematodes
WHO	It contains the related publication of filariasis, reports of elimination program, control of neglected tropical diseases, and some important links
PHIS	It contains the news and updated from filariasis elimination program
Disease database	It contains general information regarding diseases
TDR-LF	It contains knowledge about the parasite genomes for African LF and other diseases TDR is now focusing on providing capacity to use the parasite genome data and on supporting developments in applied genomics and bioinformatics
Filarial worms database	This database provides the genome sequence of organisms rapidly and broadly available to the scientific community.

filarial genome nomenclature, filarial gene mapping, and Bm genome survey sequencing (GSS). The Sanger Institute, NEB, and TIGR recently collaborated on genome sequencing of wBm and O. volvulus (Ov).

WormBase: It is a nematode biology open-access resource that includes a genome browser for Bm, C. elegans, H. contortus, and other worms, as well as gene predictions and orthology assignments for a variety of related nematodes.

FilaDB: It is a filariasis screening database with the goal of giving information on the incidence of mf, kinds of acute, chronic, and occult symptoms, as well as age, sex, and distribution region of filariasis cases for clinico-immuno surveillance and treatment of filariasis.

Filarial worm database at broad institute: The phenotypic differences between the closely related filarial species Loa loa, Wb, and Ov were studied using this database. The sequencing data on Wolbachia endosymbionts of Wb, Ov,

and Bm may also be found in the filarial worm database. In India, filarial infections continue to be a significant public health issue. There is a need for a comprehensive database, which should contain:

1. Developed connections between filariasis-related genes and their sequences in GenBank and Swiss-Prot.
2. Homology in sequence between filariasis-causing genes.
3. Pathogen information, including primary and secondary.
4. Drugs and their targets are readily available.
5. Sequences from several filarial species that have been expressed sequence tagged (EST).
6. Literature references to back up your claims.
7. Bioinformatics tools for data analysis: The database should also include epidemiological data on illness incidence, remission, and transition rates of disease sequelae by age and gender.

CURRENTLY USED ANTI-FILARIAL DRUGS

Diethylcarbamazine (DEC)

Diethylcarbamazine (DEC), a piperazine derivative, has long been the most popular and extensively used medication. DEC's anti-filarial activity was initially evaluated on cotton rats and dogs afflicted with *L. carinii* and *D. immitis*, respectively. DEC was discovered to be a promising microfilaricidal agent based on the findings. DEC was first used in a clinical study to treat human filariasis in 1947. Later, DEC was shown to have potent anti-microfilarial action against *W. bancrofti*, *B. malayi*, *O. volvulus*, and *Loa loa* infection in people. DEC works quickly by activating the immunological system of the host. DEC has been shown to have a macrofilaricidal impact in addition to its anti-microfilarial action in certain studies. During their in vitro and in vivo investigations, Peixoto et al. revealed the direct mechanism of action of DEC, seeing apoptosis and organelle destruction in *W. bancrofti*mf. Some studies used nitric oxide to improve the action of DEC against mf, and it was discovered to be a good synergist. However, DEC in combination with albendazole was shown to be successful in eliminating *W. bancrofti*mf, although the combination

treatment caused the patient to develop hydroceles[12].

Ivermectin (IVM)

It was the first commercially available macrocyclic lactone and was launched in 1981 as a broad-spectrum anthelmintic and effective macrofilaricidal medication, also known as Mectizan. It is a 22,23-dihydro semisynthetic derivative of avermectin B1, a fermentation product of the actinomycetes *S. avermitilis* that Merck discovered in the mid-1970s. In both bancroftian and brugian filariasis, IVM alone or in combination with DEC resulted in a long-term reduction of mf[13].

Suramin

Suramin was originally developed to treat trypanosomiasis and onchocerciasis. It is a hexasodium salt of 8,8'-(carbonylbis[imino-3,1-phenylenecarbonylimino(4-methyl-3,1-phenylene)carbonylimino(4-methyl-3,1-phenylene)carbonylimino])bis-1,3,5-naphthalenetrisulfonic acid. It is now the only macrofilaricidal medication that kills *W. bancrofti* and *O. volvulus*[14].

Albendazole

A benzimidazole derivative is used as an anthelmintic. This was recently tested in a clinical study to see whether it was effective as an anti-filarial medication. When used in conjunction with DEC or IVM, it proved to be more effective[15].

Levamisole

At the prescribed dosage, this is an ascaricidal medication with no adverse effects. It has also been discovered to be a microfilaricidal medication against *W. bancrofti* and *B. malayi*mf. Unfortunately, the majority of chemical anti-filarials have negative side effects. As a result, novel therapeutic medication research, particularly less dangerous natural-source medicines, is strongly encouraged. The use of biomedicines to treat illness is one of the oldest types of treatment. These biomedicines, which include plant extracts and secondary metabolites, were thought to exercise their bioefficacy by eliciting a Th1/Th2 response through immunomodulatory elicitation, either via single (Th1, Th2) or combined adjuvant action (Table 3)[16].

Table 3. Anti-filarial drugs available in the market.

Anti-filarial	Brand name	Mechanism of action
Albendazole	Albenz	Tubulin polymerization
Diethylcarbamazine	Hetrazan	Cyclooxygenase pathway
Ivermectin	Mectizan	Glutamate-gated chloride ion channels in invertebrate muscle and nerve cells of the microfilaria
Levamisole	Lepuron	L-subtype nicotinic acetylcholine receptors in nematode muscles

TREATMENT STRATEGY

Ivermectin, ALB, and DEC, which have been the medicines of choice for filariasis control, are being utilized for MDA implementation by national programs. These medicines reduce the number of mf in the body but do not kill adult worms. As a result, these medicines only offer a partial benefit to infected individuals and are often accompanied by side effects. DEC has been linked to adverse effects such as fever, gastrointestinal distress, headache, malaise, and a skin rash, all of which have been linked to decreased patient compliance. The lack of vaccinations, as well as the threat of treatment-resistant worms, needs the development of a low-cost, non-toxic, and new anti-filarial medication with long-term anti-microfilarial or macrofilaricidal action. Several medicinal substances produced from and based on plants have been used in traditional medicine. Ayurveda, Unani, and Siddha systems of medicine in India have a long history of utilizing medicinal plants or their derivatives to treat a variety of diseases. Insecticidal natural compounds of plant origin have recently been tested for the control of a range of insect pests and vectors. Anti-filarial action may be found in several medicinal plants that include pentacyclic triterpene and oleanolic acid. Research on medicinal plants utilized by indigenous healers has also led to the discovery of many anti-filarial medicines. This study focuses on anti-filarial activity in isolated chemicals, medicinal plants, and folkloric plants[17]. The structures of some most promising phytoconstituents with anti-filarial potentials are depicted in Figure 2.

NATURAL RESOURCES WITH PROMISING ANTI-FILARIAL ACTIVITY

A number of ethnobotanical Indian and globally found plants have been reported to demonstrate potential anti-filarial activity in several experimental models [18-25].

Acacia auriculiformis A. Cunn.exBenth. (Family: Fabaceae)

Acaciaside-A and acaciaside-B, triterpenoidsaponins isolated from the funicles of *A. auriculiformis*, are efficient against both microfilaria and adult *S.cervi* worms. Apart from the cestocidal action, these saponins killed 97 percent of *S. cervi* microfilaria and 100 percent of adults in 100 minutes at a dosage of 4 mg/mL. When given orally to pariah dogs naturally infected with *D.immitis* (at 150mg/kg/day for 45 days), an ethanolic extract derived from the plant's funicles was effective against both microfilaria and adult worms. Adult worms are likely to die and be expelled as a consequence of the drug's severe physiological stress. These saponins have been shown to increase lipid peroxidation in cell membranes. It has also been observed that the conjugated unsaturated system of these saponins is implicated in the

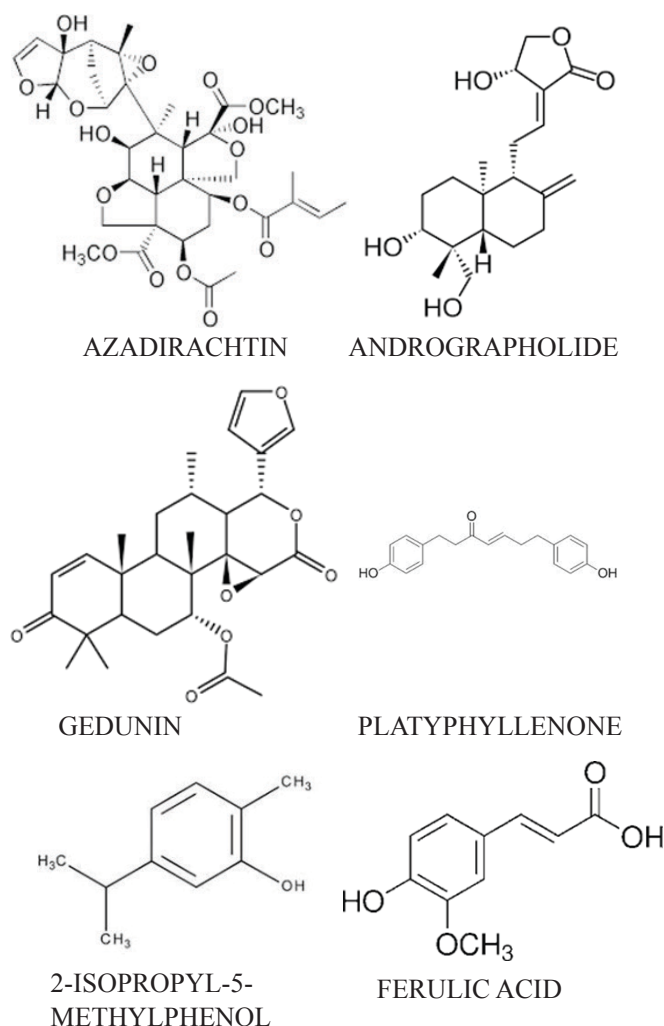


Figure 2: Promising phytoconstituents with anti-filarial potentials.

production of free radicals, which cause membrane damage in helminths via peroxidation.

Aeglemarmelos Corr. (Family: Rutaceae)

It is well-known for its usage in the treatment of filariasis with ethnobotanicals. After 48 hrs, a methanolic extract of leaves at a concentration of 100 ng/mL completely inhibited the motility of *B. malayimf*, suggesting suppression of an important physiological function in larvae. The inhibitory concentration (IC₅₀) of methanolic extract of leaves was discovered to be 70 ng/mL in another research. Polyphenolic and coumarin chemicals have been found in leaves, with dose-dependent increases in lipid peroxidation and protein carbonylation. The rise in several oxidative parameters and the resulting decrease of microfilariae motility were shown to have a high degree of correlation coefficients.

Alnusnepalensis D. Don (Family: Betulaceae)

A. nepalensis is a deciduous or semi-deciduous tree endemic

to Pakistan, southwest China, and mountainous eastern and northeastern India. In vitro on adult worms, a crude extract of this plant's leaves has anti-filarial action. In vivo findings showed that the chloroform fraction had >50 percent macrofilaricidal activity, while the methanolic fraction and n-butanol fraction had 38-40 percent macrofilaricidal activity and a female sterilizing effect against *B. malayi*. Anti-filarial action has also been found for the isolated chemical diarylheptanoid.

Andrographis paniculata Burm. F. (Family: Acanthaceae)

It is an annual plant that originated in India. Anti-filarial activity of a water-based decoction of *A. paniculata* leaves against *D. reconditum* in dogs and adult worms of subperiodic *B. malayi* has been observed.

Asparagus adscendens Roxb. (Family: Liliaceae)

Plant extracts were shown to have potent anti-filarial properties against *S. cervi*. Mfs were killed in vitro by both alcoholic and aqueous extracts. The LC50 and LC90 for aqueous extract were 8 ng/mL and 16 ng/mL, respectively, whereas the LC50 and LC90 for alcoholic extract were 3 ng/mL and 12 ng/mL.

Azadirachta indica A. Juss. (Family: Meliaceae)

It is also said to have anti-filarial properties. The anti-filarial activity of alcohol and aqueous extracts of *A. indica* flowers was tested in vitro against whole worms, nerve muscle preparations, and *S. cervi*mf. On the whole worm, the response was characterized by an initial increase in contraction rate, tone, and amplitude, as well as reversible paralysis. An irritating impact on the cuticle is the main stimulating action. In nerve-muscle preparation, spontaneous movements are inhibited, followed by reversible paralysis. Concentration was a factor in the inhibition. Alcohol and aqueous extracts both showed a similar fatal impact on *S. cervi*mf, with LC50 values of 15 ng/mL and 18 ng/mL, respectively. *S. degitata*, a filarial worm, was similarly killed by flower extract. Adults and mf of *S. cervi* were shown to be resistant to the anti-filarial action of polyphenol-rich ethanolic extract produced from the leaves of *A. indica*. Mf, as well as adult worm viability, was shown to be reduced in a dose-dependent manner. The extract induces morphological changes in the treated adult worms, such as thickening of the epithelium, cuticle, and muscle layers. In both adult and mf of *S. cervi*, major apoptotic signals such as increased chromatin condensation, fragmented chromatin, and stronger fluorescence were detected. Anti-filarial effectiveness is further aided by increased reactive oxygen species (ROS).

Bauhinia racemosa Lam.

(Family: Caesalpinaeaceae)

It is a tiny deciduous tree that's found all throughout the tropics, including India, Ceylon, China, and Timor-Leste. The n-butanol fraction of an ethanolic extract of *B. racemosa* leaves was used to separate phytochemicals from the galactolipid and catechin classes. One of the active galactolipids, (2S)-1,2-di-O-linolenoyl-3-O- α -galactopyranosyl-(1/6)-O--galactopyranosyl glycerol, emerged as the lead molecule that was active against the lymphatic filarial parasite *B. malayi*.

Buteamonosperma L. (Family: Fabaceae)

It is an Ayurvedic herb that has shown promising adulticidal efficacy against intestinal worms in several Ayurvedic formulations in India. Its leaves have considerable anti-filarial action against adult *S. cervi*, with inhibitory concentrations (IC50) of 1.25 mg/mL and 3.6 mg/mL, respectively, in methanol and hexane-ethanol extracts. Aqueous extracts of leaves and roots exhibited considerable efficacy against *B. malayi* in another research. In contrast to leaf extract, root extracts suppress mf motility in a dose-dependent manner. The presence of polyphenolic chemicals in leaves causes an increase in lipid peroxidation and protein carbonylation, which leads to their death.

Caesalpinia bonducella L. (Family: Caesalpiniaceae)

It is a tropical and subtropical perennial climbing shrub native to tropical Asia and spread globally in tropical and subtropical areas such as southern and western Africa and the Indo-Pakistan peninsula. Worm infestations are treated using the juice of the leaves and seed powder. Anti-filarial properties are present in the leaves. Microfilaricidal, macrofilaricidal, and female-sterilizing effectiveness of *C. bonducella* seed kernel extract (2g/kg) against *L. sigmodontis* and *B. malayi* in animal models.

Cardiospermum halicacabum Linn. (Family: Sapindaceae)

Plant ethanolic and aqueous extracts have been shown to have anti-filarial action against *B. pahangi*. Adult worm motility and the pattern of mf discharge from female worms were reduced in a concentration-dependent manner and time-dependent manner.

Cassia alata Linn (Family: Caesalpiniaceae)

The plant extracts were said to have an action against *S. digitata*, a model bovine filarial parasite.

Cedrus deodara Roxb. (Family: Pinaceae)

It grows in abundance at elevations of 1200 m - 3000 m across the western Himalayas. Plant wood extracts were reported to reduce formazan formation by 47.97 percent and

86.56 percent at 1 mg/mL after 1 hr and 4 hrs of exposure, respectively, and to have substantial macrofilaricidal action against *S. digitata*.

***Centrtherumanthelminticum* (Willd.) Kuntz (Family: Asteraceae)**

It is a tall, strong annual plant having anthelmintic effects, particularly for threadworms. The main component responsible for anthelmintic action is found mainly in the plant's fruits. The seed extracts, both aqueous and methanolic, inhibited spontaneous motility in the entire worm and the nerve-muscle preparation of *S. cervi*, resulting in decreased tone, amplitude, and rate of contractions. In vitro, both methanolic and aqueous extracts kill mf, with LC50 and LC90 values of 75 mg/mL and 32.5 mg/mL, respectively. At a dosage of 2 mg/mL, the fruit extracts of *C. anthelminticum* reduced formazan formation by 65.64 percent during a 4 hrs incubation period against *S. digitata*.

***Excoecariaagallocha* L. (Family: Euphorbiaceae)**

It is a mangrove species that may be found all throughout Bhitarkanika, Orissa. The anti-filarial activity of a methanol extract of leaves at a relatively low dosage (10 µg/mL) showed a dose-dependent association with filarial parasite *S. digitata* mortality in the embryonic stages. Mf motility is reduced, and both mf and eggs lose membrane integrity, resulting in death. It has been suggested as a possible drug for inhibiting development in filarial parasites as well as decreasing oxidative stress caused by chronic LF in humans.

***Ficusracemosa* Linn. (Family: Moraceae)**

It is a big deciduous tree that may be found across India. The fruits' alcoholic and aqueous extracts substantially stifle the worm's natural motions. In vitro, both extracts kill microfilariae at LC50 and LC90 of 21 ng/mL and 35 ng/mL for alcoholic extract and 27 ng/mL and 42 ng/mL for aqueous extract, respectively.

***Glycyrrhizaglabra* Linn. (Family: Fabaceae)**

Liquorice roots have a unique triterpenic acid called glycyrrhetic acid in the form of saponin called glycyrrhizic acid as a significant component. In vitro, glycyrrhetic acid is efficient against *B. malayimf* (LC100: 12.5 µM; IC50: 1.20 µM), however, it has little impact on mature worms. Synthetic amide analogs of Glycyrrhetic acid have been shown to have anti-filarial action in vitro and in vivo by removing Wolbachia, a symbiotic bacterium that parasites rely on for life.

***Hibiscus mutabilis* Linn. (Family: Malvaceae)**

Antibacterial and anti-parasitic properties are found in hibiscus extract and isolated components. Methanolic extracts of the leaves and ferulic acid extracted from the

ethyl acetate fraction of *H. mutabilis* both had anti-filarial efficacy against *S. cervimf* and microfilariae. Ferulic acid has an anti-filarial action by inducing apoptosis in the filarial worm *S. cervi* by causing oxidative stress and altering the levels of antioxidants such as glutathione, glutathione-S-transferase (GST), and superoxide dismutase (SOD).

***Hibiscus sabdariffa* Linn. (Family: Malvaceae)**

In vitro testing of crude extract of *H. sabdariffa* leaves against the human filarial parasite *B. malayi* revealed that it had anti-filarial action. Mfs were destroyed completely by the n-butanol fraction at 250 µg/mL. In vivo against *B. malayi*, leaf extract at 500 mg/kg (given for 5 days) showed macrofilaricidal efficacy (approximately 30 percent).

***Lantana camara* Linn. (Family: Verbenaceae)**

In vivo, a crude extract made from the stem of *L. camara* showed significant anti-filarial efficacy against *B. malayi* as well as sterilization of female worms. Adults were killed 43 percent of the time and female worms were sterilized 76 percent of the time when *L. camara* stem extract was given at a dosage of 1 g/kg for 5 days. This action may be caused by two isolated chemicals; oleanonic acid and oleanolic acid. In vitro, extract at a dosage of 0.031 mg/mL was used to kill all *B. malayi* worms.

***Leucasaspera* (Willd.) Linn. (Family: Lamiaceae)**

It may be found all across India, from the Himalayas to Ceylon. Plant extracts were evaluated for anti-parasitic effectiveness against the model bovine filarial parasite *S. digitata*.

***Leucasephalotes* Spreng. (Family: Labiatae)**

It is an upright, scaberulous or pubescent, sturdy annual plant with a height of 30-100 cm that grows like a weed on cultivated fields and waste lands across India, rising to 1,800 m in the Himalayas. Flower and stem extracts in alcohol and aqueous extracts suppress the filarial parasite *S. cervi*'s spontaneous movement. The alcohol extracts of the flower and stem stimulated the worm's movements at first, but then paralyzed it completely. The alcohol extract from the blossom caused reversible paralysis, while the alcohol extract from the stem caused irreversible paralysis.

***Mallotus philippensis* (Lam.) Muell. Arg (Family: Euphorbiaceae)**

It is widely used in traditional medicine to treat intestinal worms, as well as skin irritation, ringworm, and freckles. The anti-filarial activity of aqueous and alcoholic extracts of the leaves against *S. cervi* is likely related to changes in membrane permeability.

Moringaoleifera Lam. (Family: Moringaceae)

The gum extract (125 mg/mL) induces permanent loss of motility in mf and inhibits the MTT reduction potential of adult female *B. malayi* worms by approximately 56 percent. In an in vivo investigation, the extract (500 mg/kg, p. o. for 5 days) caused 69 percent adulticidal and 83 percent female worm sterilization in primary screening, while 44 percent of adult *B. malayi* worms were killed in a secondary model (*Mastomys coucha*).

Neurolaenlobata Linn. (Family: Asteraceae)

In a concentration-dependent manner and time-dependent manner, *N. lobata* extract inhibits filarial motility in mature *B. pahangi* worms. Females do not discharge microfilariae at doses of 10 µg/mL.

Piper betle Linn. (Family: Piperaceae)

It is a widely distributed plant throughout the world's tropical and subtropical areas, as well as India, with many therapeutic qualities. It has been shown to have anti-parasitic properties. The crude methanol extract (100 mg/kg) and its n-hexane fraction (30 mg/kg) both had adulticidal and female sterilizing effectiveness. In mice, the crude methanol extract (100 mg/kg) and its n-hexane fraction substantially increased the number of antibody-producing cells and hemagglutinating antibodies, as well as cell-mediated immune responses (lymphoproliferation, macrophage activation, delayed-type hypersensitivity). The crude extract, as well as its n-hexane and chloroform fractions, caused significant NO release in mouse peritoneal macrophages. The induction of a wide range of T-helper cell immunological responses may be able to counteract the immune suppression induced by *B. malayi* infection. In BALB/c mice, the n-hexane fraction elicited a type-2 cytokine response (increased IL-4 and reduced IFN- α production), while the chloroform fraction elicited a type-1 cytokine response (increased IL-4 and decreased IFN- α production).

Plumbagoindica Linn. (Family: Plumbaginaceae)

It is a perennial plant that may be found all across India. The anti-filarial activity of a methanolic extract of the root of *P. indica/rosea* was tested against adults of the cow filarial worm *S. digitata*. The worms are immobilized 83.3 percent after 6 hours at the lowest doses (0.01 mg/mL) of crude extract. At 0.0006 mg/mL, the isolated chemical 5-hydroxy-2-methyl-1,4-naphthalenedione, also known as 5-hydroxy-2-methyl-1,4-naphthoquinone (plumbagin), immobilized worms in column chromatography using petroleum ether: chloroform solvent. At 0.05 mg/mL, the isolated chemical inhibits formazan production by > 70 percent in the MTT test.

Pongamiapinnata Linn. (Family: Fabaceae)

The entire worm *S. cervi* is inhibited by the aqueous (250 µg/mL) and alcohol (120 µg/mL) extracts of fruits, as well as the alcohol extract of leaves (270 µg/mL). Aqueous extract (25 µg/mL), fruit alcohol extract (5 µg/mL), and leaf alcohol extract (20 µg/mL) all had the same impact on the nerve-muscle preparation.

Psoraleacorylifolia Linn. (Family: Fabaceae)

It is an annual plant that grows to be upright and may be found all across India. On spontaneous movements of the entire worm and the nerve-muscle preparation of *S. cervi*, which is characterized by an initial, brief, modest rise in tone of contractions followed by paralysis, an alcohol extract of leaves and seeds was shown to have anti-filarial effectiveness. Alcohol extracts of leaves and seeds were shown to impede whole worm movement at doses of 160 µg/mL, 30 µg/mL, and nerve-muscle preparation at 150 µg/mL, 20 µg/mL, respectively. In vitro, alcohol extracts of both leaves and seeds killed mf, with LC50 and LC90 values of 15 ng/mL and 25 ng/mL for alcohol extracts of leaves and 12 ng/mL and 18 ng/mL for alcohol extracts of seeds, respectively.

Ricinuscommunis Linn. (Family: Euphorbiaceae)

It is reported to have anti-*S. digitata* activity. At 1 mg/mL, the seed extract inhibits formazan production by 72.39 percent after 4 hrs of exposure in the MTT reduction test and completely suppresses motility after 100 minutes (lowest concentration). As shown by induction of mortality in the embryogenesis of the filarial parasite *B. malayi*, the methanolic extract exhibited anti-filarial efficacy in a dose-dependent manner. The extract also inhibits mf movement in a dose-dependent manner.

Saxifragastracheyion Hook.F. & Thorns. (Family: Saxifragaceae)

Some components found in the root extract of *S. stracheyi* include β -sitosterol, (+) catechin-3-gallate, and bergenin. The roots' aqueous (140 µg/mL) and alcohol (250 µg/mL) extracts block the entire worm *S. cervi*'s spontaneous movements, as shown by a rise in the amplitude and decrease in the rate of contractions, without affecting the tone of the contractions. The concentration of *S. stracheyi* extracts needed to have an equal impact on the nerve-muscle preparation was 30 µg/mL for the aqueous extract and 20 µg/mL for the alcohol extract, indicating a cuticular permeability barrier.

Solanumkhastanum Clarke. (Family: Solanaceae)

Solamargine, a steroidal alkaloid glycoside derived from *S. khastanum* mature berries, has anti-filarial properties. In 60 minutes and 88 minutes, solamargine at 4 mg/mL killed 100 percent of adults and mf of *S. cervi*, respectively.

Sphaeranthus indicus Linn. (Fam: Asteraceae)

Gorakhmundi is the Hindi name for it. Pruritus, edema, arthritis, filariasis, gout, and cervical adenopathy have all been treated by topical application of the herb paste. When exposed to *S. digitata* for 4 hrs, the leaf extract of *S. indicus* inhibited formazan production by 61.20 percent and 83.47 percent, respectively, at 1 mg/mL and 2 mg/mL.

Streblus asper Lour. (Family: Moraceae)

In the nerve-muscle preparation of *S. cervi*, aqueous and alcoholic extracts of *S. asper* induce suppression of spontaneous motility of the entire worm as well as reduced tone, amplitude, and rate of contractions. In vitro, both extracts kill mf, with LC50 and LC90 values of 90 ng/mL and 33.5 ng/mL, respectively. Against *S. digitata*, an aqueous extract of the bark of *S. asper* showed significant anti-filarial efficacy. In rats, an aqueous preparation of *S. asper* stem bark was shown to have significant macrofilaricidal action against *L. carinii* and *B. malayi*. Two cardiac glycosides, asperoside, and strebloside, have been shown to have in vitro and in vivo action against *B. malayi* at a dosage of 50 mg/kg. The stem bark of *S. asper* has been shown to have a filaricidal 'Filacid' that is both effective and harmless. The same's clinical effectiveness has also been documented. In vitro effects of asperoside and strebloside on *S. cervi* females have been observed. Both induce worm death, motility inhibition, and glucose absorption by the parasites. These glycosides also prevent [14] C-glucose from being incorporated into *S. cervi* females' macromolecules, resulting in lower profiles of enzyme activities such as glucokinase, malate dehydrogenase, and succinate dehydrogenase, implying that the lethal effects were due to significant effects on glucose metabolism. The interference of asperoside and strebloside with glutathione metabolism in adult *S. cervi* has also been observed, which causes the parasites' essential functions to be disrupted, ultimately leading to their death. Shakhota Ghana Vati (aqueous extract in tablet form), an Ayurvedic medication, was also shown to be therapeutically beneficial.

Tinosporacrispa (L.) Hook. F. & Thomson (Family: Menispermaceae)

Fever, jaundice, malaria, and worms in children are treated with a *T. crispa* stem infusion, *T. crispa* dried stems had potent anti-filarial action against mature worms of the subperiodic *B. malayi*.

Trachyspermum ammi Linn. (Family: Apiaceae)

The crude extract and a phenolic monoterpene (2-isopropyl-5-methyl phenol with a position isomer 5-isopropyl-2-methyl phenol) extracted from the hexane: ethyl acetate fraction exhibit adulticidal properties, according to an in vitro research employing adult *S. digitata* worms in an MTT reduction test. In vivo testing of the isolated active

component against *B. malayi* in *M. coucha* rodents revealed substantial macrofilaricidal and female sterility.

Vitex negundo Linn. (Family: Verbenaceae)

After 48 hrs of incubation, a root extract of *V. negundo* L. at a concentration of 100 ng/mL exhibited total loss of motility of *B. malayi* in vitro. In an in vitro system, an ethyl acetate extract of *V. negundo* leaves showed promising adulticidal efficacy against the adult filarial worm *S. cervi*. Due to the plant extract's fatal impact at lower doses in a dose-dependent manner, the treated worms were totally immobilized. The decreased amount of mitochondrial enzyme that converts MTT to formazan in the worms treated with the medication proved its impact on the worms' viability by acting at the cellular level, as shown by the MTT reduction test.

Withania somnifera Dunal. (Family: Solanaceae)

In vivolarvicidal activities of Withaferin A, isolated from *W. somnifera*, have been reported against *B. malayi* at a concentration of 7.8 µg/mL. In female worms, a decrease of 63.6 percent mf and 66.2 percent faulty embryogenesis was also observed.

Xylocarpus granatum Koenig (Family: Meliaceae)

Adult worms of the subperiodic *B. malayi* were resistant to the anti-filarial action of dried seeds extract of *X. granatum*. Gedunin and photogedunin, two potential compounds discovered from the fruit of *X. granatum*, showed anti-filarial efficacy in vitro and in vivo against the human lymphatic filarial parasite *B. malayi*. Gedunin (IC50 0.239 µg/mL, CC50 212.5 µg/mL) and photogedunin (IC50 0.213 µg/mL, CC50 262.3 µg/mL) at five daily dosages of 100 mg/kg subcutaneously showed good adulticidal effectiveness, killing 80 percent and 70 percent of adult *B. malayi* transplanted into the peritoneal cavity of jirds, respectively.

Zingiber officinale Rosc. (Family: Zingiberaceae)

Zinger is the common name for this plant. The monoterpenes and sesquiterpenes, borneol, geraniol, limonene, β-elemene, zingiberol, and linalool, are all found in small amounts in the rhizome. Chronic skin disorders, obesity, irregular bleeding after childbirth, and filariasis have all been linked to it. In dogs naturally infected with *D. immitis*, alcoholic preparations of *Z. officinale* rhizomes at 100 mg/kg decreased microfilarial concentration in blood by up to 98 percent.

CONCLUSION

The following literature study shows the significance of natural goods, particularly plant-derived test compounds,

in the treatment of a variety of diseases. Despite India's vast biodiversity and traditional knowledge accessible via Ayurveda, Unani, and Homeopathy, pharmacological use of therapeutic plants remains restricted. While some of the plants have been thoroughly examined, others are still being investigated. Not only has that, but the scientific confirmation of medicinal herbs' traditional usefulness required a comprehensive investigation. Researchers have looked into the medicinal plant's diverse bioactivity, which includes anti-cancer, anti-inflammatory, anti-bacterial, anti-oxidant, health adjuvant, and for treating skin disease, diabetes, arthritis, and epilepsy. However, there has been a limited focus on the medicinal plant used for LF. There is a scarcity of information about essential herbs that may help with filariasis. Our results highlight the need for further research into herbal medicines in order to broaden the anti-filarial treatment spectrum. In the fight against filariasis, this conventional treatment option may actually prove to be more cost-effective and patient-satisfying.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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The author did the literature survey from standard databases, collected all essential elements, and wrote this manuscript.

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