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Anthelmintic activity of 1,10-phenanthroline-5,6-dione-based metallodrugs

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Parasitic worm infections impose a significant public health burden, affecting over 2 billion people, particularly in low-income regions. The limited efficacy of current treatments highlights the urgent need for new anthelmintic agents. This study investigates the potential antiparasitic activity of 1,10-phenanthroline-5,6-dione (phendione) and its metal complexes, $[Cu(phendione)_3](ClO_4)_2.8H_2O$ and $[Ag(phendione)_2](ClO_4)$, against *Schistosoma mansoni*, the causative agent of intestinal schistosomiasis, and *Angiostrongylus cantonensis*, responsible for eosinophilic meningitis in humans. Additionally, the compounds were tested on *Caenorhabditis elegans*, a model organism for drug discovery. All compounds exhibited strong antiparasitic activity, with Cu-phendione showing the greatest potency (EC_{50} = 2.3 µM for *S. mansoni* and 6.4 µM for *A. cantonensis*). Ag-phendione also demonstrated significant activity, achieving EC_{50} values of 6.5 µM against *S. mansoni* and 12.7 µM against *A. cantonensis*. The lethal dose (LD_{50}) values in *C. elegans* were over 40 times higher, indicating selective antiparasitic effects. Cytotoxicity assays using Vero cells revealed a low toxicity profile and a high selectivity index. Given the promising biological properties of phendione and its metal complexes, these findings contribute to the growing body of research seeking to address the urgent need for new anthelmintic therapies.

Parasitic worm infections, or helminthiasis, represent a substantial but often overlooked global health burden. Affecting over 2 billion individuals, primarily in tropical and subtropical regions, these infections disproportionately impact impoverished and marginalized populations with limited access to clean water and sanitation[1]. Helminthiasis contributes significantly to morbidity and mortality, and many emerging infectious diseases of parasitic origin are zoonotic, further complicating control efforts. Recognizing the urgent need for intervention, the World Health Organization (WHO) has included helminthic diseases in its 2021 roadmap, aiming to eliminate neglected diseases by 2030[2]. Despite ongoing efforts, the arsenal of effective anthelmintic agents remains limited[3].

Schistosomiasis, caused by the intravascular trematode of the genus *Schistosoma*, stands out as one of the most significant parasitic diseases globally, particularly in terms of public health and economic impact. Affecting millions in Africa, the Middle East, South America, and the Caribbean, *S. mansoni* infection leads to chronic morbidity due to the formation of granulomas and fibrosis from trapped eggs in human tissues[4]. While praziquantel is the only drug currently used in mass treatment programs[5], its limitations, such as reduced efficacy against juvenile parasites and the emergence of drug resistance[6], have highlighted the need for alternative therapies[7].

Similarly, *Angiostrongylus cantonensis*, the rat lungworm, presents a growing zoonotic threat[8], causing eosinophilic meningitis and other neurological complications in humans[9]. This nematode, prevalent in mollusk hosts, has spread across various continents, including Africa, Southeast Asia, and the Americas, with cases often linked to travel and misdiagnosed due to the mild symptoms[10]. Despite its public health importance, there is

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no effective anthelmintic treatment for *A. cantonensis* infections, underscoring the need for new therapeutic options[11,12].

Transition metal complexes, especially those involving bioactive ligands, have emerged as a promising class of compounds in the search for novel antiparasitic drugs[13]. These complexes offer impressive chemical diversity and versatility, which depend on the metal of choice, its oxidation state, the number and type of coordinating ligands, and specific magnetic and/or optical properties[14]. This versatility allows for the rational design of compounds tailored to interact with specific biological targets, addressing the limitations of traditional anthelmintics.

Phenanthrenes, secondary metabolites produced by plants, serve as the chemical backbone for several biologically active compounds[15,16]. One such example is 1,10-phenanthroline-5,6-dione (phendione), a phenanthrene-based compound, whose metal complexes have shown significant potential due to their unique coordination chemistry and interactions with biological macromolecules[17,18]. Phendione and its metal complexes have been investigated for their antimicrobial and anticancer properties[19,20], establishing them as promising candidates for antiparasitic research[21,22]. However, their potential against helminths remains largely unexplored.

Given the limited efficacy of current anthelmintic treatments and the pressing need for novel agents, this study investigates the potential antiparasitic properties of phendione and its copper, $[Cu(phendione)_3](ClO_4)_2{\cdot}8H_2O$ – Cu-phendione, and silver, $[Ag(phendione)_2](ClO_4)$ – Ag-phendione, complexes. We evaluate their in vitro effects on *S. mansoni* and *A. cantonensis* and further explore their activity using *Caenorhabditis elegans*, a model organism for drug discovery. To assess their potential as therapeutic agents, we also performed cytotoxicity assays using Vero cells to determine their selectivity and safety profiles.

Results

The anthelmintic activities of phendione and its metal complexes (Cu-phendione and Ag-phendione) (Fig. 1) were evaluated alongside standard control drugs: praziquantel for *S. mansoni*, albendazole for *A. cantonensis*, doxorubicin for cytotoxicity in Vero cells, and ivermectin for *C. elegans*. Additionally, the simple metal salts $AgNO_3$ and $CuSO_4{\cdot}5\ H_2O$ were included for comparison (Tables 1**and** Fig. 2).

Antiparasitic activity against *Schistosoma mansoni*

Cu-phendione exhibited the highest potency, with an EC_{50} of 2.3 µM against *S. mansoni*, outperforming both phendione (EC_{50} = 18.8 µM) and Ag-phendione (EC_{50} = 6.5 µM). While praziquantel remained the most effective control drug (EC_{50} = 1.2 µM), the potency of Cu-phendione was comparable. In contrast, the simple metal salts $AgNO_3$ and $CuSO_4{\cdot}5\ H_2O$ showed no antischistosomal activity (Table 1). The negative control group (1% DMSO) displayed no significant alterations, with worms remaining motile throughout the entire incubation period (Fig. 2).

Antiparasitic activity against *Angiostrongylus cantonensis* L_1 larvae

Cu-phendione exhibited strong activity against *A. cantonensis* (EC_{50} = 6.4 µM), outperforming phendione (EC_{50} = 25.6 µM) and demonstrating similar efficacy to albendazole (EC_{50} = 10.7 µM). Ag-phendione also showed good efficacy (EC_{50} = 12.7 µM) but was less active than Cu-phendione (Table 1). In contrast, the simple metal salts $AgNO_3$ and $CuSO_4{\cdot}5\ H_2O$ showed no activity against *A. cantonensis*. Phendione treatment significantly reduced larval motility compared to the control group, while DMSO-treated larvae maintained normal activity throughout the assay (Fig. 3).

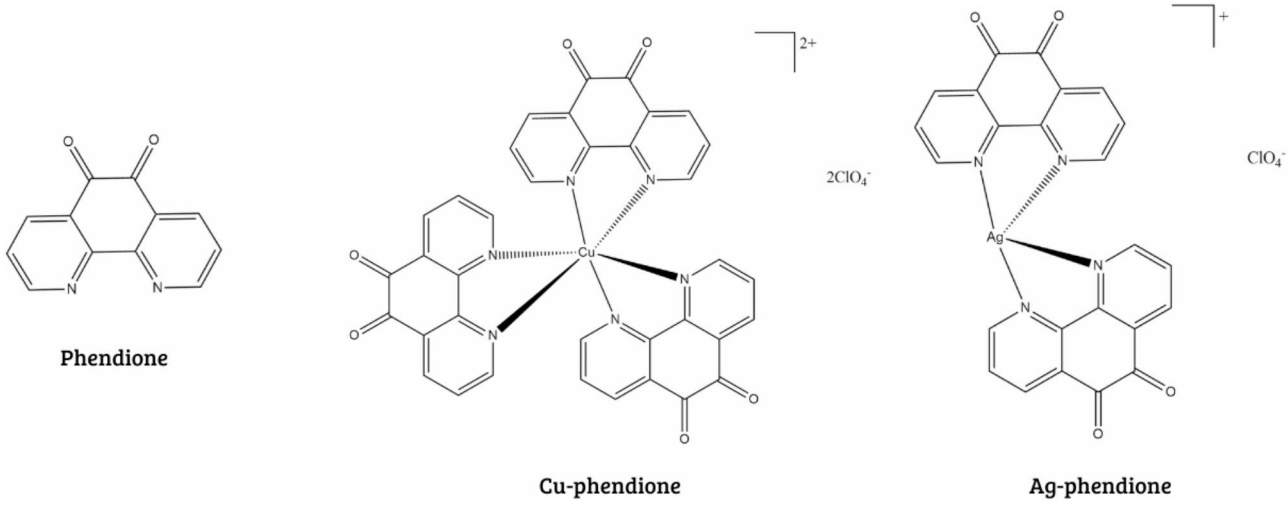

Fig. 1. Chemical structures of 1,10-phenanthroline-5,6-dione (phendione) and its metal complexes: $Cu(phendione)_3(ClO_4)_2{\cdot}8\ H_2O$ (Cu-phendione) and $[Ag(phendione)_2](ClO_4)$ (Ag-phendione).

	S. mansoni EC_{50} (μM)	A. cantonensis EC_{50} (μM)	Vero cells CC_{50} (μM)	SI for S. mansoni	SI for A. cantonensis	C. elegans LD_{50} (μM)
Phendione	18.8 ± 3.4	25.6 ± 4.1	> 200	> 10.6	> 7.81	719 ± 32.9
Cu-phendione	2.3 ± 1.1*,ł	6.4 ± 1.4*,ł	> 200	> 86.9	> 31.2	280 ± 21.6
Ag-phendione	6.5 ± 1.5*	12.7 ± 2.1*	> 200	> 30.7	> 15.5	167 ± 22.8
Praziquantel	1.2 ± 0.3*,+	ND	> 200	> 166.6	ND	ND
Albendazole	ND	10.7 ± 2.6*	> 200	ND	> 18.6	ND
Ivermectin	ND	ND	ND	ND	ND	4.1 ± 1.2
Doxorubicin	ND	ND	9.6 ± 3.3	ND	ND	ND

Table 1. Anthelmintic activity and toxicity of phendione and its metal-based complexes compared to standard drugs. ND: Not determined. SI: Selectivity index, calculated as the ratio of the CC_{50} value in Vero cells to the EC_{50} value in *S. mansoni* or *A. cantonensis* ($SI = CC_{50}/EC_{50}$). Data represent the mean ± S.D. from at least three independent experiments performed in triplicate. *$P < 0.05$ comparing Cu-phendione, or Ag-phendione, or praziquantel, with phendione. ł$P < 0.05$ comparing Cu-phendione with Ag-phendione.

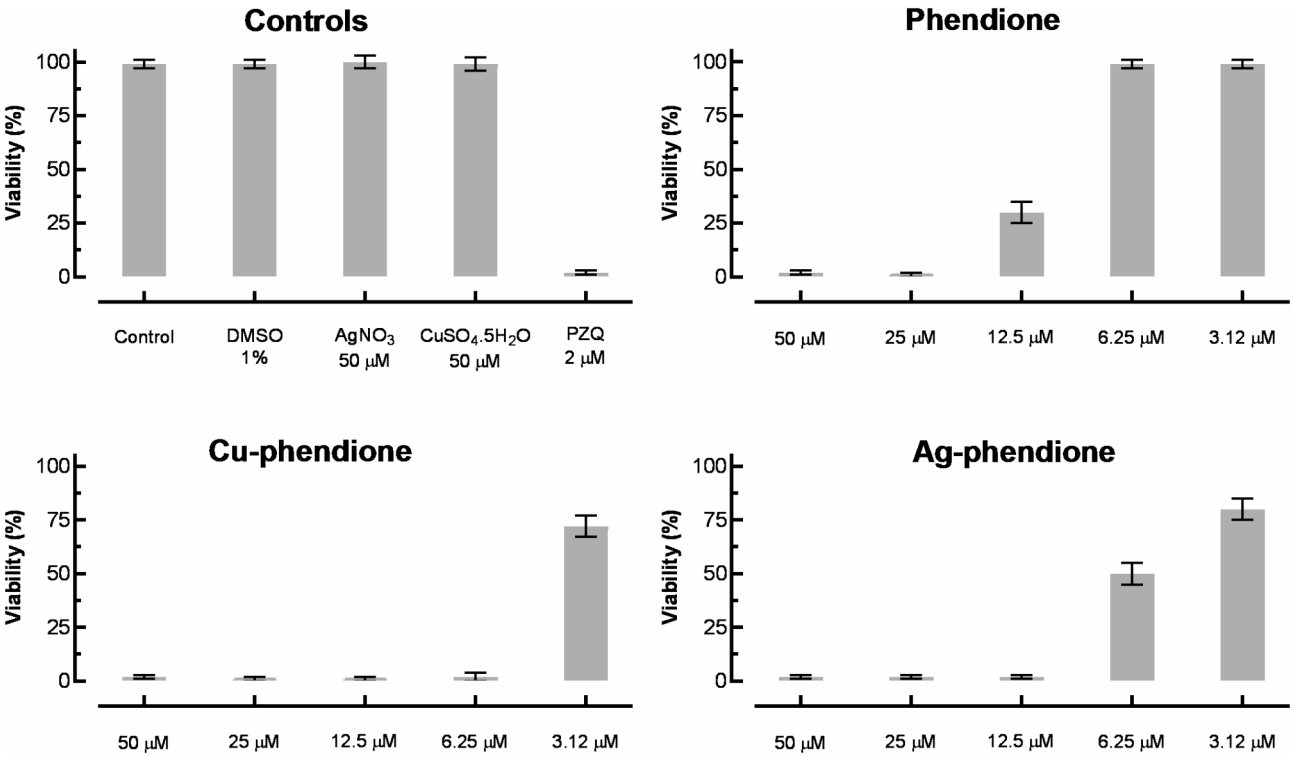

Fig. 2. Viability of adult *Schistosoma mansoni* worms after incubation with different concentrations of phendione and its metal complexes (Cu-phendione and Ag-phendione). Control groups included parasites incubated in drug-free medium, praziquantel (PZQ), metal salts ($AgNO_3$ and $CuSO_4{\cdot}5\ H_2O$), and 1% DMSO. Schistosomes were obtained from animals by perfusion 49 days post-infection. Each concentration was tested in triplicate, and worm viability was monitored for up to 72 h. Data represent the mean ± S.D. from at least three independent experiments performed in triplicate.

Toxicity and selectivity index

None of the tested compounds exhibited cytotoxicity in Vero cells at concentrations up to 200 μM (Fig. 4). In comparison, doxorubicin had a CC_{50} value of 9.6 μM, indicating that phendione and its metal complexes have significantly lower toxicity. The selectivity index (SI) values for Cu-phendione were particularly noteworthy, with SI > 86.9 for *S. mansoni* and SI > 31.2 for *A. cantonensis*, indicating high therapeutic potential. Ag-phendione also showed favorable SI values, with SI > 307 for *S. mansoni* and SI > 15.5 for *A. cantonensis* (Table 1).

The compounds were further evaluated for toxicity in *C. elegans* (Fig. 4). Cu-phendione exhibited an LD_{50} of 280 μM, significantly lower than ivermectin ($LD_{50} = 4.1$ μM), indicating lower toxicity. Similarly, Ag-phendione showed an LD_{50} of 167 μM, while phendione demonstrated the least toxicity ($LD_{50} = 719$ μM) (Table 1). These results suggest selective toxicity of the metal complexes toward parasitic helminths while minimizing the risk to non-target organisms.

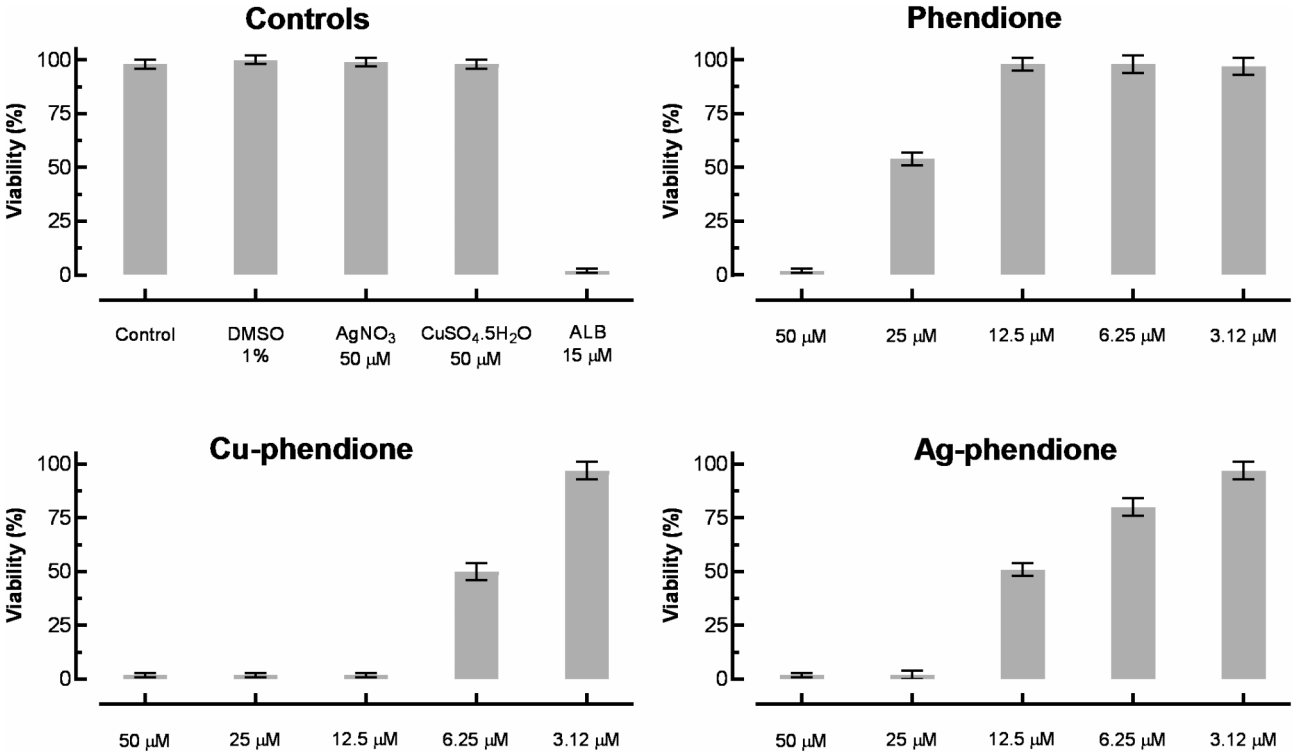

Fig. 3. Viability of *Angiostrongylus cantonensis* L1 larvae during incubation with different concentrations of phendione and its metal complexes (Cu-phendione and Ag-phendione). Control groups included larvae incubated in drug-free medium, albendazole (ALB), metal salts ($AgNO_3$ and $CuSO_4{\cdot}5\ H_2O$), and 1% DMSO. Each concentration was tested in triplicate, and larval viability was monitored for up to 24 h. Data represent the mean ± S.D. from at least three independent experiments performed in triplicate.

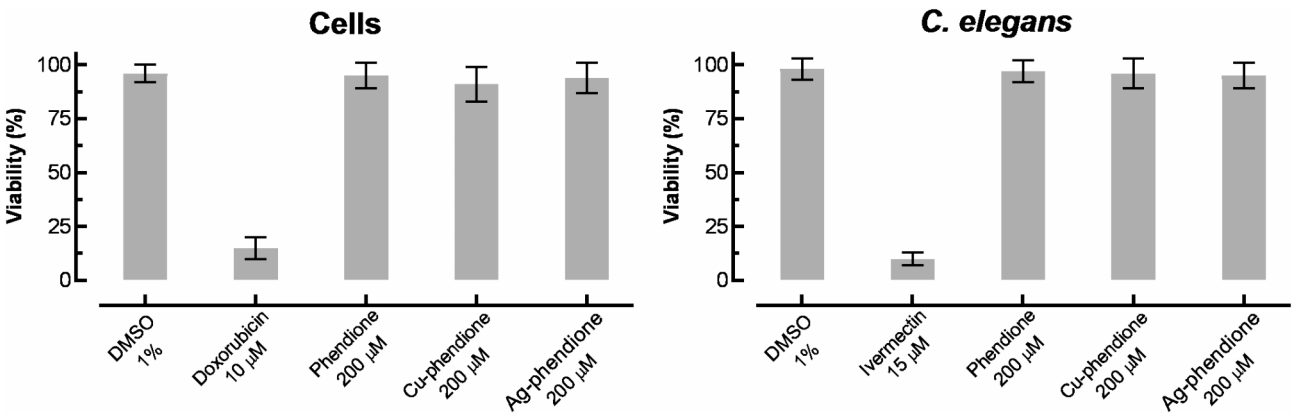

Fig. 4. Toxicity of phendione and its metal complexes (Cu-phendione and Ag-phendione) on Vero cells and *Caenorhabditis elegans*. Doxorubicin and ivermectin were used as reference drugs, while 1% DMSO-treated cells or *C. elegans* served as controls. Each concentration was tested in triplicate, with viability monitored over 72 h. Data represent the mean ± S.D. from at least three independent experiments performed in triplicate.

Discussion

This study highlights the potent antiparasitic activity of phendione and its metal complexes, particularly Cu-phendione and Ag-phendione, against *S. mansoni* and *A. cantonensis*. These results emphasize the therapeutic potential of metallodrugs in addressing parasitic infections, especially considering the limitations of existing anthelmintic treatments. Importantly, the tested compounds exhibited selective toxicity, showing minimal impact on non-parasitic organisms like *C. elegans* and low cytotoxicity in Vero cells.

Among the tested compounds, Cu-phendione demonstrated the highest potency, with EC_{50} values comparable to those of praziquantel for *S. mansoni* and albendazole for *A. cantonensis*. Its enhanced efficacy compared

to Ag-phendione aligns with previous studies indicating that copper complexes exhibit superior antiparasitic activity, such as against *Trichomonas vaginalis*[21] and *Leishmania braziliensis*[23]. Notably, the inactivity of simple metal salts ($AgNO_3$ and $CuSO_4{\cdot}5\ H_2O$) reinforces the importance of metal-ligand coordination in optimizing biological activity.

The enhanced performance of Cu-phendione may be attributed to its involvement in parasite metabolism and oxidative stress, as previously reported in studies with *S. mansoni*[24]. Recent research has also identified peptidases as potential targets of Cu-phendione in *Leishmania*[23] and *T. vaginalis*[25], while metabolic disruption and altered membrane potential have been observed in *Leishmania* species treated with Cu-phendione[22]. These findings suggest that the coordination between the metal center and phendione enhances interactions with key biological targets, increasing the parasites' susceptibility to treatment. Additionally, oxidative stress response signaling pathways may contribute to nematode death[26,27]. Further investigations are needed to elucidate the precise mechanisms underlying these interactions and optimize the design of future metallodrugs.

The schistosomicidal activity observed in this study surpasses many plant-derived products reported in the literature. For example, EC_{50} values reported for *S. mansoni* adult worms include 12.5 μM for verrucosin[28], 26.1 μM for diterpene ent-kaur-16-en-19-oic acid[29], 30 μM for neolignan licarin A[30], 31.9 μM for dehydrodieugenol B[31], 42.16 μM for carvacryl acetate[32], 50 μM for cnicin[33], licochalcone A[34], 2-oxopopulifolic acid methyl ester, and 2-oxopopulifolic acid[35], 56.8 μM for monoterpene carvacrol[36], and 81.8 μM for flavonoid kaempferol[37]. Compared to the aforementioned compounds, which are obtained directly from plants, phendiones are obtained by synthesis and are easily obtained in large quantities. The superior performance of phendione-based complexes in this study underscores their potential as more effective alternatives to many of these plant-derived compounds. Additionally, unlike the aforementioned plant-derived compounds, which require extraction and purification processes, phendiones are synthetically produced and can be easily obtained in large quantities, making them more scalable and cost-effective for therapeutic applications.

In addition to their potent antiparasitic activity, the metal complexes exhibited high selectivity. The EC_{50} values were more than 40 times higher in *C. elegans* than in parasitic worms, demonstrating selective targeting. Furthermore, the compounds showed low cytotoxicity in Vero cells, with selectivity indices exceeding 86.9 for *S. mansoni* and 31.2 for *A. cantonensis*, reinforcing their favorable safety profiles. These findings align with previous studies reporting minimal toxicity of phendione derivatives in various cell lines[21,38] and low toxicity in *Galleria mellonella* larvae[38,39], as well as in mammalian models, including mice[38] and hamsters[40].

Despite the absence of toxicity observed in in vitro and in vivo models with phendione and its metal complexes, it is important to acknowledge that metal-based drugs also present certain limitations that must be addressed to realize their full therapeutic potential. These include concerns about potential toxicity, as metals can accumulate in tissues and cause adverse effects[41]. Furthermore, the stability of metal-based complexes under physiological conditions and their interactions with off-target biomolecules may compromise their efficacy and safety[41,42]. Future research should prioritize addressing these limitations through careful optimization of metal-ligand combinations, the development of targeted delivery systems, and comprehensive safety evaluations to ensure their viability as alternative therapeutics for parasitic diseases.

Finally, future research should focus on in vivo studies to validate the efficacy, pharmacokinetics, and safety of these compounds. Investigating potential synergistic effects with established drugs, such as praziquantel or albendazole, could further enhance therapeutic outcomes. Additionally, understanding the mechanisms of action in greater detail may provide insights for developing new metallodrugs with improved selectivity and efficacy. Such advancements are particularly critical in addressing the growing challenge of drug resistance in parasitic infections. Metal-based drugs, with their unique properties and diverse mechanisms, offer a promising alternative to overcome resistance issues, as they can target different biological pathways compared to traditional therapies. This versatility underscores their potential as a valuable addition to the arsenal against drug-resistant parasitic diseases.

Conclusions

This study demonstrates the potent antiparasitic activity of phendione and its metal complexes, particularly Cu-phendione, against two major helminth species. The selective toxicity observed, combined with low cytotoxicity in mammalian cells, underscores the therapeutic promise of these compounds. These findings provide a strong foundation for further in vivo studies and preclinical development, offering new opportunities to expand the limited arsenal of anthelmintic agents. Moreover, exploring synergistic combinations with existing drugs could enhance efficacy and mitigate drug resistance, contributing to more effective treatment strategies for parasitic infections.

Methods

Compounds

1,10-Phenanthroline-5,6-dione (phendione) and its metal complexes, $[Ag(phendione)_2]ClO_4$ (Ag-phendione) and $Cu(phendione)_3(ClO_4)_2{\cdot}8\ H_2O$ (Cu-phendione) (Fig. 1), were synthesized following the protocols previously described[43]. Details of the synthesis and characterization of the compounds are provided in the Supplementary Information. These compounds were dissolved in dimethyl sulfoxide (DMSO) and stored at 4 °C until use. Praziquantel, albendazole, and ivermectin were generously provided by Ecovet Indústria Veterinária Ltda (São Paulo, Brazil), while doxorubicin was purchased from Sigma-Aldrich (St. Louis, MO, USA).

Maintenance of parasitic worms

The life cycle of *Schistosoma mansoni* (Belo Horizonte strain) was maintained at the Research Center on Neglected Diseases, Guarulhos University, using *Biomphalaria glabrata* snails as the intermediate host and Swiss

mice (*Mus musculus*) as the definitive host. Similarly, the *Angiostrongylus cantonensis* (NPDN-AC strain) life cycle was maintained by alternating between *B. glabrata* snails and Wistar rats (*Rattus norvegicus*). All animals were housed under controlled conditions (22 °C, ~50% humidity) with *ad libitum* access to food and water.

In vitro assay with adult *S. mansoni*

Adult *S. mansoni* worms were obtained by hepatic portal vein perfusion from Swiss mice, 49 days post-infection, following established protocols[44,45]. The worms were washed in RPMI 1640 medium with antibiotics and transferred to 24-well plates, with one pair of adult worms per well. Each well contained 1 mL of RPMI 1640 medium enriched with 10% fetal bovine serum, penicillin (100 U/mL), and streptomycin (100 µg/mL).

Test compounds, praziquantel, and metal salts ($AgNO_3$ and $CuSO_4{\cdot}5\ H_2O$) were added at concentrations starting from 50 µM. DMSO (1%) served as the negative control. Plates were incubated at 37 °C with 5% CO_2 for up to 72 h, and worm viability was assessed at 0, 24, 48, and 72 h using an inverted microscope. Parasite death was determined by the absence of movement for at least one minute upon gentle mechanical stimulation[46].

In vitro assay with *A. cantonensis* L1 larvae

First-stage larvae (L1) of *A. cantonensis* were isolated from the feces of Wistar rats, using the Rugai technique, and washed in RPMI 1640 medium with antibiotics. Approximately 100 larvae per well were transferred to 96-well plates[12]. The compounds, praziquantel, and metal salts were tested at concentrations starting from 50 µM, with incubation at 21 °C. Larval viability was assessed at 0 and 24 h under an inverted microscope. Movement was categorized as immobile, intermittent, slow, or highly active. Efficacy was defined as at least 60% of larvae becoming immobile within 24 h[11,12].

Lethal toxicity assay in *C. elegans*

The Bristol N2 strain of *Caenorhabditis elegans* was cultured on nematode growth medium (NGM) plates seeded with *Escherichia coli* OP50[47]. L4-stage larvae were synchronized and transferred to 96-well plates containing M9 medium, with 60 larvae per well[48]. The compounds and ivermectin were tested at concentrations starting from 1,000 µM, with 1% DMSO as the negative control. Viability was assessed after 24 h of incubation at 21 °C by observing movement[30]. Lethal toxicity was defined as 60% or more of the larvae exhibiting complete immobility[49].

Cytotoxicity assay in vero cells

Vero cells (ATCC CCL-81) were maintained in DMEM medium supplemented with 10% fetal bovine serum, penicillin (100 U/mL), and streptomycin (100 µg/mL) at 37 °C with 5% CO_2. The cells were seeded into 96-well plates at 2×10^3 cells per well and incubated with the test compounds or doxorubicin at concentrations starting from 200 µM, with 1% DMSO as the negative control. Notably, the 200 µM concentration represents the maximal solubility of the compounds under the assay conditions and adheres to standard practices for selectivity index calculations[50]. Additionally, 1% DMSO was confirmed to be non-toxic to the cells. Cytotoxicity was assessed using the MTT assay[51,52]. After 72 h, MTT solution was added, followed by 3 h of incubation. Absorbance was measured at 595 nm using an Epoch Microplate Spectrophotometer (BioTek Instruments, Winooski, VT, USA). Assays were performed in triplicate and repeated three times. Selectivity index (SI) values were calculated as the ratio of the 50% cytotoxic concentration (CC_{50}) in Vero cells to the 50% effective concentration (EC_{50}) in the parasitic helminths[53].

Data analysis

Statistical analyses were conducted using GraphPad Prism 8.0. EC_{50}, CC_{50}, and LD_{50} values were determined through sigmoidal dose-response curves[48,54]. Differences between groups were analyzed using one-way ANOVA followed by Tukey's post-hoc test, with statistical significance set at $P < 0.05$.

Data availability

All relevant data for this study are included within the manuscript. The raw data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author contributions

M.E.C., A.L.S.S., and J.d.M. contributed to conceptualization; M.E.C., T.R.T., A.C.C.B., L.F.S., and A.M.H.S., contributed to experiments and data interpretation; M.E.C. and J.d.M. contributed to writing - original draft and visualization; A.M.H.S., A.L.S.S., and J.d.M. contributed with resources, writing - review & editing; J.d.M. contributed to project administration and funding acquisition. All authors have read and agreed to the published version of the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Ethical approval

This study adhered to the ARRIVE guidelines established by the National Centre for the Replacement, Refinement & Reduction of Animals in Research (NC3Rs). All experimental protocols were approved by the Committee for the Ethical Use of Animals in Experimentation at Guarulhos University (Guarulhos, SP, Brazil), under protocol numbers 064/24 (*A. cantonensis*) and 065/24 (*S. mansoni*). The study was conducted in full compliance with Brazilian legislation on the care and use of laboratory animals.

Additional information

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