Current Research in Parasitology & Vector-Borne Diseases 7 (2025) 100256

Contents lists available at ScienceDirect

Current Research in Parasitology & Vector-Borne Diseases

journal homepage: www.sciencedirect.com/journal/current-research-in-parasitology-and-vector-borne-diseases

Exploring bioactive molecules released during inter- and intraspecific competition: A paradigm for novel antiparasitic drug discovery and design for human use

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ARTICLE INFO

Keywords:
Antiparasitics
Bioactive molecule
Drug discovery
Interspecific competition
Intraspecific competition
Mechanism of action

ABSTRACT

Many antiparasitic drugs have become obsolete and ineffective in treating parasitic diseases. This ineffectiveness arises from parasite drug resistance, high toxicity, and low drug efficacy. Thus, the discovery of novel agents is urgently needed to control parasitic diseases. Various strategies are employed in drug discovery, design, and development. This review highlights the paradigm of searching for bioactive molecules produced during inter- and intraspecific competition among organisms, particularly between microbes and parasites, as a strategy for *de novo* antiparasitic drug discovery. Competitive interactions occur when individuals of the same or different species coexist in overlapping niches and compete for space and resources. These interactions are well recognized. Therefore, bioactive molecules released during these interactions are promising targets for novel drug discovery. Compelling data indicate that microbes remain a potential source for the discovery of novel antiparasitic drugs because of their diversity. Many antimicrobial producers in nature have yet to be isolated and investigated. This body of evidence underscores the success of numerous therapeutic drugs, including penicillin, β-lactams, and tetracyclines, which have been successfully discovered and developed for treating infectious diseases. This review comprehensively covers these concepts, with a particular focus on inter- and intraspecific competition in the discovery of novel antiparasitic agents. This approach will pave the way for identifying alternative strategies to control and eradicate parasitic diseases that continue to threaten human health. Additionally, this review discusses current antiparasitic drugs and their mechanisms of action, limitations, and existing gaps. This discussion emphasizes the ongoing need to explore novel antiparasitic drugs.

1. Introduction

Parasitic diseases are illnesses caused by infections with endoparasites, such as cestodes, nematodes, protists, and trematodes, or infestations with ectoparasites, including those in the classes Arachnida and Insecta. These diseases predominantly affect populations in tropical, subtropical, and temperate regions (CDC, 2022). However, immigration and international travel have led to a global incidence of parasitic infections. Currently, over 1.5 billion individuals, representing 24% of the world's population, are infected with soil-transmitted helminths (WHO, 2023). Significant parasitic diseases include Chagas disease, filariasis, leishmaniasis, malaria, and schistosomiasis, which impact millions of individuals worldwide (Daher et al., 2022). In 2022 alone, malaria was estimated to cause 249 million infections and 608,000 deaths (WHO, 2024). In the USA, neglected parasitic diseases such as cysticercosis, toxocariasis, toxoplasmosis, and trichomoniasis affect millions of people (Cantey et al., 2021). Additionally, primary amoebic meningoencephalitis (PAM) which is a highly fatal neurological disorder, caused by *Naegleria fowleri*, also affects individuals annually in the USA. This disease also poses significant public health challenges in many countries across Africa, Asia, Australia, Europe, and Oceania (Gharpure et al., 2021).

Parasitic infections and infestations exhibit diverse clinical characteristics across different organ systems, ranging from mild symptoms to severe illness. For example, infection with *Taenia saginata*, a beef tapeworm in the class Cestoda, typically results in mild symptoms such as anal itching (Song et al., 2019; Eichenberger et al., 2020). In contrast, infection with *Taenia solium*, a pork tapeworm, can present a spectrum of

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https://doi.org/10.1016/j.crpvbd.2025.100256
Received 28 January 2025; Received in revised form 15 March 2025; Accepted 24 March 2025
Available online 25 March 2025

manifestations ranging from asymptomatic infection and mild illness to severe headaches, altered mental status, seizures, and potentially lethal outcomes (Gonzales et al., 2016; Perez et al., 2022). The clinical manifestations of parasitic diseases are caused by various mechanisms, including mechanical damage, chemical damage, organ obstruction by the parasites, induction of hyperplasia, allergic reactions to toxic wastes, and transmission of other microbes following parasitic invasion (Tungtrongchitr, 2017; Ruenchit, 2021).

The management of parasitic diseases involves both pharmacological and non-pharmacological approaches. Pharmacological treatments encompass various classes of antiparasitic drugs that target a wide range of parasitic organisms, including helminths (anticestodal, antinematodal, and antitrematodal agents), protozoans (antiprotozoal drugs), and ectoparasites (ectoparasiticides) (Campbell and Soman-Faulkner, 2022). The mechanisms of action of these antiparasitic agents are diverse and include disruption of parasite structure and function, inhibition of enzymatic activities or metabolic processes, suppression of nucleic acid and protein synthesis, interference with energy production, disruption of neuromuscular coordination, generation of free radicals, and inhibition of heme detoxification.

Non-pharmacological management strategies, such as patient isolation, personal hygiene, and sanitation, are essential for the prevention and control of parasitic diseases. Although numerous antiparasitic drugs have been approved and effectively used to treat parasitic infections for several decades - some of which possess broad-spectrum activity - the current therapeutic options remain limited due to significant toxicity and adverse effects (Partridge et al., 2017). Additionally, the efficacy of some antiparasitic agents has declined as parasites have developed resistance. For instance, multidrug resistance of *Plasmodium falciparum* to artemisinin-based combination therapies has been documented (Ward et al., 2022). Similarly, resistance to pentavalent antimonial compounds has been reported in *Leishmania* spp. from India and Sudan (Sundar et al., 2000; Maltezou, 2010). Furthermore, various adverse effects associated with antiparasitic drugs include anorexia, arrhythmias, cytopenias, hepatitis, myalgias, pancreatitis, and vomiting (Kappagoda et al., 2011). Consequently, there is an urgent need for the discovery of novel antiparasitic agents that exhibit high efficacy and low toxicity to effectively combat parasitic diseases.

Since many parasitic diseases are recognized as neglected diseases, drug discovery and development are not driven primarily by market demand (Pink et al., 2005). Additionally, emerging diseases periodically arise, prompting researchers to focus on immediate responses and preparations for potential re-emergence events. Parasitic diseases predominantly occur in regions with limited financial research support, which further contributes to the scarcity of studies dedicated to antiparasitic drug discovery (Pink et al., 2005). Nevertheless, the elimination of parasitic diseases necessitates the continuous discovery of novel antiparasitic agents.

Currently, several strategies are employed to identify new antiparasitic drugs, including drug repurposing, analog development, compound library screening, and *de novo* drug discovery (Fong and Wright, 2013; Bansal et al., 2021; Moreira et al., 2022; Shi et al., 2022). Within *de novo* drug discovery, various methodologies are utilized, such as target-based drug discovery, genome mining, and omics discovery approaches (Flannery et al., 2014; Bennuru et al., 2018; Cowell and Winzeler, 2019). This review discusses these strategies and emphasizes inter- and intraspecific competition as an additional approach for novel antiparasitic drug discovery. By advocating for the integration of this competitive strategy, this review aims to facilitate the discovery, design, and development of novel antiparasitic agents, ultimately enhancing the capacity to control and eradicate life-threatening parasitic diseases.

2. Current antiparasitic drugs

2.1. Groups of antiparasitic drugs

Antiparasitic drugs, also known as antiparasitics, are medications used to manage parasitic diseases. These diseases include infections caused by cestodes, nematodes, trematodes, and protozoans, as well as infestations with ectoparasites (Campbell and Soman-Faulkner, 2022). Antiparasitics are a subset of antimicrobial drugs, alongside antibiotics, which target bacteria, and antifungals, which target fungi. Currently, numerous classes of antiparasitic drugs are available, covering a broad range of parasitic diseases. In this review, all currently used antiparasitics and their mechanisms of action are examined by categorizing them on the basis of the type of parasite they target (anthelmintics, antiprotozoal drugs, and ectoparasiticides) (Tables 1–3).

2.2. Mechanisms of action of antiparasitic drugs

Each antiparasitic drug exhibits either static or cidal activity against various stages of parasites through distinct mechanisms. The most promising antiparasitic agents are characterized by their broad spectrum, highly selective absorption, specific sites of action, and selective toxicity to parasites. Although most currently used antiparasitic drugs were intentionally designed based on these criteria, they still possess certain limitations. This review comprehensively summarizes all reported modes of action, which will aid in understanding the common mechanisms of antiparasitics and facilitate the search for and development of new drugs.

2.2.1. Interference of energy production

Benzimidazole antiparasitic drugs, including albendazole, mebendazole, thiabendazole, and triclabendazole, exert their effects by interfering with energy production. They inhibit glucose uptake by blocking microtubule polymerization (Juliano et al., 1985; Solana et al., 1998; Furtado et al., 2016; Olivares-Ferretti et al., 2023). Benzimidazoles specifically bind to β-tubulin in nematodes and trematodes, impairing glucose uptake (Fig. 1). This binding also disrupts parasite motility and division (Solana et al., 1998). Niclosamide, another anthelmintic, inhibits oxidative phosphorylation in cestodes, resulting in impaired ATP production within mitochondria and disrupted energy production (Kulthawatsiri et al., 2023). Nitazoxanide interferes with energy production by inhibiting the enzyme pyruvate ferredoxin oxidoreductase (PFOR), which is essential for parasite energy metabolism (Hoffman et al., 2007). Melarsoprol is a prodrug metabolized to melarsen oxide, which binds to pyruvate kinase, disrupting energy production and preventing trophozoite multiplication in the parasite (Hidalgo et al., 2021). Additionally, atovaquone, an antibabesial drug, collapses the mitochondrial membrane potential of *Babesia gibsoni*, affecting the parasite's energy metabolism (Iguchi et al., 2022). Proguanil also impairs mitochondrial functions, leading to cell death (Mounkoro et al., 2021).

2.2.2. Interference with neuromuscular coordination

Many antiparasitic drugs exert their effects by disrupting neuromuscular coordination. For instance, ivermectin activates chloride ion channels in nematodes *via* γ-aminobutyric acid (GABA) receptors or glutamate-gated chloride ion channels. This activation causes hyperpolarization of neuromuscular cells, leading to flaccid paralysis (Fig. 2) (Martin et al., 2021). Ivermectin 0.5% lotion increases chloride ion concentrations in muscle cells, resulting in hyperpolarization and paralysis of head lice (Deeks et al., 2013). Diethylcarbamazine is another antiparasitic agent that induces hyperpolarization and immobilization of microfilariae (Maizels and Denham, 1992).

Levamisole and pyrantel pamoate are nicotinic agonists that target acetylcholine receptors in the somatic muscles of nematodes, causing paralysis (Martin et al., 1996). Praziquantel increases calcium influx into neuromuscular cells, leading to spastic paralysis (Abou-El-Naga,

Table 1
Current anthelmintics, mechanisms of action, and limitations.

Antiparasitic (Disease)	Mechanism of action	Limitation	Reference
Antinematodal drugs			
Albendazole [a] (ascariasis, trichuriasis, hookworm infection, enterobiasis, trichinellosis, strongyloidiasis, intestinal capillariasis, anisakiasis, and gnathostomiasis)	‣Inhibits microtubule polymerization by binding β-tubulin of nematodes, leading to impairment of cell motility, defect of cell division, and inhibition of glucose uptake; ‣Disrupts integumental integrity of cestode's protoscolex	‣Displays some adverse effects such as gastrointestinal tract disturbance (nausea, vomiting, and diarrhea), dizziness, headache, hair fall, alopecia, neutropenia, weakness, itching, fever, confusion, and allergic reactions; ‣Shows poor absorption with water	Solana et al. (1998); Aminpour et al. (2019); Turan and Metin (2020)
Diethylcarbamazine (filariasis)	‣Causes hyperpolarization and immobilization of microfilaria; ‣Alters the surface structure of microfilaria, leading to the attraction of host immune cells	‣Displays some adverse effects such as gastrointestinal tract disturbance, anorexia, dizziness, headache, malaise, and fever (from host reaction to dying parasite's protein); ‣Rapidly kills microfilaria, but not the adult	Sutanto et al. (1985); Maizels and Denham (1992); Norões et al. (1997)
Flubendazole (ascariasis, trichuriasis, hookworm infection, enterobiasis, trichinellosis, strongyloidiasis, intestinal capillariasis, and gnathostomiasis)	Binds to tubulin, resulting in disruption of microtubule structure	Shows poor absorption	Apt (1990); Spagnuolo et al. (2010)
Ivermectin (strongyloidiasis and gnathostomiasis)	Acts as an allosteric modulator to activate chloride ion channel through GABA receptor or glutamate-gated chloride ion channel of parasites, causing hyperpolarization of neuromuscular cells and flaccid paralysis	‣Causes gastrointestinal tract disturbance; ‣Difficult access to the blood-brain barrier; ‣Rapidly metabolized in the liver to inactive metabolites; ‣Ineffective to the adult stage of *Wuchereria bancrofti* or *Brugia malayi*	Martin et al. (2021)
Levamisole (ascariasis and hookworm infection)	Acts as nicotinic agonist targeting on acetylcholine receptors of nematode somatic muscle, leading to paralysis	Displays adverse effects, such as gastrointestinal tract disturbance, increased salivation, frequent urination and defecation, colic, dizziness, headache, muscle tremors, and others	Hsu (1980); Martin et al. (1996)
Mebendazole (ascariasis, trichuriasis, hookworm infection, enterobiasis, trichinellosis, strongyloidiasis, intestinal capillariasis, anisakiasis, and gnathostomiasis)	‣Inhibits microtubule polymerization by binding β-tubulin of nematodes, leading to impairment of cell motility, defect of cell division, and inhibition of glucose uptake ‣Disrupts integumental integrity of cestode's protoscolex	‣Hookworms (*Necator americanus*) show resistance; ‣Displays some adverse effects such as gastrointestinal tract disturbance, dizziness, abdominal pain, headache, hair fall, alopecia, neutropenia, weakness, itching, fever, confusion, and allergic reactions; ‣Shows poor absorption with water; ‣Rapidly metabolized in the liver to inactive metabolites	Witassek et al. (1983); Apt (1990); Lorenzini and Ruggieri (1990); Sacko et al. (1999); Furtado et al. (2016); Silber et al. (2017)
Prednisolone (trichinellosis)	Acts systemically to alleviate the effects of tissue larvae of *Trichinella spiralis*	No side effects were observed	Shimoni et al. (2007)
Pyrantel pamoate (ascariasis, enterobiasis, and hookworm infection)	Acts as nicotinic agonist targeting acetylcholine receptors of nematode somatic muscle, leading to paralysis	Hookworms (*Ancylostoma duodenale*) show resistance	Martin et al. (1996); Reynoldson et al. (1997)
Thiabendazole (ascariasis, trichuriasis, hookworm infection, enterobiasis, trichinellosis, strongyloidiasis, intestinal capillariasis, anisakiasis, and gnathostomiasis)	Inhibits microtubule polymerization	Displays some adverse effects, such as visual disturbance	Juliano et al. (1985); DrugBank Online (2024)
Antitrematodal drugs			
Bithional (fascioliasis)	‣Inhibits oxygen consumption; ‣Reduces glycolytic and oxidative metabolism; ‣Stimulates lactic acid production	Displays photosensitivity, gastrointestinal tract disturbance, abdominal pain, and urticaria	Hamajima (1973); Vanijanonta et al. (1984)
Metrifonate (schistosomiasis)	Acts as an organophosphorus cholinesterase inhibitor	Shows no significant side effects	Davis and Bailey (1969); Jewsbury (1981)
Oxamniquine (schistosomiasis)	Inhibits nucleic acid synthesis	Causes adverse neurological reactions	Pica-Mattoccia and Cioli (1985); Wong et al. (1990); Kokwaro and Taylor (1990)
Praziquantel [b] (schistosomiasis, echinostomiasis, fascioliasis, opisthorchiasis, and paragonimiasis)	Increases calcium influx into neuromuscular cells, causing spastic paralysis	‣*Schistosoma mansoni* shows resistance; ‣Causes adverse effects, such as gastrointestinal tract disturbance, malaise, headache, dizziness, low-grade fever, and rash; ‣Rapidly metabolized in the liver to inactive metabolites	Nash et al. (1982); Ismail et al. (1999); Abou-El-Naga (2020)
Triclabendazole (fascioliasis and paragonimiasis)	Inhibits microtubule polymerization by binding β-tubulin of *Fasciola* spp.	*Fasciola* spp. show resistance	Olivares-Ferretti et al. (2023); Tashibu et al. (2024)
Anticestodal drugs			
Niclosamide (diplydiasis, hymenolepiasis, and intestinal taeniasis)	‣Inhibits oxidative phosphorylation, leading to inhibition of ATP production at mitochondria; ‣Destroys scolex and segments	‣Causes gastrointestinal tract disturbance; ‣Shows poor absorption in the gastrointestinal tract; ‣Ineffective to cysticercosis	Ahkami and Hadjian (1969); Ofori-Adjei et al. (2008); Kulthawatsiri et al. (2023)
Nitazoxanide (intestinal taeniasis)	Inhibits pyruvate ferredoxin oxidoreductase (PFOR) enzyme of the parasites	Shows no evidence	Hoffman et al. (2007); McCarthy et al. (2014)

[a] Albendazole also acts as anticestodal (e.g. echinococcosis and cysticercosis), antitrematodal (e.g. clonorchiasis and opisthorchiasis), antigardial, and anti-microsporidial drug.
[b] Praziquantel also acts as anticestodal drug (e.g. diplydiasis, echinococcosis, hymenolepidiasis, and intestinal taeniasis).

Table 2
Current antiprotozoal drugs, mechanisms of action, and limitations.

Antiparasitic	Mechanism of action	Limitation	Reference
Antiamoebic drugs			
Amphotericin B	‣Causes pore formation by binding to ergosterol in parasitic cell membrane; ‣Induces apoptosis-like programmed cell death in the genus *Naegleria*	‣Exhibits severe toxicity, including gastrointestinal tract disturbance, renal toxicity, anemia, chills, fever, and headache; ‣Shows poor permeability and low cerebrospinal fluid concentrations	Goswick and Brenner (2003); Pugh and Levy (2016); Cárdenas-Zúñiga et al. (2017); Petraitis et al. (2019); Siddiqui et al. (2023)
Emetine	Inhibits protein synthesis	*Entamoeba histolytica* shows resistance	Entner and Grollman (1973); Samuelson et al. (1990)
Metronidazole	Acts as DNA synthesis inhibitor and causes DNA fragmentation	‣Causes adverse effects, such as gastrointestinal tract disturbance, headache, and dizziness; ‣Shows no activity to cystic form of amoebae	Hausen et al. (2006); Uzlikova and Nohynkova (2014); Wallner et al. (2022)
Sulfisoxazole	Inhibits dihydropteroate synthase	Displays undesirable side effects, such as hypersensitivity reactions (rashes, erythema nodosum, erythema multiforme, exfoliative dermatitis, and photosensitivity) and effects on the hematopoietic system (thrombocytopenia)	Hamilton and Sheets (1978); Kim and Kang (2016)
Tinidazole	Acts as DNA synthesis inhibitor and causes DNA fragmentation	Causes adverse effects, such as anorexia, fatigue, and gastrointestinal tract disturbance	Fung and Doan (2005)
Antigiardial drugs			
Furazolidone	‣Causes DNA damage; ‣Depletes cytoplasm; ‣Causes autophagic-like vacuoles	Causes gastrointestinal tract disturbance	Lyon (1983); Campanati and Monteiro-Leal (2002)
Quinacrine	Inhibits DNA synthesis	Causes skin discoloration	Requena-Méndez et al. (2017); Riches et al. (2020)
Antileishmanial drugs			
Liposomal amphotericin B	Binds to ergosterol in the cell membrane, leading to ion leakage and cell death	Causes infusion-related reactions, such as chest pain/discomfort, flank/abdominal pain, and dyspnea	Stone et al. (2016)
Miltefosine	‣Inhibits the phosphatidylcholine synthesis; ‣Inhibits the cytochrome *c* oxidase; ‣Disrupts the parasite Ca^{2+} homeostasis	‣*Leishmania infantum* shows resistance; ‣Displays adverse events, such as gastrointestinal tract disturbance and lack of appetite	Pinto-Martinez et al. (2017); Carnielli et al. (2019); Ware et al. (2021)
Paromomycin	Inhibits protein synthesis	‣*Leishmania infantum* and *Leishmania donovani* show resistance; ‣Displays adverse effects like nephrotoxicity and ototoxicity	Edlind (1989); Thakur (2008); Hendrickx et al. (2020)
Pentavalent antimonials (meglumine antimoniate, sodium stibogluconate)	Inhibits a type I DNA topoisomerase	‣*Leishmania* spp. show resistance; ‣Displays cardiotoxicity, cardiogenic shock, acute pancreatitis, and pancytopenia for intravenous meglumine	Chakraborty and Majumder (1988); Jeddi et al. (2011); Marques et al. (2019)
Trypanocidal drugs			
Benznidazole	‣Causes oxidative damage to *Trypanosoma* spp.; ‣Causes DNA damage to *Trypanosoma* spp.	‣Poorly tolerated; ‣Shows low effectiveness in chronic stages of Chagas disease; ‣Requires prolonged treatment regimens	Pedrosa et al. (2001); Rose et al. (2020); Mansoldo et al. (2020)
Eflornithine	Inhibits ornithine decarboxylase	Shows adverse reactions, such as gastrointestinal tract disturbance, convulsions, anemia-related bone marrow toxicity, leucopenia and thrombocytopenia, hearing impairment, and alopecia	Denise and Barrett (2001); Burri and Brun (2003)
Fexinidazole	Acts as prodrug that requires nitroreductases to generate cytotoxic species causing DNA, lipid, and protein damage	‣Shows adverse events, such as headache and vomiting; ‣Less effective in patients with severe sleeping sickness	Wyllie et al. (2012); Hidalgo et al. (2021)
Melarsoprol	Acts as prodrug that is metabolized to melarsen oxide which binds to pyruvate kinase, and disrupts energy production in the parasite, as well as preventing trophozoite multiplication	‣*Trypanosoma brucei* shows resistance; ‣Causes agranulocytosis, cardiac arrhythmias, hypertension, peripheral neuropathy, and reactive encephalitis	Fairlamb and Horn (2018); Hidalgo et al. (2021)
Nifurtimox	‣Activates nitroreductase enzymes that produce reactive metabolites effecting *Trypanosoma cruzi*; ‣Inhibits dehydrogenase activity of *Trypanosoma cruzi* and affected mitochondrial membrane potential	‣Poorly tolerated; ‣Shows low effectiveness in chronic stages of Chagas disease; ‣Requires prolonged treatment regimens	Boiani et al. (2010); Li et al. (2024)
Pentamidine	‣Blocks a polyamine transporter present in *Trypanosoma cruzi*; ‣Inhibits the putrescine and spermidine transporters in epimastigote and amastigote of *Trypanosoma cruzi*	‣*Trypanosoma brucei* shows resistance; ‣Shows adverse effects, including diabetes, myocarditis, renal toxicity, and severe hypoglycemia	Díaz et al. (2014); Alghamdi et al. (2020); Román-Álamo et al. (2023)
Suramin	Inhibits many trypanosomal enzymes including dihydrofolate reductase, thymidine kinase, and all the glycolytic enzymes	Shows no activity against cerebral trypanosomiasis as it is unable to cross the blood-brain barrier	De Koning (2020)
Antibabesial drug			
Atovaquone[a]	Collapses the mitochondrial membrane potential of *Babesia gibsoni* that affects energy metabolism	Displays adverse effects, such as diarrhea and rash when used with azithromycin	Krause et al. (2000); Iguchi et al. (2022)
Antimalarial drugs			

(*continued on next page*)

Table 2 (*continued*)

Antiparasitic	Mechanism of action	Limitation	Reference
Artemisinin and its derivatives (artemether[b], arteether, dihydroartemisinin, artesunate)	Acts as blood schizontocide by activating the free radical production	‣Displays adverse effects, such as gastrointestinal tract disturbance, dizziness, and bone marrow depression; ‣Low solubility; ‣Poor bioavailability; ‣Displays a short half-life time causing recrudescence of *Plasmodium* spp.	Classen et al. (1999); Xie et al. (2005); Li et al. (2024)
Chloroquine	Acts as blood schizontocide by inhibiting heme detoxification	‣ *Plasmodium falciparum* shows resistance; ‣Displays adverse effects, such as pruritus and retinopathy at high doses and long-term administration	Wittes (1987); Ebel et al. (2021); Singh et al. (2023b)
Lumefantrine	Inhibits detoxification to crystalline malaria pigment (hemozoin) by binding to hemin produced during hemoglobin breakdown	*Plasmodium falciparum* shows resistance	Warhurst et al. (2001); Bakari et al. (2024)
Mefloquine	Acts as blood schizontocide by inhibiting heme detoxification	*Plasmodium falciparum* shows resistance	Garavito et al. (2007); German and Aweeka (2008)
Piperaquine	Acts as blood schizontocide by inhibiting heme detoxification	*Plasmodium falciparum* shows resistance	de Villiers and Egan (2021); Okombo et al. (2022)
Primaquine	Acts as gametocide, hypnozoitocide, and tissue schizontocide through inducing reactive oxygen species (ROS) accumulation	‣Displays adverse effects, such as hemolysis, especially in G6PD deficiency persons; ‣Shows low effectiveness due to rapid metabolization into different inactive metabolites	Bonilla-Ramírez et al. (2019; Khan et al. (2022); Liu et al. (2023a)
Proguanil	Impairs multiple mitochondrial functions leading to cell death	Shows adverse outcomes, such as miscarriage, stillbirth, early neonatal death, and congenital anomalies in pregnant women	Andrejko et al. (2019); Mounkoro et al. (2021)
Pyronaridine	Acts as blood schizontocide by inhibiting heme detoxification	Shows poor bioavailability	Auparakkitanon et al. (2006); Chu and Dorlo (2023)
Quinine	Acts as blood schizontocide by inhibiting heme detoxification	‣*Plasmodium falciparum* shows resistance; ‣Shows adverse effects, such as cinchonism, hyperinsulininemic hypoglycemia, arrthymia and vasodilation, and hypersensitivity reactions	Dyer et al. (1994); Xue et al. (2013)
Anti-*Toxoplasma* drugs			
Pyrimethamine	Acts synergistically with sulfadiazine to treat toxoplasmosis by inhibiting *Toxoplasma gondii* proliferation and survival through inhibiting the dihydrofolate reductase (DHFR) and dihydropteroate synthase (DHPS) which are critical factors in folate metabolic pathway	‣Shows adverse effects, such as suppression of bone marrow, gastrointestinal tract disturbance, headache, rash, and hypersensitivity reaction; ‣Effective to tachyzoites of *Toxoplasma* spp. but no activity to bradyzoites	Ben-Harari et al. (2017); Martins-Duarte et al. (2021); Semedo et al. (2022)
Anti-balantidiasis drugs			
Iodoquinol	Acts as means of chelates toward ferrous ions, critical for amoebic metabolism	Displays adverse effects, such as seizure and encephalopathy	Fisher et al. (1993); Majeed et al. (2023)
Anti-opportunistic protozoa drugs			
Fumagillin	Interferes function of methionine aminopeptidase 2 enzyme	Displays adverse effects, such as leukopenia	Comer (1956); Watanabe et al. (2023)
Nitazoxanide	Inhibits the glucose-6-phosphate:6-phosphogluconate dehydrogenase (GlG6PD:6PGL) fused enzyme	‣Limited efficacy in the most vulnerable or malnourished patients; ‣Ineffective in immunocompromised patients	Swale et al. (2019); Martínez-Rosas et al. (2023)
Spiramycin	‣Inhibits translocation by binding to 50S ribosomal subunits; ‣Inhibits binding of donor and acceptor substrates to the ribosome; Induces rapid breakdown of polyribosomes	Shows treatment failure	Pilla et al. (1987); Brisson-Noël et al. (1988)
Trimethoprim-Sulfamethoxazole	Inhibits dihydrofolate reductase	Shows serious adverse effects sometimes	Burchall (1973); Yan et al. (2013)

[a] Atovaquone also acts as antimalarial drug.
[b] Artemether also acts as antischistosomal drug.

2020). Gamma benzene hexachloride exhibits antiscabietic activity by blocking chloride ion channels at the GABA receptors of scabies mites, resulting in hyperpolarization of neuromuscular cells (Sauviat and Pages, 2002). Permethrin, a synthetic pyrethroid approved for treating pediculosis capitis and scabies, disrupts sodium ion influx at the neuronal membranes of head lice and scabies mites, inducing depolarization (Nanda et al., 2024). Similarly, pyrethrin disrupts sodium ion channels in louse nerves (Hodoșan et al., 2023). Spinosad interferes with nicotinic acetylcholine receptors in lice, causing neuronal excitation and paralysis due to neuromuscular fatigue (McCormack, 2011).

2.2.3. *Disruption of parasite structure and function*

The integrity of a parasite's structure is critical for its viability. Benzimidazoles, a class of anthelmintics, not only interfere with the energy production of nematodes and trematodes but also disrupt the integumental integrity of cestode protoscoleces by binding to β-tubulin in larvae (Aminpour et al., 2019). Flubendazole binds to tubulin, disrupting the microtubule structure (Spagnuolo et al., 2010). Mebendazole and niclosamide disrupt the scolex and segments of cestodes (Ahkami and Hadjian, 1969; Lorenzini and Ruggieri, 1990).

In protozoans, amphotericin B induces pore formation in the membrane of *Naegleria fowleri* by binding to ergosterol (Fig. 3) (Pugh and Levy, 2016). This pore formation causes an intense efflux of ions, leading to proton influx and cell death. Additionally, amphotericin B crosses the cell membrane, inducing reactive oxygen species production and oxidative stress (Frézard et al., 2022). Liposomal amphotericin B, a unique lipid formulation, also binds to ergosterol in the cell membrane, causing ion leakage and cell death (Stone et al., 2016).

Benzyl alcohol (5% lotion) causes asphyxiation in head lice by inducing the opening of breathing spiracles, thereby interfering with

Table 3
Current ectoparasiticides, mechanisms of action, and limitations.

Antiparasitic	Mechanism of action	Limitation	Reference
Pediculicides			
Abametapir 0.74% lotion	Inhibits metalloproteinases affecting lice survival and egg development	Displays adverse events, such as rash	Bowles et al. (2018); Bowles et al. (2019)
Benzyl alcohol 5% lotion	Induces opening of the breathing spiracles, and interferes respiratory mechanism of head lice, leading to asphyxiation	Causes scalp irritation	Meinking et al. (2010)
Dimethicone 4% lotion	Inhibits water excretion of head lice by transpiration through the spiracles, causing osmotic stress and rupture to the louse gut	Shows no side effects	Burgess (2009); Yamaguchi et al. (2021)
Ivermectin 0.5% lotion or oral ivermectin	Increases chloride in muscle cells, causing hyperpolarization and paralysis	‣*Pediculus humanus corporis* shows resistance; ‣Causes pruritus	Deeks et al. (2013); Amanzougaghene et al. (2018)
Malathion 0.5% lotion or gel	Inhibits acetylcholinesterase in nervous tissues of ectoparasite	‣Resistance in head lice ‣Displays flammability and odor	Verma and Namdeo (2015); Elston (2023)
Permethrin 1% lotion or cream rinse	Induces depolarization by disrupting sodium transport at neuronal membranes of lice	*Pediculus humanus capitis* shows resistance	Audino et al. (2007); Nanda et al. (2024)
Petrolatum jelly	Blocks the breathing holes of pubic lice	Shows no evidence	Karabela et al. (2015)
Pyrethrin	Disrupts sodium channels of lice nerves	*Pediculus humanus capitis* shows resistance	Eisenhower and Farrington (2012); Hodoș;an et al. (2023)
Spinosad 0.9% suspension	Interferes with nicotinic acetylcholine receptors in lice, thereby producing neuronal excitation and paralysis from neuromuscular fatigue	Shows adverse events, such as ocular hyperemia and application-site erythema/irritation	Stough et al. (2009); McCormack (2011)
Antiscabietic agents			
Benzyl benzoate 25% lotion	Unknown mechanism	Causes irritation, and local skin reactions	Brooks and Grace (2002)
Crotamiton 10% cream	Unknown mechanism	‣Poor aqueous solubility; ‣Low bioavailability	Chen et al. (2021)
Gamma benzene hexachloride 1% lotion	Blocks chloride ion channel through gamma-amino butyric acid (GABA) receptor of scabies mites causing hyperpolarization of neuromuscular cells	‣Shows neurotoxicity; ‣Cannot be applied for pregnant women and children below 2 years-old	Sauviat and Pages (2002); Nolan et al. (2012)
Permethrin 5% cream or lotion	Induces depolarization by disrupting sodium transport at neuronal membranes of scabies mites	‣*Sarcoptes scabiei* shows resistance; ‣Displays side effects, such as itching, erythema, and xerosis in infants <2 months of age	Thomas et al. (2021); Meyersburg et al. (2022); Nanda et al. (2024)
Sulfur 5–10% ointment	Unknown mechanism	Shows unpleasant odor	Singalavanija et al. (2003)

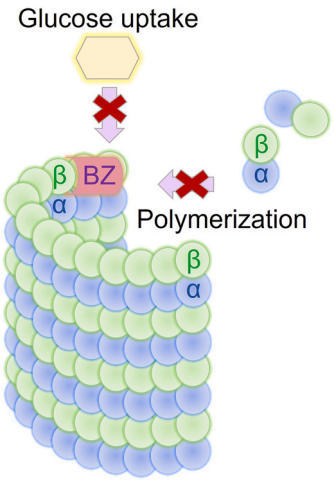

Fig. 1. Inhibition of microtubule polymerization leads to defects in glucose uptake and energy production. *Abbreviations*: α, alpha-tubulin; β, beta-tubulin; BZ, benzimidazole.

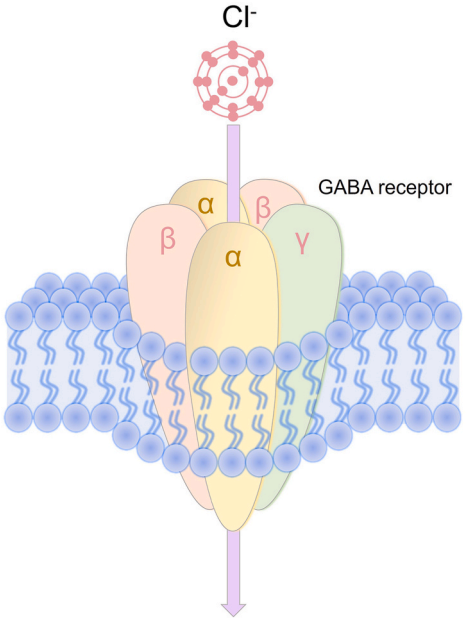

Fig. 2. Activation of chloride ion uptake through induction of the γ-amino-butyric acid (GABA) receptor. *Abbreviations*: α, alpha-subunit; β, beta-subunit; γ, gamma-subunit; Cl^-, chloride ion.

their respiratory mechanisms (Meinking et al., 2010). Dimethicone (4% lotion) inhibits water excretion in head lice through transpiration *via* spiracles, resulting in osmotic stress and rupture of the louse gut (Burgess, 2009). Petrolatum jelly, which is used to treat phthiriasis palpebrarum caused by pubic lice, exerts its therapeutic effect by blocking the breathing holes of the lice, thereby affecting their respiration and movement (Karabela et al., 2015).

2.2.4. *Inhibition of nucleic acid or protein synthesis*

Blockage of nucleic acid or protein synthesis is a common mechanism of antimicrobial agents. Metronidazole and tinidazole are DNA synthesis inhibitors (Fig. 4) (Fung and Doan, 2005; Uzlikova and Nohynkova, 2014). After reductive bioactivation by ferredoxin, a protein found in protozoans, DNA fragmentation and amoebae cell death occur (Uzlikova and Nohynkova, 2014). Oxamniquine, a drug used to treat schistosomiasis, exerts its schistosomicidal activity by inhibiting nucleic acid synthesis (Pica-Mattoccia and Cioli, 1985; Wong et al.,

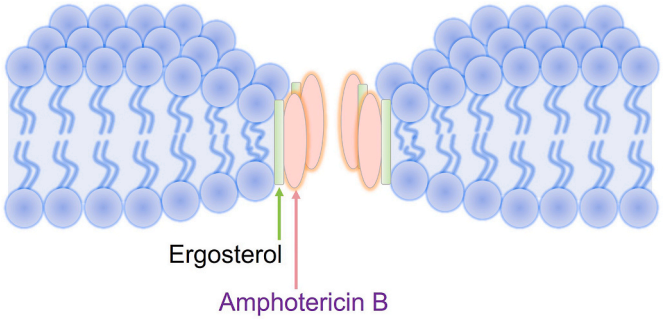

Fig. 3. Amphotericin B binds to ergosterol, forming pores in the lipid bilayer.

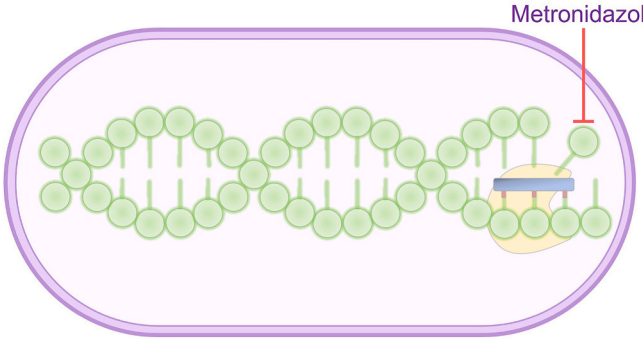

Fig. 4. Metronidazole inhibits DNA synthesis.

1990). Emetine exhibits amoebicidal activity through the inhibition of protein synthesis (Entner and Grollman, 1973). Furazolidone, an antigiardial agent, induces DNA damage in *Giardia lamblia* trophozoites. It is reduced by NADH oxidase to form toxic intermediates that damage DNA and other cellular components (Campanati and Monteiro-Leal, 2002). Quinacrine and paromomycin inhibit DNA and protein synthesis in *G. lamblia*, respectively (Edlind, 1989; Riches et al., 2020). Benznidazole causes DNA damage in *Trypanosoma* spp. (Rose et al., 2020). Fexinidazole, a nitroheterocyclic compound, acts as a prodrug requiring nitroreductases to generate cytotoxic species, which damage DNA, lipids, and proteins (Wyllie et al., 2012).

2.2.5. Inhibition of enzyme activity or interference with metabolites

Sulfonamides, such as sulfisoxazole, act as antiamoebic agents by inhibiting dihydropteroate synthase, which is involved in dihydrofolic acid synthesis (Fig. 5) (Kim and Kang, 2016). Pyrimethamine and trimethoprim inhibit dihydrofolate reductase, an enzyme related to tetrahydrofolic acid synthesis (Burchall, 1973; Ben-Harari et al., 2017). Bithional reduces glycolytic and oxidative metabolism (Hamajima,

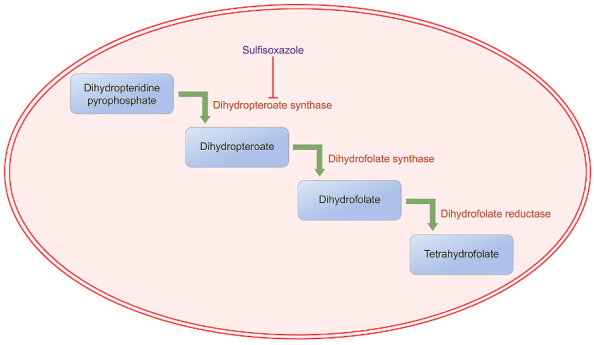

Fig. 5. Sulfisoxazole inhibits dihydropteroate synthase, which is involved in dihydrofolic acid synthesis.

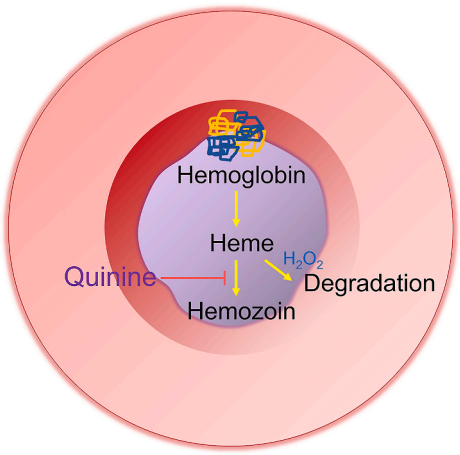

Fig. 6. Quinine interferes with heme detoxification within the parasite's digestive vacuole.

1973). Miltefosine, which is used to treat *Leishmania donovani* infections, inhibits phosphatidylcholine synthesis and cytochrome *c* oxidase (Pinto-Martinez et al., 2017). Pentavalent antimonials bind to polypeptides and inhibit type I DNA topoisomerase (Chakraborty and Majumder, 1988). Nifurtimox, a nitrofurane derivative, activates nitroreductase enzymes that produce reactive metabolites affecting *Trypanosoma cruzi*. Additionally, it inhibits dehydrogenase activity in *T. cruzi* and disrupts the mitochondrial membrane potential (Boiani et al., 2010). Eflornithine, utilized in the late stages of sleeping sickness, inhibits ornithine decarboxylase (Denise and Barrett, 2001). Suramin, a trypanocidal drug, inhibits multiple trypanosomal enzymes, including dihydrofolate reductase, thymidine kinase, and all glycolytic enzymes (De Koning, 2020). Fumagillin exhibits amoebicidal activity against *Entamoeba histolytica* by interfering with the function of methionine aminopeptidase 2 (Watanabe et al., 2023). Nitazoxanide, a nitro compound, inhibits the fusion enzyme glucose-6-phosphate 6-phosphogluconate dehydrogenase (GlG6PD6PGL) in parasites (Martínez-Rosas et al., 2023). Abametapir 0.74% lotion inhibits metalloproteinases, affecting louse survival and egg development (Bowles et al., 2018).

2.2.6. Restriction of heme detoxification

Heme detoxification is a crucial pathway for eliminating toxic byproducts generated during hemoglobin digestion. Quinine, the first antimalarial agent, inhibits heme detoxification by disrupting the digestion of heme and ferriprotoporphyrin IX within the digestive vacuole of *Plasmodium* spp., thereby preventing the conversion of heme to hemozoin (Fig. 6) (Xue et al., 2013). Additionally, chloroquine, mefloquine, piperaquine, and pyronaridine eliminate *Plasmodium* spp. by inhibiting heme detoxification (Auparakkitanon et al., 2006; Garavito et al., 2007; de Villiers and Egan, 2021; Singh et al., 2023b). Lumefantrine inhibits the detoxification of heme to crystalline malaria pigment (hemozoin) by binding to hemin produced during hemoglobin breakdown (Warhurst et al., 2001).

2.2.7. Production of free radicals

Artemisinin and its derivatives, including dihydroartemisinin and artesunate, eliminate *Plasmodium* spp. by activating free radical production (Fig. 7) (Classen et al., 1999). The free radicals bind to *Plasmodium* proteins, causing a loss of function (Classen et al., 1999). Additionally, these free radicals target heme, disrupting heme detoxification (Classen et al., 1999). Primaquine is another antimalarial drug that kills *Plasmodium* spp. by increasing reactive oxygen species accumulation (Bonilla-Ramírez et al., 2019).

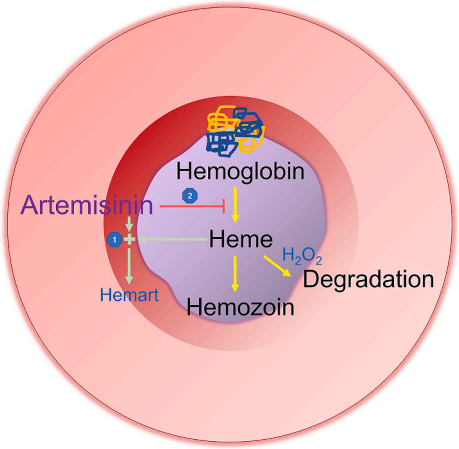

Fig. 7. Artemisinin induces free radical production and accumulation.

The mechanisms of action of anthelmintics are related primarily to three main processes: interference with energy production, disruption of neuromuscular coordination, and disruption of parasite structure and function. Additionally, some anthelmintics inhibit nucleic acid synthesis (e.g. oxamniquine), reduce oxygen consumption (e.g. bithional), and inhibit organophosphorus cholinesterase (e.g. metrifonate) (Davis and Bailey, 1969; Hamajima, 1973; Wong et al., 1990).

Antiprotozoal drugs act mainly through the inhibition of nucleic acid and protein synthesis, as well as through interference with enzyme activity or metabolic processes. In contrast, antimalarial drugs primarily involve heme detoxification inhibition and free radical production activation. Other antiprotozoal agents function by inducing pore formation (amphotericin B), triggering apoptosis-like programmed cell death (amphotericin B), causing oxidative damage (benznidazole), blocking transporters (pentamidine), interfering with metabolism (iodoquinol), and inhibiting ribosomal translocation (spiramycin) (Brisson-Noël et al., 1988; Pedrosa et al., 2001; Díaz et al., 2014; Pugh and Levy, 2016; Cárdenas-Zúñiga et al., 2017; Majeed et al., 2023).

Ectoparasiticides generally disrupt neuromuscular coordination. Additionally, some inhibit critical enzymes such as metalloproteinases (abametapir) and acetylcholinesterase (malathion), interfere with respiratory mechanisms (benzyl alcohol and petrolatum jelly), and inhibit water excretion (dimethicone) (Elston, 2023). However, the mechanisms of action of certain ectoparasiticides, including benzyl benzoate, crotamiton, and sulfur ointment, remain undisclosed. This indicates opportunities for further research.

3. Limitations of existing antiparasitic drugs

Although many antiparasitic drugs have been approved for their broad-spectrum efficacy against various parasitic diseases, there is growing concern that the current drug pipeline offers only limited options. These drugs are often used in treatments that involve considerable toxicity and adverse effects (Partridge et al., 2017). Additionally, resistance to some antiparasitics by parasites has been increasingly reported, while the toxicities and limitations of others have been obscured (Kappagoda et al., 2011). The present review extensively examines and discusses the reported limitations of antiparasitic drugs to emphasize the urgent need for novel drug discovery and development. Understanding these current limitations is crucial for advancing efforts in drug discovery and design.

3.1. Drug resistance

Recently, the WHO reported an emergency situation regarding antimicrobial resistance, highlighting that the current pipeline and recently approved antibiotics are insufficient to address the increasing emergence and spread of antimicrobial resistance (WHO, 2021). This concern extends to all groups of antiparasitic drugs, including anthelmintics, antiprotozoal agents, and ectoparasiticides. Resistance has emerged because of the frequent use of these drugs, underdosing, and genetic modifications in parasites. This underscores the critical concern of antiparasitic drug resistance as a public health problem that requires urgent preparedness (Pramanik et al., 2019).

With respect to anthelmintics, resistance is typically observed in the treatment of animal diseases; however, evidence of resistance in humans has been continuously reported, especially with the excessive use of anthelmintic drugs in many regions. Recently, mebendazole resistance was identified in *Necator americanus* hookworms, and pyrantel pamoate resistance was reported in *Ancylostoma duodenale* (Table 1) (Reynoldson et al., 1997; Sacko et al., 1999). Praziquantel, the only drug of choice for treating human schistosomiasis since the 1970s, has been used extensively in many countries, leading to the emergence of praziquantel resistance (Wang et al., 2012). For example, evidence of praziquantel resistance has been reported in Egypt (Ismail et al., 1999). Additionally, resistance of *Fasciola* spp. to triclabendazole, the only WHO-recommended drug for fascioliasis, has been documented (Tashibu et al., 2024). First reported in Australia, this resistance has since spread to several European countries, highlighting the need for new drug development.

In the antiprotozoal category, emetine resistance has been reported in *Entamoeba histolytica* (Table 2) (Samuelson et al., 1990). Resistance to miltefosine and paromomycin has been observed in *Leishmania infantum* (Carnielli et al., 2019; Hendrickx et al., 2020). Critically, pentavalent antimonials, the first-line drugs for leishmaniasis, have shown resistance in *Leishmania* spp. (Jeddi et al., 2011). Resistance to antimonials has increasingly emerged in settings where alternative drugs are limited by cost, leading to the spread of resistance and creating a significant public health crisis. Melarsoprol and pentamidine, the two main classes of trypanocidal drugs, have become less effective in treating African trypanosomiasis caused by *Trypanosoma brucei* (Fairlamb and Horn, 2018; Alghamdi et al., 2020). These scenarios represent another critical public health problem affecting clinical management.

Regarding antimalarial drugs, various *Plasmodium* species have developed resistance to chloroquine. For example, *P. falciparum* has developed chloroquine resistance, posing a major threat to global malaria control (Ebel et al., 2021). Resistance to lumefantrine, mefloquine, piperaquine, and quinine has also been reported in *P. falciparum* (Dyer et al., 1994; German and Aweeka, 2008; Okombo et al., 2022; Bakari et al., 2024). Moreover, the emergence of artemisinin resistance along the Thai-Cambodian border and its spread to Africa pose a significant global health threat, as they could render current malaria treatment regimens ineffective and jeopardize malaria control and elimination efforts worldwide (Müller et al., 2009).

In the category of ectoparasiticides, ivermectin, previously highlighted as a promising pediculicide and used in cases resistant to conventional topical pediculicides, has itself encountered resistance (Amanzougaghene et al., 2018). Resistance to malathion 0.5% lotion, permethrin 1% lotion, and pyrethrin have been observed in head lice (Table 3) (Audino et al., 2007; Eisenhower and Farrington, 2012; Verma and Namdeo, 2015). Additionally, recent observations suggest a decreasing efficacy of topical 5% permethrin cream, the standard treatment for patients with scabies (Meyersburg et al., 2022). These resistance scenarios complicate the clinical management of parasitosis.

3.2. Toxicity and adverse side effects

Most antiparasitic drugs exhibit high efficacy in treating parasitic infections. However, to exert their deleterious effects on pathogenic parasites, some require high dosages. This can result in harmful consequences not only for the parasites but also for the human host, including relative toxicity and adverse side effects. The margin of safety varies

among antiparasitic drugs (Pognan et al., 2023). Some drugs have wide safety margins, whereas others have narrow safety margins. Factors influencing the safety margin include the level and selectivity of drug absorption, which affect the drug concentration in the host (Vercruysse and Claerebout, 2014). Additionally, site-of-action selectivity and toxic selectivity toward parasites are critical factors influencing toxicity (Guengerich, 2011; Gao et al., 2022). Antiparasitic drugs with low site-of-action selectivity may adversely affect host organs when parasites are targeted. Furthermore, host hypersensitivity and immune responses during drug administration also contribute to drug toxicity (Guengerich, 2011). These factors significantly limit the clinical application of certain antiparasitic drugs.

Among anthelmintics, benzimidazoles have wide safety margins, whereas levamisole has narrow safety margins, leading to a more frequent occurrence of toxicity (Vercruysse and Claerebout, 2014). The reported adverse effects of albendazole, mebendazole, diethylcarbamazine, ivermectin, bithional, praziquantel, and niclosamide include gastrointestinal disturbances (nausea, vomiting, and diarrhea), dizziness, abdominal pain, headache, fever, and allergic reactions (Table 1) (Hsu, 1980; Nash et al., 1982; Vanijanonta et al., 1984; Sutanto et al., 1985; Ofori-Adjei et al., 2008; Silber et al., 2017; Turan and Metin, 2020). Fever often occurs due to the host's reaction to dying parasite proteins (Sutanto et al., 1985). Levamisole is associated with additional adverse effects, such as increased salivation, frequent urination and defecation, colic, and muscle tremors, in addition to gastrointestinal disturbances, dizziness, and headache (Hsu, 1980). Thiabendazole has been reported to cause visual disturbances, whereas oxamniquine application has been linked to adverse neurological reactions (Kokwaro and Taylor, 1990; DrugBank Online, 2024).

For antiprotozoal drugs, common adverse effects include chills and fever caused by amphotericin B; headache caused by amphotericin B, fexinidazole, metronidazole, and pyrimethamine; dizziness caused by artemisinin and its derivatives and metronidazole; anorexia and fatigue caused by tinidazole; and gastrointestinal disturbances (Table 2). These effects are associated with amphotericin B, artemisinin and derivatives, atovaquone, eflornithine, fexinidazole, furazolidone, metronidazole, miltefosine, pyrimethamine, and tinidazole (Lyon, 1983; Krause et al., 2000; Goswick and Brenner, 2003; Burri and Brun, 2003; Xie et al., 2005; Fung and Doan, 2005; Wyllie et al., 2012; Ware et al., 2021; Semedo et al., 2022; Wallner et al., 2022).

Renal toxicity has been reported with amphotericin B, paromomycin, and pentamidine. Pancreatitis and pancytopenia have been observed with pentavalent antimonials (Goswick and Brenner, 2003; Thakur, 2008; Marques et al., 2019; Román-Álamo et al., 2023). Toxicity to the bone marrow and hematopoietic system has been documented with amphotericin B, artemisinin and its derivatives, eflornithine, fumagillin, melarsoprol, primaquine (especially in individuals with G6PD deficiency), pyrimethamine, and sulfisoxazole (Comer, 1956; Hamilton and Sheets, 1978; Goswick and Brenner, 2003; Burri and Brun, 2003; Xie et al., 2005; Fairlamb and Horn, 2018; Hidalgo et al., 2021; Semedo et al., 2022; Liu et al., 2023a). Cardiotoxicity and cardiogenic shock have been reported with melarsoprol, pentamidine, pentavalent antimonials, and quinine (Dyer et al., 1994; Fairlamb and Horn, 2018; Marques et al., 2019; Román-Álamo et al., 2023). Hypersensitivity reactions occur with atovaquone, chloroquine, pyrimethamine, quinine, and sulfisoxazole (Hamilton and Sheets, 1978; Wittes, 1987; Dyer et al., 1994; Krause et al., 2000; Semedo et al., 2022). Encephalopathy has been observed with eflornithine, iodoquinol, and melarsoprol (Fisher et al., 1993; Burri and Brun, 2003; Fairlamb and Horn, 2018). Ototoxicity has been reported with eflornithine and paromomycin (Burri and Brun, 2003; Thakur, 2008), whereas diabetes and severe hypoglycemia are associated with pentamidine and quinine (Dyer et al., 1994; Román-Álamo et al., 2023). Additionally, alopecia, cinchonism, infusion-related reactions, retinopathy, skin discoloration, and stillbirth have been periodically recorded with eflornithine, quinine, liposomal amphotericin B, chloroquine, quinacrine, and proguanil, respectively (Wittes, 1987; Dyer et al., 1994; Burri and Brun, 2003; Stone et al., 2016; Requena-Méndez et al., 2017; Andrejko et al., 2019).

For ectoparasiticides, certain agents have been reported to cause adverse reactions. Abametapir 0.74% lotion has been associated with rashes, whereas benzyl alcohol 5% lotion, benzyl benzoate 25% lotion, and spinosad 0.9% suspension have been found to cause irritation. In addition, 0.5% ivermectin lotion and 5% permethrin cream can induce pruritus (Table 3) (Brooks and Grace, 2002; Stough et al., 2009; Meinking et al., 2010; Amanzougaghene et al., 2018; Bowles et al., 2019; Thomas et al., 2021). Malathion 0.5% lotion poses a risk of flammability, and gamma benzene hexachloride 1% lotion can cause neurotoxicity (Nolan et al., 2012; Verma and Namdeo, 2015). Some ectoparasiticides have an unpleasant odor, such as malathion 0.5% lotion and sulfur 5% ointment (Singalavanija et al., 2003; Verma and Namdeo, 2015). However, other compounds, such as dimethicone (4% lotion) and petrolatum jelly, have no documented side effects (Karabela et al., 2015; Yamaguchi et al., 2021).

3.3. *Low efficacy*

The efficacy of an antiparasitic drug typically depends on its concentration, accessibility to the parasite, and host-related factors. The concentration of the active agent is critical for maintaining sufficient levels to damage the parasite through its mechanism of action over a required period (Prichard, 1985). Additionally, accessibility of the drug to the location of the parasite is essential for effective treatment. Host physiology, including the pH conditions of various organs and the host's metabolic rate, also affects the availability and absorption of the drug to the parasite during infection (Prichard, 1985).

Within the anthelmintic drug group, limitations in absorption have been documented. For example, albendazole and mebendazole have been reported to have poor water solubility, which impairs their absorption (Table 1) (Apt, 1990; Turan and Metin, 2020). Similarly, flubendazole and niclosamide exhibit poor absorption in the intestine and gut, respectively (Apt, 1990; Ofori-Adjei et al., 2008). Some anthelmintics demonstrate stage-specific efficacy. Diethylcarbamazine rapidly kills microfilariae but is ineffective against adult worms at comparable doses (Norões et al., 1997). Ivermectin similarly shows limited efficacy against adult stages of *Wuchereria bancrofti* and *Brugia malayi*, and niclosamide is ineffective against the cysticercus stage of *Taenia solium* (Ofori-Adjei et al., 2008; Martin et al., 2021). Furthermore, the metabolism of drugs to inactive forms reduces their efficacy. Ivermectin is rapidly metabolized in the liver to inactive metabolites (Martin et al., 2021). Mebendazole and praziquantel also undergo rapid hepatic metabolism, resulting in decreased active drug levels (Nash et al., 1982; Witassek et al., 1983). Additionally, difficulty in drug accessibility to the blood-brain barrier has been reported, including for ivermectin (Martin et al., 2021).

Many antiprotozoal drugs exhibit low efficacy due to various factors. Amphotericin B has poor permeability, leading to low efficacy in treating primary amoebic meningoencephalitis (Table 2) (Petraitis et al., 2019). The inability of amphotericin B to bypass the highly selective blood-brain barrier significantly impacts its efficacy (Siddiqui et al., 2023). Suramin also faces limitations in treating cerebral trypanosomiasis, as it cannot cross the blood-brain barrier (De Koning, 2020). Like anthelmintics, some antiprotozoal agents present stage-specific limitations. For example, metronidazole is ineffective against the cystic form of *Giardia* spp., and pyrimethamine shows no activity against bradyzoites of *Toxoplasma* spp. (Hausen et al., 2006; Martins-Duarte et al., 2021). Benznidazole and nifurtimox, the only two available therapeutic options for Chagas disease, are poorly tolerated, leading to limited efficacy and frequent treatment failure in the chronic phase (Mansoldo et al., 2020). Fexinidazole is another antiprotozoal agent that is less effective in severe sleeping sickness patients (Wyllie et al., 2012). Artemisinin and its derivatives exhibit limited efficacy in malaria treatment because of their low solubility, poor bioavailability, and short

half-life (Li et al., 2024). Pyronaridine also has poor bioavailability (Chu and Dorlo, 2023). Primaquine shows low efficacy in the treatment of malaria because it is rapidly metabolized into inactive metabolites (Khan et al., 2022). Moreover, nitazoxanide has demonstrated limited efficacy in the most vulnerable or malnourished patients (Swale et al., 2019).

Among ectoparasiticides, the 10% crotamiton cream displays low efficacy in treating scabies because of its poor aqueous solubility and low bioavailability (Table 3) (Chen et al., 2021). These limitations highlight the need for improved drug formulations and the development of novel therapeutic strategies to increase the efficacy of existing antiparasitic agents.

4. Concepts and trends in novel antiparasitic drug discovery

Owing to the limitations of currently available antiparasitic drugs, the discovery and development of novel agents are urgently needed to provide better treatment options and address the limited drug pipeline. Several approaches are employed to discover effective new antiparasitic drugs, including repurposing existing drugs, developing analogs, screening available compound libraries, and searching for *de novo* compounds. These strategies are selected based on various factors, such as expertise, resources, and technology. Additionally, cost and time are critical considerations. Depending on the time needed, some drug discovery approaches are classified as short-term strategies, whereas others are considered medium- or long-term (Pink et al., 2005). This review briefly summarizes the general concepts of each approach and highlights future trends in the search for new antiparasitic drugs.

4.1. Drug repurposing

Drug repurposing is a short-term strategy for antiparasitic drug discovery. This involves identifying existing drugs that can be used for new indications, thereby enhancing antiparasitic activity or reducing toxicity (Pink et al., 2005). Using this approach, Olotu et al. (2024) identified mitomycin as a new antimalarial drug from a library of 2090 FDA-approved compounds owing to its multistage pan-inhibitor activity (Olotu et al., 2024). Additionally, sorafenib and imatinib were discovered from a list of FDA-approved protein kinase inhibitors as new antileishmanial agents for treating visceral leishmaniasis, providing new treatment options to combat increasing drug resistance (Bhattacharjee et al., 2024). These are examples of studies that employed a drug repurposing approach. Given its low resource requirements and reduced time consumption, drug repurposing is an appealing strategy for discovering novel antiparasitic drugs.

4.2. Development of analogs

The development of analogs is a medium-term strategy for antiparasitic drug development. This approach involves enhancing the efficacy of known drugs by synthesizing analogs that exhibit increased antiparasitic activity or reduced toxicity (Pink et al., 2005). For example, lipophilic *N*-alkoxyaryl FR900098 analogs, which feature lipophilic substitutions at the α position to the phosphorus atom, have been discovered as potent compounds against *P. falciparum*. These analogs act on the parasite *via* an on-target mechanism with low cytotoxicity (Bague et al., 2024). Carey et al. (2024) identified 3-nitro-2--phenyl-2*H*-chromene analogs as *T. cruzi* glucokinase inhibitors. These analogs have the potential to become new drug candidates for treating Chagas disease, for which only two drugs are currently approved and available (Carey et al., 2024).

4.3. Screening of compound libraries

The screening of compound libraries, such as the Ty-Box, COVID Box, and Global Health Priority Box, constitutes a medium-to long-term strategy for discovering new drugs. Linciano et al. (2023) identified a broad-spectrum antitrypanosomatidic agent, compound 40, through a high-throughput screening assay of 456 compounds from the Ty-Box library (Linciano et al., 2023). Chao-Pellicer et al. (2024a) discovered terconazole, clemastine, ABT-239, and PD-144418 from a collection of 160 commercially available compounds in the COVID Box library. These compounds demonstrated amoebicidal activity against two clinical strains of *Naegleria fowleri*, suggesting their potential as alternative therapeutic options for primary amoebic meningoencephalitis (Chao-Pellicer et al., 2024a). Additionally, Chao-Pellicer et al. (2024b) identified flucofuron from the Global Health Priority Box, which contains 240 compounds, as a promising therapeutic molecule against *N. fowleri* (Chao-Pellicer et al., 2024b).

4.4. De novo drug discovery

De novo drug discovery is a long-term strategy for developing novel antiparasitic agents. This approach involves identifying new active compounds that are unrelated to existing drugs (Pink et al., 2005). Novel bioactive molecules are sought by testing them against target pathogens both *in vitro* and *in vivo*. Many studies utilize well-characterized pathogen targets through virtual or experimental screenings, employing structure-based drug discovery methods. Additionally, bioinformatics is integrated to predict and design drugs on the basis of known targets, thereby shortening the investigation time.

For example, Chauhan et al. (2024) screened 30 newly synthesized amide compounds for anti-echinococcal activity (Chauhan et al., 2024). This research combined *in silico* screening with *in vitro* experimentation to evaluate the anti-echinococcal potential and identified a promising compound, N-p-tolyl-1-naphthamide, which exhibited protoscolicidal activity against *Echinococcus granulosus* (Chauhan et al., 2024). Furthermore, searching for novel bioactive molecules from natural sources, such as plants and microorganisms, is another attractive approach to drug discovery. Natural sources offer structural complexity, diversity, and historical therapeutic significance, making them valuable reservoirs for potential antiparasitic agents (Jiang et al., 2024). Examples of such natural compounds are discussed in subsequent sections.

4.5. Trends in the modern era of drug discovery, design, and development

In the modern era, various advanced technologies have shown significant potential in drug discovery and design. Historically, target-based drug discovery has integrated whole-genome analysis, next-generation sequencing techniques combined with genome mining, omics approaches, and bioinformatics (Qureshi et al., 2021). Recently, new technologies have emerged and are being integrated into drug discovery processes. Artificial intelligence-based approaches are increasingly applied to identify new drugs, reduce time and resource expenditures, and bring about a paradigm shift in the field of drug design.

For example, Mswahili et al. (2021) developed machine learning models using artificial neural networks, extreme gradient boosting, and random forest algorithms to predict the antimalarial activities of drugs against *P. falciparum* (Mswahili et al., 2021). Similarly, Moreira-Filho et al. (2023) created machine learning models to predict the schistosomicidal activity of compounds that had not been experimentally tested, facilitating rapid progression into preclinical studies of antischistosomal drugs (Moreira-Filho et al., 2023). Additionally, Linciano et al. (2023) integrated Bayesian machine learning models to characterize compounds from the Ty-Box library after high-throughput screening (Linciano et al., 2023). In addition to novel drug discovery, artificial intelligence is also being utilized to predict drug toxicity (Amorim et al., 2024).

Given that the development of a new drug is recognized as a time-consuming process, often exceeding 10 years, emerging technologies such as artificial intelligence and other innovative approaches offer new

Table 4
Bioactive molecules released during inter- and intraspecific competition and FDA approval. Parasites that were susceptible to each bioactive molecule are highlighted in bold.

Producer	Bioactive molecule	Sensitive organism	Reference
Bacteria			
Actinomycetes			
Streptomyces roseosporus	Daptomycin [a] 2003	Methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-resistant *Enterococcus* (VRE)	Debono et al. (1987)
Streptomyces antibioticus	Actinomycins	MRSA, VRE	Sharma and Manhas (2019)
Streptomyces natalensis	Natamycin [a] 2001	*Aspergillus* spp., *Candida* spp., *Cephalosporium* spp., *Fusarium* spp., and *Penicillium* spp.	Raab (1974)
Streptomyces sp. DC4-5	Iseolides	*Candida albicans*, *Trichophyton rubrum*	Zhang et al. (2020)
Streptomyces avermitilis	Avermectin B1	***Dirofilaria immitis*, *Brugia malayi*, *Onchocerca* spp., mites, cockroaches**	Campbell (1982)
	Ivermectin [a] 2012	***Strongyloides stercoralis*, *Onchocerca volvulus*, mites, lice**	Mogg et al. (1990); Ikeda et al. (2003)
Streptomyces noclosus	Amphotericin B [a] 1997	***Leishmania donovani*, *Naegleria fowleri***	Valli et al. (2024)
Streptomyces krestomuceticus	Paramomycin [a] 1969	***Leishmania major***	Singh et al. (2023a)
Lactic acid bacteria			
Leuconostoc mesenteroides	2-hydroxypropanoic acid [a] 2020	*Streptococcus mutans*	Gu et al. (2023)
Lactobacillus plantarum	Cyclodipeptides	*Acinetobacter baumannii*	Yap et al. (2021)
	Organic acids	*Aspergillus niger*, *Aspergillus oryzae*, *Aspergillus flavus*, *Trichoderma longibrachiatum*, *Fusarium graminearum*	Zhao et al. (2022)
Lactobacillus acidophilus	Lactic acid	*Clostridium difficile*	Yun et al. (2014)
	Bacteriocin	***Enterocytozoon bieneusi***	Mossallam et al. (2014)
Lactobacillus reuteri	Unidentified agent	***Cryptosporidium parvum***	Waters et al. (1999)
Lactobacillus johnsonii	Bile-salt-hydrolases	***Giardia lamblia***	Travers et al. (2016)
Lactococcus lactis	Nisin	***Acanthamoeba castellanii***	de Carvalho Clímaco et al. (2022)
Enterococcus faecalis	Bacteriocin AS-48	***Trypanosoma brucei*, *Leishmania donovani***	Abengózar et al. (2017); Martín-Escolano et al. (2019)
Marine bacteria			
Pseudoalteromonas spp.	Alterins	*Vibrio parahaemolyticus*, *Vibrio harveyi*	Desriac et al. (2020)
Streptomyces sp. KMM 9048	Aureolic acids	*Bacillus subtilis*, *Enterococcus faecium*, *Staphylococcus aureus*, *Staphylococcus epidermidis*	Kalinovskaya et al. (2017)
Vibrio cholerae	Valine-glycine repeat protein G3	*Aeromonas hydrophila*	Liu et al. (2023b)
	Hemolysin A [b] 2017	*Vibrio cholerae*	Ruenchit et al. (2017)
Bacillus licheniformis	Ieodoglucomide C	*Aspergillus niger*, *Botrytis cinereal*, *Colletotrichum acutatum*, *Rhizoctonia solani*, *Candida albicans*	Tareq et al. (2015)
Bacillus amyloliquefaciens	Peptide W1	*Sclerotinia sclerotiorum*, *Fusarium oxysporum*	Wen et al. (2022)
Serratia marcescens	2,4-di-tert butyl phenol	*Fusarium foetens*	Kharat et al. (2022)
Streptomyces sp.	Marinopyrrole A	***Toxoplasma gondii***	Martens et al. (2022)
Pseudomonas aeruginosa	Hydroxyquinoline compounds	***Plasmodium falciparum***	Martínez-Luis et al. (2019)
	Pyocyanin [b] 2021	***Naegleria fowleri***	Ruenchit et al. (2021)
	Pyocin	*Pseudomonas aeruginosa*	Heo et al. (2007)
Pseudomonas otitidis	Unidentified agent	***Naegleria fowleri***	Ruenchit et al. (2021)
Enterobacter cloacae	Unidentified agent	***Naegleria fowleri***	Ruenchit et al. (2021)
***Lysobacter* spp.**			
Lysobacter lactamgenus	Cephabacins	*Escherichia coli*, *Bacillus subtilis*	Lee et al. (2008)
Lysobacter sp. ATCC 53042	Lysobactin	*Escherichia coli*, *Klebsiella aerogenes*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pyogenes*, MRSA, VRE	Bonner et al. (1988); Hou et al. (2011)
Lysobacter enzymogenes	Heat-stable antifungal factor	*Aspergillus nidulans*, *Candida albicans*, *Colletotrichum fructicola*	Lin et al. (2021)
	Unidentified agent	*Aphelenchoides fragariae*, *Caenorhabditis elegans*, *Heterodera schachtii*, *Meloidogyne javanica*, *Pratylenchus penetrans*	Chen et al. (2006)
Others			
Amycolatopsis rifamycinica	Rifamycin [a] 2018	*Mycobacterium tuberculosis*	Surette et al. (2021)
Burkholderia ubonensis	Bacteriocin-like compound	*Burkholderia pseudomallei*	Marshall et al. (2010)
Escherichia coli	Colicins	*Escherichia coli*	Calcuttawala et al. (2021)
	Microcins	*Escherichia coli*, *Samonella enteritidis*, *Salmonella typhimurium*	Corsini et al. (2010)
Fungi			
Marine fungi			
Chromocleista sp.	*p*-hydroxyphenopyrrozin	*Candida albicans*	Park et al. (2006)
Trichoderma sp.	Trichodin A	*Candida albicans*	Wu et al. (2014)
Penicillium citrinum	Citrinin derivative	*Bacillus subtilis*	Sabdaningsih et al. (2020)
Ascomycota sp.	Diorcinol	*Acinetobacter baumanii*, *Enterococcus faecalis*, *Escherichia coli*, *Staphylococcus aureus*	Tian et al. (2015)
Aspergillus fumigatus	Fumagillin	***Entamoeba histolytica***	Watanabe et al. (2023)
	Diketopiperazines	***Trypanosoma brucei***	Watts et al. (2010)
Nectria inventa	Diketopiperazines	***Trypanosoma brucei***	Watts et al. (2010)
Endophytic fungi			

(*continued on next page*)

Table 4 (*continued*)

Producer	Bioactive molecule	Sensitive organism	Reference
Botryosphaeria sp.	Botryosphaerins	*Candida albicans*, *Saccharomyces cerevisiae*, *Penicillium avellaneum*, *Gaeumannomyces graminis*, *Fusarium moniliforme*, *F. solani*, *F. oxysporum*, *Pyricularia oryzae*, *Panagrellus redivivus*, *Caenorhabditis elegans*	Yuan et al. (2009); Chen et al. (2015)
Endolichenic fungi			
Chrysosporium sp.	Unidentified agent	*Colletotrichum* sp.	Kannangara et al. (2009)
Fusarium proliferatum	Unidentified agent	*Enterococcus faecalis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanni*, *Pseudomonas aeruginosa*, *Enterobacter agglomerans*	Tan et al. (2020)
Nemania primolutea	Unidentified agent	*Enterococcus faecalis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanni*, *Pseudomonas aeruginosa*, *Enterobacter agglomerans*	Tan et al. (2020)
Daldinia eschsholtzii	Unidentified agent	*Enterococcus faecalis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanni*, *Pseudomonas aeruginosa*, *Enterobacter agglomerans*	Tan et al. (2020)
Xylaria grammica	Grammicin	*Meloidogyne incognita*	Park et al. (2021); Kim et al. (2021)
Others			
Glarea lozoyensis	Caspofungin [a] 2001	*Candida* spp., *Aspergillus* spp.	Valérie and Herbrecht (2003)
Parasites			
Toxoplasma gondii	Unidentified agent	***Neospora caninum***	Sundermann and Estridge (1999)
Pristionchus pacificus	Unidentified agent	*Caenorhabditis elegans*	Quach and Chalasani (2020)
Schistosoma mansoni	Unidentified agent	***Schistosoma intercalatum***	Tchuenté et al. (1996)
Plasmodium falciparum	Unidentified agent	***Plasmodium falciparum***	Chen et al. (2014)
Plasmodium juxtanucleare	Unidentified agent	***Plasmodium gallinaceum***	Paul et al. (2002)
Nippostrongylus brasiliensis	Unidentified agent	*Staphylococcus aureus*, *Escherichia coli*, *Salmonella enterica*, *Klebsiella pneumoniae*	Pillay et al. (2023)
Trypanosoma brucei	Unidentified agent	***Trypanosoma brucei***	Balmer et al. (2009)

[a] FDA-approved agents and year of approval.
[b] Bioactive agents discovered in previous studies at the author's institute.

hope for disruptive growth in drug discovery and development. These technologies increase the efficiency and effectiveness of identifying promising drug candidates, optimize their efficacy and safety profiles, and ultimately accelerate the availability of novel antiparasitic agents.

5. Inter- and intraspecific competition: A paradigm of *de novo* antiparasitic drug discovery and design

Competition, or competitive interaction, is a mutually negative interplay between two individual organisms, whether of the same species or different species, that coexist in an overlapping niche and compete for the same resources (Gause and Witt, 1935; Cordeiro et al., 2014). "Interference competition" and "antagonistic interaction" are alternative terms referring to competitive interactions that involve the inhibition, suppression, or killing of other inhabitants in the same ecosystem. These interactions increase resource availability through the production of biological weapons. Microbial species have long been known to compete with one another, and this phenomenon has guided antimicrobial drug discovery for decades. Ancient Egyptians applied poultices of moldy bread to infected wounds, an empirical practice explained by microbial competition (Pećanac et al., 2013). In the present review, both inter- and intraspecific competitions are examined in detail, and evidence supporting their role in antiparasitic drug discovery is highlighted (Table 4).

5.1. Interspecific competition

Interspecific competition is a negative interaction in which two organisms of different species compete for limited food and space (Lang and Benbow, 2013). Such competition shapes community dynamics and drives evolutionary changes within specific niches. It has also led to the discovery of novel antimicrobial compounds and bioactive molecules (Tyc et al., 2014; Lutz et al., 2016). Many studies have demonstrated such interactions among species of bacteria, fungi, and parasites. However, competition among viruses or between viruses and other microbes is rare. This rarity likely occurs because viruses are intracellular microbes that persist within host cells. Existing data on interspecific competition provide critical empirical evidence for the paradigm of novel antiparasitic drug discovery.

5.1.1. Interactions between bacteria, and between bacteria and other microorganisms

In microbial communities, interspecific competition among different bacterial species, or between bacteria and other microbes, has been reported for many decades. Certain bacteria produce antimicrobial compounds (e.g. antibiotics, bacteriocins, ethanol, fatty acids, hydrogen peroxide, lytic enzymes, and organic acids) as weapons against competing species in natural communities, including soil, water, and host body microcosms. This is known as the interaction-mediated induction of antimicrobial compound production (Tyc et al., 2014; Darbandi et al., 2022). These biological weapons have inspired researchers to discover novel therapeutics to combat increasing drug resistance and limited efficacy.

Actinomycetes, particularly those in the genus *Streptomyces*, are well-known gram-positive bacteria that produce many of the antimicrobials used clinically, including aminoglycosides, β-lactams, glycopeptides, macrolides, and tetracyclines (Mast and Stegmann, 2019). *Streptomyces* spp. produce these bioactive secondary metabolites to outcompete other microorganisms in shared habitats such as soil (Procópio et al., 2012). All of these molecules are species-specific substances, including antibiotics, antifungals, and antiparasitics (Procópio et al., 2012). For example, *Streptomyces roseosporus*, which was isolated from soil on Mount Ararat in Turkey, produces the cyclic lipopeptide antibiotic daptomycin. Daptomycin displays bactericidal activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) by causing depolarization of the bacterial cell membrane to increase its permeability (Table 4) (Debono et al., 1987). The FDA approved this antibiotic in 2003. *Streptomyces* sp. DC4-5, which was isolated from a stony coral of the genus *Dendrophyllia*, produces iseolides (glycosylated macrolides) with potent antifungal activity against the human pathogens *Candida albicans* and *Trichophyton rubrum* (Zhang et al., 2020). In terms of antiparasitic agents, *Streptomyces avermitilis* produces the macrocyclic lactone "avermectin B1" and its derivative "ivermectin," which are well-known anthelmintic and arthropod-toxic compounds (Campbell, 1982). Ivermectin, approved by the FDA, is used for strongyloidiasis and onchocerciasis, as well as for scabies and other ectoparasitoses (Mogg et al., 1990; Ikeda, 2003). *Streptomyces noclosus* produces amphotericin B, which is active against *Leishmania* spp. and *Naegleria fowleri*, whereas

Streptomyces krestomuceticus produces paramomycin, an aminoglycoside effective against leishmaniasis (Singh et al., 2023a; Valli et al., 2024).

Lactic acid bacteria of the genus *Lactobacillus* also produce antimicrobial peptides and bacteriocins that inhibit or kill other bacterial species. *Clostridium botulinum*, *Listeria monocytogenes*, and *Salmonella typhi* are among the pathogens killed by lactic acid bacteria-produced bioactive molecules (Anjana and Tiwari, 2022). These molecules help control the native microbiota and are employed as probiotics for human health (Anjana and Tiwari, 2022). Lactic acid bacteria are also used in food preservation because of their antimicrobial properties (Mokoena et al., 2021). For example, *Leuconostoc mesenteroides* produces lactic acid, a compound approved by the FDA as "generally recognized as safe, " that inhibits *Streptococcus mutans*, the pathogen causing dental caries. Co-culturing with *L. mesenteroides* significantly reduces biofilm formation by *S. mutans*, highlighting its role as an oral probiotic (Table 4) (Ju et al., 2016; Gu et al., 2023). *Lactobacillus plantarum* produces acetic, lactic, and phenyllactic acids, which display antifungal activity against *Aspergillus niger*, *A. oryzae*, *A. flavus*, *Trichoderma longibrachiatum*, and *Fusarium graminearum*. These findings indicate the potential use of *L. plantarum* as a fungal inhibitor for food preservation (Zhao et al., 2022).

Regarding antiparasitic agents, no consistently effective treatment currently exists for intestinal microsporidiosis caused by *Enterocytozoon bieneusi*. Tubulin-binding benzimidazoles and fumagillin have proven ineffective (Franssen et al., 1995; Lallo et al., 2013). By applying the concept of competitive exclusion, Mossallam et al. (2014) discovered that *Lactobacillus acidophilus* produces bacteriocin with anti-microsporidial effects against *E. bieneusi*. This represents a potentially safe therapy for intestinal microsporidiosis (Mossallam et al., 2014). Waters et al. (1999) reported that the use of *Lactobacillus reuteri* as an intestinal probiotic can control *Cryptosporidium parvum* infection (Waters et al., 1999). Travers et al. (2016) demonstrated that *Lactobacillus johnsonii* secretes bile-salt hydrolases that convert nontoxic bile components into highly toxic forms for *Giardia lamblia*, a protozoan parasite causing giardiasis, a neglected parasitic disease (Travers et al., 2016). *Lactococcus lactis* produces the natural antimicrobial peptide nisin, which shows amoebostatic activity against *Acanthamoeba castellanii* trophozoites. It induces cell cycle arrest and interferes with DNA replication (de Carvalho Clímaco et al., 2022). *Enterococcus faecalis* produces the bacteriocin AS-48, which exhibits trypanocidal activity against *Trypanosoma brucei* by inducing reactive oxygen species production and mitochondrial depolarization. AS-48 is more effective and less cytotoxic than benznidazole, the current reference drug, suggesting promising potential as an antichagasic agent (Martín-Escolano et al., 2019). AS-48 also displays leishmanicidal activity against *Leishmania donovani* amastigotes and promastigotes by inducing plasma membrane permeabilization and mitochondrial dysfunction, demonstrating its potential as a new and safe leishmanicidal agent (Abengózar et al., 2017).

Marine bacteria constitute another promising group of biologically active compound producers. Marine biodiversity, from surface to deep-sea environments, is vast and complex, leading to a wide variety of bioreactive agents (Fleury, 2021). Thus, marine bacteria are reservoirs for discovering and developing new bioactive molecules. For example, *Pseudoalteromonas* spp. isolated from the hemolymph of healthy oysters produce alterins, which are antibacterial cyclolipopeptides that bind lipopolysaccharides. These compounds inhibit the growth of human and aquaculture pathogens such as *Vibrio parahaemolyticus* and *V. harveyi* (Table 4) (Desriac et al., 2020). *Bacillus licheniformis*, an aquatic bacterium, produces ieodoglucomide C and ieodoglycolipid with antifungal activity against plant pathogens (*Aspergillus niger*, *Botrytis cinereal*, *Colletotrichum acutatum*, and *Rhizoctonia solani*) and the human pathogen *Candida albicans* (Tareq et al., 2015).

Marine bacteria are considered promising sources for antiparasitic drug discovery because of their abundance and diversity of bioactive compounds (Zhang et al., 2023). Marine *Streptomyces* spp. produce marinopyrrole A, an alkaloid that strongly inhibits *Toxoplasma gondii* tachyzoites (Martens et al., 2022). Martínez-Luis et al. (2019) reported that marine *Pseudomonas aeruginosa* produces hydroxyquinoline compounds (3-heptyl-3-hydroxy-1,2,3,4-tetrahydroquinoline-2,4-dione, 2-heptyl-4-hydroxyquinoline, and 2-nonyl-4-hydroxyquinoline) that have antiparasitic effects on the chloroquine-resistant *P. falciparum* W2 strain (Martínez-Luis et al., 2019). A subsequent Thai study also demonstrated that pyocyanin secreted from *P. aeruginosa* can inhibit the growth of *N. fowleri* trophozoites, suggesting its role in providing a competitive advantage in overlapping ecosystems (Ruenchit et al., 2021). Moreover, a study revealed that cell-free culture supernatants from *Pseudomonas otitidis* and *Enterobacter cloacae*, strains isolated from a freshwater canal, suppressed growth and caused morphological changes in *N. fowleri* trophozoites (Ruenchit et al., 2021).

Lysobacter species, which belong to the family *Xanthomonadaceae*, are another potential source for novel antiparasitic drugs. They are widely distributed in freshwater, plant, and soil environments (Fukuda et al., 2013; Lin et al., 2015; Lee and Whang, 2021). Owing to their lytic effects on other organisms, *Lysobacter* spp. produce many bioactive substances (de Bruijn et al., 2015). *Lysobacter lactamgenus* produces cephabacins, which are beta-lactam antibiotics (Lee et al., 2008). *Lysobacter* sp. ATCC 53042 produces lysobactin, which adversely affects *Escherichia coli*, *Klebsiella aerogenes*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Streptococcus pyogenes* (Table 4) (Bonner et al., 1988). *Lysobacter enzymogenes* secretes a heat-stable antifungal factor *via* an enzyme secretion system, acting as a weapon against *Aspergillus nidulans*, *Candida albicans*, and *Colletotrichum fructicola* (Lin et al., 2021). *Lysobacter enzymogenes* strain C3 produces antagonistic enzymes and toxins that are active against a range of plant-parasitic nematodes, including *Aphelenchoides fragariae*, *Caenorhabditis elegans*, *Heterodera schachtii*, *Meloidogyne javanica*, and *Pratylenchus penetrans*. These enzymes degrade eggshells and reduce egg viability (Chen et al., 2006). However, their effects on human-parasitic nematodes and other parasites remain unexplored.

In addition to Actinomycetes, *Lysobacter*, lactic acid bacteria, and marine bacteria, other bacterial species also produce bioactive molecules that may serve as drug discovery sources. For instance, *Amycolatopsis rifamycinica*, which is isolated from soil, produces rifamycin, an antibacterial agent approved by the FDA in 2018 (Table 4) (Surette et al., 2021). Certain uropathogenic *Escherichia coli* strains produce microcins, low-molecular-weight proteins active against *E. coli* O157: H7, *Salmonella enteritidis*, and *S. typhimurium*, enabling them to outcompete other bacteria in the same habitat (Swann, 1983; Corsini et al., 2010).

These data suggest that bacteria remain promising sources of novel antiparasitic drugs due to their variety of species, wide range of habitats, and strong experimental evidence. Therefore, extensive investigations of various bacterial species based on competitive interactions are still highly intriguing approaches for drug discovery and development.

5.1.2. Interactions between fungi, and between fungi and other microbes

Fungi are another major source of antimicrobial agents used in current medical practice. A famous example is the competitive interaction noted by Alexander Fleming in 1928 between *Penicillium notatum* (mold) and *Staphylococcus* spp. (bacteria). This classic discovery led to penicillin, the first known antibiotic (Gaynes, 2017). Such historical evidence demonstrates that fungi produce antimicrobial or bioactive molecules when competing with other microorganisms.

Marine fungi are compelling sources of biologically active compounds. The ability of bacteria, parasites, and other bacteria to survive in complex marine communities drives them to produce a wide array of antimicrobial compounds with cytoprotective properties. These compounds offer promising sources for antibiotics (Yurchenko, 2022). For example, *Chromocleista* sp., a deep-sea fungus, produces *p*-hydroxyphenopyrrozin, which exhibits antifungal activity against *C. albicans* (Table 4) (Park et al., 2006). *Penicillium citrinum*, which is isolated from a marine sponge, secretes a citrinin derivative that displays antibacterial

activity against *Bacillus subtilis* in malt extract medium (Sabdaningsih et al., 2020). For antiparasitics, *Aspergillus fumigatus*, which is isolated from deep-water sediment, produces fumagillin, an amoebicidal agent that is active against *Entamoeba histolytica* (Watanabe et al., 2023). Clinical trials for human amebiasis began in 1949 (Watanabe et al., 2023). Watts et al. (2010) demonstrated that *A. fumigatus* and *Nectria inventa* produce diketopiperazines that inhibit *Trypanosoma brucei* growth (Watts et al., 2010).

Botryosphaeria sp. MHF, an endophytic fungus of *Maytenus hookeri*, produces botryosphaerins that inhibit *Candida albicans*, *Saccharomyces cerevisiae*, and *Penicillium avellaneum* UC-4376 (Table 4) (Yuan et al., 2009). *Botryosphaeria* sp. P483, an endophytic fungus from *Huperzia serrata*, produces botryosphaerins that show antifungal and nematocidal activity against phytopathogenic fungi (*Gaeumannomyces graminis*, *Fusarium moniliforme*, *F. solani*, *F. oxysporum*, *Pyricularia oryzae*) and nematodes (*Panagrellus redivivus* and *Caenorhabditis elegans*) (Chen et al., 2015).

Endolichenic fungi reside within the thalli of lichens, which are symbiotic organisms composed of fungi and algae or cyanobacteria. These fungi produce many secondary metabolites and are thus promising sources of novel antimicrobial compounds (Wethalawe et al., 2021). *Chrysosporium* sp. 2, an endolichenic fungus from *Parmotrema* sp., *Usnea* sp., and *Pseudocyphellaria* sp., produces antifungal agents that are active against plant-pathogenic fungi such as *Colletotrichum* sp. (Kannangara et al., 2009). *Fusarium proliferatum*, *Nemania primolutea*, and *Daldinia eschsholtzii*, endolichenic fungi isolated from *Parmotrema rampodense*, produce bioactive molecules with antibacterial activities against *Enterococcus faecalis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa*, and *Enterobacter agglomerans* (Table 4) (Tan et al., 2020). *Xylaria grammica*, another endolichenic fungus, produces grammicin, which is strongly nematicidal against the plant parasite *Meloidogyne incognita* (Kim et al., 2021; Park et al., 2021).

Glarea lozoyensis produces caspofungin, an echinocandin approved by the FDA. Caspofungin exerts fungicidal effects against *Candida* spp. and fungistatic effects on *Aspergillus* spp. by blocking β(1,3)-D-glucan synthesis in the fungal cell wall (Table 4) (Valérie and Herbrecht, 2003).

5.1.3. Interactions between parasites, and between parasites and other organisms

Parasites live on or within different hosts to gain resources for growth, metamorphosis, maturation, and reproduction. Within the host, parasites coexist with many other organisms, including other parasites of different species. To outcompete rivals, parasites develop various strategies. For example, *Toxoplasma gondii* outcompetes *Neospora caninum* when equal numbers of both tachyzoites are cocultured in the same host cells (Table 4) (Sundermann and Estridge, 1999). Quach and Chalasani (2020) reported that *Pristionchus pacificus* and *Caenorhabditis elegans*, which share overlapping bacterial diets for rotting plant material, compete with one another (Quach and Chalasani, 2020). Among *Schistosoma* species, *S. mansoni* is competitively dominant over *S. intercalatum* (Tchuem Tchuenté et al., 1996). Paul et al. (2002) found that two avian malaria parasites, *Plasmodium gallinaceum* and *P. juxtanucleare*, compete during fertilization in the mosquito bloodmeal. This competition contributes to the restricted global distribution of *P. gallinaceum* (Paul et al., 2002). McQueen and McKenzie (2006) reported that *Plasmodium vivax* and *P. falciparum* compete for red blood cells during coinfections. *Nippostrongylus brasiliensis*, an intestinal helminth, releases broad-spectrum bactericidal molecules against both gram-positive (*S. aureus*) and gram-negative (*E. coli*, *S. enterica*, *K. pneumoniae*) bacteria (Pillay et al., 2023). These findings encourage further investigations into bioactive molecules that may serve as potential antiparasitic therapies.

5.2. Intraspecific competition

Intraspecific competition is a mutually negative interplay between organisms of the same species that compete for limited resources (Lang and Benbow, 2013). Under natural conditions, coinfections or multiple-strain infections are common, leading to intraspecific competition that shapes the ecology and evolution of microorganisms.

For example, among two strains of *P. aeruginosa*, one strain produces pyocin, which confers a competitive growth advantage over the other strain (Heo et al., 2007). A study in Thailand revealed that a non-O1/non-O139 *Vibrio cholerae* strain produced and secreted hemolysin to suppress *V. cholerae* O1, a pandemic strain, during copersistence in aquatic habitats (Table 4) (Ruenchit et al., 2017). Among parasites, Chen et al. (2014) reported competition between different strains of *P. falciparum* during *in vitro* culture adaptation. Certain parasites present growth advantages, leading to the loss of some parasite populations (Chen et al., 2014). Balmer et al. (2009) demonstrated strong intraspecific competition between different *T. brucei* strains during co-infection in mice. A less virulent strain enhances host survival by suppressing a more virulent strain. Although the precise mechanisms remain unknown, understanding these suppression phenomena may reveal bioactive molecules for therapeutic development (Balmer et al., 2009).

6. Gaps and opportunities in the discovery, design, and development of novel antiparasitic drugs

The development of new antiparasitics remains essential to address pharmaceutical shortages and to overcome clinical management limitations of parasitic infections. Despite the declining prevalence of most parasitic diseases, many remain life-threatening, especially in low-resource settings where neglected parasitic diseases persist. These populations urgently need effective treatment options to improve health and reduce mortality.

De novo drug discovery is one strategy to meet this need. Although time-consuming, it represents a valuable long-term investment. A literature search of MEDLINE/PubMed *via* PICO identified 1252 articles on novel antiparasitic drug discovery (search terms were “drug,” “new,” “novel,” “parasitic disease,” “parasitic infection,” “parasitosis,” and “therapeutic”). Identifying novel bioactive molecules from natural sources such as plants and microbes is a compelling approach because of their complexity, diversity, and historical therapeutic importance. Many potential antibiotic or bioactive molecule producers remain uncultured or neglected. A search of MEDLINE/PubMed revealed only 15 articles related to antiparasitic discovery from natural sources, highlighting a gap that warrants further exploration. Ecological studies and investigations of microbial variation in diverse niches may increase the chances of discovering new drugs. Multiple antimicrobial agents, antibiotics, bacteriocins, ethanol, fatty acids, hydrogen peroxide, lytic enzymes, and organic acids, have been further analyzed as potential antiparasitic leads.

Biochemical and molecular biological research involving the chemical substances and processes found in plants, animals, and microorganisms, combined with advanced analytical techniques such as genomics or other big data approaches, will increase the likelihood of discovering novel therapeutic agents for parasitic diseases. To search for novel bioactive molecules, high-throughput screening, combined with molecular approaches such as metabolomics and proteomics, can be applied to identify potent metabolites and peptides. Compared to the benefits of seeking out known competitions and functionally annotate the compounds of interest, identifying new compounds in unexplored environmental niches, such as phytomicrobiome, animal microbiome, fermented foods, and sediments, using high-throughput screening appears more compelling due to their diversity. Structure-based discovery using bioinformatics and artificial intelligence can also be integrated to identify highly effective, drug-target-specific antiparasitic drugs. Moreover, employing molecular biology-based approaches to design

therapeutic agents can improve the bioavailability, efficacy, and pharmacokinetics of antiparasitic drugs, as well as help overcome toxicity issues. For example, nanotechnology can facilitate more effective control and treatment of parasitic diseases through improved delivery of antiparasitic drugs *via* the use of liposomes, nanoemulsions, and polymeric nanoparticles, among other nanocarriers (Sun et al., 2019).

Antibody-drug conjugates represent another promising technology. They have already demonstrated success in cancer drug development, suggesting their potential applicability in the design of novel antiparasitic agents. In addition, the ligation of a novel bioactive molecule to a penetrating peptide - forming peptide-drug conjugates - has been explored as an alternative antimalarial therapy (Palombi et al., 2023). Such approaches could also be applied to other drugs that currently have limited target accessibility.

Another promising strategy is molecular hybridization, in which two distinct drug cores are fused *via* functional groups or bonds, producing a single unit with greater pharmacological potency than the sum of its individual components. For instance, incorporating benzimidazole and oxadiazole cores into a single molecule has yielded compounds that exhibit potent anticancer, antimicrobial, anti-inflammatory, antioxidant, anticonvulsant, antidepressant, antihypertensive, and antitubercular activities. This breadth of activity highlights the increased success rate that molecular hybridization can bring to drug discovery (Bhat et al., 2024).

More recently, the supramolecular factor hypothesis has emerged in drug design, allowing researchers to virtually predict and develop agents capable of destroying pathogens with highly remarkable selectivity and efficacy (Regen, 2024). To further reduce toxicity during drug design, bioinformatic tools or artificial intelligence can be employed to predict efficient structural modifications before synthesis and experimental testing. This predictive approach enhances safety and streamlines the process of developing effective antiparasitic therapies.

7. Conclusions

Antiparasitic drugs are crucial tools for managing clinical and public health problems caused by parasites. Currently, preventive vaccines are not available, and drug resistance, limited efficacy, and side effects hinder treatment outcomes. The urgent need for novel therapeutic agents can be met through strategies such as drug repurposing, the development of analogs, screening of compound libraries, and *de novo* drug discovery. Among these, the search for bioactive molecules released during inter- and intraspecific competition offers a paradigm for exploring new antiparasitic drugs. The studies highlighted in this review show many successful discoveries of antimicrobial and bioactive compounds through these competitive interactions. Various organisms, including bacteria (Actinomycetes, lactic acid bacteria, marine bacteria, *Lysobacter*), fungi (marine fungi, endophytic fungi, endolichenic fungi), and parasites themselves, produce a wide range of active agents, such as antibiotics, bacteriocins, lytic enzymes, organic acids, peptides, and toxins. These findings suggest that many antiparasitic producers remain undiscovered in nature. Combining ecological and competitive interaction concepts with structure-based discovery may identify highly effective antiparasitic drugs.

Ethical approval

Not applicable.

Funding

This work was supported by the Siriraj Research Development Fund (grant number IO-R016637003) and the Chalermphrakiat Grant from the Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand.

Declaration of competing interests

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

I thank my colleagues at the Department of Parasitology, Faculty of Medicine Siriraj Hospital, Mahidol University, for their support during the writing of this review. I am indebted to Weluga Bootsongkorn for technical support. I also appreciate the facilities provided by the institution. Additionally, I am grateful to my peers at the Stanford Byers Center for Biodesign, Stanford University, for providing a stimulating academic environment.

Data availability

The data supporting the conclusions of this article are included within the article.

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