***Review Article***

 Burden of Soil-transmitted Helminths and Anthelmintic Resistance

**Abstract**

This review focused on the health effects of nematode parasite but it is not out of place to mention the importance and menace of plant parasitic nematodes in crop farming. Nematodes are round, elongate bilaterally symmetrical worms. Most nematodes are dioecious, although a few monoecious species are known. Knowledge of the different stages in relation to their growth and development is the basis for understanding the epidemiology and pathogenesis of helminth diseases as well as in their treatment. Parasitic nematodes of humans inhabit tissues or body fluids (Filarial worms) and the intestinal tract. Nematodes found in the intestinal tract are called gastrointestinal (GI) nematodes or soil-transmitted helminths (STHs) because of their faecal-soil-oral route of transmission. The ability of parasitic nematodes to survive within their host has been attributed to their body form and structure. A non-bony skeleton and non-segmented smooth body allows motility in curves and folding of the GI tract. STHs increase poverty, contribute to morbidity and mortality, impair development and reduce productivity. The Treatment of nematode infection faces challenges due to the development of resistance by target nematodes therefore, there is need for alternative. Innovative approaches, including the exploration of novel compounds and biopesticides derived from natural sources, hold promise for expanding the therapeutic landscape. Future research should, therefore, prioritize the scientific validation of various alternative therapies, such as phytotherapy, to ensure robust management practices that bolster animal health and welfare while minimizing reliance on conventional anthelmintics.

Keywords: phytotherapy, Filarial worms, nematode parasite, anthelmintic resistance

**Introduction**

According to reports, parasites especially helminth parasites of humans are found mostly in the tropical parts of the world and may not make much sense to people from the temperate regions except for those parasites infecting livestock and pet animals. Therefore, this review intends to provide a brief background about parasitic nematodes, especially the soil-transmitted group and their menace in developing countries. As one of the neglected tropical diseases (NTDs), soil-transmitted helminths have not received the required global attention despite the huge number of people infected or at risk of infection. Prevention and control strategies are not entirely effective because of the problems of anthelmintic resistance (AR) and the dwindling efficacy of the current regime of anthelminthics. Also, the problems of parasitic nematode resistance and dwindling efficacy of current anthelminthics and the urgent need for alternative low cost anthelminthics were highlighted.

Helminths are flat or round-bodied worms of two important phyla- Platyhelminthes (flatworms) and Nematodes (roundworms) [1]. Many are free living while others have adopted a parasitic lifestyle. The free living groups are often aquatic or terrestrial and beneficial in the environment because they aid in the degrading of organic matter[2]. Generally, helminths pass through series of stages during their development- egg, larva (juvenile) and adult stages. Knowledge of the different stages in relation to their growth and development is the basis for understanding the epidemiology and pathogenesis of helminth diseases as well as in their treatment [3] The Platyhelminths are flat worms. Members are bilaterally symmetrical with dorso-lateral flattening [4]. Their body form is acoelomate with triple layers- ectoderm, mesoderm, and endoderm filled with spongy loose connective tissues. Outermost cover is a cuticle derived from the ectoderm [4,5]. Two most important classes include Trematoda and Cestoda[4]. This review will dwell more on the nematodes.

Nematodes are among the most abundant animals on earth[6]. It is estimated that the number of species is between 40,000 to 10 million. They are found everywhere on land, marine and freshwater habitats either free-living or parasitizing animals and plants[7,8]. Many nematodes are unimportant to humans and therefore attract little attention. Some however cause diseases of humans, animals and plants[9].

Nematodes are round, elongate bilaterally symmetrical worms. Most nematodes are dioecious, although a few monoecious species are known. Parthenogenesis also exists in some. Sexual dimorphism usually occurs in dioecious forms, with females growing larger than the males[7,10,11]. The main sense organs are the cephalic (amphids), and caudal (phasmids) papillae, and in certain free-living species the ocelli. These organs are for chemoreception. The presence or absence of phasmids is phylogenetically important and used to separate the classes into Adenophorea (= Aphasmidia, without phasmids) and Secernentea (= Phasmidea, with phasmids)[12,12,13].

 Their anterior and posterior ends are pointed with an acellular cuticle and there is a through-gut with a mouth and a sub-terminal anus. The two most common human nematode parasites are A. lumbricoides know as largest round worm of man and the hookworms [14–16].

### Distribution and Life cycle of parasitic nematodes

Parasitic nematodes of humans inhabit tissues or body fluids (Filarial worms) and the intestinal tract. Nematodes found in the intestinal tract are called gastrointestinal (GI) nematodes or soil-transmitted helminths (STHs) because of their faecal-soil-oral route of transmission[10]. They are the most common helminth infections worldwide and affect the poorest and most deprived communities. More than 2 billion people (about 24% of world population) are infected with helminths globally, and of this number, 1.45 billion are attributed to at least one species of STH[17]. The infections are widely distributed in tropical and subtropical areas in sub-Saharan Africa, the Americas, China and East Asia[18].

Table 1: Distribution of human GI nematodes

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| --- | --- | --- | --- |
| Species | Estimated number infected (millions) | Distribution | Mode of Transmission |
| A. lumbricoides | 819  | Global but more in the tropical regions. | Ingestion of egg containing infective stage (L2). |
| Hookworms | 438.9 | Global but more in the tropical regions | L3 penetrate skin. |
| T. trichiura | 464.6 | Global but more in the tropical regions. | Ingestion of egg containing infective stage (L2). |
| E. vermicularis | 209  | Worldwide. | Ingestion or inhalation of egg. |
| S. stercoralis | 30  | Global but more in the tropical regions. | Auto-infection/L3 penetration. |

(Modified with permissions from Stepek et al 2006).

Over 270 million preschool-age and over 600 million school-age children live in areas where these parasites are transmitted [17,19]

In humans the main species are *Enterobius* *vermicularis*, *Ascaris* *lumbricoides*, *Necator* *americanus*, *Ancylostoma* *duodenale*, *Trichuris* *trichiura* and *Strongyloides* *stercoralis*[20]. Their life cycle is simple and direct. Adult females sexually produce eggs that hatch releasing first larval instar (L1), the L1 develop through second (L2), third (L3) and fourth (L4) larval instars that mature to adult. Infection is by ingestion of infective stage (L2 in the egg, for *A. lumbricoides,* and *T. trichiura*) or penetration of host skin (L3 of *N. americanus*, *A. duodenales* and *S. stercoralis*) [18,21].

### Burden of nematode parasite infections

Burden of diseases, especially those caused by STHs is greatest amongst the poor and those living in pastoral communities[22–24]. STHs infect more than 1 billion people most of which are poorest of the poor[25], and together with other NTDs, STHs increase poverty, contribute to morbidity and mortality, impair development and reduce productivity[20,26]. In the developing world lack of social amenities such as good drinking water, and sanitation, coupled with crowded living conditions, illiteracy and poor health care systems increases the susceptibility to NTDs in general, but particularly STHs. There is a complex vicious cycle between poverty and STHs, and infection with STH has been a contributing factor to poor economic growth[27]. STH infections have profound effects on the host, and the morbidity increases as the worm load in the host increases. The disability-adjusted life years (DALYs) lost (that is the number of healthy years lost to premature death or disability) due to STH infection is more than that of malaria or measles[28]. Recently, STH was reported to account for 5.18 million DALYs lost, with 3.23, 1.31, and 0.64 million DALYs caused by hookworm, *A. lumbricoides* and *T. trichiura* respectively[29].

The common symptoms associated with the STH infections include, stomach or abdominal pain, diarrhoea, nausea, loss of appetite[30]. Fatality may arise where there is obstructive complication of the gut in the case of *A. lumbricoides* infection. Severe hookworm infection and even *T. trichiura* infections cause iron-deficiency anaemia[8,28]. The extent of hookworm induced anaemia is a factor of the intensity of worm infection with either or both of the two hookworm species; *A. duodenales* suck more blood than *N. americanus*. Hookworm induced anaemia is promoted by occupational disposition as most of the people infected are mainly rural dwellers who are predominantly farmers working in plantations where their daily activities expose them to infection. The anaemic status of the farmers affects their physically ability which negatively impact on their work output therefore negatively affecting the general family income. The family purchasing power is affected leading to poor nutrition and inability of the body system to fight off other infections leading to more infections thus maintaining the vicious cycle of poverty and diseases[31–33]. The danger of hookworm-induced anaemia is more in pregnancy, as report has shown that the severity of iron-deficiency anaemia is much greater in pregnant women when compared with non-pregnant mothers. Anaemia in pregnancy lead to low birth weight and still birth and has contributed significantly to maternal mortality in developing world[34–36].

In addition to competing and depriving hosts of nutrients, *Ascaris* sp produces ascarase that impair host digestion of protein leading to severe malnutrition of the host. Nutritional status of a host determine how a host cope with STH and other infections[37–39]. Malnutrition and anaemia in population where STHs are endemic, usually have detrimental effects on host physical inability. It also causes stunted growth, and poor cognitive and social development amongst children. Severe infection with STHs in children affect their school attendance leading to poor academic performance and quality of skills[27–29].

The gastrointestinal nematodes abrade and damage intestinal mucosa leading to secondary bacterial infections[28]. Hyper-infection and disseminated form of strongyloidiasis, and other forms of nematode infections leave their host with large population of larval migrans, that migrate and lodge in and damage many vital body organs, such as the brain, heart, lungs, and the eyes, often with fatal consequences[29]. Infection with STHs in immunocompromised or immunosuppressed individuals is one the factors responsible for secondary bacterial infections as well as downregulation of the Th1 immune response especially in tuberculosis (TB) and human immunodeficiency virus (HIV)[34], leading to rising cases of TB and HIV in developing countries[40].

The effect of GI nematodes is not restricted to humans. GI nematodes pose serious problems to livestock farmers[41]. They cause great socio-economic problem globally with negative impact on farm profitability[42]. Nematode infection in livestock causes reduction in skeletal growth, weight gain and milk production[43,44]. The most common GI nematodes infecting and affecting ruminant animals include *Haemonchus* *contortus*, *Telodorsagia* *circumcinta*, *Trichostrongylus* spp, *Ostertagia* *ostertagia*, *Oesphagostomum* spp, and *Cooperia* spp [45,46]. In the UK GI nematode infections have been implicated in an annual loss of £84 million on sheep farming, compared to £24 million and £8 million lost to footrot and scab, [47,48] whereas in Australia it is reported to cost about 1 billion Australian dollars annually and tens of billions of dollars worldwide[49].

Though this review focused on the health effects of nematode parasite but it is not out of place to mention the importance and menace of plant parasitic nematodes in crop farming. *Meloidogyne* and *Globodera* spp alone cause an average annual crop loss of about US$70 billion globally. Some parasitic nematodes of plant and the problems they cause have been reviewed elsewhere[37].

 The ability of parasitic nematodes to survive within their host has been attributed to their body form and structure. A non-bony skeleton and non-segmented smooth body allows motility in curves and folding of the GI tract. Their pseudocoel fluids act as circulatory medium to distribute food to tissues. A protective cuticle covers the entire body surface and resists host enzymic activities but does not protect from dehydration[37].

 The nematode cuticle is an exoskeleton encasing the entire body except small cuticle-lined openings at the pharynx, anus, excretory pore and vulva[50,51]. It consists of a collagenous extracellular matrix and is secreted in layers[37]. Moulting and replacement occurs five times through development to adult. During synthesis material is secreted and deposited by hypodermal cells to the outer membrane where they remain in close contact with the membrane as the mature cuticle[52]. After embryonic cuticle synthesis, subsequent cuticle is laid underneath old ones which are removed during moulting. Moulting is achieved by proteinases, some of which are members of the papain family C1 but other enzymes are also involved[53]. The cuticle prevents osmotic and radial swelling of the nematode body. It forms a barrier between the animal and its environment, and maintains body morphology and integrity and plays a vital role in locomotion via attachment to body wall muscles. Moulting of the cuticle allows growth[37,38,51,52,54].

On the outermost part of the epicuticle is the glycocalyx- surface coat, which is constantly shed and resynthesized. It consists of secretory and excretory products from such organs as amphids, phasmids or rectum and is mainly made up of proteins, glycoproteins or carbohydrates[53]. The shedding and re-synthesis of the glycocalyx helps to lubricate the cuticle surface for smooth movement and defence against predators[53]. The epicuticle is about 6.4µm thick and is known as the ‘’true’’ cuticle. It is non-collagenous but consists of highly cross-linked non-soluble proteins- the cuticlin. The cortical zone is electron dense and made up of collagens and cuticulins. Its electron density varies across the cuticle surfaces. The other layer, the median zone, is poorly defined. It consists of varied structures such as vacuoles, struts, globular bodies etc., all deposited in a fluid medium. The fluid medium is believed to function in dissipating stress arising from movement of the animal[55].

Variations occur among nematode stages and species in the number of definable layers, ultra-structure and thickness of cuticle in relation to body diameter.

The cuticle contains three types of extracellular molecules; collagen-like proteins, cuticlins and glycoproteins[56]. In the *C. elegans* genome more than 160 genes encode for cuticle collagens, with about 30 genes encoding for cuticlins, 8 of the cuticlin genes have been identified[38,50,51,54,56,57].

### Nematode resistance to anthelmintic

Treatment of GI nematode/STH infections is usually with one or a combination of two or all three classes of synthetic anthelmintics,- benzimidazoles, nicotinic acetylcholine agonists and macrocyclic lactones[58], whose modes of action range from neuromuscular transmission inhibition to blockage of metabolic pathways[59]. Currently there is no vaccine with full and effective protection against parasitic nematode infection [60] therefore putting pressure on the available anthelmintics. The intensive use of drugs and the dependence of treatment of nematode infection on only a few drugs with similar mode of action has put pressure on the drug candidates with resultant loss of potency due to development of resistance by target nematodes [49,52,58,61] The history of anthelmintic resistance (AR) dates back to late 1950s when *H. contortus* and horse strongyle worms were reported to have developed resistance to phenothiazine, one of the earliest anthelmintics[62]. Nematode resistance to anthelmintics is a crisis in certain livestock industries and seems to be more in the small ruminant animals[46]. The problem of resistance to the current drugs in use as anthelmintics was made worse by the inability of big pharmaceutical companies to invest in the discovery of new drugs with different mode of action against target nematode parasites for obvious reasons of fear for profit return on investment[58,60–63]. Most reports of nematode resistance are for small ruminants, for instance there are wide reports for resistance of parasites of sheep and goat as well as small strongyles of a non-ruminants (horses) which were associated with benzimidazole class of anthelmintics[46], though there are cases of resistance of pig nematode parasites against levamisole, morantel group of anthelmintics. There are also reports of ovine/caprine parasite resistance to ivermectin[64,65].

This problem was exacerbated by nematode genetic diversity and the ability to develop resistant genes leading to multi-drug resistance (MDR). High prevalence of nematode multi -drug resistance [66,67] exists in several parts of the world, such as Africa [68–70], Australia [49,71], Europe [72,73] Malaysia [74] and USA [75]. A serious consequence of MDR was the abandonment of sheep farming in parts of South Africa because of wide spread anthelmintics failure to control worms[67].

 Though the greatest problem is in treatment of ruminants, resistance also exists in human populations [76–79]. Among the STHs, there are reported cases of *N. americanus* resistance to mebendazole [80–82] and *A. duodenale* against pyrantel in Australia [83,84]. The factors influencing resistance in human anthelmintics include; frequency of treatment, single dose regime, target treatment/mass drug administration and under dosing [32,42,85–87]. Resistance among parasitic nematodes is a growing problem that has made the development of novel alternative anthelminthic very imperative[88]. The novel alternative anthelmintic such as the plant cysteine proteinases (CPs) should be able to attack other body targets other than the physiological system[38]. Therefore, there is urgent need to develop alternative drug candidate with multi-target property against nematode parasites. Such drug candidate will not only be an option to current anthelmintics but reduce the chances of development of resistance by target organisms.

**Conclusion**

In conclusion, intestinal parasitic infections remain a public health problem in rural areas of low-income and middle-income settings of tropical and subtropical zones, affecting human and animal health and welfare. Conventional anthelmintics are facing the serious challenge of multi-drug resistance. Addressing anthelmintic resistance in nematode parasites necessitates a multifaceted approach that incorporates both alternative treatments and sustainable management practices. The pressing issue of anthelmintic resistance necessitates the urgent development of alternative drugs and strategies for nematode control. As the efficacy of traditional anthelmintics declines due to the increasing adaptability of nematode parasites, reliance on a limited arsenal of existing treatments poses significant risks to both agricultural and human health. Innovative approaches, including the exploration of novel compounds and biopesticides derived from natural sources, hold promise for expanding the therapeutic landscape. Future research should, therefore, prioritize the scientific validation of various alternative therapies, such as phytotherapy, to ensure robust management practices that bolster animal health and welfare while minimizing reliance on conventional anthelmintics.

**Disclaimer (Artificial intelligence)**

**Option 1:**

**Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.**

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