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Present drugs and future perspectives in treating soil-transmitted helminthiasis

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Soil-transmitted helminthiases caused by *Ascaris lumbricoides*, *Trichuris trichiura*, and hookworm (*Ancylostoma duodenale* and *Necator americanus*) are responsible for the infection of approximately 1.5 billion people worldwide, mostly in tropical and subtropical regions. Preventive chemotherapy is the mainstay of control, which is the regular administration of anthelminthic drugs, mainly albendazole and mebendazole to at-risk populations. As benzimidazoles face a risk of developing drug resistance and have shortcomings in their therapeutic profile, efforts have been made to develop alternative anthelminthics. The aim of this review is to provide a state-of-the-art update on available treatments and ongoing efforts in Research and Development (R&D) for the three main soil-transmitted helminth infections. Recent findings on the use of drug combinations and advanced drug candidates such as oxantel pamoate and emodepside and how these drugs fulfill the target product profile will be reviewed. Lastly, progress in drug discovery will be summarized.

KEYWORDS

soil-transmitted helminthiasis, drug development, anthelminthics, albendazole, mebendazole

Introduction

Soil-transmitted helminthiases are caused by one of the three major soil-transmitted helminths (STHs), *Ascaris lumbricoides*, *Trichuris trichiura*, and hookworm (*Ancylostoma duodenale* and *Necator americanus*). The fourth species the threadworm *Strongyloides stercoralis* is largely neglected. STHs are responsible for the infection of approximately 1.5 billion people worldwide, mostly in tropical and subtropical regions (1), and are a considerable global health burden (2). The burden of STH infections includes dietary deficiencies, anemia, physical and cognitive retardation in children, and reduction in work performance in adulthood (1).

In STH endemic areas, the cornerstone of control by the World Health Organization (WHO) is preventive chemotherapy (PC), which is the regular administration of anthelminthic drugs without prior diagnosis to at-risk populations.

Parasitological surveys are conducted to identify the settings where PC is needed, define treatment frequency, and monitor progress. The initial coverage aim of 75% treatment in the high-risk group of school-age children was recently expanded to two other high-risk

populations of STH-related morbidity: preschool-age children and women of reproductive age (3).

However, the number of drugs currently recommended to treat and control STH infections is restricted, including four drugs, with two benzimidazoles (albendazole and mebendazole) at the forefront. Between 2010 and 2020, approximately 1.9 billion tablets of albendazole and 1.4 billion tablets of mebendazole were donated for the control of STH in school-age children (3). Levamisole and pyrantel pamoate are rarely used (4). The combination of albendazole-ivermectin was added in 2017 as a recommended treatment to the essential medicine list (5).

A key 2030 target set recently for STH control aims to achieve and maintain the elimination of STH-attributable morbidity in preschool- and school-age children. In order to achieve these targets, the development of additional anthelminthic drugs or a combination of existing anthelminthics was recommended (3). In the past years, increasing efforts in the field of drug discovery and development for STH infections have been witnessed. The aim of this review is to provide a state-of-the-art update on available treatments and ongoing efforts in Research and Development (R&D) for the three main STH infections. A recent review gave an in-depth overview of ivermectin and moxidectin, which are two excellent drugs against *Strongyloides stercoralis* (6). In this review, I will first summarize recent evidence on the performance of the four recommended drugs. Next, I will highlight recent findings on the use of drug combinations. Advanced drug candidates such as oxantel pamoate and emodepside and how these drugs fulfill the target product profile will be reviewed. Lastly, progress in drug discovery will be summarized.

Recommended treatments for soil-transmitted helminthiasis

Standard drugs on the essential medicine list by WHO for STH infections include the two benzimidazoles (albendazole and mebendazole), levamisole, and pyrantel pamoate. Ivermectin is the recommended treatment for infections with *S. stercoralis* and is recommended in combination with albendazole for STH infections (5).

Albendazole is the most widely used drug in preventive chemotherapy programs (3). In a systematic review and meta-analysis conducted in 2017, cure rates of 79.5%, 30.7%, and 95.7% for albendazole against hookworm, *T. trichiura*, and *A. lumbricoides* were calculated. The corresponding egg reduction rates were 89.6%, 49.9%, and 98.5% (7) (Table 1). While these figures can serve as excellent benchmarks, they are based on studies conducted over several decades using a wide range of trial methodologies. Nonetheless, studies investigating albendazole conducted in the past 5 years, after conducting the systematic review (e.g. 8–15), confirm these findings. Reassuringly, the efficacy of albendazole against *A. lumbricoides* and hookworm was high in all studies. Recent findings have highlighted the presence of a food effect resulting in differences in cure rates against hookworm within fed and fasted participants in Ethiopia (97.4% vs 74.2%) and confirmed a lower efficacy in moderate versus light infections (43% vs 94.6%) (15) as well as a lower sensitivity of *N. americanus* versus *A. duodenale* (13).

Cure rates against *T. trichiura* were very low in the majority of studies, with cure and egg reduction rates as low as 6% and 16%, respectively. The highest cure rates with albendazole against *T. trichiura* were observed in Indonesia (cure rate of 46.2%) (16) and Timo-Leste (cure rate of 50%), studies, however, had low sample sizes.

Several studies have investigated whether a relationship exists between the presence of putative benzimidazole resistance single-nucleotide polymorphisms (SNPs) in the β-tubulin gene of *T. trichiura* and other STHs. However, putative benzimidazole resistance SNPs were not found to be higher after treatment (17).

For mebendazole, cure rates put forth by the systematic review were 32.5%, 42.1%, and 96.2% against hookworm, *T. trichiura*, and

TABLE 1 Efficacy (geometric mean egg reduction rates and cure rates) of treatments against soil-transmitted helminthiasis.

Treatment	*T. trichiura*		*A. lumbricoides*		Hookworm	
	CR (%)	ERR (%)	CR (%)	ERR (%)	CR (%)	ERR (%)
Albendazole (400 mg)[a]	30.7	49.9	95.7	98.5	79.5	89.6
Mebendazole (500 mg)[a]	42.1	66.0	96.2	98.0	32.5	61.0
Pyrantel pamoate (10 mg/kg)[a]	20.2	47.5	92.6	94.3	49.8	71.9
Levamisole (2.5 mg/kg)[a]	29.5	28.3	97.3	96.4	10.3	61.8
Albendazole-ivermectin (400 mg/200 µg/kg)	60.0[a]	95.5[a]	96.7[a]	99.9[a]	83.7[a]	94.7[a]
	14/66/49[b]	70/99/98[b]	94/100/99[b]	100/100/100[b]	88/59/72[b]	99/97/99[b]
Albendazole-moxidectin (400 mg/8 mg)	65.6[a]	92.2[a]	92.9[a]	99.1[a]	76.7[a]	95.7[a]
	34.5[c]	96.8[c]	100[c]	100[c]	75.0[c]	98.8[c]
Oxantel pamoate (20 mg/kg)[a]	75.7	85.0	21.8	35.8	23.8	39.5
Emodepside (30 mg)[d]	89.0	99.8	93.8	99.9	95.0	99.9
Tribendimidine[a]	5.9	41.3	96.5	88.1	83.4	91.6

a) Data from systematic reviews and network meta-analyses (4, 7). b) Data from recent randomized controlled trials in Côte d'Ivoire, Lao PDR, and Pemba, Tanzania (8). c) Data from a recent randomized controlled trial on Pemba, Tanzania (9); d) data from a recent randomized controlled trial on Pemba, Tanzania (10). CR, cure rate; ERR, egg reduction rate (based on geometric mean).

A. lumbricoides. Egg reduction rates calculated were 61.0%, 66.0%, and 98.0% (7). Studies conducted in the past 5 years confirmed that mebendazole has low efficacy against hookworm and *T. trichiura* while being an excellent drug for *A. lumbricoides*. Recent studies have reported cure rates of 13.0-30.8% against hookworm, 6.8-33.9% against *T. trichiura*, and 96.9-100% against *A. lumbricoides* (18–20). The only exception is an alarmingly low cure rate of 59.6% with a single dose of 500 mg of mebendazole against *A. lumbricoides* in Ethiopia, which should be assessed further (21). Two studies confirmed that a multiple dose of mebendazole reveals a considerably higher efficacy against hookworm and *T. trichiura* infection (18, 19). However, a treatment scheme consisting of six dosages is incompatible with preventive chemotherapy programs. Lastly, a child-friendly formulation of mebendazole was developed in 2018 (22), which despite different tablet characteristics reveals a nearly identical efficacy profile (23) that will greatly facilitate the treatment of young children.

Levamisole and pyrantel pamoate are not used in routine deworming programs and only a handful of research studies that have used these drugs as monotherapy or in combination and evaluated the efficacy in the past recent years were conducted (16, 24, 25). A combination of albendazole and pyrantel pamoate was found not to improve the cure rate or egg reduction rate in children with *T. trichiura* infection (24). On the other hand, the combination of albendazole and levamisole showed an improved cure rate for light *T. trichiura* infection (16); however, the results would need to be confirmed in additional trials.

Drug combinations

In order to increase the spectrum of activity and to be prepared for threatening drug resistance, the use of drug combinations has been suggested by experts and policymakers for the treatment of STH infections. A list of available co-administration treatments has been put forth ranked by the current evidence and whether the drugs are already marketed and available (4). Albendazole-ivermectin is the top-ranked drug combination. As the co-administration of albendazole-ivermectin has been widely used against filarial infections, from a regulatory perspective, the treatment could be integrated into PC programs in a fast manner. It is worth highlighting that ivermectin has excellent efficacy against *S. stercoralis* and hence the use of ivermectin as a partner drug would also target this neglected STH species (26, 27). Albendazole-ivermectin was recently proposed as an improved treatment strategy for STH infections and placed on the WHO essential medicine list (4, 5, 28). A meta-analysis was conducted to prepare the dossier for submission to the WHO essential medicine list. The findings suggested good tolerability and higher efficacy of albendazole-ivermectin against *T. trichiura* compared to single-dose albendazole treatment. Based on four studies that were identified, albendazole-ivermectin was significantly associated with lower risk (risk ratio (RR) = 0.44, 95% confidence interval (CI) = 0.31-0.62) for *T. trichiura* infection after treatment compared to albendazole alone (28). Yet, the authors concluded that large-scale randomized controlled trials are required to confirm these results. In three countries (Pemba, Tanzania; Lao PDR; and Côte d'Ivoire), a randomized, double-blinded, placebo-controlled trial was therefore conducted among 600 participants in each site to compare the efficacy and safety of monotherapy of albendazole to albendazole-ivermectin against *T. trichiura* to provide further evidence for this new treatment. The coadministration of albendazole-ivermectin was well tolerated with a similar number of adverse events in both treatment arms. However, unexpectedly, we observed a very low efficacy in Côte d'Ivoire (cure rate: 12.9%; egg reduction rate: 69.2%), which is in sharp contrast to the efficacy observed in other countries (8). In more detail, a statistically significant difference was found in cure and egg reduction rates between monotherapy and combination therapy in Pemba, Tanzania and Lao PDR signifying the superiority of the combination treatment. In Côte d'Ivoire, a statistically significant difference between monotherapy and combination therapy was not found for both cure and egg reduction rates.

The underlying reasons for the lack of drug efficacy are yet to be fully elucidated. Possible confounding factors (age, sex, and infection intensity) of the low efficacy of the albendazole-ivermectin combination could not be identified. There were no potential candidate benzimidazole-resistance mutations at codons 167, 198, and 200 in the β-tubulin gene in any of the mapped Amplicon Sequence Variants (ASVs) from Pemba, Tanzania and Lao PDR (unpublished observation).

However, two contributing factors could be determined which are *T. trichiura* strain differences and the gut microbiome. In more detail, phylogenetic analysis of the ITS-2 rDNA locus revealed that the ASVs from all samples from Pemba, Tanzania and Lao PDR clustered together whereas those from Côte d'Ivoire clustered separately. Primers targeting the mitochondrial nad1, nad4, and the major β-tubulin gene generated ASVs, mapping to the appropriate reference sequences from all samples from Pemba, Tanzania and Lao PDR but not from any samples from Côte d'Ivoire. Phylogenetic analysis of the ribosomal ITS-1 and ITS-2 markers placed the *Trichuris* from Côte d'Ivoire populations in a clade that includes *Trichuris* sp. from non-human primates and pigs but is separate from the clade containing *T. trichiura* from the Laos and Pemba populations (29).

Moreover, using samples from one of the study villages in Lao PDR showed that a large majority of cured patients who received the combination therapy (albendazole-ivermectin) presented a distinct gut microbial composition hinting towards a compositional aspect of the gut microbiome driving decreasing response to albendazole-ivermectin treatment of *T. trichiura*. These observations require analyzing additional human stool samples collected in Côte d'Ivoire (30).

To facilitate weight-based regimens, which are complex in preventive chemotherapy programs, a fixed-dose formulation of albendazole with a high dose of ivermectin is currently under development (31–33). An adaptive phase II/III randomized controlled trial has been undertaken in STH endemic sites in Ethiopia, Kenya, and Mozambique to evaluate an oral fixed-dose combination of 400 mg albendazole and either 9 or 18 mg ivermectin with the goal of providing a simplified treatment formulation (33).

Another co-administration therapy researched in the past years is albendazole-moxidectin (9, 34, 35). Moxidectin, like ivermectin,

is a macrocyclic lactone that was approved in 2018 by the US Food and Drug Administration (FDA) as a treatment for onchocerciasis in patients over the age of 12 years (36). Several exploratory studies suggested that it might be a good partner drug in combination treatment against STH infections while being less effective in monotherapy (35). A recent head-to-head comparison revealed an egg reduction rate of 96.8% for moxidectin-albendazole, which was inferior to ivermectin-albendazole (ERR 99.0%, difference of -2.2%-points (95% CI -4.2 to -1.4)), while as expected, both combination treatments resulted in significantly higher efficacy than albendazole, moxidectin, or ivermectin (9). Like ivermectin, moxidectin has a high efficacy against *S. stercoralis* infections (37) and, hence, adding a macrocyclic lactone to albendazole does not only increase efficacy against *T. trichiura* infections but will also be beneficial for infections with *S. stercoralis*.

In Table 2, I have summarized how these two drug co-administrations would fulfill the suggested target product profile for soil-transmitted helminthiasis (38).

The essential characteristics of a novel drug against STH infections include a broad spectrum of activity that is safe for preventive chemotherapy programs, offers a simple dosing and ideally a single-dose treatment, reveals no cross-resistance to existing drugs, and is affordable (38).

The two combination treatments (albendazole-ivermectin and albendazole-moxidectin) have two drawbacks; first, the clinical efficacy in terms of cure rate is still below an ideal threshold of 80% against *T. trichiura*, yet the egg reduction rates, which are the main drivers for morbidity reduction, are high. Second, neither moxidectin nor ivermectin is currently approved for children. Efforts are ongoing to develop a child-friendly formulation of

TABLE 2 Target product profile for drugs for soil-transmitted helminthiasis.

Product Characteristics	Albendazole-ivermectin (Albendazole-moxidectin)	Oxantel pamoate	Emodepside	Tribendimidine
Route of administration: Oral (essential)	+++	+++	+++	+++
Activity (spectrum): Minimal: Active at least against adult stages of principal geohelminths, including *Ascaris*, hookworms (*Ancylostoma and Necator*), *Trichuris*, and *Enterobius* at the target dose. Added value: Additionally active against *Strongyloides*, cestodes, and/or trematodes in multiple doses (<=3 days) or at higher single doses	+++	+	+++	++
Activity (stages): Minimal: Active against lumen-dwelling adults. Active against ova or egg-producing (stop transmission) adults. Added value: Active against migrating larvae and tissue stages of STHs	+++	+++	+++	+++
Active against resistant organisms: Novel molecule (dissimilar to existing compounds for geohelminths – neuromuscular blockers or tubulin antagonists). Drug with low potential for inducing resistance – novel mode of action	++	+++	+++	+++
Dosing schedule: Single dose	+++	+++	+++	+++
Clinical safety: The safety profile includes long-term safety and mild side effects (not worse than existing agents); side effects in uninfected individuals are minimal. Safe for administration without medical supervision, especially if given without screening.	+++	+++	Not known	Not known
Clinical efficacy: High efficacy: >90% cure (>95% egg reduction) of *Ascaris* and both Hookworm infections; >80% cure (>90% egg reduction) of *Trichuris* infections	+	+	+++	+
Compatibility with potential partner drugs: Concomitant treatment with ivermectin, praziquantel, or benzimidazole anthelminthics. Possible to partner to improve spectrum or cure rates or reduce the risk of resistance.	NA	+++	Not known	Not known
Drug-drug Interactions: No interaction with ivermectin, benzimidazoles, or drugs for malaria or HIV/AIDS	+++	+++	Not known	+++
Use in pregnant/lactating women: Minimum: Safe during trimesters 2 and 3 of pregnancy and lactation. No teratogenetic signals in toxicology Added value: Safe during all trimesters of pregnancy	+++	+++	Not known	Not known
Use in infants and children: Safe for use from 1 year of age	+	+++	Not known	Not known
Cost per treatment: Affordable at point of use, therefore equivalent to the cost of current treatments	++	+++	Not known	+++

+++ drug fully meets criteria, ++ drug fulfills partially criteria, + drug reveals limitations fulfilling this product characteristic, NA, not applicable. The target product profile was presented in (38).

ivermectin (39). Pediatric studies with moxidectin in children from 4 to 11 years are also currently ongoing (https://clinicaltrials.gov/ct2/show/NCT03962062).

Other drug combinations have been researched in the recent past including pyrantel pamoate and oxantel pamoate, which will be discussed further below, as well as the Chinese anthelminthic tribendimidine (4). Several of the drug combinations showed highly promising results with high cure and egg reduction rates against STH infections. For example, a high cure rate of 84% was observed with a triple dose of albendazole, pyrantel pamoate, and oxantel pamoate against *T. trichiura* (40). Tribendimidine combined with ivermectin revealed a high efficacy against hookworm infections (41). However, as oxantel pamoate and tribendimidine are not marketed yet by stringent regulatory authorities, these combinations will not become available in the near future.

Advanced development candidates

Two drugs can be classified as late-stage candidates, namely, oxantel pamoate and emodepside, as they have already been tested in Phase II clinical trials against STH infections. Tribendimidine is a drug registered in the Chinese market but further studies would be required before the drug would obtain registration outside China.

Oxantel pamoate

Oxantel pamoate is a tetrahydropyrimidine derivative that has been marketed for veterinary use for several decades. Currently, oxantel pamoate is only approved and marketed for human use in some countries of South America and Asia for children from 6 months of age in combination with pyrantel pamoate (Quantrel®). Oxantel pamoate is currently being developed in the European Union-funded project "Establishment of a pan-nematode drug development pipeline", Helminth Drug Development Platform (HELP, www.eliminateworms.org) in order to register the drug for the treatment of *T. trichiura* infections at a stringent regulatory authority (42). Oxantel pamoate has high efficacy against *T. trichiura* but low activity against *A. lumbricoides* and hookworm infections. Based on a recent network meta-analysis, a 20 mg/kg single dose of oxantel pamoate yields a cure rate of 76% (4). Details on the drug and the suggested clinical development plan for oxantel pamoate endorsed by Swissmedic have been summarized in a recent review (43). The HELP-funded activities include the development of a child-friendly formulation and a regulatory-compliant Phase I study comparing single administration versus single administration on three consecutive days. A two-week repeated-dose toxicity study including pharmacokinetics and local tolerability and reversibility of findings (if any) in *in vitro* and *in vivo* genotoxicity testing and one regulatory-compliant Phase III study in *T. trichiura*-positive patients are required for approval (43).

Emodepside

Emodepside, registered as a veterinary drug for the treatment of gastrointestinal helminths in dogs and cats, was already highlighted a decade ago as a potential drug candidate for STH infections (38). Emodepside belongs to the N-methylated cyclooctadepsipeptides and is a semisynthetic derivative of PF1022A, a fermentation product of a fungus (*Rosellinia* sp.), which is part of the microflora of the leaves of *Camellia japonica* (44). Preclinical studies confirmed that the drug has excellent activity against all major nematode species used in the laboratory, i.e., *Trichuris muris*, *Ancylostoma ceylanicum*, *Necator americanus*, and *Strongyloides ratti*, with a significantly higher activity than the currently recommended treatments (45). Studies using *C. elegans* and filarial nematodes revealed that the calcium- and voltage-activated potassium channel SLO-1 is the major receptor triggering emodepside's action (44).

In 2014, Bayer and the Drugs for Neglected Diseases initiative (DNDi) started a collaboration to develop an emodepside for onchocerciasis. Phase I studies were completed and a Phase II study is currently ongoing (44). This development program allowed the conducting of two Phase IIa studies against *T. trichiura* and hookworm infections. In these studies, emodepside revealed high efficacy against *T. trichiura* and hookworm infections. At a dose of 15 mg, emodepside cured *T. trichiura* infections, while 25-30 mg achieved cure rates of 94 and 95%, respectively (10). The further development of emodepside against STH infections has been launched in partnership with Bayer AG.

Tribendimidine

Tribendimidine, inspired by the veterinary drug amidantel, is a drug discovered by Chinese researchers at the National Institute of Parasitic Diseases (NIPD) in Shanghai and developed by Xinhua Co., Ltd. in Shandong, China (46). Tribendimidine has a similar activity profile as albendazole with excellent activity against *A. lumbricoides* and hookworm infections (4). It also has remarkable activity against *O. viverrini* and *C. sinensis* infections (47). Efforts to develop it as a next-generation therapy for hookworm infections were launched with the aim of using the FDA's Tropical Disease Priority Review Voucher (PRV) program (48) to fund the development. While this program has been a game changer for the development of several drugs (49), tribendimidine did not qualify for obtaining a PRV as the drug would not achieve superiority to the standard of care marketed in the US, i.e., six doses of mebendazole, which has a high efficacy against hookworm infection (18). The development of tribendimidine for registration at a stringent regulatory authority was therefore put on hold.

With regard to the TPP, oxantel and tribendimidine would fulfill many criteria, yet both drugs do not have a spectrum of activity against all STHs and hence would ideally be administered as combination chemotherapy. For emodepside, several characteristics such as affordability are unknown currently as the compound is under development.

Research on novel drugs for soil-transmitted helminth infections

Table 3 summarizes compounds that are in the discovery phase or have been researched against laboratory models of soil-

TABLE 3 Compounds studied *in vitro* and *in vivo* in laboratory models for soil-transmitted helminthiasis.

Compound class	*In vitro* activity	*In vivo* activity	Reference
Dihydrobenzoxazepinones	EC_{50} against *T. muris*: 21->100 µM; 2 compounds showed 50% activity 100 µM against ex vivo *H. polygyrus* L3	ND	(50, 51)
Open scaffold collection SN00797439 (oxadiazole and pyrrolidine core)	90.1% of *T. muris* L1 dead at 100 µM	ND	(52)
Polypyridylruthenium(II) complexes	Rubb12-mono: L3 (IC_{50} = 3.1 ± 0.4 µM) and adult (IC_{50} = 5.2 ± 0.3 µM) *T. muris*	66% reduction with three doses of 5 or 10 mg/kg in faecal egg count in *T. muris*-infected mice	(53)
Sertraline, paroxetine, and chlorpromazine	Decreased motility against *T. muris* and hatching of *A. caninum* (IC_{50} values from 0.7 to 18.2 µM)	ND	(54)
Artemisia campestris essential oil	ND	5000 mg/kg revealed a worm burden reduction of 72% against *H. polygyrus*	(55)
Camel milk	ND	Camel milk administered at 66 ml/kg resulted in a worm burden reduction of 82.91% against *H. polygyrus*	(56)
Cry5B	ND	A combination of Cry5B and tribendimidine revealed a 41% worm burden reduction in *A. ceylanicum*-infected hamster	(57)
Duranta erecta L. (Verbenaceae) fruits	ND	No activity against *H. polygyrus in vivo*	(58)
Chamomile Methanolic Extract	IC_{50} = 0.162 mg/mL against *H. polygyrus*	CME-800 revealed a worm burden reduction of 85% against *H. polygyrus*	(59)
Approved drug library	Sulconazole/econazole and pararosaniline/cetylpyridinium were identified as lead candidates based on activity against *A. ceylanicum* and cheminformatics/data mining analyses	Pararosaniline impacted *A. ceylanicum* fecundity	(60)
Novel albendazole and mebendazole formulations	Increased activity compared to standard drugs observed against *H. polygyrus in vitro* and *in vivo*		(61)
Yeast Particle-encapsulated terpenes	Activity observed against *T. muris* and hookworm at doses >33 µg/ml	ND	(62)
Ferrocenyl and ruthenocenyl derivatives of albendazole	70% activity against *T. muris* adults at 200 µM	Low activity	(63)
Ketamine	ND	6 mg ketamine orally showed high activity in *A. ceylanicum*-infected hamster	(64)
Mentha pulegium	ND	At 400 mg/kg, *M. pulegium* showed a worm burden reduction of 80.23%: M. pulegium extracts at 4000 mg/kg showed a worm burden reduction of 71.6%:	(65, 66)
In-depth study of commercially available anthelminthics	Tests against larval and adult stages across species reported	Moxidectin and milbemycin oxime showing the highest activity against *H. polygyrus* (ED_{50} values of 0.009 and 0.006 mg/kg, respectively), and moxidectin and abamectin being the most effective drugs against *T. muris* (ED_{50} values of 0.2 and 0.5 mg/kg, respectively)	(67)
Ten plants used by health practitioners in Botswana	Several plant extracts revealed moderate activity against hookworms	ND	(68)
Grifolin, neogrifolin from *Albatrellus confluens* and derivatives	No activity against hookworm and *Strongyloides ratti*	ND	(69)
FDA-approved aspartyl protease inhibitors	Motility inhibition of adult *T. muris* at 50-100 µM	ND	(70)
Benzimidazole and aminoalcohol derivatives	Compounds studied against larval and adult stages of *T. muris* and *H. polygyrus*	ND	(71)

(Continued)

TABLE 3 Continued

Compound class	*In vitro* activity	*In vivo* activity	Reference
Laurus nobilis essential oil	ND	*L. nobilis* at 2400 mg/kg orally completely eliminated the egg output and revealed a 79.2% worm burden reduction of *H. polygyrus*	(72)
Myrtus communis	ND	1200 mg/kg of *M. communis* revealed a reduction of 99.70% in faecal egg counts and a 71.12% worm burden reduction of *H. polygyrus*	(73)
Ocimum basilicum essential oil	IC_{50} of 0.138 mg/mL against *H. polygyrus* larvae	Estragole administered at 100 mg/kg resulted in a worm burden reduction of 82.91% against *H. polygyrus*	(74)
Thiosemicarbazide and 1,2,4-triazole derivatives	ND	30% worm burden reduction against *H. polygyrus* with a 5-day treatment of compound II-1	(75)
Brown alga *B. bifurcata*	5 mg/mL extracts from *B. bifurcata* induced a complete inhibition of the larval development of *H. polygyrus* and adult worms	ND	(76)
Lophira lanceolata	Aqueous and ethanol extracts revealed activity against L1 and L2 stages of *H. polygrus*	ND	(77)

A search was done on Pubmed for recent activities (past 6 years (2017-2023)) testing compounds in laboratory models of human soil-transmitted helminthiasis using the following search terms ("drug discovery" OR "in vitro", OR "in vivo" AND (hookworm OR "*Trichuris muris*" OR "*Strongyloides ratti*" OR "*Ascaris*" OR *Necator americanus* OR *Heligmosomoides polygyrus* OR *Ancylostoma ceylanicum*)). ND, not done.

transmitted helminth infections in the past 6 years (2017-2023). Reassuringly, efforts on STH R&D are taking place at different academic institutions. *H. polygyrus* is the most widely used model. Many innovative compounds was studied, ranging from a wide range of natural compounds to compounds already marketed for other diseases, hence, drug repurposing (67, 70). The most advanced compound entering preclinical studies is the *Bacillus thuringiensis* Cry5B, which shows a broad spectrum of anthelminthic activity *in vitro* and *in vivo* (78, 79).

Conclusion

The past decade has witnessed significant efforts in developing alternative treatments for STH infections. Safe and effective treatments are pivotal to making progress towards the elimination of STH infections. A first milestone was reached when the first drug combination for STH infections albendazole-ivermectin was placed on the WHO essential medicine list in 2017. Yet, there is a need to understand the lack of responsiveness of this combination on *T. trichiura* in Côte d'Ivoire. It is not known whether this is a phenomenon unique to Côte d'Ivoire or common in other settings. Pilot efficacy testing is therefore necessary before countries plan to implement albendazole-ivermectin on a large scale as currently done in Uganda. Oxantel pamoate and emodepside are excellent late-stage candidates, which will hopefully increase the small armamentarium for the treatment of STH infections in the near future. While these drugs are nearing the finish line, access strategies should be carefully considered.

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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