Plant Products in the Treatment and Control of Filariasis and Other Helminth Infections and Assay Systems for Antifilarial/Anthelmintic Activity

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Abstract

Lymphatic filariasis, onchocerciasis, loaisis, and other helminth infections cause serious health problems especially in resource-limited tropical and subtropical developing countries of the world, and more than 2 billion people are infected with at least one helminth species. From times immemorial, man looked up to the plant kingdom in search of anthelmintics, antifilarials, and remedies for parasite-induced health problems. Although more than 50% of drugs in modern medicine are derived from plants or leads from plants, a success story of plant-based anthelminthics or antifilarials is yet to be told. In the last 5 decades, more than 100 plant products were reported to be beneficial in the treatment or control of these parasitic infections but they could not be developed into viable drugs for a variety of reasons. This review focuses on the plant products reported to be useful in the control and treatment of human helminth infections with the main emphasis on filariasis and the *in vitro* and *in vivo* systems available for assaying anthelmintic activity.

Introduction

Since the time man first discovered the plant kingdom as a rich and convenient source of food, he returned to this kingdom repeatedly and found there remedies for illness too. As a result, several knowledge bases of how to treat or prevent illness and diseases using plants were generated. Some of this knowledge was passed on through generations by "word" ("folk medicine") and some was compiled and practiced, such as Ayurveda in India, Kampo and traditional Chinese medicine (TCM) in Japan, Taiwan, and China. Today, about 50% of the drugs used in modern medicine are of plant origin [1] and the success stories include the mito-inhibitor vinca alkaloids vincristine & vinblastin (from *Vinca rosea)* and their semisynthetic analogues vinorelbine and vindesine as anticancer agents, the topoisomerase II inhibitors etoposide and teniposide which are semisynthetic isomers of the cytotoxic podophyllotoxin from *Podophyllum* spp., the taxanes and camptothecins, also anticancer agents [2], and the antimalarial artemesinin and its derivatives from *Artemesia annua* [3]. However, there are very few success stories related to antifilarial or anthelmintic activity, with the possible exception of ivermectin which is a macrocyclic lactone derived from *Streptomyces avermitilis*. This review focuses on the plant products reported to show activity against human helminth parasitic infections with the main emphasis on filarial infections and the *in vitro* and *in vivo* systems employed to assay the (antifilarial) activity.

The Parasites

The helminth parasites represent an extreme in the spectrum of pathogens as they are probably the only multicellular pathogens infecting man and animals. The helminth parasites comprise two very distantly related taxa: (1) the round worms or nematodes belonging to Nemathelminthes (Class: Nematoda); and (2) the flatworms or Platyhelminthes (Class: Cestoda and Trematoda).

Worldwide, more than 2 billion people are infected with at least one helminth species [4]. The majority of these infections occur in resource-limited tropical and subtropical developing countries of the world, where over half of the population may harbor infections [5]. Of the various helminthic infections in man, those caused by filarial parasites are particularly important because of the huge loss of man-hours they cause.

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The filarial parasites (Class: Nematoda; Superfamily: Filarioidea) include approximately 500 species infecting almost all vertebrates except fish. The parasites reside in lymphatics, connective tissues, or body cavities of the vertebrate hosts, and the infection is transmitted by a blood-sucking arthropod vector.

The filarial species infecting only humans are: *Wuchereria brancrofti, Brugia malayi,* and *B. timori*, which are responsible for lymphatic filariasis (LF) causing debilitating disease manifestations such as "elephantiasis" and hydrocele, *Onchocerca volvulus* that causes "river blindness", and *Loa loa* causing "loiasis" ("calabar swelling"). Other prevalent but benign human filariids are: *Acanthocheilonema perstans, Acanthocheilonema streptocerca*, and *Mansonella ozzardi,* as well as the less frequent minor species: *W. lewisi, B. beaveri, B. guyanensis, M. semiclarum, Dipetalonema arbuta, D. sprenti, Microfilaria bolivarensis*, and *M. rodhaini*.

LF is a major disease with ever increasing prevalence in the developing world and the second leading cause of permanent and long-term disability. Globally, about 1 billion people live in areas endemic to LF (80 countries) and thus are exposed to the risk of infection. About 120 million suffer from the infection or the chronic filarial disease manifestations such as edema of limbs, breast, external genitalia, or hydrocele [6].

It is estimated that medical treatment for acute and chronic LF manifestations costs millions of dollars each year across the endemic regions. In India alone over 10 million people per year seek treatment for LF, which accounts for a total of 30 million dollars per annum. It is thought that the measurable health care costs of treating LF are small in proportion to the individual and societal costs from lost productivity. The contribution of LF to tropical disease burden in terms of *disability adjusted life years* (DALY) – which basically indicates the amount of healthy life expectancy lost because of a disease or disability caused by it, or risk factor, including both mortality and morbidity – is around 5.94 million globally and over 2.62 million for India [7].

LF infection is spread by *Anopheles, Culex, Aedes,* and *Mansonia* species of mosquitoes. During a blood meal, the mosquito takes up the stage 1 larvae or microfilariae (mf) circulating in the blood of an infected human. In the mosquito, mf undergoes two molts to become stage 3 infective larvae (L_3) which enter the human host during a blood meal of the vector. L_3 penetrate through the local connective tissue and enter the lymphatic vessels [8] where they take 2 to 12 months to develop into adult worms through two molts. Mature male and female worms mate and produce the progeny, mf, which enter the bloodstream from where they are picked up by the mosquito during its blood meal, and the life cycle continues.

Onchocerciasis is the second major filarial disease group and affects around 18 million people, mainly in tropical Africa and Latin America [9]. The infection is presented as a spectrum of dermal and ocular lesions resulting from the presence of microfilariae in the skin and eyes. The severity of the pathology which may cause blindness has attracted a massive international effort to reduce the impact of onchocerciasis through vector control and by mass chemotherapy [10].

Among non-filarial nematode infections, the soil-transmitted helminths (STH) commonly known as intestinal worms are the most common infections worldwide and constitute an important community health problem. The causal parasites are: *Ascaris lumbricoides, Trichuris trichiura*, and the hookworms *Ancylostoma duodenale* and *Necator americanus*. Recent estimates suggest that *A. lumbricoides* infects over 1 billion people, *T. trichiura* 795 million, and hookworms 740 million. The greatest numbers of STH infections occur in sub-Saharan Africa, the Americas, China, and East Asia [11]. STH affect most frequently children and produce diarrhea, abdominal pain, general malaise, and weakness that may affect working and learning capacities and impair physical growth and activity. Hookworms cause chronic intestinal blood loss leading to anemia [12–16]. A list of human helminth infections other than filariasis is given in **Table 1**.

In vitro and *in vivo* Systems for Screening Potential Antifilarials

Being multicellular advanced organisms displaying considerable host specificity, the helminth parasites pose several challenges in the development of convenient and reliable laboratory test systems for assaying plant and synthetic products for anthelmintic and antifilarial activity. In the case of the filarial parasite, there are two main challenges: first, there are 16 distinct human filarial parasite species and the efficacy of the products may show species specificity and parasite stage-specificity. For instance, a product may show about 80% efficacy against adult worms of *Onchocerca* spp. but only show an identical or acceptable activity against the larval microfilariae stage of *B. malayi* (unpublished observation). Consequently, to maximize the exploration, a given product, whether active or inactive against one parasite, has to be tested against life stages of multiple species. The second challenge is the availability, maintainability, and responses of some of the target parasites/parasite life stages *in vitro* and transmission of infection to nonhuman laboratory animal models. For example, the most prevalent lymphatic filariid, *W. brancrofti*, is seldom used for *in vitro* or *in vivo* screening. This is because the infection cannot be transmitted to or maintained in small laboratory animals. As a result we do not have a convenient screening model of this parasite and a source of the parasite life stages for *in vitro* use.

However, our improved understanding in the recent decades of the biology and host parasite interactions helped us developing not only useful *in vitro* systems but also successful transmission of human infections into small and larger laboratory animals for *in vivo* screening [18–31].

The different *in vitro* screen systems developed over the decades and employed for screening plant and synthetic products are given in **Table 2**. The assays employ one or more life stages (L_3, mf, or adult worms) of the parasite depending upon the feasibility or type of activity (larvicidal, microfilaricidal, or macrofilaricidal) desired. The endpoints used in the assays include inhibition (in the parasite) of: motility, reduction of a tetrazolium salt to its formazan, parasite specific glutathione-S-transferase, enzymes involved in antioxidant generation or free radical scavenging, molting of L_3 to L_4, embryogenesis, and mf release from female worms. The assays are employed as prescreens either singly or as a battery of two or more assays and the most frequently used battery consists of motility assay and 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) reduction assay. Using this battery, a product is considered active if it causes complete inhibition in motility and/or > 50% inhibition in MTT reduction. The advantage of the assays are that a) a large number of products can be screened, b) they require a small amount of the test product for the assay, and c) the assays can be completed within 24–48 hrs [32,33]. Investigators have also used 120 hr incubation in order not to miss products that act slowly [34]. The main disadvantage of the *in vitro* pre-screens is that they detect

Table 1 Human helminth infections (other than filariasis) [17].

Disease	Parasite	Habitat	Infective agent/route	Intermediate host	Clinical manifestations
Nematode infections					
Ancylostomiasis	*Ancylostoma duodenale, A. ceylanicum, Necator americanus*	Intestine	L_3/per os, skin	None	Creeping eruptions, anemia, gastrointestinal (G.I.) manifestations, pot-belly, puffy face
Ascariasis	*Ascaris lumbricoides*	Intestine	Eggs/per os	None	G.I. disturbances: intestinal colic, obstruction, carbohydrate depletion, physical and mental retardation, allergy
Trichuriasis	*Trichuris trichiura*	Intestine	Eggs/per os	None	Diarrhea, dysentery, pain, rectal prolapses
Enterobiasis	*Enterobius vermicularis*	Intestine	Eggs/per os	None	Abdominal pain, dysentery, pruritus, rectal prolapses
Trichinellosis	*Trichinella spiralis*	Intestine, muscle	Encysted larvae/per os	None	G.I. disturbances, myositis, myocarditis, neurological symptoms, urticarial rash, fatal toxemia
Strongyloidiasis	*Strongyloides stercolaris*	Intestine	L_3/skin	None	G.I. disturbances
Trematode infections					
Schistosomiasis	*Schistosoma mansoni, S. haematobium, S. japonicum, S. mekongi, S. intercalatum*	Vasculature of G.I. or genito-urinary systems	Cercariae/ skin	Snail	*Acute*: Dermatitis, fever, chills, nausea, abdominal pain, diarrhea, malaise, and myalgia *Chronic:* Bloody diarrhea *(S. mansoni)* or hematuria *(S. haematobium)*
Cestode infections					
Taeniasis and Echinococcosis (hydatid disease)	*Taenia solium, T. saginata, Diphyllobothrium* spp., *Hymenolepis* spp., *Echinococcus multiloccularis*	Intestine	Eggs or cysts/ per os	Pig/cow/fish	Abdominal discomfort, diarrhea, loss of appetite. Anemia in people with the fish tapeworm, neurological problems (rare)

Table 2 *In vitro* antifilarial assay systems.

Assay(s) (Measure/endpoint of the antifilarial activity)	Parasite(s)	Parasite life stage employed	References
Single assays			
Motility (irreversible inhibition of motility of parasite/viability)	*Litomosoides carinii, Brugia malayi, Acanthocheilonema viteae*	Mf	[35]
	B. malayi	Adults	[36]
	B. malayi	L_3	[37]
	B. malayi	Adults, mf	[38]
Mf release inhibition	*B. malayi*	Adults	[38]
MTT reduction (inhibition of MTT reduction/viability)	*Onchocerca volvulus, O. gutturosa*	Female adults	[39]
GST Inhibition (Inhibition in parasite GST activity/viability)	*B. pahangi, B. malayi*	Mf, L_3, adults	[40]
Molting inhibition (Inhibition of L_3 to L_4 molting)/anti-*Wolbachia*	*B. malayi*	L_3	[41]
Octapamine stimulation (tonic paralysis by altered membrane potentials/viability)	*A. viteae*	Adults	[42]
Two-assay battery			
Motility; reduction in lactate excretion (viability)	*B. patei and B. malayi*	L_3, adults	[43]
Motility; inhibition of respiration (viability)	*L. carinii*		[44]
Motility; MTT reduction (viability)	*Setaria cervi*	Adult, mf	[45]
	O. volvulus	Adults	[46–49]
	O. gutturosa	Adults	[47]
	O. ochengi	Adults, mf	[50]
	A. viteae	L_3, adults, mf	[51, 52]
	B. malayi	Adults, mf	[28, 53]
	S. digitata	Adults	[54]
Motility; GST inhibition (viability)	*S. cervi*	Adult (female)	[55]
Multiple assay battery			
Motility; MTT reduction; inhibition of microfilaria release (embryostatic effect; viability)	*B. malayi*	Adults, mf	[56]
	B. pahangi	Adults	[57, 58]
Antioxidant enzyme inhibition (inhibition of xanthine-oxidase, superoxide dismutase, catalase, glutathione peroxidase/viability)	*B. pahangi*	Adults	[57, 58]
	L. carinii, S. cervi	Adults	[59]

antifilarial activity of only those products which do not require metabolic activation to active pharmacophore. As a result several products that are negative *in vitro* but which may show activity after bitransformation in the host are missed. It is therefore necessary to include in the *in vitro* incubations a metabolic activation system such as the liver microsomal fraction (S9 mix) rich in most of the cytochrome P450 isoforms. An (expensive) alternative is testing all products, whether active or inactive *in vitro*, in suitable animal models of the infection.

Although tests employing animal models are labor intensive, expensive, lengthy, and often difficult to scale-up, they are sufficiently reliable, and the conclusions drawn from them are frequently transferable to human infection, provided sufficient care is taken in the selection of the host-parasite system.

Our understanding of the host-parasite interactions and immune responses of the host in human filariasis and in a variety of animal models of the human infection has greatly improved in recent years [20, 60–62] and as a result we now have well-characterized animal models for assaying antifilarial activity (**Table 3**).

Historically, attempts to transmit the human filarial infections to laboratory animals were unsuccessful. This necessitated the use of alternative animal models for antifilarial drug discovery programs. One of the earliest models is *Litomosoides carinii* infection in the cotton rat. Introduced in 1944 [63], this was used as a primary screen and was instrumental in the discovery of the microfilaricide diethylcarbamazine (DEC). However a major drawback with this model was that the host can only be infected through the vector but not by manual injection of infective larvae. So, there is no way of knowing how many, if at all, infective larvae had been introduced into the host by the vector. This is important for reproducible 1) determination of the percent yield of adult worms (= % larvae surviving and developing in to adult worms), and 2) quantifying the macrofilaricidal and worm sterilizing effect of the test drug. Another model which was established in '70s is *Acanthocheilonema viteae* in the jird (*Meriones unguiculatus)* and in *Mastomys coucha.* These models overcame the deficiencies of the *L carinii*/cotton rat model and were considered acceptable [64] as a surrogate primary screen for products against human *O. volvulus* infection. However, for a long time there was still no rodent model for human lymphatic filarial infections with *W. bancrofti* and *B. malayi*. The real breakthrough came with the successful transmission of *B. malayi* to the rodents jird [65, 66] and *Mastomys coucha* [18, 67, 68] and recently, to nonhuman primates [25, 29, 31, 69]. In *M. coucha* the infection is introduced by subcutaneous injection of a known number of L_3. In jird, in addition to the s. c. route, the infection can also be initiated by intraperitoneal instillation of a known number of adult worms or L_3. The latter method not only makes the animal microfilaremic in a short period but is especially useful for assaying macrofilaricidal efficacy of products by following the fate of instilled worms. Both the rodent models show high and sustained microfilaraemia for prolonged periods which is advantageous for assaying microfilaricides. An additional feature of the *M. coucha* is its susceptibility to develop filarial disease manifestations (unpublished observation).

Among nonhuman primates, the leaf monkeys (*Presbytis* spp.) were found to be especially susceptible to *B. malayi* infection [25, 29] and among them the Indian leaf monkey displays responses similar to those shown by human subjects harboring the infection, including the recurrent febrile and limb edema episodes, hydrocoele, and eosinophilia [29].

With the availability of adequate animal models of human filarial infection, the new product screening protocol has been revised by the WHO. At the authors' Institute the protocol conducted is largely based on WHO recommendations and is as follows:

Prescreen: In vitro motility and MTT assays using adult worms and mf of *B. malayi* for short-listing. This is followed by IC_{50} (the concentration at which the parasite motility is inhibited by 50%) determination using the same assays and CC_{50} (cytotoxic concentration at which 50% of cells are killed) determination using VERO Cell line C1008 (African green monkey kidney cells) [33, 89–91].

Primary screening: Jird bearing i. p. instilled adult worms of *B. malayi.*

Confirmation of efficacy: L_3-initiated infection of *B. malayi* in *M. coucha* or jird.

Dose optimization studies: L_3-initiated infection of *B. malayi* in *M. coucha.*

Efficacy in a non-rodent or nonhuman primate model (previously called as tertiary screen): L_3-initiated infection of *B. malayi* in non-rodent/nonhuman primate model.

Assay Systems for Screening Plants against Helminth Parasites Other Than Filariae

In vitro (primary) screens

For screening potential synthetic or plant derived anthelmintics (other than antifilarials) several nematode, cestode, and trematode parasites have been used in *in vitro* systems (**Table 4**). The selection of parasites for the *in vitro* systems is apparently based on considerations such as easy availability, adaptability to laboratory conditions, ease in handling, and, when the human parasite cannot be used, the similarities between human and surrogate parasite responses to known drugs and/or taxonomical proximity of the species chosen. This approach would appear justified by several instances of intergeneric chemotherapeutic responses within the same family. Among nematodes, such a relationship is known to exist between murine oxyurid and *Enterobius vermicularis* with piperazine; between *Nippostrongylis muris* and trichostrongyles of sheep and cattle or hookworms of man and dog with bephenium and between *Strongyloides ratti* and *S. stercolaris* with dithiazanine [92].

In vivo

Tables 5 and **6** show a list of animal models for primary and secondary screening, respectively. The *in vivo* primary and secondary screening would strengthen the results obtained in the *in vitro* prescreening. The *in vivo* screens will also demonstrate whether the spectrum of activities can be extended to the related parasites in different hosts and to efficacy in human subjects.

Parasites having a short and direct life cycle needing no vector would obviously need less time and labor and would be economical to generate results. *Hymenolepsis nana*, a human tapeworm, in natural condition, is cycled through intermediate host (*Tribolium confusum*) but also attains maturity in one and the same host within 15 days of incubation of eggs. This system will also facilitate the assessment of drugs against cysticercoides and adult worms in the same infected animal. Small hosts with minimum genetic variations and easily available in adequate numbers are usually preferred for reproducibility.

Inspite of all the care exercised in selecting the best host-parasite system, the results obtained in experimental hosts can not totally

Table 3 Animal models of nonhuman and human filarial infections.

Parasite	Host	Vector	Initiation/introduction of infection	Site of adult worms/ microfilariae	Reference
1. Rodent and non-rodent models of nonhuman filarial infections					
Litomosoides carinii#	*Sigmodontis hispidus*#	Mite	L_3 (s. c.)	Pleural cavity/blood	[63, 70–74]
	Mastomys coucha				
	Meriones unguiculatus				
Acanthocheilonema viteae	*M. unguiculatus*	Tick	L_3 (s. c.)	Subcutaneous and internal connective tissues/ blood	[75, 76]
	M. lybicus				
	M. persicus				
	M. coucha				
	Mesocricetus auratus				
Brugia pahangi	*M. unguiculatus*	Mosquito	L_3 (s. c.), adult worms (i. p.)	Testes, heart, lungs/ blood	[69, 75, 77–79]
	M. coucha				
	CDI and Balb/c mice				
	Dog	Mosquito	L_3 (s. c.)	Lymphatics/blood	
	Cat				[80]
Dirofilaria immitis	Dog	Mosquito	L_3 (s. c.)	Heart, pulmonary arteries, venae cavae/ blood	[41, 80]
2. Rodent and non-rodent models of human filarial infections					
*B. malayi**	*M. unguiculatus**	Mosquito	L_3 (s. c.), adult worms (i. p.)	Lymphatics, testes, heart, lungs/blood	[21, 53, 66, 68, 69, 81–83]
	*M. coucha**		L_3 (s. c.)		
	Balb/c mice		L_3/adult worms (i. p.)		
B. malayi	Dog	Mosquito	L_3 (s. c.)	Lymphatics/blood	[69, 80]
	Cat				
3. Nonhuman primate models of human filarial infections					
*B. malayi***	*Erythrocebus patas*	Mosquito	L_3 (s. c.)	Lymphatics/blood	[25, 29–31, 69, 84–86]
	Nyticebus coucang				
	Galago crassicaudatus panganiensis				
	Papio cynocephalus				
	Cercopithecus aethiops				
	Macaca mulatta				
	*Presbytis entellus***				
	P. melalophos				
	P. cristata				
Wuchereria bancrofti	*P. entellus*	Mosquito	L_3 (s. c.)	Lymphatics/blood	[87]
Breinlia sergenti	*Nycticebus coucang,*	Mosquito	L_3 (s. c.)	Peritoneal cavity	[80, 88]
	Papio anubis, Erythrocebus patas				
Loa loa	*Mandrillus leucophaeus*	Chrysops	L_3 (s. c.)	Subcutaneous and connective tissues/blood	[80, 88]
Onchocerca volvulus	*Pan troglodytes*	Simulium	L_3 (s. c.)	Subcutaneous tissues/ blood	[80, 88]

Earlier used as a primary screen. * Models currently employed as a primary screen for assaying potential antifilarial products at CDRI. ** Models employed as final preclinical confirmation (previously called as tertiary screen) assays at CDRI

be translated to the target parasite in its natural host because the different compounds behave differently in different hosts (absorption, kinetics, resorption and distribution, etc.) [104]. This might be crucial for decision making regarding whether or not it should enter successive steps of drug development program. The different *in vitro* and *in vivo* systems, their utility and drawbacks have been recently reviewed by Keiser [101].

Plants for Filariasis

In modern medicine the drugs used for lymphatic filariasis are diethylcarbamazine (DEC) [70] and ivermectin [105], and a single-dose treatment with DEC or ivermectin, or combination of DEC or ivermectin with albendazole is currently employed in an attempt to control the infection. DEC and ivermectin are microfilaricides and therefore only useful in reducing transmission and pathology. New drugs are required to improve treatment by killing the adult worms (macrofilariae), which are long-lived, and to replace the currently used drugs before drug resistance starts appearing [106].

Table 4 *In vitro* parasite systems (other than filaria) for screening anthelmintic activity.

Parasite (host)	Life stages	Assay(s)/measure of the anthelmintic activity	References
Nematodes			
Trichostrongylus colubriformis (human infection)	Eggs, L_3 (infective larvae), adult worms	Egg hatch inhibition assay (EH), larval development assay (LD), larval migration inhibition (LMI), adult worm viability	[93–96]
Haemonchus contortus (ruminants)	Eggs, infective larvae, adult worms	Egg hatch inhibition assay (EH), larval migration inhibition (LMI)	[93, 97, 98]
Ancylostoma caninum (human) *Necator americanus* (human)	Larvae, adults	Motility/irreversible inhibition of motility	[93]
Ascaris suum (pig & human) *A. lumbricoides* (human) *Ascaridia galli* (chicken/turkey) *Heterakis gallinarum* (chicken/turkey) *Toxocara canis*	Adult worms, 2nd stage larva	Motility/irreversible inhibition of motility	[99, 100]
Cestodes			
Raillietina echinobothrida (fowl)	Adult worms	Motility/irreversible inhibition of motility	[99]
Trematodes			
Paramphistomum sp. (cattle, sheep, goat)	Adult worms	Motility/irreversible inhibition of motility	[99]
Schistosoma mansoni *Fasciola hepatica* *Echinostoma caproni* (all human infections)	Adult worms	Motility/irreversible inhibition of motility	[101]

Table 5 Helminth parasites used for *in vivo* primary screening* [17, 100, 102, 103].

Parasite	Host/intermediate host	Infective agent/route	Model for	Clinical correlation@
Nematodes				
Ascaris suis (suum)	Mouse/none	Eggs/per os	Ascariasis	+++
Necator amaricanis	Hamster/none	L_3/skin	Ancylostomiasis	+++
Ancylostoma ceylanicum	Hamster/none	L_3/per os	-do-	+++
Nippostronglys brasiliensis	Hamster/none	L_3/per os	-do-	+++
Cestodes				
Hymenolepis nana	Mouse/beetle#	Eggs/per os	Taeniasis	+++
H. diminuta	Rat/beetle	Eggs/per os	-do-	++
Trematodes				
Fasciola hepatica	Rat, rabbit/snail	Metacircariae/per os	Fascioliasis	++
F. gigantica	Rat/rabbit/snail	-do-	-do-	++
Schistosoma mansoni	Mouse, hamster/snail	Cercariae/skin	Schistosomiasis	+++
S. japonicum	Mouse/snail	-do-	-do-	+++
	Hamster/snail	-do-	-do-	++
	Rabbit/snail	-do-	-do-	++
	Guinea pig/snail	-do-	-do-	++

Intermediate host not obligatory; @ scale: ++ = moderate; +++ = high

Table 6 Test models for *in vivo* secondary screening [17].

Parasite	Host/intermediate host	Model for	Clinical correlation
Nematodes			
Ascaridia galli	Chicken/none	Ascariasis	+++
Toxocara canis	Dog/none	-do-	++
Toxascaris leonina	Cat/none	-do-	++
Ancylostoma caninum	Dog/none	Ancylostomiasis	+++
A. brasiliense	Dog, cat/none	-do-	+++
A. tubaeforme	Cat/none	-do-	++
Cestodes			
Taenia hydatigna	Dog/ruminants	-do-	+++
T. taeniaeformis	Cat/rodents	-do-	+++
Dipylidium caninum	Dog/fleas	Taeniasis	+++
T. pisiformis	Dog/rabbit	-do-	+++
Cysticercus pisiformis (larva of *T. taeniaeformis*)	Rabbit	Cysticercosis	++
Echinococcus cyst (intermediate stage of *E. granulosus*)	Rabbit	Hydatid disease	++

In the last few decades a lot of emphasis has been laid on the development of antifilarial agents from plant or natural products by many investigators [32,48,82,107,108] and to develop traditional plant-based medical preparations incomplementary or alternative medicines (CAM) supported by scientific validation of efficacy and safety and quality control of the preparations. Although there are few specific reports on the antifilarial properties of plant extracts or products, it is not unusual to find these indications cited amongst a general list of medicinal plants [109,110]. Some plants are reported to be active against tissue dwelling nematodes and various filarial species and are used in traditional systems of medicine [111]. **Table 7** shows a list of plants studied for activity against filarial parasites [112]. Some of these are tested for their antifilarial activity mostly *in vitro* and some *in vivo*. Among these, *Streblus asper*, a plant used in traditional medicine for lymphedema, is the only plant that has been studied extensively and systematically *in vitro* as well as *in vivo* and whose active constituents were chemically characterized. A preparation of plant decoction named "filacid" made from the stem bark of *S. asper* has been administered to over 5000 filarial patients at a filaria clinic in Varanasi, India, during the period 1970–1987 [113,114] and was found to be effective in the treatment of filarial lymphedema, filarial chyluria, and other conditions of the disease. In comparative trials, other plants used in traditional medicine were found to be less effective (viz. *Crataeva nurvala* [7%], *Argyreia nervosa* [48%], *Butea monosperma* [12%]) than "filacid" in the treatment of filarial lymphedema [112,113]. Later, the stem bark extract was found to be active against several filarial species including *B. malayi in vitro* and *in vivo*. The active principles were identified as two cardiac glycosides, asperoside and strebloside [107]. For onchocerciasis, there are relatively fewer reports of plant-based traditional medicine in the literature. *Aloe barteri* was cited for the treatment of *O. volvulus*-induced skin conditions [109]. Another plant, *Cassia aubrevellei*, which is believed in Liberia to be useful in skin conditions associated with onchocerciasis, was found to be inactive against female parasites recovered from nodules of patients [115]. On the contrary, the plant extract increased the density of skin microfilariae [116]. Extracts of some Cameroonian plants like *Carapa procera, Pachypodanthium staudth*, and *Polyalthia sauveolens* were also found to be effective against filarial parasites. The active principles of these plants were identified as carapolide A and oliverine and were tested against *O. volvulus in vitro* by Titanji et al. [117]. Cardol, a phenolic compound isolated from *Anacardium occidentale* is reported to be active against bovine filariid *S. cervi in vitro* [118]. Other *in vitro*/*in vivo* investigations of plant extracts have also been reported against various filarial species [116,119–123]. Both aqueous and alcoholic extracts of the leaves of *Mallotus philippensis* and *Sencio nudicaulis* were effective in inhibiting the movements of the nerve-muscle (n.m.) preparation of *S. cervi.* The stimulatory response of acetylcholine was blocked by the aqueous extract on whole worm movements [124]. The effect of *S. nudicaulis* extracts was different from that produced by the calcium channel blocker nifedipine on the whole worm and n.m. preparation. While nifedipine blocks the stimulant effect of Ach, the extract of *S. nudicaulis* fails to do so. This response bears similarity with DEC, which also does not block AchE response. However, interpretation of these activities in terms of target filarial infections *in vivo* is difficult.

The majority of the filaricidal applications of plant products reported in the early literature are for the treatment of guinea worm (*Dracunculus* sp.) which was earlier considered as a filarial parasite but is now included in a separate group. Plant extracts are in many cases applied externally to the sore caused by guinea worm indicating that most of the observed effects may be due to direct topical effect of the agent on the parasite or wound. Several plant products were also reported active when given orally. Root decoction of *Combretum micranathum* was reported to help in expelling guinea worms in infested patients; inflammation around the lesions was also reduced [125]. The leaves of *Elaeophorbia drupifera* and *Hilleria latifolia* taken in combination with a palm soup preparation were found to be guinea wormicidal [125].

In laboratory investigations several plant products were identified with antifilarial activity. *In vitro*, macrofilaricidal activity was shown by ethanolic and aqueous extracts of the medicinal plant *Cardiospermum halicacabum* against *B. pahangi* in terms of reduced motility of both male and female adult worms and reduced microfilarial release and motility (ethanolic extract) [126]. Methanolic extracts of the root of *Vitex negundo* L. (containing alkaloids, saponin, and flavonoids) and leaves of *Aegle marmelos* Corr. (containing coumarins) produced complete loss of motility of microfilariae of *B. malayi* [127]. Extracts of *Butea monosperma* leaves and roots showed significant inhibition of motility in a dose-dependent manner of *B. malayi* microfilariae [32]. In animal models, crude extract and hexane fraction of marine red alga *Botryocladia leptopoda* killed adult filarial parasites of *L. sigmodontis* and *A. viteae* and caused sterilization of *B. malayi* female worms [128]. Crude extract and chloroform fraction of the stem portion of the plant *Lantana camara* showed adulticidal and female worm sterilizing activity against *B. malayi* in *M. coucha* and in jirds with i.p. instilled *B. malayi* adult worms. Oleanonic and oleanolic acids isolated from the hexane and chloroform fractions showed considerable antifilarial activity on *B. malayi in vitro*. Inhibition of motility and subsequent mortality of adult worms of *S. digitata* was produced *in vitro* by extracts of *Cedrus deodara, Ricinus communis, Sphaeranthus indicus*, and *Centratherum anthelminticum* in decreasing order [54]. Crude extract (and an active fraction of it) of *Trachyspermum ammi* fruit inhibited motility and killed *S. digitata* worms *in vitro* and showed macrofilaricidal and female sterilizing efficacy *in vivo* against *B. malayi* in *M. coucha*. The active compound was isolated and found to be a phenolic monoterpene [129]. Potential micro- and macrofilaricidal efficacy against *B. pahangi* was shown by ethanol extract of leaves of *Neurolaena lobata*, a Guatemalan medicinal plant [58]. Aqueous, butanol, and hexane extracts of *Caesalpinia bonducella*-seed kernel demonstrated microfilaricidal, macrofilaricidal, and female-sterilizing efficacy against *L. sigmodontis* in cotton rats and microfilaricidal activity against *B. malayi* in *M. coucha* [130].

Plants for Helminthiasis (Other Than Filariasis)

The literature concerning the use of plants as anthelmintics (**Table 8**) is more extensive [158,159] and preparations from many of these plants are in current use. With few exceptions, e.g. the investigation by Kiuchi et al. [111] on tissue dwelling nematodes, the majority of them are effective against intestinal helminths. The most widely known and investigated anthelmintics of plant origin are ascaridole, derived from *Chenopodium ambrosoides* [158] and the phloroglucinols aspidin and deaspidin, from the male fern *Dryopteris filix mas*. They are used effectively to treat tapeworm infections [160]. Some of the plant

Table 7 Plant products with activity in filariasis or against the parasites.

Name of the plant	Family	Part used/product	Activity against	Reference
Adenia gummifera	Passifloraceae	Root	Filariasis, hydrocoele	[131]
Aegle marmelos Corr.	Euphorbiaceae	Leaf	Mf of *B. malayi (in vitro)*	[32, 127]
Afstonia boonei	Apocynaceae	Bark, fresh latex, fresh stem bark	Loaiasis, filarial swellings	[132–134]
Agrimonia eupatoria	Rosaceae	Agrimophol	*Schistosoma* sp *Taenia* sp	[135]
Alstonia congensis	Apocynaceae	Latex	Loaiasis, filarial swellings (bandaged along with crushed bark of *Erythrophleum guineense*)	[109]
Alstonia scholaris	Apocynceae	Latex, bark	Filariasis, elephantiasis	[136]
Aloe barteri	Liliaceae	Leaf	Guinea worm, disease causing white skin patches (onchocerciasis?)	[109]
Ammannia multiflora	Lythraceae	Leaf	Sight problems, including those caused by filaria	[131]
Andrographis paniculata	Acanthaceae	Dried leaf	Filariasis, mf of *D. reconditum* in dogs *(in vivo* and *in vitro)* and adults of *B. malayi* in rodents	[120]
Argyreia speciosa	Convolvulaceae	Whole plant	Filariasis, parasitic skin diseases, active *in vitro* against *S. cervi*	[137, 138]
Azadirachta indica	Meliaceae	Leaf, flower	*S. digitata (in vitro)*	[139, 140]
Boerhavia repens	Nyctaginaceae	Immature shoots	Elephantiasis	[109]
Botryocladia leptopoda	Rhodymeniaceae	Red algae	*L. sigmodontis, A. viteae, B. malayi (in vivo)*	[128]
Butea monosperma	Leguminosae-Papilioneae	Root and leaf	Mf of *B. malayi (in vitro)*	[127]
Caesalpinia bonducella	Caesalpiniaceae	Seed kernel	*S. digitata (in vitro), L. sigmodontis, B. malayi (in vivo)*	[130]
Calotropis gigantea	Asclepiadaceae	Leaf, latex	Filariasis, elephantiasis, skin changes, *S. digitata (in vitro)*	[109, 140, 141]
Calotropis procera	Asclepiadaceae	Whole plant/milky juice, dried aerial parts, root, bark, latex	Guinea worm; filariasis, elephantiasis	[109, 136, 142–144]
Carapa procera	Meliaceae	Dried fruit, seed	Filariasis, *O. volvulus (in vitro)*, parasitic skin disease	[117, 145]
Cardiospermum halicacabum	Sapindaceae	Plant	*B. pahangi* adult and Mf *(in vitro)*	[126]
Cassia alata	Leguminosae	Fresh leaf juice	Parasitic skin disease	[117, 122]
Cassia aubrevellei	Leguminosae	Root, bark	Onchocerciasis, skin microfilaricidal, active *in vitro* against *O. volvulus* mf	[138]
Cassia occidentalis	Leguminosae	Leaf, seed	Guinea worm, parasitic skin diseases acute lymphedema, skin changes	[109]
Cassia tora	Leguminosae	Dried leaf	Parasitic skin diseases	[109, 141]
Cayaponia martiana	Cucurbitaceae	Root	Elephantiasis	[109]
Cedrus deodara	Pinaceae	Plant extract	*S. digitata* adults *(in vitro)*	[54]
Centratherum anthelminticum	Asteraceae	Plant extract	*S. cervi, S. digitata* adults *(in vitro)*	[54]
Cinnamomum culilawan	Lauraceae	Bark	Rubeifacient for filarial lymphangitis	[109]
Cleistopholis glauca	Annonaceae	Dried bark	Filariasis, inactive *in vitro* against *O. volvulus*	[109]
Clerodendrum capitum	Verbenaceae	Root	Elephantiasis	[109]
Crossopteryx febrifuga	Rubiaceae	Fresh fruit juice	Eye filaria	[125]
Cyrotomium fortunei	Polypodiaceae	Dried rhizome	Filariasis	[133]
Daniella thurifera	Leguminosae	Gum	Parasitic skin diseases	[146]
Delonix elata	Leugminosae	Whole plant	Filariasis, elephantiasis	[109]
Dichrostachys cinerea D. glomerata	Leguminosae	Dried stem bark, inner bark	Elephantiasis	[142, 147]
Dombeya amaniensis	Steruliaceae	Root	Filariasis/lymphatic disorders	[148]
Eclipta alba	Compositae	Dried whole plant	Elephantiasis	[109]
Elaeophorbia drupifera	Euphorbiaceae	Leaf	Guinea worm, filariasis	[131, 145]
		Leaf	Guinea worm, used with *Hilleria latifolia*	[109]
Elephantopus scaber	Compositae	Dried root	Filariasis	[141]
Emicostema littorale	Gentianaceae	Whole plant	Filariasis, microfilaricidal *in vitro* against *Conispiculum guindiensis*	[125]
Erythophleum guineense	Leguminosae	Crushed bark	Loaiasis (filarial swellings), used with *Alstonia congensis*	[149]
Erythophleum ivorense	Leguminosae	Dried stem bark	Loaiasis (filarial swellings) used in *O. volvulus*	[119]
Eucalyptus robusta	Myrtaceae	Leaf	Microfilariasis	[109]
Guiera senegalensis	Combretaceae	Leaf	Parasitic skin diseases, guinea worm inflammatory swellings	[109]
Hilleria latifolia	Phytolaccaceae	Whole plant, leaf	Guinea worm, used with *Elaeophorbia drupifera*; filariasis, *O. volvulus (in vitro)*	[109, 150]

continued next page

Table 7 Plant products with activity in filariasis or against the parasites. *(continued)*

Name of the plant	Family	Part used/product	Activity against	Reference
Jatropha curcas	Euphorbiaceae	Seed oil, leaf, whole plant	Guinea worm, rubefacient for parasitic skin diseases	[122, 125, 141]
Kigelia africana	Bignoniaceae	Whole plant	Elephantiasis of scrotum	[109]
Lantana camara	Verbenaceae	Stem	*A. viteae, B. malayi*	[108]
Limeum ptercarpum	Molluginacaeae	Aerial parts	Filariasis	[141]
Lawsonia inermis	Lythraceae	Leaf	*S. digitata (in vitro)*	[140]
Lycopodium rubrum	Lycopodiaceae	Whole plant	Elephantiasis	[151]
Mallotus philippensis	Euphorbiaceae	Leaf	*S. cervi (in vitro)*	[124]
Melia azidirachta	Meliaceae	Bark	Filariasis, component (15 %) of FILARIN	[152]
Microglossa afzelii	Compositae	Dried leaf	Filariasis, *O. volvulus* (inactive *in vitro*)	[124]
Mussaenda elegans	Rubiaceae	Leaf	Elephantiasis	[109, 125]
Myrianthus arboreus	Moraceae	Dried stem bark	Filariasis, *O. volvulus* (inactive *in vitro*)	[109]
Newbouldia laevis	Bignoniaceae	Root and leaf	Elephantiasis, scrotal elephantiasis, orchitis	[122, 153]
Neurolaena lobata	Asteraceae	Leaf	*B. pahangi* adults *(in vitro)*	[58]
Ocimum sanctum	Lamiaceae	Leaf	*S. digitata (in vitro)*	[140]
Ochrocarpus africanus	Guttiferae	Root/resinous sap	Parasitic skin diseases	[109]
Odyendea gabunensis	Simaroubaceae	Dried stem bark	Filariasis, *O. volvulus* (inactive *in vitro*)	[154]
Pachyelasma tessmanii	Leguminosae	Dried fruit	Filariasis, *O. volvulus (in vitro)*	[122]
Pachylobus edulis	Buseraceae	Bark	Parasitic skin diseases	[141]
Pachypodanthium staudtii	Annonaceae	Dried stem bark	Filariasis, *O. volvulus (in vitro)*	[117, 122]
Physedra longipes	Cucurbitaceae	Whole plant	Elephantiasis of scrotum	[117, 122]
Phychotria tanganyikensis	Rubiaceae	Leaf	Elephantiasis	[109]
Raphia farinifera	Palmae	Dried fruit	Filariasis, *O. volvulus (in vitro)*	[155]
		Dried leaf	Filariasis, *O. volvulus (in vitro)*	[122]
Ricinus communis	Euphorbiaceae	Plant extract, leaf	*S. digitata* adults *(in vitro)*; Mf of *B. malayi (in vitro)*	[32, 54, 127]
Richiea caparoides	Capparidaceae	Leaf, root	Filariasis; guinea worm	[122, 141]
Rynchosia hirta	Leguminosae	Whole plant	Filariasis, elephantiasis	[156]
Sargentodoxa cuneata	Sargentodoxaceae	Dried stem	Filariasis	[147]
Sencio nudicaulis	Asteraceae	Leaf	*S. cervi* mf *(in vitro)*	[109]
Sphaeranthus indicus	Asteraceae	Plant extract	*S. digitata* adults *(in vitro)*	[54]
Streblus asper	Urtaceae	Stem bark	Filarial lymphedema, micro- and macro-filaricidal, *S. cervi, L. carinii, B. malayi, A.viteae, B. malayi*	[107, 113, 114, 123, 157]
Trachyspermum ammi	Apiaceae	Fruit	*S. digitata* adults *(in vitro), B. malayi (in vivo)*	[129]
Terminalia chebula	Combretaceae	Not known	Filariasis	[109]
Tinospora cordifolia	Menispermaceae	Not known	Filariasis (acute lymphedema, skin changes)	[112]
Xerodermis stuhlmannii	Leguminosae	Root	Elephantiasis	[138]
Vitex negundo L.	Euphorbiaceae	Root, leaf	Mf of *B. malayi (in vitro)*	[32, 127]
Zingiber officinale	Zingiberaceae	Fresh rhizome	Filariasis, *D. immitis* (microfilaricidal) (acute lymphedema)	[121, 152, 154]

products are vermicides while others are vermifuges. Oil of chenopodium (ascaridole) is effective against *Ascaris* and hookworms but is highly toxic. Aspidum is one of the oldest used anthelmintics obtained from the rhizomes of the fern *Dryopteris filix mass.* Polyhydric phenol is its active principle (filicic acid and filicin). The product has specific action against intestinal cestodes: *Diphyllobothrium, Taenias, Hymenolepis* spp and others, and acts probably by paralyzing the muscles of parasites. However, the drug is toxic and causes polyneuritis and paralysis of the iris. Santonin is the oil obtained from the seeds of *Artemisia maritima*. Flowering tops of this plant were used by physicians of Greece as early as 60 AD. The decoction of the stem bark of *Zanthoxylum liebmannianum* decreased the count of intestinal nematode eggs in naturally infected sheep while the chloroform extract was found to be toxic to *Ascaris suum*. Alpha-sanshool from *Z. liebmannianum* was found to be the active compound. However, alpha-sanshool induced tonic-clonic seizures in mice and thus has some toxicity [161]. Thymol obtained from *Thymus vulgaris* is a monohydric phenol (methyl isopropyl phenol) and is used as vermicide in eliminating hookworms and *Trichinella spiralis*. Thymol is not active against *Ascaris, Trichuris*, and *Enterobius.* It is neurotoxic and affects kidneys. Pelletierin is an alkaloid obtained from the pomegranate tree, *Punica granatum,* and is active against *Taenia* sp. but causes headache, dizziness, nausea, vomiting, and diarrhea with colic pain; it is also known to be neurotoxic. Arecanut, the seed of *Areca catechu* is also known for its anthelmintic action; its active principle is arecoline, a colorless liquid. Dried flowers of *Hagenia abyssnica*, commonly called as "Kousso" or Cusso, are used against tapeworm (*Taenia* sp.) infections. Their active principle is identified as kosatxin. Palasonin derived from *Butea frondosa* and its piperavine salts were found to be active against *A. lumbricoides* [162]. Although these are not advantageous over existing synthetic anthelmintics (benzimidazole derivatives and ivermectin), they are effective in expelling the worms if used as a purgative. Interestingly, some plant anthelmintics directly inhibit the worms' motility due to cholinergic agonist/antagonist action as in the case of arecolin. However, the action of all these agents depends on several host factors too.

Table 8 Plants with activity against helminths other than filariidae.

Name of the plant	Family	Part/product used	Target parasite	Reference
Albizzia anthelmintica A. lebbek	Mimosaceae	Bark	*Hymenolepis diminuta*	[167]
Allium sativum	Liliaceae	Bulbs	Nematodes*, helminths	[173]
Areca catechu	Arecaceae	Seed	*Ascaria* sp.	[135]
Azadirachta indica	Meliaceae	Leaf	Helminthes*	[139]
Bauhinia purpurea	Caesalpiniaceae	Leaf	Helminthes*	[174]
Butea frondosa	Papilionaceae	Seed	*A. lumbricoides* in man, *T. canis* in dogs	[162, 175]
Camellia sinensis	Theaceae	Green tea	Infective larvae of *Teladorsagia circumcincta* and *Trichostrongylus (in vitro)*	[176]
Carica papaya	Caricaceae	Seed, latex	Rat tapeworm, intestinal nematode	[168, 177, 178]
Centratherum anthelminticum	Asteraceae	Seed	Tapeworm	[179]
Chenopodium ambrosioides	Chenopodiaceae	Leaf, seed (oil of chenopodium)	*Ascaris* sp, hookworm	[173]
Coriandrum sativum	Apiaceae	Crude extract of seed	*Haemonchus contortus (in vitro* and *in vivo)*	[172]
Cucurbita maxima	Cucurbitaceae	Seed	Helminths*	[175, 177, 179]
Cucurbita pepo	Cucurbitaceae	Seed	*Hymenolepis nana, Dicrocoelium dendriticum*	[175, 177, 179]
Cyathocline purpurea	Asteraceae	Essential oil of aerial part	Tapeworm and hookworm	[177]
Datura metel	Solonaceae	Fruit or flower	*A. galli*	[180]
Delonix regia	Caesalpiniaceae	Flower	*H. contortus*	[179]
Digenea simplex	Rhodophyceae	Kainic acid	*Ascaris* sp.	[135]
Embelia schimperi	Myrsinaceae	Dried fruit	*Hymenolepis diminuta (in vitro* & *in vivo)*	[165]
Evolvulus alsinoides	Convolvulaceae	Crude extract	Helminths*	[180]
Flemingia vestita	Fabaceae	Root, tuber-peel	*Trematode, cestode, A. suum, A. lumbricoides*	[99]
Ficus glabrata, F. spp.	Moraceae	Latex	*A. suum, Strongiloides, Trichuris, S. obvelata*	[164, 181]
Limnophila repens	Scrophulariaceae	Oil	Helminths*	[175]
Leucas caphalotes	Lamiaceae	Leaf	Helminths*	[174]
Luffa echinata	Cucurbitaceae	Seed	Helminths*	[175]
Mallotus philippinensis	Euphorbiaceae	Fruit (kamalin)	*Diphyllobothrium latum*	[175]
Matteuccica orientalis	Onocleaceae	Root	*Fasciola hepatica*	[182]
Millettia thonningii	Papilionaceae	Seed	*Schistosoma mansoni*	[183]
Onobrychis viciifolia Scop.	Fabaceae	Plant (as forage)	*H. contortus*	[169]
Piliostigma thoningii	Caesalpiniaceae	Bark	*A. galli*	[184]
Polygonum glabrum	Polygonaceae	Leaf	Helminths*	[185]
Psorelea corylifolia	Papilionaceae	Seed	Helminths*	[175]
Quisqualis indica	Combretaceae	Quisqualic acid	Nematodes*	[177]
Taverniera abyssinica	Leguminosae	Dried root	Nematodes*	[186]
Urginea indica	Liliaceae	Bulb	*A. suum*	[187]
Struthiola argentea	Thymelaeaceae	Plant	Helminth *(in vitro)*	[171]
Teloxys graveolens (Willd.)	Chenopodiaceae	Plant	*F. hepatica, A. galli*	[170]
Zanthoxylum liebmannianum	Rutaceae	Stem bark	Intestinal nematode of sheep, *A. suum*	[161]

* Parasite(s) not specified

The oil fractions from *Limnophila conferta* syn. *L. repens* Benth and *L. heterophylla* (Roxb) Benth syn. var. reflexa (Benth) Hook. f. belonging to Scrophulariaceae, and from *Buddleja asiatica* Lour (Buddeleia), *B. neemda* Ham. ex Roxb. syn. *B. asiatica* Lour. and *B. globasa* Hope belonging to the family Buddlejaceae were found to show good anthelmintic activity [163].

The latex of some species of *Ficus* (Moraceae) has been traditionally used as vermifuge in Central and South America. However, due to high acute toxicity (hemorrhagic enteritis), lateces are not recommended for use in traditional medicine [164]. Extract of the dried fruits/crushed seeds of *Embelia schimperi* Vatke, belonging to the family Myrsinaceae, is used by the Masai people of Tanzania and Kenya who believe that it eliminates adult *Taenia saginata*, the beef tapeworm. It was effective against tapeworms *Hymenolepis diminuta* in a rat model. No significant *in vivo* effect was observed against *H. microstoma*, the trematode *Echinostoma caproni*, and the nematode *Heligmosomoides polygyrus* in mice, although the worms could be killed *in vitro*. These results indicate that the crushed seeds of *E. schimperi* taken orally by the Masai people, indeed have an anthelmintic activity against human intestinal tapeworms [165]. The West African legume *Millettia thonnigii* is used in Ghana as an anthelmintic and as a purgative [166]. A chloroform extract of the seeds of *Millettia thonningii* which is known to be molluscicidal and cercaricidal was topically applied to mouse skin 2 and 24 hours prior to exposure to *S. mansoni* cercariae. The presence of *M. thonningii* extract components on the surface of the skin appeared to be effective in preventing subsequent establishment of infection. The compound responsible for the activity is thought to be the isoflavonoid alpinumisoflavone. The aqueous extract of *Albizzia anthelmintica* bark showed high anthelmintic activity (68–100%) against experimental *H. diminuta* infection in albino rats; it was not toxic. The water extract from *A. lebbek* bark was less effective against the cestode and was toxic to rats at a high dose [167]. Papaya latex (*Carica papaya*) showed an antiparasitic efficacy against *Heligmosomoides polygyrus* in a mice model [168].

Sainfoin (*Onobrychis viciifolia*) extracts containing condensed tannins inhibited the migration of 3rd-stage larvae of *Haemonchus contortus* [169]. 5,7-Dihydroxyflavanone (pinocembrine) from the acetone extract of *Teloxys graveolens* (Willd.) Weber

(Chenopodiaceae) exhibited fasciolicide, ovicide, and larvicide activities on newly excysted *Fasciola hepatica*, on infective eggs of *A. galli*, and on stage 3 larvae of *Stomoxys calcitrans*, respectively [170]. One of the flavones from *Struthiola argentea* (Thymelaeaceae) identified as 5,6,2′,5′,6′-pentamethoxy-3′,4′-methylenedioxyflavone, demonstrated the most potent anthelmintic activity with 90% inhibition of larval motility *in vitro* [171]. The crude aqueous and hydro-alcoholic extracts of the seeds of *Coriandrum sativum* (Apiaceae) inhibited hatching of eggs of *H. contortus* completely in a dose-dependent manner. The hydro-alcoholic extract showed better *in vitro* activity against adult parasites than the aqueous one [172].

Conclusions and Prospects

From times immemorial, the plant kingdom has been a veritable source of medicinal agents, and there are several success stories of plant derived drugs even in modern medicine. However, our efforts to discover plant products or develop new drugs on plant-based leads for the control and treatment of filariasis and other helminth infections have not been met with much success. In the last five decades, more than 100 plant products were reported to be beneficial in the treatment or control of these parasitic infections but they could not be developed into viable drugs for a variety of reasons. New animal models of human infection developed in recent years improved our understanding of host parasite interactions and provided us better models to identify anthelmintic/antifilarial activity of plant products. It is expected that the newer assay batteries coupled with quality controlled systematic plant identification, collection, storage, processing, etc., and the state-of-the-art technology of chemical "fingerprinting" of the products would help us build some success stories in the area of filariasis/helminth infections.

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