

REVIEW ARTICLE

Emerging Resistance to Albendazole in Soil-Transmitted Helminths

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ABSTRACT

Soil-transmitted helminths (STHs) are significant pathogens affecting approximately 1.5 billion people globally, with the highest prevalence in sub-Saharan Africa, South America, and Asia. This study examined the effectiveness of albendazole, a widely used anthelmintic drug, in treating STH infections, particularly focusing on its potential resistance. Despite its effectiveness in many cases, recent studies have indicated a concerning trend of reduced efficacy, particularly against species such as *Trichuris trichiura*. This study reviewed literature from the past decade, identifying key studies that demonstrate a decline in albendazole's effectiveness across various populations, including school-aged children in multiple regions. The findings proposed that while albendazole remains the primary treatment option, its effectiveness varies significantly based on geographic and demographic factors, raising concerns about the emergence of drug resistance. This study emphasizes the need for ongoing monitoring and potential pharmacological combinations to enhance treatment efficacy and address the threat of resistance. Ultimately, the research highlights the complexity of managing STH infections and the necessity for tailored intervention strategies.

Keywords: Soil-transmitted helminths; tropical disease; albendazole resistance; combination therapy

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Highlights:

1. Although albendazole is a commonly used medication for soil-transmitted helminths (STHs), its efficacy seems to be waning, thereby requiring additional research to analyze potential resistance.
2. Many studies have pointed out a decreased efficacy of albendazole, despite none having verified resistance, indicating that the medication remains efficacious in specific groups, geographical areas, and dosage regimens where STH infections are prevalent.

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INTRODUCTION

Soil-transmitted helminths (STHs) are a group of pathogens that infect humans, along with bacteria, viruses, protozoa, and fungi (Schlosser-Brandenburg et al., 2023). STHs infect an estimated 1.5 billion individuals worldwide, with sub-Saharan Africa,

South America, and Asia having the highest prevalences (Lebu et al., 2023; World Health Organization, 2023). The main STH species that result in most of the infections are known as nematodes, which include the roundworm (*Ascaris lumbricoides*), whipworm (*Trichuris trichiura*), hookworms (*Ancylostoma duodenale* and *Necator*



americanus), and threadworm (*Strongyloides stercoralis*) (Lebu et al., 2023).

Asia has one of the highest STH infection prevalence rates globally. A systematic review and meta-analysis established that 39.60% of individuals in Southeast Asia were infected, compared to 19.86% in the Eastern Mediterranean and 37.10% in Africa (Agrawal et al., 2024). In China, there have been three different national surveys on STH infections: the first reported an infection rate of approximately 53.58%; the second indicated a decrease to 19.56%; and the third revealed a continuous decline to 4.49%, with an estimated 29.12 million infected people (Chen et al., 2021; Zhu et al., 2023). Another Asian country, namely Indonesia, has a relatively high prevalence of STH infections, especially among individuals with low income, a lack of education, poor sanitation, and inadequate access to toilets and clean water facilities (Ayele et al., 2019; Sari et al., 2021). East Timor, as another developing country, also conducted its own national survey more than ten years ago, revealing a 55% STH infection rate in its capital city (Australian Agency for International Development et al., 2012).

Anthelmintic medications have worked exceptionally well against STH infections. Prior research confirmed that between 2010 and 2020, roughly 1.9 billion tablets of albendazole and 1.4 billion tablets of mebendazole were administered for disease control in school-age children (Montresor et al., 2020). Levamisole and pyrantel pamoate have also been utilized once in a while, according to a different study (Moser et al., 2019). Meanwhile, in 2017, a combination of albendazole and ivermectin was noted as a suggested treatment on the fundamental pharmaceutical list (Keiser, 2023). Albendazole, a fundamentally anthelmintic drug, works by clogging up the microtubule capacities of parasites, hindering the polymerization of beta-tubulin into microtubules, subsequently disrupting glucose uptake and transport, which inevitably leads to glycogen deficiency in the parasites (Trevor et al., 2015; Chai et al., 2021). These activities enable a wide spectrum that performs best in ending ascariasis as well as infections caused by hookworms, pinworms, and whipworms (Trevor et al., 2015). Research conducted in India publicized an 88.6% cure rate for ascariasis and 100% for hookworm infections with albendazole (Ulaganeethi et al., 2023). Furthermore, the World Health Organization (2023) recommends the twice-yearly administration of 400 mg of albendazole to all high-risk groups, including children and pregnant women.

A few studies determined that albendazole is, to a great degree, safe without any noteworthy side effects when administered at recommended dosages for one to three days (Chai et al., 2021). Nonetheless, prolonged use of albendazole for the

treatment of helminthiasis may trigger several impacts, such as liver problems, unfavorably susceptible responses, neutropenia, and eventually, drug resistance (Rashwan et al., 2016; Krücken et al., 2017; Moser et al., 2019). These outcomes can lead to an emergency situation, since albendazole has been the ultimate treatment against STH infections. Hence, this study reviewed research from the last ten years regarding the emergence of albendazole resistance. The objective of this study was to investigate the efficacy of albendazole, a commonly used anthelmintic medication, for the treatment of STH infections, with a special emphasis on potential resistance.

RESEARCH METHODOLOGY FOR THE NARRATIVE REVIEW

Our study employed a narrative review methodology with a descriptive approach to synthesize existing evidence on albendazole's declining efficacy and potential resistance in STH infections (Sukhera, 2022). We conducted a literature search across multiple databases (Google Scholar, PubMed, PLOS, and Frontiers) using several keywords, such as "resistance of albendazole" or "reduced effectiveness of albendazole," "schoolchildren," and "cross-sectional study." The literature search was limited to articles published within the last ten years to prioritize recent evidence for our review study. The initial screening yielded 36 articles, from which we selected four eligible studies that matched our research focus. As a narrative review, this study qualitatively synthesized key findings rather than generating or analyzing new statistical data.

MECHANISM OF ALBENDAZOLE IN THE TREATMENT OF SOIL-TRANSMITTED HELMINTH INFECTIONS

Albendazole, chemically known as methyl 5-(propylthio)-2-benzimidazolecarbamate, contains an active metabolite that attaches to beta-tubulin, hence preventing its polymerization (Bloom & Ryan, 2020). Adult worms become immobile and die as a result of this activity, which prevents the cytoplasmic microtubule production and glucose intake of the parasites. It also stops the hatching of parasite eggs (Trevor et al., 2015; Bloom & Ryan, 2020; Chai et al., 2021).

Although albendazole has low bioavailability, it increases when taken with food. Moreover, absorption can be boosted fivefold when albendazole is paired with high-fat diets. Through first-pass hepatic metabolism, albendazole is quickly transformed into albendazole sulfoxide, which peaks two to five hours after consumption. Albendazole sulfoxide is present in all tissues, including cerebrospinal fluid, and has 70% protein

binding in plasma (Zhang et al., 2019; Bloom & Ryan, 2020; Malik & Dua, 2023).

The mean half-life of albendazole ranges from 8 to 12 hours, with excretion likely occurring through the biliary tract. The transformation of the drug to albendazole sulfoxide occurs within the intestinal epithelium, where the metabolite is subsequently excreted directly into the lumen (Bloom & Ryan, 2020).

RESISTANCE TO ALBENDAZOLE IN THE TREATMENT OF SOIL-TRANSMITTED HELMINTH INFECTIONS

Albendazole, like any other medications used for treating infections caused by other living organisms, has its own side effects as well. Adverse events, such as liver problems, neutropenia, and drug resistance, may arise when albendazole has been used for a quite long period of time (Rashwan et al., 2016; Krücken et al., 2017; Moser et al., 2019; Chai et al., 2021). Research conducted within the past decade, as shown in Table 1, demonstrated a reduced effectiveness of albendazole against STHs, potentially suggesting the emergence of resistance.

ALTERNATIVE MEDICATIONS FOR THE TREATMENT OF SOIL-TRANSMITTED HELMINTH INFECTIONS

Levamisole, pyrantel pamoate, and the two benzimidazoles (albendazole and mebendazole) are

standard medications for STH infections included in the World Health Organization's Model List of Essential Medicines. Ivermectin is recommended as the drug of choice for *Strongyloides stercoralis* infections, while a combination therapy of albendazole and ivermectin shows efficacy against other STH species (Keiser, 2023). Albendazole has demonstrated reassuring effectiveness against *Ascaris lumbricoides* and hookworms in certain parts of the world. Nevertheless, its performance against *Trichuris trichiura* is markedly suboptimal, as most trials reported very low cure and egg reduction rates, with figures as low as 6% and 16%, respectively (Keiser, 2023). Higher cure rates for *Trichuris trichiura* infections (50% in Timor-Leste and 46.2% in Indonesia) have been observed, though these findings derived from studies with small sample sizes (Anto & Nugraha, 2019).

Experts and policymakers have recommended the utilization of pharmacological combinations in the treatment of STH infections to broaden the spectrum of activity and to be ready for the threat of drug resistance. A list of treatments with drug co-administrations has been proposed based on the available data and the current advocacy and accessibility of the medications (Moser et al., 2019). Among the proposed regimens, albendazole-ivermectin has emerged as the most utilized medication combination. From a regulatory standpoint, the albendazole-ivermectin co-administration might be quickly incorporated into preventive chemotherapy programs, as this

Table 1. Reduced effectiveness of albendazole in the treatment of soil-transmitted helminths

Research, country	Study design, population	Results
Krücken et al. (2017), Rwanda	A cross-sectional study involving 150 children aged 6–10 years, randomly recruited from 12 participating schools, resulting in 100 children per school	The overall cure rates in children with confirmed infections were 69.9% with the Mini-FLOTAC method and 88.6% by wet mount microscopy. The effectiveness of albendazole in school-based deworming for <i>Ascaris lumbricoides</i> infections in southern highland Rwanda was inconsistent and generally inadequate. Given the role of surviving parasites in the development and dissemination of resistance, these results should be considered as a warning.
Humphries et al. (2017), Ghana	A cross-sectional study involving primary school children aged 6–13 years	The overall cure rate after a single-dose administration of albendazole in five communities was 36%. The lowest cure rate recorded was 0% in Jato Akuraa, while the most elevated cure rate was 82% in Cheranda.
Hailu et al. (2018), Ethiopia	A cross-sectional study of 409 primary school (grades 1–7) students aged 6–14 years	Albendazole for hookworm infections provided a lower cure rate at 76.8%, compared to praziquantel for <i>Schistosoma mansoni</i> infections, which achieved a cure rate of 91.4%.
Budiapsari et al. (2021), Indonesia	A cross-sectional analytical study of 250 schoolchildren in grades 1–6	The investigation identified one child with a <i>Trichuris trichiura</i> infection. While albendazole therapy resulted in a favorable cure rate for <i>Ascaris lumbricoides</i> and hookworm infections, <i>Trichuris trichiura</i> infections still required particular care. The widespread use of anthelmintic medications in the last 50 years is particularly concerning due to the potential for drug resistance, which has been a worry since the dawn of contemporary chemotherapy.

combination has been widely used in the treatment of filarial infections. It is important to note that ivermectin is quite effective against *Strongyloides stercoralis*. Hence, utilizing it as a companion medication would also target the underutilized STH species (Buonfrate et al., 2019; Gandasegui et al., 2022).

DISCUSSION

Albendazole, the primary and most popular treatment for STH infections, has exhibited a decline in efficacy, prompting the concern to become the subject of this paper. According to a prior study by Krücken et al. (2017), albendazole administration generated different overall cure rates depending on the diagnostic methods: 88.6% with the wet mount method compared to only 69.9% with the Mini-FLOTAC method. These findings are consistent with a study by Humphries et al. (2017), which also discovered that single-dose albendazole was administered in a very ineffective and incompetent manner, reducing its efficacy and failing to eradicate the majority of STH infections.

The efficacy of albendazole and praziquantel as treatments for specific STH infections, specifically those caused by hookworms and *Schistosoma mansoni*, was compared in a study conducted by Hailu et al. (2018). The findings indicated that albendazole therapy only eliminated hookworms in 76.8% of cases, whereas praziquantel therapy eradicated *Schistosoma mansoni* in 91.4% of instances. Similarly, additional care must be taken to treat *Trichuris trichiura* infections (Budiapsari et al., 2021). The widespread exposure to benzimidazoles, such as albendazole, may hasten the evolution of genetically mediated resistance in human nematode parasites (Albonico et al., 2015).

This study focuses more on reviewing the most frequently used medication, albendazole, for the treatment of STH infections. In order to offer a narrative evaluation on the decreased effectiveness of albendazole use in the population, which, if left unchecked, may result in drug resistance, this study relies on recent research from the last ten years. However, the absence of direct examination of the authors' living environment contributes to a significant limitation in this study, resulting in a very limited amount of data.

CONCLUSION

Albendazole is generally considered the treatment of choice for STH infections. Despite its continued widespread use, the effectiveness of albendazole as a therapeutic agent appears to be declining. Nevertheless, while numerous studies have indicated a decrease in effectiveness, none have provided confirmed evidence of resistance. This research suggests that albendazole remains effective in certain

populations, regions, and modes of use where STH infections are prevalent. Future research is expected to further explore the efficacy of combination therapies and investigate genetic markers associated with resistance to better address the evolving challenges of STH infections.

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CONFLICT OF INTEREST

There are no conflicts of interest among the authors.

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AUTHOR CONTRIBUTION

AAW contributed to the conceptualization and design, analysis and interpretation of the data, article drafting, critical revision, collection and assembly of the data, study material provision, and final approval of the article. AML contributed to the analysis and interpretation of the data, critical revision, collection and assembly of the data, study material provision, and final approval of the article. LBG contributed to conceptualization and design, critical revision, study material provision, and final approval of the article. BBG contributed to the analysis and interpretation of the data, critical revision, collection and assembly of the data, study material provision, and final approval of the article. EF contributed to the analysis and interpretation of the data, critical revision, collection and assembly of the data, study material provision, and final approval of the article. SHGF contributed to the analysis and interpretation of the data, article drafting, critical revision, study material provision, and final approval of the article.

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