PRAZIQUANTEL DEPENDENCE IN SCHISTOSOMIASIS: ADVANCES IN THERAPEUTICS AND PHARMACEUTICAL TECHNOLOGIES

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ABSTRACT

Schistosomiasis, a serious neglected tropical infection with high prevalence, especially in Brazil, critically depends on Praziquantel (PZQ), which, despite its advantages, faces limitations such as inactivity against immature forms and increasing resistance in Mass Drug Administration (MDA) areas. This demonstrates that multiple rounds of MDA result in a lower Egg Reduction Rate (ERR), highlighting the urgent need for new strategies. The objective of this study is to review the literature on pharmacological alternatives for the treatment of schistosomiasis, focusing on the screening of new drugs, bioactive compounds, and innovative pharmaceutical technologies. The goal is to reduce the exclusive dependence on PZQ and optimize the treatment methodology to mitigate the development of new resistant strains of the parasite. Pre-clinical research reveals the promising potential of alternative agents with low cytotoxicity and multimodal action: Thiazole derivatives induce mortality, paralysis, inhibition of oviposition, and damage to the parasite's tegument in vitro; and Nanomaterials such as SC-5%CuO cause dose-dependent paralysis and, in vivo, eliminate eggs and liver fibrosis. Combination therapies demonstrate superior efficacy in modulating pathology, with Mefloquine (MFQ) and GNPs (Ginger Nanoparticles) preventing the formation of granulomas, and the combination of GNPs + PZQ reducing granulomas and accelerating their inactivation. These findings support the transition to diversified pharmaceutical strategies that not only combat the parasite but also reverse chronic pathology, which is essential for more sustainable control and for mitigating parasitic resistance.

Keywords: *Schistosoma mansoni*; Resistance; Treatment; Future.

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INTRODUCTION

Schistosomiasis, a potentially fatal infection due to hepato-splenic and gastrointestinal alterations, is caused by blood helminths of the genus *Schistosoma spp.* and is classified by the World Health Organization (WHO) as one of the main neglected tropical diseases. It is estimated that more than 250 million people are infected worldwide, another 800 million are at risk of infection, and approximately 300,000 individuals die annually (WHO, 2025). In the Americas, Brazil accounts for more than 90% of cases, with a highlight on the Northeast region (Facchini *et al*., 2018). Pernambuco is the state with the highest mortality and hospital admission rate for schistosomiasis, a rate 5 times higher than the average; in 2024 alone, 1,669 cases were reported. Historically, municipalities in the Zona da Mata and Agreste regions had the highest prevalence and incidence, but currently, several cases have been registered along the entire Pernambuco coast and in the metropolitan region of Recife (Pernambuco, 2025). In addition to the clinical impact, the disease represents a significant economic and social burden: hospitalizations, therapeutics, early disability, and loss of labor productivity increase public healthcare system costs and perpetuate cycles of poverty. Furthermore, the infection causes stigmatization, psychological suffering, and deterioration of quality of life, configuring a persistent obstacle to human and socioeconomic regional development.

Currently, praziquantel (PZQ) is the only drug recommended by the WHO for the treatment and control of schistosomiasis (WHO, 2025). Despite its high parasitological cure rate, low cost, and favorable safety profile, PZQ has limitations such as the lack of activity against immature forms, which compromises the complete eradication of the parasite in treated individuals. Additionally, there are reports of decreased sensitivity and development of resistance in some strains, particularly in regions that carry out Mass Drug Administration (MDA), which raises concerns about the sustainability of exclusive PZQ treatment (Crellen, *et al*., 2016).

These restrictions reinforce the need for continuous investigation of new therapeutic strategies and complementary approaches for the effective treatment and control of schistosomiasis. This study aims to review the literature on pharmacological alternatives for the treatment of schistosomiasis, with an emphasis on the screening and development of new drugs, bioactive compounds, and innovative pharmaceutical technologies, aiming to reduce the exclusive dependence on PZQ and to optimize the treatment methodology for schistosomiasis so that the development of new resistant strains is mitigated.

METHODOLOGY

The methodological strategy adopted in this study was a narrative review of the literature through a critical analysis of different and promising therapeutic alternatives for schistosomiasis. This type of review is characterized by a broad approach that aims to describe and discuss the state of the art of a given topic and answer questions from a theoretical and/or contextual perspective. Narrative reviews play a relevant role in continuing education, as they allow the reader to access, synthesize, and update knowledge on a specific topic in a short period of time (Silva, *et al*., 2021).

The bibliographic material search was conducted between July and September 2025 in the following databases: National Library of Medicine (PubMed), SCIELO (Scientific Electronic Library Online), and NCBI (National Center for Biotechnology Information). The following terms were crossed: “alternative”, “treatments”, “for”, “schistosomiasis”, “resistance” and the Boolean operators AND and OR in English and Portuguese. The selection criteria were full-text, open-access articles with pre-clinical or clinical trials that addressed new drugs, natural compounds, or pharmaceutical technologies for the treatment of schistosomiasis, published in the last 10 years. Initially, titles and abstracts were screened by two independent reviewers. Potentially relevant studies were read in their entirety to confirm eligibility, and any disagreements between the reviewers were resolved by consensus or by a third reviewer.

In contrast, articles that addressed other aspects related to schistosomiasis, incomplete articles, theses, dissertations, TCCs (undergraduate theses), and articles published in scientific event proceedings and outside the selected time frame were excluded from the analysis. The analysis and synthesis of the articles are expressed qualitatively and quantitatively, highlighting trends, research gaps, the effectiveness of the proposed compounds and technologies, and study limitations. Comparisons with the standard treatment (praziquantel) were emphasized whenever the studies presented comparative data.

RESULTS AND DISCUSSION

In total, 154 articles were found, of which 4 were selected according to the established criteria. An analysis roadmap was developed that included authorship, country, year of publication, study design, main statistical tests, and results. PZQ is the only drug used in mass preventive chemotherapy (Mass Drug Administration – MDA) programs against schistosomiasis, constituting a central pillar in the control of the disease on a global scale. Its relevance comes from a set of pharmacological, operational, and economic advantages, such as: high effectiveness against all *Schistosoma* species that infect humans; chemical stability; good tolerability and safety profile, with generally mild and transient adverse effects; oral administration in a single dose; and low cost. On the other hand, the available doses of PZQ still do not meet the global demand of infected patients, besides having limitations, such as the lack of effectiveness against immature stages and the risk of the emergence of resistant and/or tolerant *Schistosoma* strains (Crellen *et al*., 2016).

Crellen and colleagues (2016) highlight, in a study of 6 primary schools in different districts of Uganda, that children infected with *S. mansoni* showed greater resistance to PZQ when subjected to more rounds of MDA, based on the quantification of eggs in feces before and after treatment with 40 mg/Kg of PZQ and 400 mg of Albendazole. Schools that performed 8-9 rounds of administration (high) had an average Egg Reduction Rate (ERR) of 92.10%, significantly lower (95% CI) than those that had done 5 rounds (medium) and 1 round (low), which had an ERR of 98.04 and 97.81, respectively. Furthermore, it was proposed that schools with high MDA had high prevalence (84%) and infection intensity > 400 eggs per gram (EPG) even after 9 rounds of MDA, suggesting a selection pressure from the drug causing resistance in parasites that have considerable genetic variability (Crellen *et al*., 2016). In addition, the persistence of a high egg load in the feces of children after nine successive rounds of praziquantel (PZQ) treatment raises central concerns about the sustained effectiveness of MDA and the possibility of the emergence of parasitic resistance. A first aspect to be considered is the selective pressure exerted by the repetitive use of a single drug, even with the high incidence of schistosomiasis. In MDA programs, individuals are treated regardless of whether they have an active infection, which continuously exposes parasite populations to PZQ. This context favors the survival and dissemination of strains naturally less susceptible to PZQ, creating a conducive environment for the selection of resistant variants. Experimental and field studies have already demonstrated the existence of phenotypic and genotypic

variability among *Schistosoma spp.* populations, which suggests that selective pressure can, in fact, amplify sub-populations with lower sensitivity to PZQ.

The results obtained highlight the need for new therapeutic alternatives. In this context, substances such as thiazole derivatives, calcium silicate nanoparticles with 5% copper oxide (SC-5%CuO) and ginger extract, and ginger-derived nanoparticles (GNPs) showed promising action against *S. mansoni* (Barbosa *et al*., 2019, El Nour *et al*., 2020 and El Wahab *et al*., 2021). The new pharmaceutical technologies studied by Barbosa (2019) and El Nour (2020) showed low cytotoxicity for monocyte cells, in the case of thiazole derivatives, (CC50 between 125.6 µM and 1582.9 µM) and for melanocytes, in the case of SC-5%CuO. Furthermore, according to Barbosa (2019), almost all thiazole derivatives demonstrated lethal activity (mortality) and induced a decrease in the parasite's motor activity *in vitro*. Additionally, within a 24-hour drug-worm exposure period, it was observed that all compounds promoted the separation of couples, inhibition of oviposition, and morphological changes in the parasite's tegument. El Nour (2020), in turn, found that worms exposed to SC-5%CuO at concentrations of 10, 5, and 2.5 µg/mL showed a sharp depression in worm movements, showing a dose-response relationship and complete loss of motility *in vitro* occurring in 4, 6, and 12 hours, respectively. El Wahab's studies (2021) showed an absolute decrease in the total worm load in the 6th week in the group treated with ½ dose of GNPs and ½ dose of mefloquine (MFQ), and in the 10th week in groups treated with PZQ and MFQ, respectively ($P < 0.001$) compared to the untreated infected control group. In summary, the new technologies investigated have high therapeutic potential by inducing lethality and paralysis of the parasites, in addition to reducing the worm load in the host, all with a low cellular toxicity profile.

There was also a reduction in granulomas with the use of SC-5%CuO and ginger derivatives. According to the findings of El Nour (2020) and El Eahab (2021), *in vivo* treatment with the SC-5%CuO compound resulted in a hepatic histological picture that demonstrated a reduction in granulomatous inflammation, elimination of eggs, and fibrosis, although inflammatory infiltration persisted in the chronic phase. In contrast, treatment with Mefloquine (MFQ), alone or combined with nanoparticles (GNPs), led to the total absence of hepatic granulomas. The combination of GNPs and PZQ, on the other hand, proved effective in significantly reducing the size and number of granulomas, promoting egg degeneration, and changing the type of inflammatory granuloma to a fibrocellular (less active) granuloma, while the spleen, under the action of SC-5%CuO, showed varying degrees of egg degeneration surrounded by inflammation. The presented histological results provide crucial evidence on the curative and anti-fibrotic potential of new treatment strategies, focusing on the reversal of hepatic pathology induced by helminth eggs. The ability to prevent the formation of granulomas (MFQ/GNPs) or to accelerate their inactivation and regression (GNPs/PZQ) is fundamental for the development of treatments that can reverse the chronic tissue damage of the disease. Furthermore, ginger derivatives, in particular, showed a significant role when combined with PZQ, potentiating its effects and resulting in a reduction in worm load and egg deposition similar to that of isolated PZQ.

PZQ has limitations against immature stages and does not act directly on the processes of inflammation and liver fibrosis. Therefore, the combination of drugs emerges as a promising alternative to overcome these limitations. In this context, artemisinin derivatives (e.g., artesunate, artemether) have an effect on young forms of the parasite, complementing the effect of PZQ and reducing early re-infections. In addition, compounds with anti-inflammatory, anti-fibrotic, and antioxidant properties (curcumin, resveratrol, N-acetylcysteine) and modulators of the renin-angiotensin pathway have shown potential in reducing the granulomatous response, oxidative stress, and collagen deposition, mitigating the progression of liver fibrosis, which is the main morbidity in hepato-splenic and intestinal schistosomiasis. Thus, combined therapies can bring dual benefits: greater antiparasitic efficacy and a reduction in chronic morbidity associated with schistosomiasis. However, the adoption of these

strategies requires robust clinical studies that confirm their safety, efficacy, and viability in public health programs.

CONCLUSION

While Praziquantel (PZQ) is essential for the treatment and control of schistosomiasis, especially in Mass Drug Administration (MDA) programs, it has limitations against immature parasite stages and carries the risk of selecting for resistant strains. This highlights the urgent need for new therapeutic strategies. New approaches have shown promise. Thiazole derivatives, calcium silicate nanoparticles with copper oxide (SC-5%CuO), ginger nanoparticles (GNPs), and drug combinations with mefloquine and artemisinin have demonstrated potential in reducing parasite load, inducing worm lethality and paralysis, all while exhibiting low cytotoxicity. These new therapies have also shown the ability to reduce granulomatous inflammation, cause egg degeneration, and lead to the regression of liver fibrosis. This points to their potential to mitigate the chronic morbidity of the disease. Combining PZQ with compounds that have anti-inflammatory, anti-fibrotic, and antioxidant properties offers a dual benefit: greater antiparasitic efficacy and tissue protection. In summary, combined therapies and new pharmaceutical technologies represent promising alternatives to overcome PZQ's limitations. However, further clinical studies are needed to validate their large-scale safety and effectiveness.

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