Chapter

Filariasis

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Abstract

Filariasis is one of the most debilitating tropical neglected diseases with high morbidity rate and less rate of mortality with various clinical symptoms. According to the World Health Organization (WHO) reports, about 120 million people from 81 countries are infected at present, and an estimated 1.34 billion people live in areas endemic to filariasis and are at risk of infection. Currently available drugs are only effective against the larval stage of the worms with side effects, and their repetitive use gives rise to drug resistance. Till date, no effective vaccine is available for the treatment of filariasis; to fulfill this need, new drug development becomes the priority for the researchers. This chapter reviews different synthetic and natural origin drugs, drug targets, and use of bioinformatics to discover new antifilarial agents which can control this debilitating disease, including the types of filariasis, their prevalence, and eradication programs which are discussed.

Keywords: filariasis, drug targets, antifilarials, bioinformatics

1. Introduction

A variety of parasitic diseases which are associated with morbidity and mortality have received less attention worldwide. Among these, filariasis is one of the most debilitating neglected tropical diseases. Filariasis is a vector-borne disease transmitted by arthropod vector which is endemic in the tropics and subtropics that results in social stigma. It is a group of human and animal infectious diseases caused by nematode parasites generally called "filariae" that include several hundred species of worms that are slender and elongated and are parasitic in tissues of various vertebrate hosts. This parasite known to cause human infections belongs mainly to the genera *Wuchereria*, *Brugia*, *Onchocerca*, *Dipetalonema*, *Mansonella*, and *Loa*. They reside either in lymphatics or muscles, connective tissues, body cavities, etc. of vertebrate hosts. They may be classified into three main groups based on the habitat of the adult worm, i.e., the cutaneous group, the lymphatic group, and the body cavity group. Based on the habitat of the adult worm, a few of the filarial species infecting man and the disease caused by them with their intermediate hosts are listed in **Table 1**. The infection is transmitted by intermediate hosts which are always blood-sucking arthropods of the order Diptera. Only two genera, *Wuchereria* and *Brugia*, are mainly responsible for human lymphatic filariasis. The common animal parasites are *Setaria digitata* and *S. cervi* (bovine), *Dirofilaria immitis* (dog), *D. uniformis* (rabbit), *Litomosoides carinii* and *Dipetalonema vitae* (gerbils), *Brugia pahangi* (cat), and *Acanthocheilonema viteae* (jird).

According to recent surveys, about 120 million people in 81 countries of the world are infected from this disease, and 1.34 billion people who live in endemic areas are at high risk of this life-threatening infection [1]. To eradicate filariasis

Filarial worm	Habitat	Intermediate host	Disease
Wuchereria bancrofti	Lymphatics	Mosquito sp.	Elephantiasis
Brugia malayi	Lymphatics	Mosquito sp.	Malayan filariasis
B. timori	Lymphatics	Mosquito sp.	Timor fever
Loa loa	Connective tissue	*Chrysopsis* sp. (*C. dimidiata*)—Horse flies	Loaiasis
Mansonella ozzardi	Serous membranes	*Culicoides* sp. (*C. furens*)—biting midges	Ozzard's filaria
Onchocerca volvulus	Skin	*Simulium* sp. (*S. damnosum*)—black flies	Onchocerciasis

Table 1.
List of filarial worms with their habitats and intermediate host infecting humans.

globally, research plans are needed to design effective drugs and drug targets, new vector control strategies, and diagnostic techniques. At the same time, the treatment of filariasis also requires disease-specific clinical care and patient education with counseling to eradicate this disease. Moreover, statistical analysis along with bioinformatics tools of the mass drug administration (MDA) surveillance reports should be carried out which could provide new opportunities to get an insight into the proteins or genome which may contribute to its inhibition process.

In current surveillance report, five World Health Organization (WHO) regions are endemic with lymphatic filariasis (LF). Worldwide, 1.39 billion people require preventive chemotherapy. In Southeast Asia region, 877 million people of 9 countries and 432 million people of 39 countries in the Africa region are brutally affected from this disease and require proper treatment. From the Western Pacific Region which includes the Mekong Plus region and the Pacific region, nearly 40 million people are at a risk of lymphatic filariasis. Cambodia, China, Cook Islands, Niue, the Marshall Islands, Palau, the Republic of Korea, Tonga, Vanuatu, Viet Nam, and Wallis and Futuna are the countries of this region that successfully eradicated this disease, whereas American Samoa, Brunei Darussalam, Fiji, French Polynesia, Kiribati, Lao People's Democratic Republic, Malaysia, Federated States of Micronesia, New Caledonia, Papua New Guinea, Philippines, Samoa and Tuvalu are the 13 countries where lymphatic filariasis remains endemic [1, 2].

2. History of filariasis

In India first, ancient documented evidence of filariasis was reported in *Sushruta Samhita* (approximately 600 BC) by the famous physician Sushruta. According to some records, the first reliable documentation of filariasis was reported in the late fifteenth and early sixteenth centuries. In 1849 William Prout explained the pathological condition of chyluria in which the passage of lymph occurs in urine, a condition associated with lymphatic filariasis. The French surgeon Jean Nicolas in 1863 was the first person who observed the microfilariae in the hydrocele fluid. For the first time, in 1872 Timothy Lewis observed the microfilariae in the human blood in India. In 1876, Joseph Bancroft recovered female filarial worms and named them *Filaria bancrofti*, which later merged in the genus *Wuchereria*. In 1877, Sir Patrick Manson discovered the main cause of transmission of filariasis, by studying the parasitic development of microfilariae in the mosquito stomach that was fed on

the blood of an infected gardener and thus reported that filariasis is transmitted by the mosquito. In 1960 and 1977, two other filarial worm species were identified and named as *Brugia malayi* and *B. timori*, respectively.

3. Filariasis: an overview

Among all the filariasis, lymphatic filariasis is the most debilitating which causes disability in humans. *Wuchereria bancrofti* and *Brugia malayi* or *B. timori* are the main cause of lymphatic filariasis, each of which is transmitted by the bite of a specific insect vector. The various vectors that cause LF belong to the genera *Anopheles*, *Culex*, *Aedes*, and *Mansonia*. According to the WHO, increase in the microfilarial density in the infected individuals and the feeding rate of vector population are the causes of high transmission rates of filariasis in a particular area. *Onchocerca volvulus* and *Loa loa* are the two other filarial worms that reside in the cutaneous and subcutaneous tissues of the host and cause onchocerciasis and loaiasis, respectively. *Wuchereria bancrofti* and *O. volvulus* are the two filarial worms which do not require an animal host as reservoir.

Data collected from the survey depicted the picture of depressive illness of an individual caused by LF and estimated 5.09 million disability-adjusted life years (DALYs) [3–5]. In infants microfilaremia starts at the age of 5 after acquiring infection, but the actual signs of filariasis (including hydroceles) appear during puberty. Previous survey reports indicated that once the individual acquired infection chances of cure becomes very low [6].

Filarial worms inhabiting the lymphatic system live up to 8 years and release millions of microfilariae into the bloodstream. The WHO started the Global Alliance to Eliminate Lymphatic Filariasis (GPELF) in 2000 with the goal of eradicating this disease by 2020 through the use of MDA [7]. In the history of public health, GPELF is the most successfully expanding global health program. Fifty-three out of the 81 endemic countries have started mass drug administration to halt the transmission of filariasis. Two strategies have been developed to achieve the target of eliminating filariasis. According to the first strategy, single annual doses of diethylcarbamazine or ivermectin plus albendazole will be provided to the entire endemic area to prevent the disease. The second strategy is to reduce disability rate by providing knowledge about how to maintain hygiene and skin care, to those with lymphedema and performing surgery in patients with hydrocele. The investment for chemotherapy to control this disease is approximately US$ 105–208 million per year during 2015–2020. The WHO determined two objectives, which include "70% of endemic countries demanding MDA will have to enter post-intervention surveillance by 2016" and "all other endemic countries have to complete the post-intervention surveillance by 2020" [8, 9]. The abovementioned antifilarial drugs are only effective against the microfilariae and have no effect on the adult worms which therefore provide a partial treatment to the infected individuals. Repetitive use of these drugs resulted in drug resistance. Till date no vaccines are developed, and treatment depends only on the antifilarial. Researchers are developing various new antifilarials and combination therapies to overcome this disease [10].

4. General life cycle of filarial worm

Man is the definitive host of filarial worm, in whose lymphatic system, the adult worms reside. Adult females discharge the live embryo called microfilariae (290 μ). Microfilariae flow in the peripheral blood and can survive for a considerable time

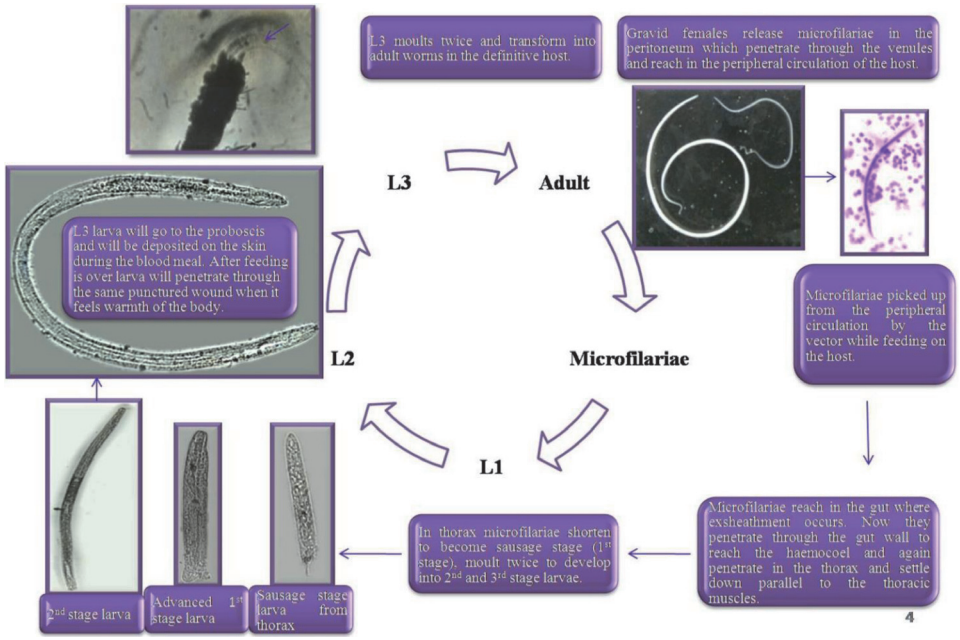

Figure 1.
Life cycle of filarial worm Setaria cervi *given by Prof. Wajihullah and Dr. Sharba Kausar.*

without undergoing metamorphosis until they are taken up by the intermediate host, i.e., the culicine mosquitoes during their blood meal. After reaching in the mosquitoes, microfilariae undergo development and become infective-stage larvae as described in **Figure 1**.

5. Diagnosis of lymphatic filariasis

LF is primarily diagnosed using the immunochromatographic card test kit via antigen detection methods (which also detects latent infections). The traditional diagnosis of LF is performed by microscopy to detect circulating microfilariae. Molecular xenomonitoring of parasites in mosquitoes, serological testing, ultrasonography, PCR tests, lymphoscintigraphy, detection of exposure to transmission in children via antibody detection, and the recently introduced filariasis test strip (FTS) are some of the other diagnostic approaches that are currently used.

6. Biological point for designing new drug

A clear knowledge of parasite physiology is very important to identify drug targets for understanding the mode of action of antifilarial drug. Sometimes compounds are also tested, without prior knowledge of the target. Compounds which are effective against the whole parasite are defined as hits, while compounds that are found to be active in vivo are considered as leads. Lead compounds require standardization for increasing their efficacy. Once a compound is optimized, it can be tested clinically in patients and defined as a "drug candidate." Based on the physiological processes and symptoms, a drug should be formulated and designed to combat the disease. To overcome filariasis a number of drug targets should be covered for developing new antifilarial, viz., macrofilaricidal and microfilaricidal

drugs, drugs preventing exsheathment in microfilariae and drugs that can cause hindrance in the movement of microfilariae. Different biochemical pathways are summarized in **Table 2** which are used in designing new drugs. On the other hand,

***Wolbachia* bacteria**		
Wolbachia are proteobacteria 61 potential drug targets (outer membrane proteins, ribosomal proteins, DNA polymerases, mutases, ligases, isomerases, cell division proteins, transferases, synthetases, reductases, etc.) and four potential vaccine extracellular targets such as putative peptidoglycan lipid II flippase, deoxycytidine triphosphate deaminase, GTP cyclohydrolase II, and RNA pyrophosphohydrolase	Contribute to the nucleotide pool of nematodes	Tetracycline was resulted in the depletion of these *Wolbachia* resulting in the upregulation of phosphate permease gene, required for nucleotide synthesis Another study with doxycycline showed that *Wolbachia* depletion was associated with a reduction in the levels of vascular endothelial growth factors (VEGFs) that are essential for lymphangiogenesis (18)
Wolbachia cell division protein FtsZ a GTPase	Bacteria-specific filamenting temperature-sensitive protein (important in bacterial cytokinesis) that was expressed in all developmental stages of *B. malayi*	*E. coli* FtsZ inhibitor berberine, a natural alkaloid, was examined by researchers against GTPase activity of FtsZ in *B. malayi*, and it was observed that at 10–40 mM concentration, berberine had adversely affected production of microfilariae as well as motility of adult females of *B. malayi*
N-Myristoyltransferase		
Myristoyltransferase (NMT)	The addition of myristic acid, a 14-carbon unsaturated fatty acid, to the N-terminus of glycine in a subset of proteins via myristoyl-CoA:protein N-myristoyltransferase (NMT) promotes their binding to cell membrane	A known NMT enzyme inhibitor in tripanosomatids, DDD85646, and its analog DDD100870, were tested against *B. malayi* NMT proteins and provided IC50 values of 10 nM and 2.5 nM, respectively
Proteins and amino acids		
	Free amino acids are required for intracellular osmoregulation and protein synthesis	
S-adenosylmethionine methyltransferase, methionine adenosyltransferase, and S-adenosylhomocysteine hydrolase	Are required for the conversion of methionine to homocysteine in the methionine	
Enzyme prolyl-4-hydroxylase has been reported to	Play a vital role in the biosynthesis of this collagen	
Transaminoglutamase	Play a significant role in the growth, development, and maturation of the nematode	A pseudosubstrate, monodansylcadaverine (MDC), and active site inhibitors cystamine or iodoacetamide were found to inhibit L3-stage parasite mobility in a dose-dependent manner that was associated with irreversible biochemical lesions, resulting in the death of the parasite

Proteins and amino acids		
Retinoic acid-binding proteins (RABPs)	Parasitic nematodes require lipophilic retinol for various biological processes, such as embryogenesis, differentiation, and growth For inter- as well as intracellular movement	Ivermectin(II) was found to compete efficiently with retinol for the retinol-binding sites on RBP of the parasite but not for the host RBP sites
Biogenic amines and polyamines		
Norepinephrine (NE), histamine, 5-hydroxytryptamine (5-HT), and dopamine	Biogenic amines play a role in neuromuscular activity and behavioral coordination in nematodes	
Monoamine oxidase (i.e., MAO), acetylcholinesterase, and dopamine-b-hydroxylase		DEC, levamisole, and centperazine were found to inactivate these enzymes
Dopamine-b-hydroxylase		
Octopamine		
Putrescine, spermine, and spermidine	Are required for growth, differentiation, and macromolecular synthesis in all living organisms as constituents of the polyamine salvage pathway	
S-adenosylmethionine decarboxylase (SAMDC)	Which is required for polyamine biosynthesis	Berenil and aromatic methylglyoxal bis (guanylhydrazone) analogs are inhibitors of an important regulatory enzyme
Carbohydrate metabolism		
Fructose 1,6-diphosphate aldolase	Its immunogenic component in filarial worms is distinguishable from that of mammals, thus identifying it as possible vaccine target238	
Phosphoenolpyruvate carboxykinase	Inhibited by DEC	
Fumarate reductase	Inhibited by DEC and benzimidazoles	
Succinate dehydrogenase	Inhibited by DEC	
Phosphofructokinase	Blocked by antimonial stibophen in *B. pahangi* and *L. carinii* when compared to isofunctional mammalian enzyme	
Glucose uptake	Altered by DEC, amoscanate, and arsenicals	
Utilization of glucose	Decreased by levamisole	
Lipid metabolism		
Quinones	Play a role in filarial electron transport	
Geranyl geraniol	Unknown role	The biosynthesis of genanyl geraniol and dolichols was inhibited by mevinolin

Lipid metabolism		
Juvenile hormones	Regulators of larval development	
Dolichols	Required for glycoprotein synthesis	
Isopentyl pyrophosphate	IPP constituent of filarial tRNA	
HMG-CoA reductase is a rate limiting enzyme	Involved in the isoprenoid pathway of filaria	Inhibited by mevinolin
Folate metabolism		
Enzymes, such as reductases, transferases, synthases, dehydrogenases, hydrolases, mutases, ligases, and deaminases	Are involved in the interconversation of folate analogs observed in the synthesis of different tetrahydrofolate cofactors by macrofilariae. Specifically, dihydrofolate reductase activity, which is commonly observed in macrofilariae, was found to be absent in the microfilariae of *B. pahangi*	DEC and suramin were found to inhibit some enzymes involved in folate metabolism
10-Formyl FH4 dehydrogenase enzyme	Which was found to play a vital role in the regulation of the endogenous FH4 cofactor concentrations, was more active in *B. pahangi* than in mammals	
Glutathione		
Glutamate-cysteine ligase (rate-g-glutamyl transpeptidase)	Glutathione has been proposed to constitute the antioxidant system (g-glutamyl cycle) that extends the survival of filarial parasites in mammalian hosts, thereby protecting them from host-mediated membrane lipid peroxidation	Arsenicals depletes filarial glutathione (262–264) Phytocompounds such as plumbagin, curcumin, and a phenoxyacetic acid derivative were found to inhibit filarial GST In a report of a homology modeling approach via in silico analysis of the filarial GST of *B. malayi*, albendazole, and a methyl-substituted chalcone showed non-competitive type of inhibition of GST activity
Glutathione-transferases (GSTs)	The major detoxifying systems in filarial parasites and can detoxify cytotoxic products of lipid peroxidation via the conjugation of glutathione (GSH) to various endogenous xenobiotic electrophiles	

Table 2.
Antifilarial targets for designing drugs.

vaccine development and mosquito repellent practices such as the use of insecticide nets, body lotions, insecticides spray, coils, etc. along with good knowledge of sanitization can prevent vector development which together helps in combating filarial worm infection in a community. The pathology associated with lymphatic filariasis like elephantiasis, hydrocoele, and lymphedema is due to the hyporesponsiveness of D4+ T cells of the host immune system [11–13]. Therefore, immunological studies are also playing an important role in the field of drug development. Drugs are also designed to combat symptoms associated with filariasis, viz., drugs used for the treatment of lymphatic filariasis (drugs effective against adenolymphadenitis, funiculitis, epididymo-orchitis, lymphedema, hydrocele, chyluria,

chylocele, lymph scrotum) and drugs used in the treatment of other manifestations like asymptomatic microfilaremia, occult filariasis, onchocerciasis, and loaiasis.

7. Currently used antifilarial drugs

7.1 Diethylcarbamazine (DEC)

Diethylcarbamazine (DEC), a piperazine derivative, is the most common and widely used drug over many decades. The antifilarial activity of DEC was first tested against *Litomosoides carinii*- and *Dirofilaria immitis*-infected cotton rats and dogs, respectively [8]. The observations revealed DEC as a potential microfilaricidal agent. Clinical trial of DEC was started in 1947 against human filariasis. Later, strong antimicrofilarial activity of DEC was also observed against *W. bancrofti*, *B. malayi*, *O. volvulus*, and *Loa loa* infection in humans [14–17]. DEC acts rapidly by stimulating the host immune system. In some reports macrofilaricidal effect of DEC was also recorded along with its antimicrofilarial activity [18–21]. Peixoto et al. [22] described the direct mechanism of action of this drug during their in vitro and in vivo studies; they observed apoptosis and organelle damage of *W. bancrofti* microfilariae by DEC [22]. To enhance the effect of DEC against microfilariae, nitric oxide was induced by some researchers and was found to be a good synergist [23]. However, DEC combined with albendazole [24] revealed an effective killing of *W. bancrofti* microfilariae, but the combination therapy increased the development of hydroceles in the treated patient [25].

7.2 Ivermectin (IVM)

It is a broad-spectrum anthelmintic and an effective macrofilaricidal drug introduced in 1981 also known as Mectizan [2], which was the first commercially available macrocyclic lactone. Chemically, it is a 22,23-dihydro semisynthetic derivative of avermectin B1, which is a fermentation product of actinomycetes *S. avermitilis* discovered by Merck in the mid-1970s [11–32]. IVM alone or in combination with DEC [8] resulted in long-term suppression of microfilariae in both bancroftian and brugian filariasis [20, 33, 34].

7.3 Suramin

Suramin [35] initially was a drug used to cure trypanosomiasis and onchocerciasis. Chemically it is an 8,80-(carbonylbis[imino-3,1-phenylenecarbonylimino(4-methyl-3,1-phenylene)carbonylimino])bis-1,3,5-naphthalenetrisulfonic acid hexasodium salt. Presently it is the only macrofilaricidal drug that is effective against *W. bancrofti* and *O. volvulus*.

7.4 Albendazole

This anthelmintic drug is [24] a benzimidazole derivative. Recently this has been used in a clinical trial to check out its efficacy as antifilarial drug [36]. Its efficacy was increased when administered in combination with either DEC [8] or IVM [2].

Antifilarial agent	Recommended dose	Route of administration	Mechanism of action	Filarial worm	Side effects
Diethyl carbamazine (piperazine derivative)	6 mg/kg for 12 days (individual treatment) 6 mg/kg in 24 hours (weekly/monthly/single annual dose in mass treatment) for treating *W. bancrofti* infection	Oral	Alterations in arachidonic acid metabolism of host endothelial cells and microfilariae, resulting in blood vessel constriction and host granulocyte and platelet aggregation; apoptosis and org nelle damage	*W. bancrofti* infection	Encephalitis and retinal hemorrhage. Increasing dose include systemic reaction: nausea, GIT upset, malaise, body aches, and anorexia. Localized reactions: abscess formation, lymphadenitis, and transient lymphedema
	3–6 mg/kg for 6–12 days (individual treatment) 3–6 mg/kg in 24 hours (6 times at weekly or monthly in mass treatment) for treating *B. malayi* and *B. timori* infections			*B. malayi* and *B. timori* infections	
	8 mg/kg for 14 days For the treatment of occult filariasis			Occult filariasis	
Table salt + Diethylcarbamazine	0.1% for 6 months treatment of LF			*W. bancrofti* (lymphatic filariasis)	
	0.3% for 3–4 months *B. malayi* is endemic			*B. malayi*	
Ivermectin (macrocyclic lactone)	400 mg/kg single dose treatment 4800 mg/kg for 6 months treatment *of B. malayi* and single dose remove microfilariae *W. bancrofti*	Oral	Targets glutamate gated Cl- and K+ ion channels in nematodes, results in hyperpolarization that causes paralysis of the body wall muscle and pharynx. The drug also affects ligand-gated chloride ion channels gated by GABA. It competes with retinol for the retinol-binding site on retinol-binding proteins (RBPs) in the parasite only	Bancroftian and brugian filariasis	Same as DEC, and special care must be considered, such as avoiding its use in cases of pregnancy and in children younger than 5 years old
Suramin	66.7 mg/kg in 6 incremental weekly doses (3.3, 6.7, 10.0, 13.3, 16.7, 16.7 mg/kg for the first and sixth weeks, respectively)	Intravenous (10% solution in water)	It adversely affects enzymes associated with glucose catabolism and destabilizes DNA and protein kinase enzymes in filarial worms	*W. bancrofti*, *O. volvulus*	Fatal collapse, albuminuria, ulceration, and persistent high fever; polyuria, tiredness, tenderness, anorexia, and increased thirst; among others are some of the milder side effects

Antifilarial agent	Recommended dose	Route of administration	Mechanism of action	Filarial worm	Side effects
Levimazol	An initial dose of 100 mg followed by the same dose twice daily for 10 days was found to be as effective as the total oral dosage of DEC at 126 mg per kg body weight	Oral	Acts as nicotinic receptor agonist that causes prolonged activation of the excitatory nicotinic acetylcholine (nACh) receptors on the body wall muscle of parasites, leading to spastic muscle paralysis in the worm	*W. bancrofti*, *B. malayi*	No side effects at recommended doses
Albendazole (benzimidazole) Albendazole+ DEC	Albendazole (400 mg) + diethylcarbamazine (DEC) (6 mg/kg)	Oral	Block tubulin polymerization, thereby inhibiting microtubule formation. It also inhibits parasite intestinal cells, preventing glucose uptake leading to the death of the parasite	Macrofilaricidal	Embryotoxicity and teratogenicity
Albendazole+ ivermectin	Albendazole (400 mg) + ivermectin (150–200 mg/kg)				

Table 3.
Summary of the recommended doses of currently used antifilarials.

Antifilarial agent	Action	Parasite	Dose	Reference
Trisubstituted pyrimidine derivatives (the amino group and 4-aminophenyl group at the second position plays an important role in exerting antifilarial activity)	ATP-dependent DNA topoisomerase II inhibitory activity	*S. cervi*	10–40 mg/ml	[38, 39]
2-Sulfanyl-6-methyl-1,4-dihydropyrimidines		*B. malayi* (in vitro) *B. malayi–Mastomys coucha*	25 and 50 μM 100 mg/kg	
Indole derivatives B-carboline		*L. carinii–S. hispidus* (cotton rats) *A. viteae–M. natalensis*	30 mg/kg for 5 days 50 mg/kg for 5 days	[40–43]
b-Carbolines (substituted 9Hpyrido[3,4-b] indoles)		*L. carinii, A. viteae* and *B. malayi* in a *M. coucha* model	50 mg/kg for 5 days	
Quinoline and related compounds 7-chloro-4-(substituted amino)quinolines		*A. viteae*		[44–47]
3-Nitro-4-quinolones via ipso-nitration	Thymidylate kinase inhibitory activity	*Brugia malayi*	IC50 2.9 mM	
Quinolones compound 7-chloro-4-(substituted amino)quinolines	Evaluation against DNA topoisomerase II enzyme, compound	Screened in vivo against *A. viteae*	200 mg/kg for 5 days	
3-Nitro-4-quinolones	*Brugia malayi* thymidylate kinase inhibitory activity	*B. malayi*	IC50 2.9 mM	
Glycoside cinnamoyl glycosides		*S. cervi*	MIC (3.40 nM), IC50 (6.90 nM) and LC50 (25 nM) values, CC50 value of approximately 103 nM	[48]
Cinnamoyl glycosides	Chromatin condensation and DNA fragmentation; this compound also damaged the cuticular sheath of the microfilariae	*W. bancrofti*	MIC and IC50 values were 4.4 nM/ml and 8.96 nM/ml, respectively	
Dioxocine 3,6-epoxy dioxocines		*B. malayi–M. coucha*	IC50 values (0.4 mg/ml and 1.8 mg/ml, with selectivity indices (SI) of 100 and 22.2 with respect to macrofilariae and microfilariae, respectively	[49]

Antifilarial agent	Action	Parasite	Dose	Reference
Compound		*B. malayi* in jirid	Found to be potent in terms of both in vitro (IC50 1.6 mg/ml and 3.5 mg/ml for macrofilariae and microfilariae, respectively) and in vivo antifilarial activity, 200 mg/kg	
Alcohols cyclohexanol, 2- substituted propanol Cyclooctanol derivatives		*A. viteae* and *L. carinii* in rodents *A. viteae* in rodent	100% macrofilaricidal activity (at a dose of 200 mg/kg for 5 days) 81% sterilization of female worms (at a dose of 100 mg/kg for 5 days) against	[50]
Triazine	DHFR (dihydrofolate reductase) inhibitors, good inhibitory activity (approximately 74%) against PARP (polyadenosine diphosphate ribose polymerase)enzyme	*B. malayi*	Almost 100% loss of motility of filarial worms at 20 mg/ml showed better activity (IC_{50} 10.90 mM) when compared with standard antifolate (positive control) compounds, i.e., trimethoprim (IC_{50} 12.92 mM) and pyrimethamine (IC_{50} 20.10 mM	[51, 52]
Benzopyran (coumarin)		*B. malayi–M. coucha* *B. malayi*–jirid model	When administered orally at a dose of 300 mg/kg for 5 days showed 53.6% macrofilaricidal and 46% microfilaricidal activity At a dose of 100 mg/ kg for 5 days, showed 75% adulticidal and 50% microfilaricidal activity	[53–55]
Naphthalene derivative 1,4-naphthoquinones	1,3-Dimethyl substitution on the butylamino side chain favors an increased lipophilicity with potentially improved binding to the active site, which results in elevated macrofilaricidal activity (133)	*Setaria digitata*	ED50 value of 2.6 mM after a 24 h incubation and 0.91 mM after a 48 h incubation	[56]
Thiazolidine heterocyclic thiazolidine compounds compound (31) and compound (32)		*B. malayi*	IC50 values of 5.2 mM and 1.78 mM LD50 values of 349 mM and 17.59 mM, respectively	[14]

Antifilarial agent	Action	Parasite	Dose	Reference
Butylated hydroxy anisole (BHA)	Oxidative stress-induced apoptosis was found to be its major killing mechanism (135)	*S. cervi*	At 100 mM was found to be a potent adulticide	[15]
Piperazine benzoyl piperazine derivatives (two compounds, viz., compound (34) and compound (35) containing a 4-chloro (para) substituent and 3-methyl (meta) substituent on the aromatic ring)		*S. cervi*	Worms were immotile following treatment with these two compounds at a concentration of 8 mg ml ^{1}	[16, 17, 57]
Pyrrolidine chalcone derivative (36) containing the pyrrolidine-methoxy group	Showed a significant suppression of glutathione-S-transferase (GST) activity in the macrofilariae of female *S. cervi* at a concentration of 3 mM in vitro	*S. cervi*	100% inhibition	
Diaminoalkane N1,Nn-xylofuranosylated diaminoalkanes		*B. malayi–M. coucha* *B. malayi*–jirid	At 50 mg kg 1 provided approximately 38.7% recovery of macrofilariae and 63.80% sterilization of female parasites The same compound also showed 33.5% adulticidal action along with 50% sterilization of female worms	[58]
Secondary amines		*A. viteae*	At a dose of 200 mg/kg for 5 days exhibited 100% macrofilaricidal activity, whereas compound elicited a microfilaricidal response of approximately 93%	[59]
Glycyrrhetinic acid derivatives and the benzylamide analog		*B. malayi*	Killing microfilariae and macrofilariae at 50 and 25 mM, respectively The IC50 values were found to be 2.2 mM against microfilariae and 8.8 mM against macrofilariae of the worm	[60]
		B. malayi–jirid	At a dose of 100 mg/kg for 5 days exhibited 40% adulticidal activity	

Antifilarial agent	Action	Parasite	Dose	Reference
Nitazoxanide and tizoxanide	The researchers further reported that both compounds reduced microfilarial production and impaired embryogenesis in female worms. They also suggested that mitochondria in the worms may be a possible target of NTZ (41) and TZ (42) because in addition to damaged worm tissues, they found alterations in the mitochondria	*B. malayi*	Macrofilariae were found completely immotile after 6 days when cultured with these two compounds at concentrations of 20 mg/ml On day 8 of culture at concentrations of 2.5 mg/ml, both drugs also caused a 50% decrease in worm viability Microfilarial motility was also hampered by these compounds at concentrations exceeding 5 mg/ml, and the worms were completely immotile following treatment with 20 mg/ml (after 48 h)	[61]
Nitazoxanide Nitazoxanide + silver nanoparticles	Inhibit TCA cycle enzymes	*S. cervi*	100% mortality of microfilariae at 100 μg/ml 100% mortality of microfilariae at 30 μg/ml	[62, 63]
Anthraquinone 3-methylcatechol with a substitution of acylium ions	Marked effects on intrauterine embryos of parasite	*B. malayi* infection in humans	At 5 ppm (18–19 mM) showed 100% mortality within 1, 5, and 3 days against microfilariae and adult male and female worms	[64]
Sulfonamide sulfonamide chalcones		*B. malayi*	IC50 value was found to be 4.4 mM, LD50 value of 188 mMt 500 mM concentration after 48 h of incubation	[65]
Benzothiazole novel chalcone–benzothiazole hybrids	It showed higher binding interactions at the active site of BmTMK (*B. malayi* thymidylate kinase, an essential enzyme for nucleotide metabolism in B. *malayi*).	*B. malayi*	IC50 values of 2.12 mM and 1.63 mM, respectively, for adult worms as well as microfilariae MIC value of 5 mM for both the forms IC_{50} value was 95.3 mM	[66]
Thiazole chalcone–thiazole derivatives		*B. malayi–jirid* *B. malayi–M. coucha*	At a dose of 100 mg/kg for 5 days showed 100% embryostatic activity Exerted approximately 49% macrofilaricidal activity and	[67]

Antifilarial agent	Action	Parasite	Dose	Reference
Benzimidazole derivatives HOE 33258 mebendazole, Flubendazole 2,2′-Dicarbomethoxyamino-5,5′-dibenzimidazolyl ketone	At 5 × 2.5 mg/kg and 1 × 25 mg/kg in jirds and 1 × 100 mg/kg in cats when administered by subcutaneous injection A dose of 3 mg/kg (i.p.) and 50 mg/kg (oral) × 5 days of Comp. 82/437 At a dose of 150 and 200 mg/kg for 5 days	*L. carinii* and *D. immitis* Evaluated in jirds (*Meriones unguiculatus*) and cats (*Felis catus*) infected with *Brugia pahangi* *L. carinii* in cotton rats *Dipetalonema viteae* and *Brugia malayi* in *Mastomys natalensis*	Macrofilaricidal. It also killed developing larvae in jirds. It was not microfilaricidal Eliminated almost 100% of adult worms and microfilariae It killed 100% of the macrofilariae and 97% of the microfilariae	[68–79]
Silver	Nanosilver	*B. malayi*	LD_{50} concentration (by trypan blue exclusion) of 101.2 mM and an IC_{50} value of 50.6 mM (complete microfilariae population found immotile). At 4.6 mM only, nanosilver caused a 50% decrease in the motility of the parasite	[80]

Table 4.
List of synthetic and naturally originated antifilarials.

Plant	Extract	Target	Antifilarial efficiency	Author
Streptomyces sp. 17,944	Three new tirandamycins	*B. malayi*	Inhibit the asparaginyl-tRNA-synthetase (BmAsnRS) enzyme at an IC50 value of 30 mM	[81]
Streptomyces sp. 9078	Depsipeptide	*B. malayi*	IC50 value of 50 mM	[82]
Streptomyces sp. 4875	Four adipostatins (alkyl resorcinols) potent among the compounds	*B. malayi*	Kill the worms at 1 mM concentrations	[83]
Lantana camara	Crude extract	*A. viteae*	LC_{100} 62.5 μg/ml	[84]
		B. malayi	LC_{100} 500 mg/ml	
	Chloroform, n-butanol and aqueous	*B. malayi*	LC_{100} 250 μg/ml	
	Fractions of n-hexane oleanonic acid	*B. malayi*	LC_{100} 31.25 μg/ml	
	Oleanonic acid		LC100 62.5 μg/ml	
	Crude extract 1 g/kg × 5 days	*A. viteae/M. coucha* model	95.05% reduction in Mf 23.65% effective against adult	
		B. malayi transplanted/ M. unguiculatus	80% effective against adult	
Taxodium distichum	A001 (crude ethanolic extract of aerial part) F001 (hexane fraction) K003(labda-8(20),13-diene-15-oic acid) and K004 (metasequoic acid A) SF1 (fraction) SF_4 (fraction)	*B. malayi*	mf (LC100 3.91 μg/ml) than adult worms (LC_{100} 15.63 μg/ml) IC_{50} values for the respective parasite stages were found to be 1.95 and 10.00 μg/ml mf (LC100 7.83 μg/ml) adult worms (LC100 31.25 μg/ml) mf (LC_{100} 31.25 μg/ml) and adult worms (LC_{100} 125 μg/ml) mf (LC_{100} 7.83 μg/ml) than adult (LC_{100} 31.25 μg/ml) mf (LC_{100} 62.5 μg/ml) adult (LC_{100} 125 μg/ml)	[85]
	A001 (500 mg/kg × 5 days; orally) K003 (100 mg/kg × 5 days) exerted At 100 mg/kg dose, both K003 and K004 K003 (100 mg/kg × 5 days)	*B. malayi/M. unguiculatus* *B. malayi/M. coucha model*	100% effective against Adult >95%; remarkable embryostatic activity Produced >25% macrofilaricidal activity Exerted 53.94% macrofilaricidal	

Plant	Extract	Target	Antifilarial efficiency	Author
Azadirachta indica	Alcoholic extract of flowers Aqueous extract of flowers	*S. cervi*	Mf(LC50 of 15 ng/ml) (LC90 ¼ 23 ng/ ml), mf(LC50 of 18 ng/ml) (LC90 ¼ 25 ng/ ml)	[86–88]
	Methanolic extract of leaves Ethanolic extract of leaves	*S. cervi*	Mf 100% mortality at 200 μg/ml in 135 min Mf 90% mortality at 200 μg/ml in 135 min	
	Ethanolic extract of *A. indica* leaves	*S. cervi*	Showed significant worm reduction at 25 lg/ml and highest mortality at 100 lg/ml after 24 h of incubation when applied against the microfilariae	
Eucalyptus tereticornis	Ursolic acid obtained from the leaves	*B. malayi*	LC100 50 mM and IC50 8.84 mM against microfilariae, and LC100 100 mM and IC50 35.36 mM against adult worms	[89]
Senecio nudicaulis	Aqueous leaf extract Alcoholic leaf extract	*Setaria cervi*	Both the extracts exhibited macrofilaricidal activity LC50 10 ng/ml and LC90 15 ng/ml LC50 5 ng/ml and LC90 12 ng/ml	[90]
Hibiscus sabdariffa	n-Butanol insoluble fraction of leaf extract	*B. malayi*	At 250 mg/ml concentration demonstrated a high microfilarial motility	[91]
	At a dose of 500 mg/kg × 5 days 1 g/kg × 5 days	*B. malayi*–jirid model *B. malayi*–M. *coucha* model	Showed 30% macrofilaricidal activity Showed 57% macrofilaricidal activity	
Trachyspermum ammi	Methanolic extract of fruit The 2-isopropyl-5-methyl phenol (thymol) was the active component Its positional isomer (i.e., 5-isopropyl-2-methyl phenol, carvacrol,) also showed promising result	*S. digitata*	IC_{50} 0.067 and 0.019 mg/ml after 24 h and 48 h, respectively IC_{50} were 0.024 mg/ml and 0.002 mg/ml after 24 h and 48 h incubation, respectively Macrofilaricidal IC_{50} values were 0.025 mg/ml and 0.004 mg/ml after 24 h and 48 h incubation, respectively.	[92]
	2-Isopropyl-5-methyl phenol at a dose of 50 mg/ kg for 5 days	*B. malayi–M. coucha*	Macrofilarial mortality of 58.93%	

Plant	Extract	Target	Antifilarial efficiency	Author
Bauhinia racemosa (B. racemosa)	Galactolipid (n-butanol fraction) obtained from ethanolic extraction of the leaves	*B. malayi*	The MIC values against adult worms 3.9 mg/ml and 15.6 mg/ml against microfilariae The IC_{50} values were 1.25 mg/ml and 1.607 mg/ml, respectively, against adult worms and microfilariae	[93]
	50 mg/kg × 5 days	*B. malayi infection*	58.3% adult worm mortality	
Piper betel	Crude methanolic at a dose of 100 mg/kg	*B. malayi–M. coucha*	Suppress mf most effectively and showed 26% efficacy against adult worm	[94]
Hibiscus mutabilis	Active ferulic acid, from the leaves	*S. cervi*	Approximately 97 and 90%, of reductions in viability of microfilariae and adult worms, respectively	[95]
Caesalpinia bonducella	Crude extract from the seed kernel	*B. malayi*	96% macrofilaricidal activity	[96]
Melaleuca cajuputi	The flower extract	*B. pahangi*	Halted the release of mf and worm mobility after 6 days at 1000 mg/ml	[97]
Xylocarpus granatum	Aqueous–ethanolic extract fruit extract	*B. malayi*	IC_{50} value of 15.46 and 13.17 mg/ml against macrofilariae and microfilariae, respectively	[98]
	The ethyl acetate soluble fraction demonstrated		An IC_{50} value of 8.5 and 6.9 mg ml^{-1} against macrofilariae and microfilariae, respectively	
	At a dose of 50 mg/kg for 5 days	*B. malayi–M. coucha*	53% macrofilaricidal and 63% embryostatic effects	
	Gedunin (64) Photogedunin		Mf (IC_{50} 2.03 mg/ml) Adult (IC_{50} 0.239 mg/ml) Mf (IC_{50} 2.23 mg/ml) Adult (IC_{50} 0.213 mg/ml)	
	Gedunin at a dose of 100 mg/kg for 5 days Photogedunin at a dose of 100 mg/kg for 5 days	*B. malayi–M. coucha*	Killed 80.0% of the transplanted adult worms 70.0% adult worm mortality	
Vitex negundo (*V. negundo*) and *Aegle marmelos* (*A. marmelos*)	The root extract *from V. negundo* and the leaf extract from *A. marmelos*	*B. malayi*	At a concentration of 100 ng/ml caused a complete loss of microfilarial motility after 48 h of incubation	[99]
Aegle marmelos	Methanolic extracts of *Aegle marmelos* Corr. (Rutaceae) leaves	*S. cervi*	(IC_{50}) was 0.168 mg/ml	[100]

Plant	Extract	Target	Antifilarial efficiency	Author
Diospyros peregrina	n-Butanol extract (NBE) of *D. peregrina* stem bark on *Setaria cervi*	*S. cervi*	Mf (IC_{50} 56.1 μg/ml, (IC_{50}), adult (IC_{50} 57.6 μg/ml) Mf (LD100 187.17 μg/ml) after 24 h of treatment	[101]
Cajanus scarabaeoides (L)	The polyphenol-rich ethanolic extract obtained from the stem part	*S. cervi*	LD_{50} values were 2.5, 10 and 35 μg/ml, against the oocytes, microfilariae (Mf) and adults, respectively	[102]
Ficus racemosa	Alcoholic and aqueous extract of fruits of *F. racemosa*	*Setaria cervi*	LC_{50} and LC_{90} were 21 and 35 ng/ml, respectively, for alcoholic, while for aqueous extracts were 27 and 42 ng/ml, respectively	[103]
Botryocladia leptopoda	The crude ethanolic extract from the marine red alga *B. leptopoda*	*A. viteae* *L. sigmodontis* *Brugia malayi*	LC_{100} of 62.5 mg ml^{-1} LC_{100} of 31.25 mg ml^{-1} LC_{100} of 125 mg ml^{-1}	[104]
	At a dose of 200 mg/kg for 5 days	*L. sigmodontis–cotton rats* *A. viteae–M. coucha and* *B. malayi–M. coucha*	Exhibited 71.6% 63.2% (ethanolic extract) and 45% (hexane fraction) macrofilaricidal activity, respectively	
Haliclona oculata	The methanolic extract Chloroform fraction and its one chromatographic fraction	*B. malayi*	Mf (IC_{50} 5 mg/ml) Adult (1.88 mg/ml) Showed antimacrofilarial activity IC_{50} 1.80 mg/ml and 1.62 mg/ml, respectively, whereas concentrations of 1.72 mg/ml and 1.19 mg/ml were effective against microfilariae	[105]
	At a dose of 100 mg/kg for 5 days the methanol extract, chloroform fraction, and chromatographic fraction (contain four major alkaloids: xestospongin-C, araguspongin-C, mimosamycin, and xestospongin-D), respectively	*B. malayi–jirid*	Revealed 51.3%, 64% and 70.7% macrofilaricidal activities in the methanol extract, chloroform fraction, and chromatographic fraction, respectively.	
Haliclona exigua	Methanol extract, the n-butanol-soluble fraction Chloroform fraction Araguspongin C	*B. malayi*	(LC_{100} 31.25 mg/ml) (LC_{100} 15.6 mg/ml) Macrofilaricidal activity at 15.6 mg/ml	[106]

Plant	Extract	Target	Antifilarial efficiency	Author
Eucalyptus globulus	The leaf extract from *E. globulus* was active in vitro	*B. malayi*	IC_{50} values 62.5 and 31.2 mg/ml, respectively, against adult worms and microfilariae	[107]
	At a dose of 100 mg/kg for 5 days	*B. malayi–M. coucha model and transplanted B. malayi jirid*	Exhibited 66.7% adulticidal activity and an embryostatic effect	
Terminalia bellerica, Terminalia chebula, Terminalia catappa	Leaf extracts in different solvents	*Setaria cervi*	The methanol extract exhibited more than 80% activity at the highest dose level of 10 mg/ml. The IC_{50} obtained in methanol extracts are 2.7, 1.96 and 2.58 mg/ml	[108]
Moringa oleifera	The gum extract obtained from *M. oleifera* showed at a dose of 500 mg/kg for 5 days In contrast, at a dose of 1000 mg/kg for 5 days	*B. malayi* *B. malayi–jirid* *B. malayi–M. coucha*	Mf (LC_{100} 1000 mg/ml) Adult (LC_{100} 125 mg/ml) Mf (IC_{50} > 1000 mg/ml) Adult (IC_{50} 74.33 mg/ml) Extract showed 69% adulticidal activity and sterilized 83% of the female worms Extract showed 44% adulticidal activity	[109]
Butea monosperma	The leaf and root extract Methanol and hexane–ethanol fraction of the leaf extract	*B. malayi* *S. cervi*	Microfilarial motility in a dose-dependent manner Showed IC_{50} values of 1.25 and 3.6 mg/ml, respectively, against macrofilariae	[110, 111]
Ricinus communis	Methanolic extract of the seed	*B. malayi*	90% death in the developmental stages of the parasite	[112–114]
Rutin and hesperetin		*S. digitata*	Showed macrofilaricidal activity a 500 mg/ml	
Naringenin		*B. malayi*	Showed macrofilaricidal activity at 125 mg/ml IC_{50} value at2.5 mg/ml	
	At 50 mg/kg	*B malayi–Meriones and B. malayi-M. coucha*	Eliminate adult worms 73 and 31%, respectively	
Flavone Chrysin			Exhibit macrofilaricidal activity at 62.5 mg/ml and inhibit the adult motility at 31.2 mg/ml Showed macrofilaricidal activity at 2.50 mg/ml	

Table 5.
List of naturally originated antifilarials are summarized below.

7.5 Levamisole

This is an ascaricidal drug with no side effects at the recommended doses. It has also been found as a microfilaricidal drug against the microfilariae of *Wuchereria bancrofti* and *Brugia malayi* [37].

Unfortunately, most of the chemical antifilarials are characterized by adverse side effects. The list of currently used antifilarials with their side effects is summarized in **Table 3**. Hence, researches on exploring new therapeutic drugs, especially less hazardous drugs of natural origin, are highly recommended. The application of biomedicines to treat disease is among the oldest forms of therapy. These biomedicines including plant extracts and their secondary metabolites were believed to exert their bioefficacy through immunomodulatory elicitation of Th1/Th2 response, either by single (Th1, Th2) or mixed adjuvant activity. Therefore, in the context of filariasis, synthetic and naturally originated antifilarials are summarized in **Tables 4** and **5**.

8. Role of bioinformatics in filarial research

Bioinformatics is a science of computer-based analysis for the biological datasets in which biology and computer science are mutually helping and influencing each other in the field. Bioinformatics has increased the understanding of molecular mechanism of various cellular processes. Nowadays bioinformatics covers several fields of biological sciences and drug discovery to overcome biological problems.

8.1 Genomic approach in filarial research

Genomic research in bioinformatics is a useful technique used to understand the structure and function of all the genes within an organism. Genomics help to find the particular gene and other biological aspects in the entire genome sequence of the organism. Screening of drug targets can also be done using the genomics approach. Casiraghi et al. [115] had carried out phylogenetic analysis using bioinformatics of 11 filarial and Spirurida nematodes and identified the sequence of mitochondrial cytochrome oxidase-I (COI).

Hoerauf et al. [116] detected the mutual interaction between the intracellular bacteria (endobacteria) and filarial nematodes, which is further used as antifilarial drug targets. Nuchprayoon et al. [117] identified the genetic diversity using phylogenetic analysis parsimony tool (PAUP) between the DNA sequences of two strains of *Wb* found in Myanmar and Thailand. Ghedin et al. [118] reported the nuclear genome draft of *Bm* (95-Mb), which contains 88,363,057 bp sequences with 17.84% protein coding sequence [118]. The full genome sequences are available at NEMBASE4 database. Investigators identified a variety of filarial parasite genes and their novel functions that are involved in miRNA regulation and processing.

8.2 Proteomic approach in filarial research

Proteomics approach involved highly efficient methods of protein separation like two-dimensional-poly acrylamide gel electrophoresis (2DPAGE) and detection, using modern tools of bioinformatics. Proteomic analysis of the several stages of *Bm* has identified 557 *Bm* proteins and 11,508 protein coding genes which helps to define various proteins by using reverse-phase liquid chromatography-tandem mass spectroscopy.

Afterwards Bennuru et al. [119] have also done the same in identifying the excretory/secretory (ES) and somatic proteins of adult, mf, and infective stages of

larvae of *Brugia malayi*. Some workers gathered the molecular information of the particular protein of interest through 3D structure which plays a significant role in drug designing and vaccine development for lymphatic filariasis. In 2005 Bhargavi et al. [120] analyzed the 3D model of GST of *Wuchereria bancrofti* and *Brugia malayi* for better drug development. For the development of potential drugs, novel drug targets are modeled using bioinformatics approach including either ligand-based drug designing (LBDD) or structure-based drug designing (SBDD). LBDD provides crucial understanding of the interaction between the drug target and ligand molecule and provides information about the biologically active molecules [121]. Currently 3D quantitative structural activity relationship (QSAR) and pharmacophore modeling of small molecules are carried out to define their minimum necessary structural characteristics through which it inhibits the target. These 3D structure analyses of a protein were designed from the experimental-based method such as X-ray crystallography, NMR, electron microscopy, etc. If an experimental data are not available for the target proteins, homology modeling is carried out to build the 3D structure using target protein sequence [122].

Potential inhibitor can be designed on the basis of their binding sites or can be identified from the small-sized molecule databases such as Cambridge Structural Database [123], ChemBank [124], DrugBank [125], PubChem [126], and ZINC database [127] and databases that are available at Lignad.Info: molecule database [128] to inspect the biological activity of the particular protein.

Name	Description	URL
DBEMFDD diseases database	It is an annotated bibliography for filariasis, malaria, dengue, and diarrhea. It also contains the findings of the literature survey	http://ideas.repec.org/p/ess/wpaper/id2032.html
FilaDB	Database on filaria detection, clinico-immuno monitoring, and management has been developed for Kasturba Hospital and private practitioners to screen the filarial infection	http://www.jbtdrc.org/FilaDb.htm
NEMBASE2	Contains the EST sequence for *Brugia malayi* and other nematodes	http://www.nematodes.org/nematodeESTs/nembase.html
Filaria Journal	Full and freely access journal of filariasis	*http://www.filariajournal.com/*
Wormbase	It is an online database for the biology and genome of the *Ce* and related nematodes	http://www.wormbase.org
WHO	It contains the related publication of filariasis, reports of elimination program, control of neglected tropical diseases and some important links	*http://www.who.int/topics/filariasis/en/*
PHIS	It contains the news and updated from filariasis elimination program	http://umis.doh.gov.ph/fila
Disease database	It contains the general information regarding diseases	*http://www.diseasesdatabase.com/ddb4824.htm*
TDR-lymphatic filariasis	It contains knowledge about the parasite genomes for African lymphatic filariasis 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	*http://www.who.int/tdrold/diseases/lymphfil/default.htm*
Filarial worms database	This database provides the genome sequence of organisms rapidly and broadly available to the scientific community.	*http://www.broadinstitute.org/annotation/genome/filarial_worms/MultiHome.html*

Table 6.
List of online databases for lymphatic filariasis are as follows.

8.3 Web-based available resources for LF

Web-based biological data plays a significant role in bioinformatics which plays a significant role in analyzing biological data for large amount of nucleotide sequences, amino acid sequences, and 2D or 3D structures for the broad range of organisms and their drug targets. Currently, there are only few databases available for LF (**Table 6**), but the specified database for LF is not available, which is an urgent need in the field of drug development and to overcome the emerging drug resistance. Some of the important databases which are available for LF research have been discussed below.

NEMBASE: It contains databases containing information of filarial nematodes such as filarial biology and pathology, nomenclature of filarial genome, mapping of filarial gene, and *Bm* genome survey sequencing (GSS). Recently, genome sequencing of *wBm* and *Onchocerca volvulus* (*Ov*) was also included with the Sanger Institute, NEB, and TIGR.

WormBase: It's an open access database repository for nematode biology which contains the genome browser for *Bm*, *C. elegans*, *H. contortus*, etc., and the gene predictions and orthology assignments from a range of related nematodes.

FilaDB: It is a database for screening filarial patients with the objective of providing information on the incidence of mf and types of acute, chronic, and occult manifestations and age, sex, and distribution area of filariasis cases for clinico-immuno monitoring and management of filariasis.

Filarial worm database at broad institute: This database used to study the minute phenotypic difference between the closely related filarial species of *Loa loa*, *Wb*, and *Ov* (*http://www.filariasiscenter.org/brugia-malayigenomics-and-bioinformatics-resources*). Filarial worm database also has the sequence data on *Wolbachia* endosymbionts of *Wb*, *Ov*, and *Bm*. Filarial diseases are still remaining as a major public health concern in India. There is a need of comprehensive database, which should contain:

a. Curated links between genes relevant to filariasis and their sequences in GenBank and Swiss-Prot.

b. Sequence homology between different filariasis causing genes.

c. Primary and secondary information of pathogens.

d. Availability of various drugs and their targets.

e. Expressed sequence tagged (EST) sequences from different filarial species.

f. Supporting references from published literatures.

g. Bioinformatics tools to analyze those data. Database should also contain the epidemiological data on age and gender-wise incidences of disease, remission, and transition rates of disease sequelae.

9. Conclusions

Filariasis is one of the most disabling and disfiguring neglected tropical diseases with various clinical manifestations and a high morbidity rate. Repetitive use of antifilarials has given rise to drug resistance. Most of them are effective against

microfilariae and have no effect on the adult worms. Till date numbers of antifilarial targets have been explored, but their evaluation with reference to assay feasibility, target validation, drugability, toxicity, resistance potential, and structural information needs to be discovered in the future. There is a need to explore the mechanism through which drug resistance occurs so that new effective combination therapy could be discovered at an early stage.

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