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Natural products in antiparasitic drug discovery: advances, opportunities and challenges

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Parasites infect hundreds of millions of people, result in significant disability rates and mortality and lead to devastating social and economic consequences, especially in developing countries and regions. Traditional medicines have been used for centuries to treat parasitic diseases. Some natural products (NPs) and their derivatives have been derived from these medicines and applied in clinical settings, attracting the attention of the scientific community throughout history. With the development and application of revolutionized technologies over the past few years, more promising compounds have been found from natural resources and provided new possibilities for the development of novel antiparasitic drugs. In this review, we aimed to discuss the strategies used for developing drugs from natural resources and mainly describe the causative pathogens, epidemiology and current treatment of parasitic diseases. Promising NPs and their derivatives are listed, and their effectiveness, potential mechanism and structural optimization are described. Subsequently, the advantages and limitations of the drug development process and the role of technologies in this process are discussed. A prospective analysis of research on and development of antiparasitic drugs based on NPs is presented. The high attrition rates, accessibility, sustainable supply, IP constraints and other problems still hinder the development of NPs; however, the therapeutic significance and broad clinical utilization of approved natural product-derived drugs, exemplified by quinine, artemisinin, and ivermectin in treating parasitic diseases, underscore that natural products remain a highly promising reservoir of chemical agents. Their exceptional structural diversity and marked bioactivities continue to stimulate scientific interest in novel antiparasitic drug discovery. In combination with the recent development and application of revolutionized technologies, NPs will provide a stronger basis for drug discovery and will continue to provide major contributions to human and veterinary health.

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1 Introduction

Parasites are a group of eukaryotic pathogens that include protozoa, helminths and arthropods, which partially or entirely complete their life cycle within their host organisms. Parasites infect hundreds of millions of people, resulting in significant mortality with devastating social and economic consequences,[1,2] especially in tropical and subtropical regions of the world. Most parasitic diseases are neglected tropical diseases (NTDs) and spread through various modes of transmission, including surfaces (scabies and psoroptes), infected vectors (Chagas disease, lymphatic filariasis, *etc.*), and contaminated food and/or water (echinococcosis).[3,4] Although some vaccine candidates, including ChAd63-KH for leishmaniasis,[5] the PfSPZ vaccine and ChAd63 for malaria,[6] and recombinant proteins of Tc24 with Th1 adjuvants for African trypanosomiasis, have been investigated,[3] only chicken coccidiosis vaccines have been used.[7] Today, there are no vaccines available against major parasitic infections in humans, and medication is still used only for control and prevention of parasitic diseases. However,

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owing to the poor compliance of individuals and the poor safety, low efficacy, resistance and high cost of drugs, the utility of conventional drugs is limited and decreased.[2] The management of parasitic diseases is a great challenge.[8] Therefore, it is necessary to find new therapeutic agents against parasitic infections.

For centuries, traditional medicines have been used to treat parasitic diseases. Some prominent plants such as *Cinchona* and *Artemisia annua* have been screened and used by humans for a long time and are applied in clinical settings today to treat malaria in Africa and China, respectively. Currently, 70–95% of the population in developing countries continue to rely on medicinal plants for their primary Pharmacopeia,[9] and 80% of 122 plant-derived drugs were discovered from traditional medicines.[10] Considering that the plants present good features such as good safety, strong effects, affordability and long clinical practice in humans and animals, the WHO has established the use of plants as a traditional medicine strategy.[11] Natural product platforms derived from traditional medicines have shown potential for the management of many parasitic diseases.

Natural products (NPs) derived from plants, animals and microorganisms have played an important role in drug discovery since the early days of medicine, especially for treating infectious diseases.[12] Compared with the synthetic counterparts, NPs with a high degree of bioavailability not only provide remarkable prototype drugs such as artemisinin, avermectin, morphine, berberine, taxol, quinine, and camptothecin for treating diseases, but also offer special features with enormous scaffolds and diverse structures for synthesizing new chemical entities (NCEs), such as avermectin.[13] Currently, more than 1000 NCEs derived from natural sources are approved for

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Table 1 Available drugs and promising natural products for the representative parasitic diseases

Disease	Causative pathogen	Treatment		Promising natural products and their analogs
		Current drugs	Disadvantage	
Protozoal disease				
Leishmaniasis	*Leishmania donovani*, *L. infantum* for VL; *L. tropica* and other species for MCL and CL	Pentamidine, pentavalent antimonials, amphotericin B[a], miltefosine	Resistance for pentamidine and antimonials; high cost for amphotericin B; the contraindicated in pregnancy of miltefosine; toxic effects and parenteral route of all drugs	*Arnica montana* tincture; jacoumaric acid, corosolic acid
Chagas's disease	*Trypanosoma cruzi*	Nifurtimox; benznidazole	Benznidazole is not effective against the chronic phases; long treatment course; adverse effects	Ascosalipyrrolidinone A; valinomycin; terpinen-4-ol
African trypanosomiasis	*T. brucei rhodesiense*; *T. gambiense*	Suramin, pentamidine, melarsoprol, eflornithine	Pentamidine and suramin are effective only on the early haemolymphatic stage; pentamidine needs parenteral administration; poorly tolerated	7,8-Dihydroxyflavone; 1,12-dehydro-13-oxo-plakortide Q; manadoperoxides I and B; 2,7-dibro-mocryptolepine; 12-isomanadoperoxide B
Malaria	*Plasmodium* spp.	Quinine[b], chloroquine[a], primaquine[a], mefloquine[a], artemisinin[b], atovaquone[a]	Resistance, low compliance, cost and toxin of these drugs	Dioncophyllines F; dehydroantofne; tylophoridicine; tsitsikammamine C; puberulic acid; fortunilide A
Toxoplasmosis	*Toxoplasma gondii*	Dihydrofolate reductase inhibitors (pyrimethamine, trimethoprim), dihydropteroate synthetase inhibitors (sulfadiazine, sulfamethoxazole, sulfadoxine)	Most drugs acts only against the tachyzoite, didn't affect the cysts and cross the blood–brain barrier; the undesirable side-effects and the resistance of pyrimethamine were appeared widely	*Trametes versicolor* (Turkey tail) methanol extract; propolis and wheat germ oil; abscisic acid; manzamine A; sigmosceptrellin-B; plakortide
Helminths				
Schistosomiasis	*Schistosoma mansoni*, *S. haematobium*, *S. japonica*	Oxamniquine and praziquantel	Oxamniquine only effective against *S. mansoni*, and praziquantel does not kill immature worms. The resistance to praziquantel was appeared	Ectracts of *Agave lophantha*, *Furcraea selloa* and *Solanum elaeagnifolium*; artemisinin (artesunate or artemether); 4-nerolidylcatechol; menadione
Lymphatic filariases and onchocerciasis	*Brugia malayi*, *Wuchereria bancrofti*, and *Onchocerca volvulus*	Diethylcarbamazine or ivermectin[b] in combination with albendazole; moxidectin	Diethylcarbamazine cannot be used in *O. volvulus*-endemic areas, albendazole only used in combination therapy, and ivermectin does not eliminate adult worms; the resistance, high cost, and adverse effects are appeared	Anthraquinone K; 7-fluoro-6-oxybenzoxaborole; A-1574083 (tylosin A analog); doxycycline

Table 1 (*Contd.*)

Disease	Causative pathogen	Treatment: Current drugs	Disadvantage	Promising natural products and their analogs
Ectoparasites				
Scabies	*Sarcoptes scabiei*	Permethrin[a], ivermectin[b]	The poor or limited ovicidal action of permethrin, and the resistance are appeared	*Tinospora cordifolia* lotion; tea oil; clove oils; eugenol, juglone, octadecanoic acid-tetrahydrofuran-3,4-diylester
Ticks	*Ornithodoros* spp., *Otobius* spp., *Hyalomma* spp., *Ixodes* spp., *Dermacentor* spp., *Amblyomma* spp., *Boophilus* spp., *Rhipicephalus* spp.	Permethrin[a], ivermectin[a], fluralaner, *etc.*	The resistance, high cost, and adverse effects are appeared	Some plant essential oils, such as MyggA® Natural (Bioglan, Lund, Sweden) and Citriodiol®

[a] Represent the antiparasitic drugs were derived from NPs. [b] Represent the antiparasitic drugs were NPs.

clinical use, and in international databases, 10 000 patents are authorized by governments.[14] During 1970–1980, the investigation of NPs peaked in the Western pharmaceutical industry. Newman & Cragg[15] found that among all FDA-proven drugs (1881) between 1981 and 2019, 49.44% (930) were directly and indirectly derived from NPs. For parasitic diseases, approximately 60% of drugs are derived from NPs.

With an estimated 300 000 to 500 000 plant species and approximately 2 million lower-level organisms worldwide, these resources provide a chemotherapeutic pool for finding novel compounds.[16] According to the Medicinal Plant Names Services (MPNS), approximately 28 187 species of plants are utilized in medicine, accounting for nearly 7.5% of all plant life.[17,18] They may provide insights into the efficacy and safety of novel compounds. However, considering the time-consuming and labor- and cost-intensive nature of traditional extraction, isolation and identification, many groups and pharmaceutical companies have experienced a slow decline in the discovery of novel NPs over the past two decades, and only small parts of natural resources have been exploited. Promisingly, a range of revolutionized technologies (including genomics, metagenomics, proteomics and metabolomics) are providing an unprecedented opportunity and new welcome impetus for researchers and pharmaceutical companies to discover antiparasitic drugs from natural resources.[11] The WHO Program of Tropical Diseases has declared that NPs are still a crucial priority for the management of parasitic diseases.[3] In this paper, we review the opportunities and challenges encountered during the discovery of antiparasitic drugs from natural resources (Table 1).

2 Current control strategies for parasitic diseases

2.1 Protozoa

Protozoa are eukaryotic unicellular organisms that are free-living in water or other organisms, and protozoan parasite infection leads to high rates of mortality and morbidity worldwide. In this review, we focus on the current control strategies against *Leishmania* spp., *Trypanosoma* spp., *Plasmodium* spp., and *Toxoplasma* spp.

Malaria caused by five species of *Plasmodium* remains a massive problem in many regions of the world,[19] and there were 247 million cases of malaria and 619 000 deaths in 2022 worldwide.[20,21] Although malaria vaccine pilots were launched in 2019 by the Ministries of Health of some Africa countries and organizations, a 5-month-old girl has received the world's first malaria vaccine recently (RTS, S/AS01 or RTS, S). In 1820, quinine (**1**), the first antimalarial agent, was isolated from *Cinchona* tree bark and is widely used to treat malaria,[22] and classic amino alcohols and 4-aminoquinolines (**2–4**) were developed over the last century. Tafenoquine (**5**) and primaquine (**6**) from the 8-aminoquinoline scaffold are recommended in combination with other antimalarials to prevent relapse of *P. vivax* and *P. ovale* infections[23] (Fig. 1A). In addition, artemisinin's derivative, dihydroartemisinin (**8**), as well as artesunate (**9**)

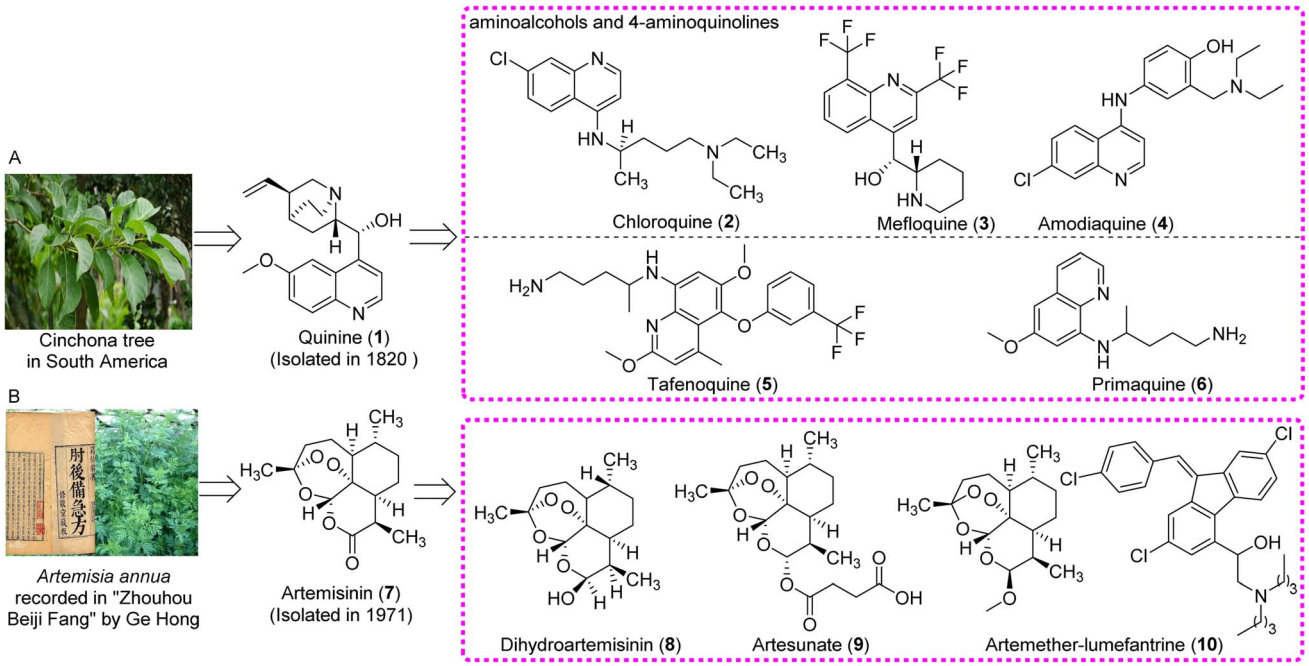

Fig. 1 Two successful examples of antimalarial drugs ((A) for quinine and (B) for artemisinin).

and artemether-lumefantrine (**10**), was approved by the WHO[20] (Fig. 1B). Currently, chemoprevention strategies, based on mass drug administration (MDA), remain the most important and efficient methods for controlling malaria. The history of chemotherapy for controlling malaria is intimately linked with the history of herbal medicinal products. Over the past few decades, significant progress has been made in new approaches to control and eliminate malaria, including the identification of new druggable targets, promising drug candidates, and several new therapies. Despite this measurable progress for screening NPs, no NCEs have been licensed. Of course, the annual number of malaria cases still persists, highlighting the vital need for new medicines.[24]

Leishmaniasis is a disease caused by an obligate intracellular parasite that contains over 20 *Leishmania* species. The main forms of the disease are cutaneous leishmaniasis (CL), which is characterized by self-healing ulcers; mucocutaneous leishmaniasis (MCL), which involves progressive

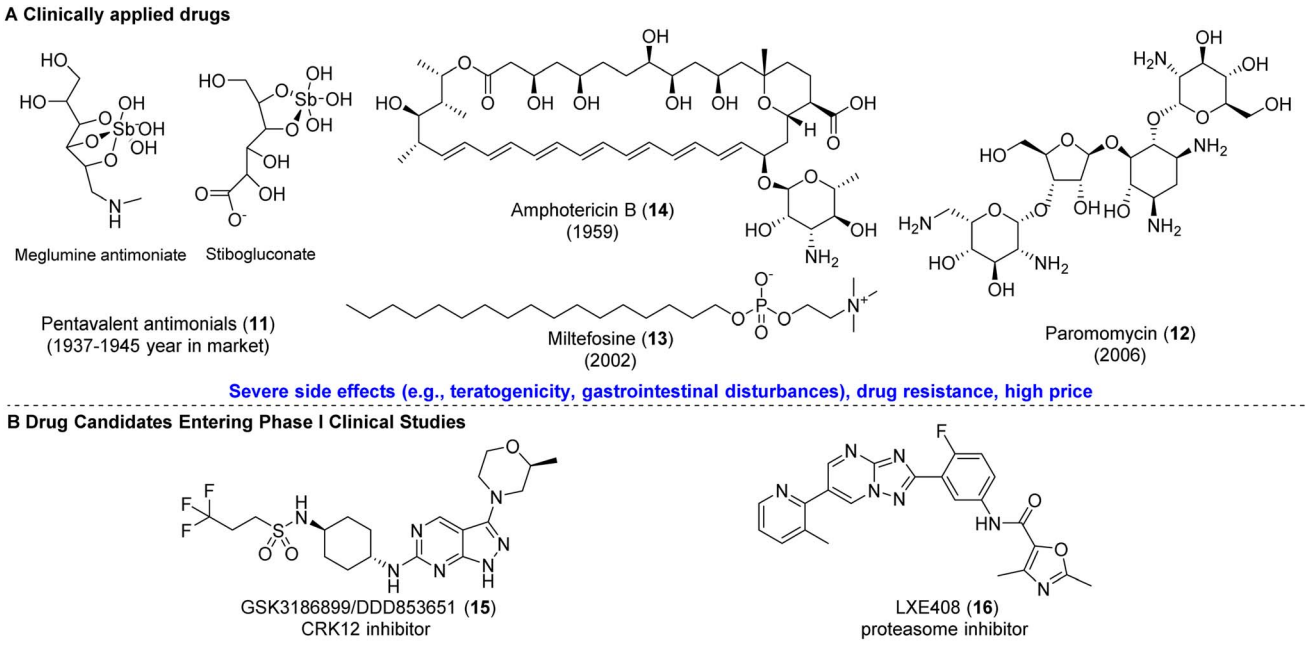

Fig. 2 Current chemicals or antibiotics used to treat leishmaniasis (A). Drug candidates for the treatment of leishmaniasis (B).

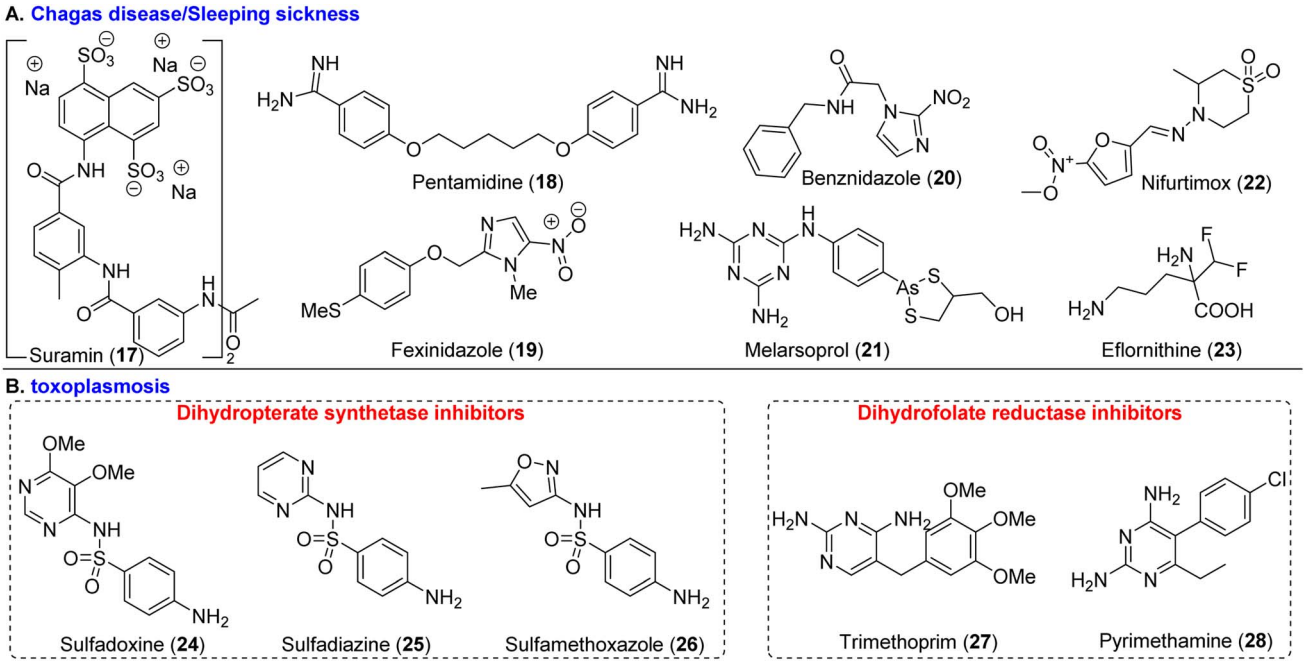

Fig. 3 Current chemicals or antibiotics used to treat American trypanosomiasis and human African trypanosomiasis (A) and toxoplasmosis (B).

nasopharyngeal infections; and visceral leishmaniasis (VL), which is also known as kala-azar,[25,26] and over 90% of VL occur in poor rural and suburban areas of Bangladesh, Brazil, Ethiopia, Sudan, India and South Sudan.[27,28] According to the Global Burden of Disease (GBD) study conducted in 2019, it was estimated that between 498 000 and 862 000 new cases of leishmaniasis occur worldwide each year.[29] Currently, there is no perfect vaccine or suitable drug to eradicate leishmaniasis completely,[30] and the treatment of leishmaniasis mainly relies on pentavalent antimonials (**11**), paromomycin (**12**), miltefosine (**13**), amphotericin B (**14**) and other drugs. Among these, amphotericin B (**14**) is a breakthrough antibiotic against leishmaniasis and was isolated from *Streptomyces* spp.[31] (Fig. 2A). Due to the development of extensive resistance to pentavalent antimonials (**11**) and the toxic effects, parenteral route and high cost of other drugs, these drugs are gradually being limited. Although some NCEs have progressed into phase I clinical research, including the CRK12 inhibitor GSK3186899/DDD853651 (**15**) and proteasome inhibitor LXE408 (**16**),[32] no new drugs have been approved in recent decades (Fig. 2B).

Trypanosoma brucei and *T. cruzi* are the pathogens causing human African trypanosomiasis (sleeping sickness) and American trypanosomiasis (Chagas disease), respectively. These diseases are prevalent in low- and middle-income countries and cause a large number of deaths (approximately 12 000 people per year).[33–35] Significant progress has been achieved in treating sleeping sickness; however, drugs and developmental pipelines for Chagas disease urgently need to be investigated, although the novel drug nifurtimox (**22**) invented by Bayer was approved by the FDA in Q3 2020.[36] Moreover, the curative effect of current drugs is limited; pentamidine (**18**) and suramin (**17**) are effective only against the early hemolymphatic stage, and benzimidazole (**20**) is effective only in children aged 2–12 years whose recent infection is in the acute phase of Chagas disease but not against the chronic stage.[37] Pentamidine (**18**) requires parenteral administration, and some drugs are poorly tolerated and difficult to administer. Hence, drugs with novel structures and mechanisms of action different from those of current drugs (**17–23**) are needed[38] (Fig. 3A). However, due to their unsuitable structural and pharmacokinetic properties, numerous drug candidates have failed to advance to the later stages of clinical development. Some traditional medicines and NPs have presented clinical efficacy in treating complementary neurological disorders associated with sleeping sickness and other disease sites in adipose tissue, skin, cardiac muscle, *etc.*, and have attracted the interest of many researchers.[39]

Toxoplasma gondii is an apicomplexan obligate intracellular parasite.[40] The parasite occurs in nature as oocysts, bradyzoites, and replicating tachyzoites, and the last form is the hallmark of active disease.[41,42] According to the GBD estimate, the disease affects about one-third of the population, and causes 1.2 million disability-adjusted life years (DALYs) for >190 000 annual cases.[43] In particular, chronic infections frequently become reactivated in individuals infected with HIV who have advanced to AIDS due to immunocompromise, leading to a significantly elevated risk of mortality.[44] Treatment of toxoplasmosis usually involves a combination of two enzyme inhibitors to block folate synthesis, including dihydropterate synthetase inhibitors, such as sulfadoxine (**24**), sulfadiazine (**25**), and sulfamethoxazole (**26**), and dihydrofolate reductase inhibitors, such as trimethoprim (**27**) and pyrimethamine (**28**). Among them, pyrimethamine is one of the most effective drugs against *T. gondii*.[42] However, most

drugs act only against the tachyzoite and do not affect cysts; undesirable side effects and resistance to pyrimethamine also appear widely[45] (Fig. 3B).

Considering that *T. gondii* may cross the blood–brain barrier and then establish persistent infection in a drug-resistant bradyzoite stage,[46,47] an ideal agent should achieve therapeutic, systemic, brain and eye concentrations that are effective in the organs and active against the acute replicating tachyzoite and latent bradyzoite stages.[48] Anyway, although many NPs have been investigated and explored, no suitable leads or drug candidates have been found.

2.2 Helminths

Helminths, multicellular invertebrates, comprise nematodes or round worms, cestodes or tapeworms, and trematodes or flat worms, which are among the most persistent public health problems caused by human and veterinary infections.[49,50] More than 1 billion humans are infected with helminths annually worldwide; helminths are present in various parts of the body system, and can lead to serious pathological outcomes.[51,52] At present, anthelmintic drugs, which are used to eliminate helminth parasites in host organisms, have solved a major problem in animal husbandry and made an important contribution to the problem of human malnutrition and disease.[26] However, drugs that treat the parasitic worms after the bloodstream, lymphatics or other tissues are infected are limited, and drugs that treat resident adult worms causing diseases such as river blindness and lymphatic filariasis are still needed. In addition, the increasing prevalence and severity of resistance of human and animal pathogenic helminths have become global phenomena, necessitating the search for new bioactive agents.[53,54]

Schistosomes (*Schistosoma mansoni*, *S. haematobium*, and *S. japonica*) infect over 200 million people and cause more than 250 000 deaths globally every year.[55] Schistosomes are multicellular pathogens with complex life cycles and biological properties causing schistosomiasis, the treatment of which relies on the chemicals oxamniquine (**29**) and praziquantel (**30**);[2] however, oxamniquine (**29**) is only effective against *S. mansoni*, and praziquantel (**30**) does not kill immature worms (Fig. 4A). Moreover, possible resistance to praziquantel has been reported; thus, relying on praziquantel monotherapy is risky.[56] Due to the complex life cycle of schistosomes, the development of new safe and effective drugs to target parasites at all stages is still hard.

Lymphatic filariases and onchocerciasis are caused by *Brugia malayi*, *Wuchereria bancrofti*, and *Onchocerca volvulus*, respectively.[57,58] *B. malayi* infection has spread to southeast Asia, *W. bancrofti* has the estimated 120 million cases in 83 countries, and *O. volvulus* affects nearly 37 million people in 34 countries, with small foci in southern and central America.[59] In 1987, Merck Laboratories registered the first formulation of ivermectin (**32**), and then as the only drug used in a control program for annual or semi-annual dosing, it was officially approved by the FDA in 1996 for the treatment of onchocerciasis and strongyloidiasis.[60] In 2018, moxidectin (**31**) was approved by the FDA for the management of onchocerciasis in patients over 12 years old, which was repositioned as a veterinary medicine.[61,62] Along with the recurrent donations and MDA campaigns of ivermectin, the spread of lymphatic filariases and onchocerciasis has been partly controlled in some endemic regions over the past few decades. The combination of diethylcarbamazine (**33**) or ivermectin with albendazole (**34**) has become the basis of a global program for the elimination of lymphatic filariasis (Fig. 4B). However, due to the risk of adverse effects, diethylcarbamazine and ivermectin could not be used to eliminate *O. volvulus* and adult worms, respectively. Albendazole can only be used in combination therapy.[2] Moreover, the

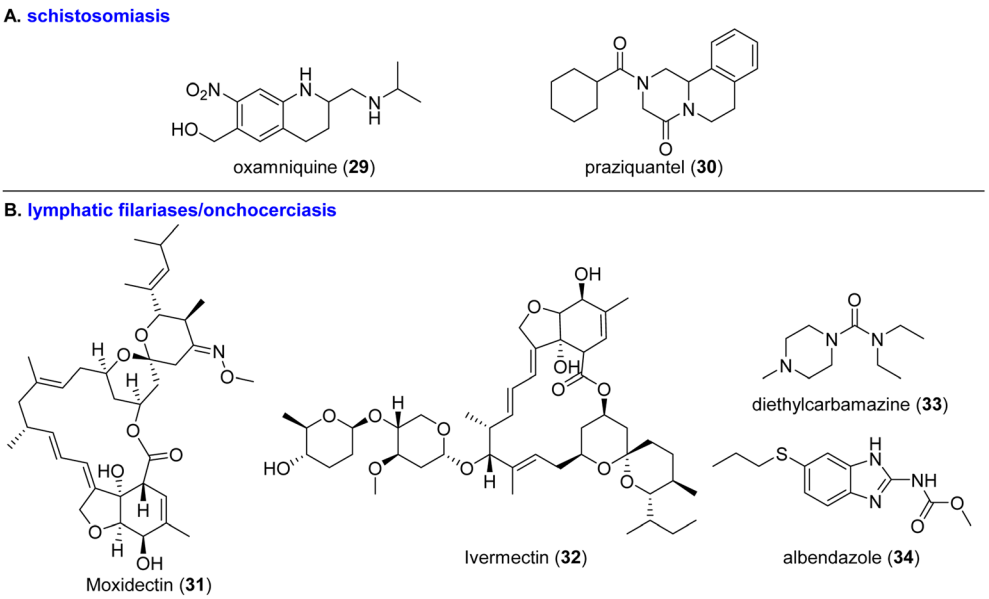

Fig. 4 Current chemicals or antibiotics used to treat schistosomiasis (A) and lymphatic filariases and onchocerciasis (B).

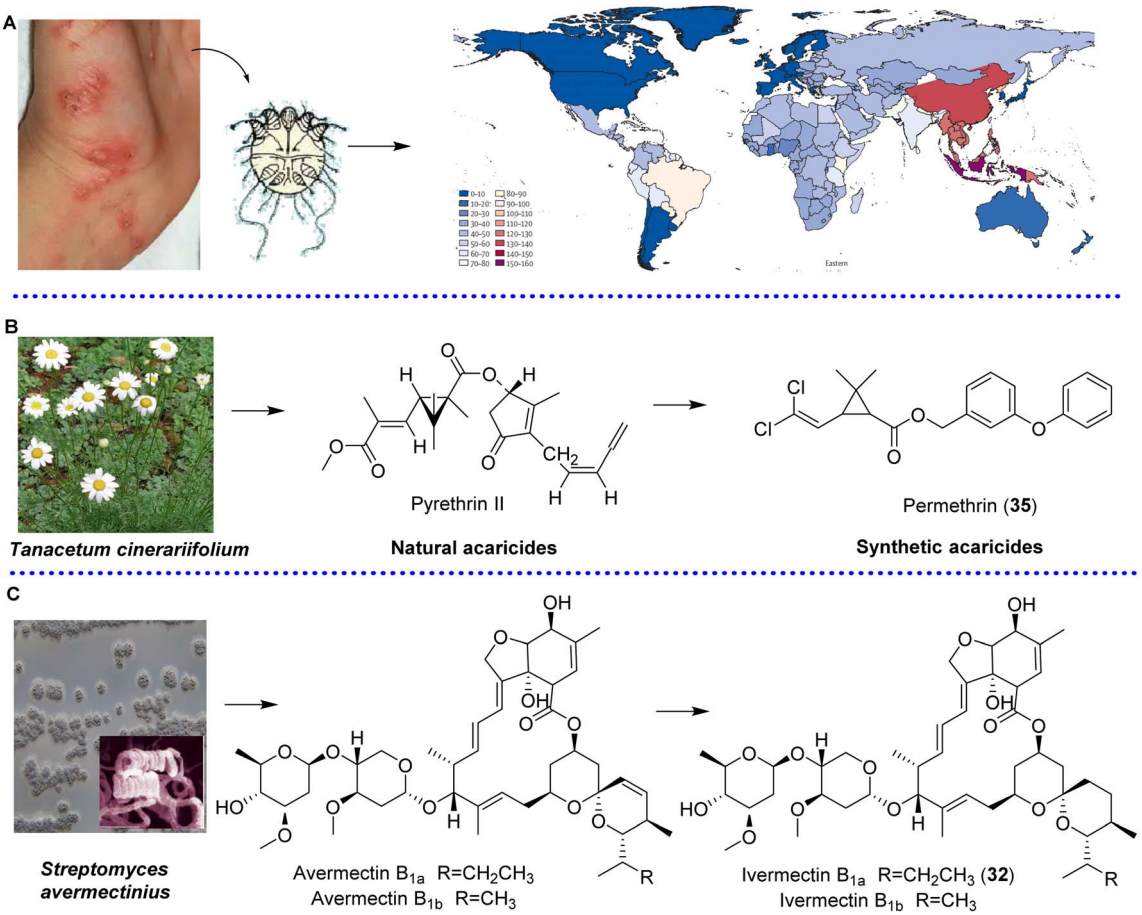

Fig. 5 Epidemiology of scabies (A),[69] and history of permethrin (B) and ivermectin development (C) in clinical applications.

development of resistance to these drugs affects their clinical application. Hence, a new chemical class with slow action, oral use, and low cost (ideally a single oral dose) is needed against all parasite stages in humans.[4]

2.3 Ectoparasites

Ectoparasites (such as fleas, ticks, lice, flies, or mites) and vector-borne diseases have a major impact on the health and productivity of hosts; in addition, ectoparasites cause a constant risk for the survival and well-being of the public and animals worldwide by transmitting diseases such as Crimean-Congo hemorrhagic fever, Q fever caused by *Coxiella*, babesiosis and hymenolepiasis caused by *Hymenolepis*.[63–66]

Currently, the vast majority of human and animal ectoparasites are still arthropods. Mites can live freely in the environment and can also parasitize plants, humans or domestic animals. Scabies is an important parasitic disease of the skin caused by the ectoparasite *Sarcoptes scabiei* var. *hominis*, which is associated with debilitating itch and major morbidity worldwide and leads to severe bacterial infection and immune-mediated diseases in humans.[67] It can occur across all age groups, and affect 150–200 million people yearly (Fig. 5A). In 2017, scabies was added to the WHO list of NTDs;[68] it was responsible for 0.21% of DALYs studied by the GBD in 2015 worldwide. In tropical regions, the burdens of scabies in children, elderly people and adolescents are greater[69] (Fig. 5A). As the first-line treatment used topically, permethrin (**35**) (5%) derived from natural pyrethrins from *Tanacetum cinerariifolium*, which is efficient after 1 week repeating, indicates poor or limited ovicidal action (Fig. 5B). In addition, due to emerging resistance, scabies is becoming less sensitive to permethrin therapy,[70] and the efficacy of permethrin has been reduced in Australia for the past 20 years.[71] Ivermectin (**32**) (Fig. 5C), the only oral drug currently available for the treatment of scabies, is primarily prescribed for patients with severe crusted scabies and patients with intercurrent infections or eczematous skin lesions in scabies-endemic areas or in facilities where large-scale use of effective drugs is required to control outbreaks.[72] However, along with ivermectin-based MDA strategy is widely used to control scabies in clinic, the resistance appears inevitable.[73] Since the first documented case from human infestations in Australia in 1994,[74] there have been reports on the resistance of *Sarcoptes scabiei* to ivermectin *in vitro* and *in vivo*. In 1997, mites grown *in vitro* in the presence of ivermectin survived for 1 hour; however in 2006, this time increased to 2 hours.[75] Moreover, considering that ivermectin is poorly metabolized in both humans and animals, after the large-scale use in human and livestock, ivermectin and its metabolites are

constantly released into the environment mainly *via* feces (90%), the potential ecotoxicity in freshwater systems from agriculture or latrines and others should be given more attention,[76] and the environmental fate should be taken into account. Of course, some neurotoxins that selectively target the arthropod nervous system were also used for controlling ectoparasite infections.[77] Considering that permethrin and ivermectin are all derived from natural resources, NPs have attracted great interest. Our group analyzed and reviewed the global research profile of anti-ectoparasitic agents for animals from Jan. 2015 to Jun. 2020. Among 284 papers published by international journals, 204 papers (71.83%) aimed to obtain active NPs, and more than 16% papers focused on investigating acaricidal activity of NPs against *Sarcoptes* and *Psoriasis* mites.[78]

Among blood-sucking arthropods, ticks are second only to mosquitoes in causing harm from a public health and veterinary viewpoint.[79] Due to the severity of tick-borne diseases, many livestock breeders spend a significant portion of their annual input costs on managing and controlling ticks and the diseases they transmit.[80] According to statistics, the annual loss was estimated at $720 million in Africa, $100 million in Australia, and up to $1 billion per year in South America.[81] In Brazil, the cattle tick (*Rhipicephalus microplus*) alone has caused $3.24 billion economic losses,[82] and other tropical and subtropical regions are likely to face similarly severe impacts. Currently, many commercially available chemicals including macrocyclic lactones, organophosphates, pyrethroids, carbamates and others were widely used to control ticks.[83] The long-term, high-scale use of these chemical drugs has led to problems such as drug resistance and drug residues, which seriously affect the treatment of the disease. At present, the use of botanicals for the control of domestic animal parasites has received renewed attention due to their safety, effectiveness and low price. Pavela *et al.*[84] have recently stated that more than 200 plant species were used as herbal preparations to repel ticks from livestock by traditional communities worldwide. Additional studies have recommended that an integrated strategy is used to control ticks based on the rotation and combinations of acaricides, immunization and biological control, and practices against ticks.[85] House management, pasture alternation and/or rotation, and nutritional management should also be focused on.[86]

3 Strategies for developing drugs from natural resources

Typically, a successful drug discovery campaign spans 10–15 years, and high attrition rates and costs always hinder antiparasitic drug discovery. Hence, the number of new compounds in clinical development is very low and clinical needs are unlikely to be met. To improve the success rate of drug discovery by relatively few working organizations, people have tried to find new agents from natural resources over the past century, and some strategies for drug development have been applied (Fig. 6).

3.1 Isolation and identification of NPs from natural sources

The use of a bioassay-guided isolation method or a direct phytochemical isolation method to find active NPs from medicinal plants, marine microorganisms, and other natural resources remains the main strategy or approach. Some active NPs could be used as antiparasitic agents directly. Although the traditional use of plants and animals for hundreds of years ensures that isolated NPs exhibit bioactivities, the ability to isolate and purify active compounds remains limited. In addition, this workflow is time-consuming and labor- and cost-intensive; some known compounds are found repeatedly; and more promising or target compounds with low contents may be missed. Due to the presence of synergistic effects, compounds with better activity may not necessarily be obtained in many active crude extracts.

In the past decade, novel extraction technologies have been developed to improve extraction yields and downstream detection efficiency, such as high-speed countercurrent chromatography,[87] semipreparative liquid chromatography, supercritical fluid extraction,[88] deep eutectic extraction,[89] and high-intensity pulsed electric fields combined with semibionic extraction.[90] An idealized system coupled with online affinity screening, separation and identification was developed to improve the efficiency of discovering active ingredients from extracts. Through this approach, bioactive compounds can be detected at an early stage; thus, the bioactivity-guided isolation process is shortened and unnecessary efforts, costs, and working times are reduced.[91]

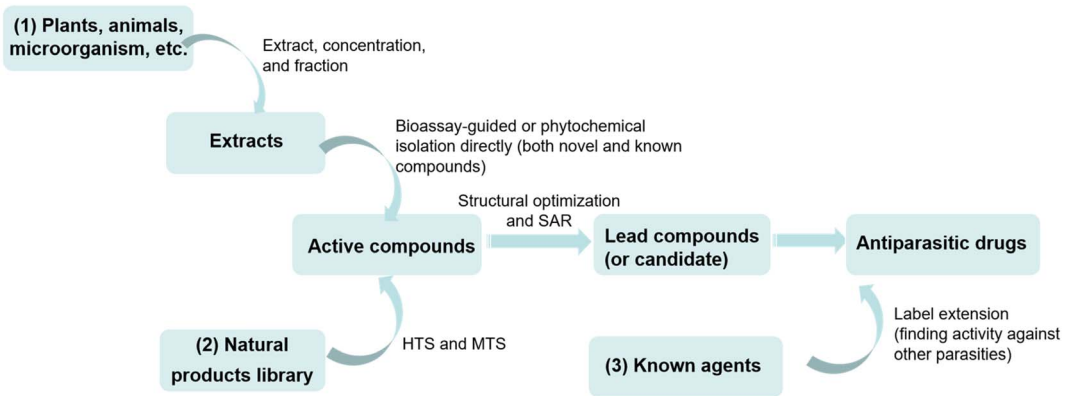

Fig. 6 Main strategies used to develop drugs from natural resources.

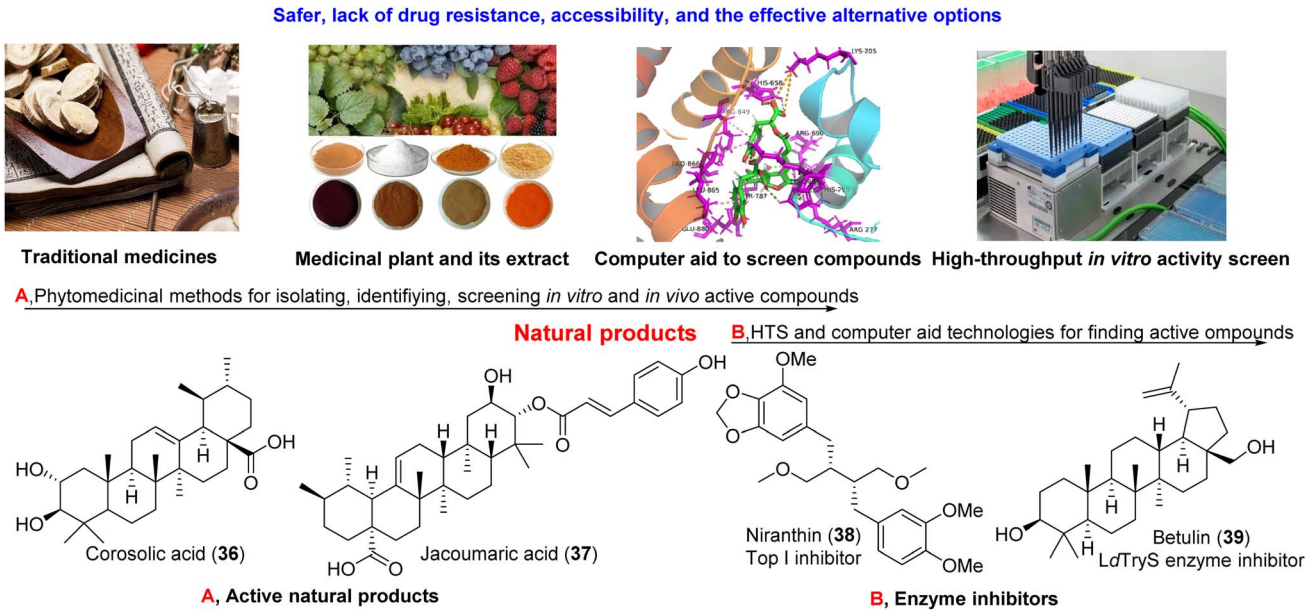

Fig. 7 Main strategies for finding active NPs from natural sources based on phytochemical analysis (A) and high-throughput screening (B).

The application of metabolomics in NP research combines two concepts, *i.e.*, metabolic profiling with the introduction of photodiode arrays and HRFTMS detectors that were coupled with HPLC, NMR spectroscopy and LC-MS.[92] It could identify active components at the early fractionation step and predict which structures might be bioactive.[93,94] For example, a family of triterpenoid compounds from *Psidium guajava* leaves were found with antileishmanial activity in the amastigotes stage, including corosolic acid (**36**, $IC_{50} = 0.0021$ μM) and jacoumaric acid (**37**, $IC_{50} = 0.0021$ μM), using metabolomics (Fig. 7A).[92] In addition, a number of prefractionation strategies coupled with sensitive NMR technology have been reported for separation, which addressed isolation and structure-elucidation bottlenecks. When combined with a high-throughput screening (HTS) strategy, higher hit rates and faster screen speeds were realized (Fig. 7B).[95] For example, through high-throughput screening, the topoisomerase I inhibitor niranthin (**38**)[96] was discovered to alter the DNA topology of *Leishmania promastigotes* with an EC_{50} value of 1.26 μM; inhibiting the polyamine pathway can kill *Leishmania*, and targeting this pathway, betulin (**39**)[97] was efficiently screened out through high-throughput screening.

The development of sequencing technologies has accelerated the process of discovering drugs from NPs. Genome mining techniques have emerged as a powerful approach to discover and identify potential interesting products[98,99] or novel compounds from bacteria and fungi, specifically through the identification of secondary metabolites derived from biosynthetic gene clusters encoding novel bioactive metabolites, such as the polyphenolic polyketide antibiotic clostrubin, which was identified from *Clostridium beijerinckii* using this technology.[100] Since the 1960s, mass spectrometry has been extensively utilized to characterize small molecules and NPs through their fragments.[101] In parallel, the proteomics have been applied to expedite the identification process of small-molecule agents. Moreover, chemical proteomics with the affinity principle between compounds and targets has been widely used to find the potential targets of NPs and then to design novel agents.[102,103] In addition, the combination of cell membrane-coated technology and sequencing technology can more effectively screen the active ingredients in NPs. The biomimetic environment created by cell membranes greatly enhances the accuracy and efficiency of the screening process.[104]

NPs retain their pivotal role in drug discovery, particularly in pioneering therapeutics with novel mechanisms of action. Although escalating challenges in identifying natural compounds with superior bioactivity and cost-efficiency have diminished pharmaceutical industry investment in this field over recent decades, the convergence of interdisciplinary technological advancements now presents two strategic pathways: rational development of existing natural product frameworks, or systematic discovery of new bioactive candidates. Throughout these processes, methodical observation, critical analysis, and transformative innovation constitute essential determinants of successful outcomes.[105]

3.2 New application of existing drugs

Considering that NP-based drug discovery represents a complex endeavor and hard work that requires an integrated interdisciplinary approach, many NP groups have been eliminated in most large pharmaceutical companies in the U.S. Under this condition, methods to extend the label or activity of existing NP treatments for other human ailments have gained the interest of many people and companies. This strategy may enable pharmaceutical companies to reduce the economic cost of discovering new drugs and increase the new application and economic value of existing products.[3] Historically, many antiparasitic drugs were developed for other purposes. For instance,

Table 2 Natural product databases

Database	Number of entries	Additional information	Ref.
Super Natural 3.0	355 000	2D structure; vendor information for over 449 005 compounds	42
Universal Natural Product Database	197 201	3D structures assembled from Chinese database	43
Chinese Natural Product Database	53 000	Has been used in a virtual screen for PPAR-γ agonists	44
Drug Discovery Portal	40 000	All based on available samples	45
iSMART	20 000	Compounds from traditional Chinese medicines	46
Database from historical medicinal plants, DIOS	6702	It has been used in several virtual screening campaigns	47
AfroDb	1000	Compounds from medicinal African plants	48
NuBBE	640	Compounds from Brazilian sources	49
MarinLit	40 542	Marine natural products research	50
Microbial Natural Products Database	16 000	Compounds from microbial	51
The Natural Products Atlas (https://www.npatlas.org/)	33 372	13 068 compounds from bacterial and 20 304 from fungal sources	52
Dictionary of Natural Products	270 000	Some of them are considered vital components of many modern drugs	53

moxidectin (**31**), a veterinary anthelminthic agent that is an analog of ivermectin, has progressed to phase II clinical trials for controlling lymphatic filariasis and onchocerciasis.[106,107] Ivermectin is used not only for filariasis/onchocerciasis but also for ectoparasites.[108] In addition, some commercial drugs with anti-inflammatory, antiviral or other activities present antiparasitic activity, such as auranofin approved by the FDA for the treatment of rheumatoid arthritis, which exhibits activity against *Toxoplasma gondii in vitro* and *in vivo*.[109] During the past three decades, the pharmaceutical industry has provided limited support for specific drug discovery programs. This approach would reduce the cost and time to market; for example, artemisinin and its derivatives with antimalarial activity were also used to treat schistosomiasis in clinical trials.

3.3 NP library and HTS

Employing automation tools, miniaturized assay formats, and large-scale data analysis, the HTS strategy enables the screening of approximately one million compounds daily from the NP library, enabling the rapid detection of biological activity within a minimal time frame.[109] Compared with the traditional approach, advances in these technologies would decrease drug screening time, shorten drug discovery timelines and enhance hit-to-lead development.[110] However, for the HTS approach, a high-quality and abundant NP library is a crucial prerequisite for achieving effective screening. Currently, a corresponding trend is developing lead compounds from NP libraries or libraries of NP hybrids, NP analogs and NP-inspired molecules using HTS technology, such as the Dictionary of NPs, Drug Discovery Portal, Chinese Natural Product Database, iSMART, AfroDb, NuBBe, MarinLit and Super Natural II[111–122] (Table 2). Among them, the Dictionary of NPs containing 270 000 compounds was considered as authoritative and comprehensive data in the NP field.[122,123]

Due to the complex life cycle and difficult culture conditions of parasites compared with other pathogens, it is difficult to screen active NPs with low concentrations *in vitro* or *in vivo.* The strategy based on target-based HTS and medium-throughput screening (MTS) in whole-parasite assays against specific proteins and whole parasites has been developed and used to identify NCEs from NP libraries. With the continuous development of HTS technologies, some impedance-based methods based on cell monitoring products or custom "in-house" systems for the target application have been developed to assess anti-schistosomiasis activity based on their mobility measurements.[124,125] These methods will ultimately screen NPs beyond small research laboratory-based proof-of-principle studies, and more lead compounds may be found. Furthermore, chemoinformatic methodologies are now being integrated with genomics, *in silico* screening, and the cocrystallization of proteins with small molecules, to accelerate the discovery of antiparasitic drugs.[126,127] From heterogeneous cell-based screens, a machine learning approach for defining antimalarial drug was developed.[128] Although a large gap remains between enzyme inhibitors and antiparasitic agents, some encouraging results have been obtained.[129,130]

3.4 Optimization of the NP structure

Lead optimization is a key process in which medicinal chemistry is used to optimize the structure of NPs and find new compounds; this is the most crucial process in drug discovery stage to address several problems, including bioavailability, metabolism and toxicity. Between 1981 and 2019, 43.2% of FDA-approved commercial drugs were indirectly derived from NPs, which were optimized.[131] Chemical scaffolds of NPs have historically been sources of inspiration for the development of novel molecules[132] that can retain the antiparasitic activities of parent NPs, which are beneficial in this aspect; thus, the use of parent NPs to design and synthesize novel agents has received much attention. Apart from NPs such as paclitaxel that can be directly used in clinical applications, most bioactive NPs with excellent biological activity often suffer from limitations such as poor stability, low solubility, toxicity, and inadequate bioavailability. Implementing simple structural modifications to address these application challenges represents a highly effective optimization strategy.[133] Additionally, chemical

modifications through approaches such as bioisosterism, active substructure hybridization, and local modification, as well as constructing a series of derivatives based on core scaffolds, serve as a crucial means for discovering potential drug candidate molecules.[134]

Moreover, the advancement of Computer-Aided Drug Design (CADD) technologies has enabled the use of computational tools to predict and optimize interactions between lead compounds and their biological targets, significantly accelerating both the discovery and optimization processes of lead compounds.[135] Fragment-Based Drug Design (FBDD) has emerged as another robust approach, where small molecular fragments demonstrating target binding affinity can be systematically developed into more potent compounds through structure elaboration.[136]

Given the significant contributions and application potential of NPs in the field of antiparasitics, the advancement of these technologies has once again reignited enthusiasm for developing natural product-based antiparasitic drugs. Recently, public-private partnership (PPP) has been established to promote antiparasitic drug discovery, which will enhance the development of an active compound into a drug candidate together with interdisciplinary expertise.[137,138] More medicinal chemists, parasitologists, biologists, pharmacologists, botanists and companies have participated in this project to develop novel antiparasitic drugs.

3.5 Development of adjuvant therapy drugs from natural resources

An ideal medicine will not only directly kill the pathogens but also indirectly alleviate the inflammatory and immune responses caused by these pathogens. For antiparasitic agents, adjuvant therapy is very important because it inhibits the inflammatory response and oxidant stress of the body induced by parasites and enhances the immunity of humans and animals to improve the quality of life.[139] Compared to direct antiparasitic therapy, adjuvant therapy with traditional medicines and NPs is more feasible for this disease in the current situation. For instance, ruxolitinib (**40**) could be combined with antimalarial therapy to regulate the long-term immune response of the host (Fig. 8).[24] In the natural drug discovery field, finding the adjuvant therapy drugs from natural resource has been paid more attention.

T. gondii infection causes multiple organ or tissue injury and central nervous system disease and leads to the death of animals or humans;[44] thus, recovering injured tissues is very important for controlling the development of toxoplasmosis. Resveratrol (**41**),[140,141] coixol (**42**),[142] and ginsenoside Rh2 (**43**)[143] ameliorate *Toxoplasma gondii* infection-induced liver, lung and neuronal injuries by inhibiting the inflammatory response (Fig. 8). Considering that elevated IgE levels occurred in 96% of patients with crusted scabies, the upper limit of normal for 17 times, an immunotherapy strategy or natural

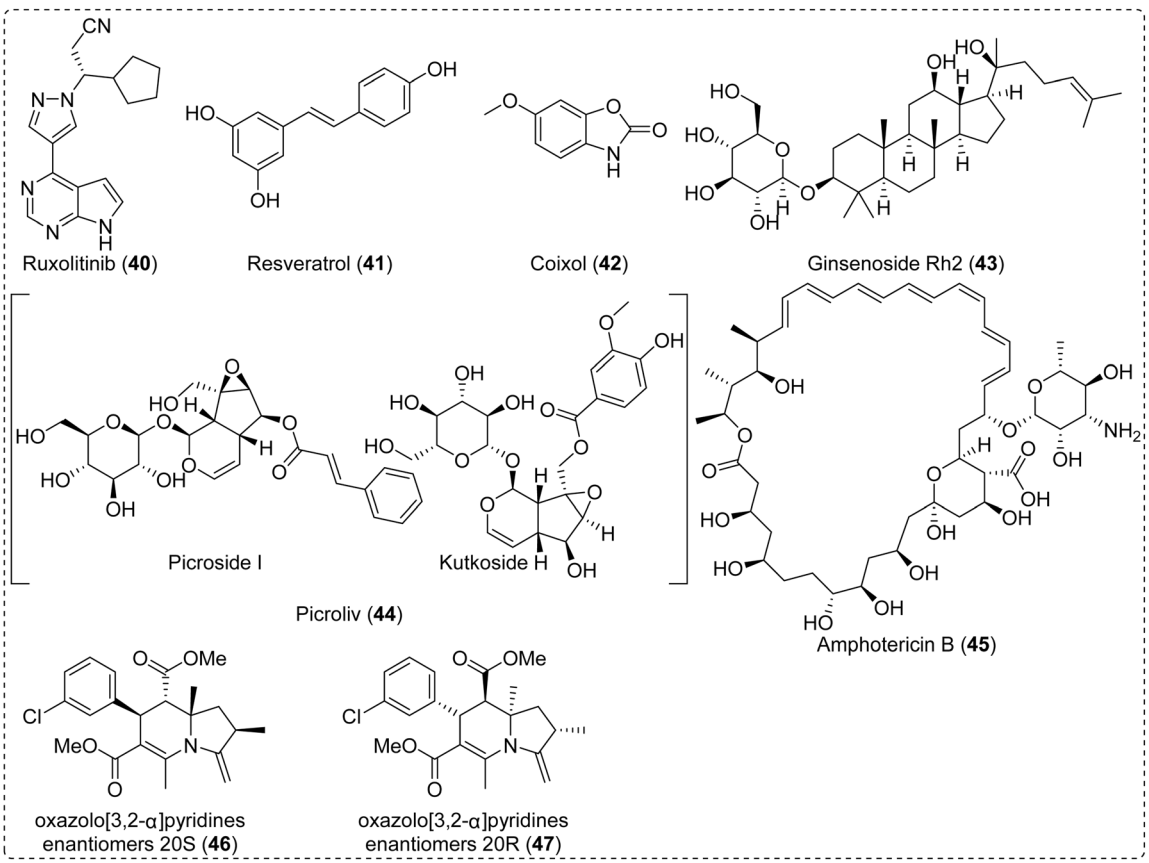

Fig. 8 Application of NPs in the treatment of parasitic diseases.

immunomodulatory drugs were applied in the clinic combined with ivermectin.[144] As an adjuvant (Fig. 8), picroliv (**44**) has been proposed to enhance the efficacy of anti-leishmania drugs and has shown therapeutic index in phase I and phase II clinical trials.[145] For schistosomes, some NPs not only decreased worm burden and egg production but also demonstrated antifibrotic and immunomodulatory activities, which improved the status of the human body. Hence, adjuvant therapy is an important strategy for treating parasitic diseases. However, further research is still needed to investigate its mechanism of action and evaluate its clinical efficacy, so as to provide scientific and valuable treatment strategies for parasitic diseases.

Besides having broad application prospects in adjuvant therapy, NPs can also enhance drug activity, improve treatment efficacy, and overcome drug resistance when used in combination with pharmaceuticals, representing an effective strategy for disease treatment that has been widely studied in the context of cancer and infectious diseases.[146–149] In particular, formulating NPs with drugs into new dosage forms, such as nanoparticles, has significantly enhanced the application potential of this therapeutic strategy. Some active compounds also demonstrated this activity, such as chitosan with amphotericin B (**45**), contributing to a therapeutic approach for the control of *leishmaniasis*.[150] In addition, a number of studies have demonstrated that NPs could contain drugs that overcome the multidrug resistance (MDR) of parasites.[151] The 1,4-dihydropyridine family of compounds containing oxazolo[3,2-α] pyridines units that are enantiomers 20S (**46**) and 20R (**47**) reversed the resistance to daunomycin and miltefosine in the *L. tropica* strain with 6.7-fold and 8.7-fold reversion indices, respectively (Fig. 8).[152] Although the above-mentioned strategies have been studied in the treatment of parasitic diseases, related research remains limited due to the specific characteristics of parasitic research.

Of course, while many NPs may possess various unique and promising potentials in anti-parasitic applications, not all are suitable for clinical use. Some NPs may have issues such as toxicity, low bioavailability, or unclear mechanisms of action. Therefore, adequate preclinical and clinical studies are essential to ensure their safety and efficacy.

4 Natural products and current natural drugs against parasitic diseases

In history, many plants are used as medicinal herbs for the treatment of human and animal parasitic diseases, and play an important role in ensuring public health security worldwide. Accompanied by the development of modern chemical techniques for isolating and identifying NPs, in particular the discovery of substances with anti-malarial activity, a new era was opened in the discovery of active NPs from plants. Especially since 2010, the WHO has insisted that NPs should be developed as alternatives for the treatment of CL;[153,154] NPs, such as quinones, alkaloids, flavonoids, terpenes, lignans, and some marine microorganism secondary metabolites, have found direct medicinal application as pharmaceutical entities because they exhibit fewer side effects and effective properties. In this section, we summarize the history of research and development of natural product-based antiparasitic drugs and recent research progress of promising NPs based on different sources of NPs (plants, microorganisms, and marine organisms) up to 2024. According to the guide of the Drugs for Neglected Diseases Initiative (DNDi) and other criteria, we only described and listed compounds with good activity and high safety (*e.g.* for *Leishmania* spp. and *P. falciparum* strains, $IC_{50} \leq 0.1$ μM and/or SI > 100). According to the type of compounds, a list of taxonomic groups including alkaloids, quinones and flavonoids, terpenes, essential oils and others is supplemented (Tables 3–6).

4.1 Plants

4.1.1 Alkaloids. Alkaloids are the most critical class, exhibiting broad-spectrum activities against a wide array of diseases, and could be potential drug leads due to their properties. As the first antimalarial chemotherapy derived from nature source, quinine has been identified and isolated from *Cinchona* tree bark since 1820, and then was widely used worldwide to treat malaria due to many advantages such low price, high efficacy, and parenteral administration.[22] In order to meet the needs of Southeast Asia during World War II, the total synthesis of the compound was advanced, and some derivatives with better potency and lower toxicity were developed.[155] In addition, the attempt to synthesize quinine led to the development of methylene blue and the dye industry.[3] In 2006, although the WHO stopped recommending it as a first-line treatment for malaria due to its high toxicity and resistance, quinine continues to play a critical role in the management of chloroquine-resistant *Plasmodium vivax* malaria in pregnancy.[22] For severe malaria in adults and children, quinine is recommended if artesunate and artemether are not available. Although the mechanism underlying antimalarial action is not fully understood, the quinoline group of this compound could act to cap hemozoin to digest the hemoglobin of parasites.[3,156] In addition to quinine, classic amino alcohols and 4-aminoquinolines, including chloroquine (**2**), mefloquine (**3**), and amodiaquine (**4**), were developed and used over the last century for malaria treatment (Fig. 1A).

Considering the promising prospects of NPs to find novel anti-malarial agents, great efforts have been dedicated to this field. From 2010 to 2017, a total of 1524 compounds were assayed against *Plasmodium*.[157] Among these, 39% (594) were described as new NPs and 29% (442) had $IC_{50} \leq 3.0$ μM. Some of these NPs including isoquinoline, quinoline, quinazoline, and indole alkaloids have the potential to be developed into antimalarial drugs by targeting gametocytes (Fig. 9A), such as cryptolepine (**48**) from *Cryptolepis sanguinolenta*,[158] strictosamide (**49**) from *Nauclea pobeguinii*,[159] protopine (**50**), allocryptopine (**51**), and berberine (**52**) from *Argemone mexicana*,[160,161] and febrifugine (**53**) from *Dichroa febrifuga*,[162,163] which presented antimalarial effects in preclinical or clinical tests.[164] In Table 3, the compounds with $IC_{50} \leq 0.1$ μM and SI > 100 are listed.[165–170] Although research into NPs with the potential to

Table 3 Promising alkaloids and their analogs against parasitic diseases

Compounds	Parasitic	Species	Activity	Ref.
7-Oxostaurosporine	*Leishmania* sp.	*Streptomyces sanyensis*	IC_{50} = 0.0075 μM against *L. amanzonensis* promastigotes; 0.0012 μM against *L. donovani* promastigotes; 0.0002 against *L. amanzonensis*, amastigotes	269
40-Demethyl-40-oxostaurosporine	*Leishmania* sp.	*Streptomyces sanyensis*	IC_{50} = 0.037 μM against *L. amanzonensis* promastigotes; >0.089 μM against *L. donovani* promastigotes; 0.005 against *L. amanzonensis*, amastigotes	269
Staurosporine	*Leishmania* sp.	*Streptomyces sanyensis*	IC_{50} = 0.00017 μM against *L. amanzonensis* promastigotes; 0.0045 μM against *L. donovani* promastigotes; 0.0224 μM against *L. amanzonensis*, amastigotes	269
Streptocarbazole B	*Leishmania* sp.	*Streptomyces sanyensis*	IC_{50} = 0.0224 μM against *L. amanzonensis* promastigotes; >0.089 μM against *L. donovani* promastigotes	269
Renieramycin A	*Leishmania* sp.	*Neopetrosia* species	IC_{50} = 0.35 μM against *L. amanzonensis*	271
Dihydrocorynantheine	*Leishmania* sp.	*Corynanthe pachyceras*	IC_{50} = 3 μM against *L. major*	166
Corynantheine	*Leishmania* sp.	*Corynanthe pachyceras*	IC_{50} = 3 μM against *L. major*	166
Corynantheidine	*Leishmania* sp.	*Corynanthe pachyceras*	IC_{50} = 3 μM against *L. major*	166
Buchtienine	*Leishmania* sp.	*Kopsia griffithii*	IC_{50} < 3.15 μM against *L. donovani* promastigotes	167
Duguetine β-*N*-oxide	*Leishmania* sp.	*Duguetia furfuracea*	IC_{50} = 0.11 μM	168
Dicentrinone	*Leishmania* sp.	*Duguetia furfuracea*	IC_{50} = 0.01 μM	168
Viridamide A	*Leishmania* sp.	*Oscillatoria nigroviridis*	EC_{50} = 1.5 μM against *L. mexicana*	168
Ancistectorine *N*-methyl A1	*P. falciparum*	*Ancistrocladus tectorius*	IC_{50} = 0.08 μM (against K1 strain), SI = 646 (against L6 cell)	160
Ancistectorine *N*-methyl A2	*P. falciparum*	*Ancistrocladus tectorius*	IC_{50} = 0.08 μM (against K1 strain), SI = 705 (against L6 cell)	160
Ancistectorine 5-*epi*-A2	*P. falciparum*	*Ancistrocladus tectorius*	IC_{50} = 0.03 μM (against K1 strain), SI = 3340 (against L6 cell)	160
Dioncophyllines F	*P. falciparum*	*Ancistrocladus ileboensis*	IC_{50} = 0.045 and 0.09 μM (against K1 and NF54 strains), SI = 3340 (against L6 cell)	161
Dehydroantofne	*P. falciparum*	*Ficus septica*	IC_{50} = 0.028 μM (against 3D7 strain), SI > 1964 (against L929 cell)	162
Tylophoridicine	*P. falciparum*	*Ficus septica*	IC_{50} = 0.058 μM (against 3D7 strain), SI > 966 (against L929 cell)	163
Dimethylisoborreverine	*P. falciparum*	*Flindersia amboinensis*	IC_{50} = 0.06 and 0.02 μM (against K1 and FCR3 strains), SI = 68 265 (against HEK 293 and HeLa cells)	163
Tsitsikammamine C	*P. falciparum*	Marine sponge *Zyzzya* sp.	IC_{50} = 0.013 and 0.018 μM (against 3D7 and Dd2 strains), SI = 276 200 (against HEK 293 cells)	164
Thiaplakortone A	*P. falciparum*	Marine sponge *Plakortis lita*	IC_{50} = 0.051 and 0.0066 μM (against 3D7 and Dd2 strains), SI = 76 591 (against HEK 293 cells)	165
Berberine, piperine	*R. microplus*	—	EC_{50} values were 6.76 mM and 6.04 mM, respectively, with larvicidal activity	232

block the transmission of malaria remains in its infancy and needs to be vigorously pursued, it still has broad research prospects and merits.[157]

Moreover, a small number of NPs present antileishmanial activities (Fig. 9B). Corynantheine (**54**), dihydrocorynantheine (**55**) and corynantheidine (**56**) with the indole core from the bark of *Corynanthe pachyceras* exhibited inhibitory activity (IC_{50} 3 μM) against *L. major* by inhibiting its ETC,[171] and buchtienine (**57**) from *Kopsia griffithii* showed the remarkable activity (IC_{50} < 3.15 μM) against *L. donovani* promastigotes.[172] Aporphine alkaloids, duguetine β-*N*-oxide (**58**) and dicentrinone (**59**), isolated from *Duguetia furfuracea*, exhibited antileishmanial activity, with IC_{50} values of 0.11 μM and 0.01 μM, respectively.[173] Structural optimization using the framework of NPs with strong biological activity as the core is a crucial strategy for identifying lead compounds with enhanced efficacy and broader application prospects. Istanbullu *et al.*[174] evaluated derivatives of thiazolopyrimidine and found that the derivatives (**65**) exhibited the

Table 4 Promising quinones and flavonoids and their analogs against parasitic diseases

Compounds	Parasitic	Species	Activity	Ref.
Plumbagin	*Leishmania* sp.	*Plumbago* species	IC_{50} = 2.24 μM against *L. donovani* amastigotes and 5.87 μM against *L. amazonensis* amastigotes	185
2-Methyl-5-(30-methyl-but-20-enyloxy)-[1,4] naphthoquinone	*Leishmania* sp.	*Plumbago zeylanica*	EC_{50} = 1.9 and 3.46 μM against promastigote and amastigote forms of *L. donovani*	179
Burmanin A	*Leishmania* sp.	*Diospyros burmanica*	IC_{50} = 0.053 μM against *L. major*	183
Joziknipholones A	*P. falciparum*	*Bulbine frutescens*	IC_{50} = 0.14 μM against K1	301
Joziknipholones B	*P. falciparum*	*Bulbine frutescens*	IC_{50} = 0.23 μM against K1	184
Rufigallol	*P. falciparum*	—	IC_{50} = 35 nM against D6 *Pf* strain	184
Gambogic acid derivative	*P. falciparum*	Original compound from *Garcinia* resin	IC_{50} = 0.0102 and 0.0123 μM (against Dd2 and 3D7 strain), SI = 142, 118 (against HEK293 cell)	302
Menadione	*S. mansoni*	—	At oral dose of 40 mg kg^{-1}, menadione reduced the worm burden (48.57%) in female BALB/c mice infected with *S. mansoni*, and reduced the number of eggs in the liver of infected mice by 53.57%	303
Casticin	Helminths	—	Mice treated with 20 mg per kg per day casticin for 14 consecutive days reduced worm burden and presented antifibrotic activity	304

Table 5 Promising terpenes and their analogs against parasitic diseases

Compounds	Parasitic	Species	Activity	Ref.
Avarone	*Leishmania* sp.	*Dysidea avara*	IC_{50} = 28.21 μM against *L. infantum* promastigotes; 20.28 μM against *L. tropica* promastigotes 海洋生物	270
Avarol	*Leishmania* sp.	*Dysidea avara*	IC_{50} = 7.42 μM against *L. infantum* promastigotes; 7.08 μM against *L. tropica* promastigotes; 3.19 μM against *L. infantum* amastigote	123
Linalool	*Leishmania* sp.	*Croton cajucara*	IC_{50} = 28 nM and 143 nM against promastigotes and intracellular amastigotes of *L. amazonensis* by destroying kinetoplastid and mitochondrial swelling followed by cell lysis in parasite	305 and 306
Isoiguesterin	*Leishmania* sp.	*Salacia madagascariensis*	IC_{50} = 0.198 and 0.082 μM against *L. donovani* and *L. mexicana*, respectively	307
20-*Epi*-isoiguesterinol	*Leishmania* sp.	*Salacia madagascariensis*	IC_{50} = 0.079 μM against *L. donovani*	307
Mesabalide III	*Leishmania* sp.	*Maesa balansae*	IC_{50} = 5 nM against L. infantum intracellular amastigotes	200
Mesabalide IV	*Leishmania* sp.	*Maesa balansae*	IC_{50} = 9 nM against L. infantum intracellular amastigotes	308
Fortunilide A	*P. falciparum*	*Chloranthus* species	IC_{50} = 0.0052 μM (against Dd2 strain), SI = 1700 (against WI38 cell)	196
Fortunilide B	*P. falciparum*	*Chloranthus* species	IC_{50} = 0.019 μM (against Dd2 strain), SI = 163 (against WI38 cell)	196
Dichapetalin A	*S. hematobium*	*Dichapetalum crassifolium*	The dichapetalin A presented *in vitro* antischistosomal activity against clinical isolates of *S. hematobium* with IC_{50} of 151.1 μg mL^{-1}	204
Hederacochiside C	*S. hematobium*	*Pulsatilla chinensis Regel*	It showed potential antischistosomal and immunomodulatory effect	309
β-Cyclocitral	*R. appendiculatus*	*Gynandropsis gynandra*	It has more than 90.0% repellence rate at 0.1% at 5 min	231
α-Ionone	*R. appendiculatus*	*Gynandropsis gynandra*	It has more than 90.0% repellence rate at 0.1% at 5 min	231
Cedrene	*R. appendiculatus*	*Gynandropsis gynandra*	It has more than 86.7% repellence rate at 0.1% at 5 min	231
1-α-Terpineol	*R. appendiculatus*	*Gynandropsis gynandra*	It has more than 89.9% repellence rate at 0.1% at 5 min	231

Table 6 Promising essential oils and other NPs and their analogs against parasitic diseases

Extracts or compounds	Parasitic	Species or major compositions	Activity	Ref.
Palstimolide (macrolide)	*Leishmania* sp.	*Marine Cyanobacteria*	IC_{50} = 4.67 μM against *L. infantum* amastigote	310
2-[(3,4-Dihydroxyphenyl) methylene]-6-hydroxybenzofuran-3(2*H*)-one (phenolics)	*Leishmania* sp.	—	EC_{50} = 0.33–0.40 μM and 4.58 μM against promastigotes of *Leishmania* spp. and amastigotes of *L. donovani*	311
Asuarinin (phenolics)	*Leishmania* sp.	*Punica granatum*, *Casuarina*	EC_{50} = 0.52 μM against *L. donovani*	312
Orthidine F derivative	*P. falciparum*	*Aplidium orthium*	IC_{50} = 0.0086 μM (against K1 strain), SI > 15 000 (against L6 cell)	313
Carmaphycin B derivative (cyclodepsipeptides)	*P. falciparum*	*Symploca* sp.	IC_{50} = 0.0033 μM (against Dd2 strain), SI = 379 (against HepG2 cell)	314
Puberulic acid	*P. falciparum*	Culture broth of the *Penicillium* sp. FKI-4410 fungus	IC_{50} = 0.0547 and 0.0547 μM (against K1 and FCR3 strains), SI = 5720 (against MCR5 cell)	262
Divaricatic acid	*S. mansoni*	*Canoparmelia texana*	IC_{50} was 100.6 μM *in vitro*. It could cause death, motile changes and ultrastructural damage to worms	263
Brazilian red propolis	Helminths	Bee	It 25 μg mL^{-1} caused 100% mortality of adult parasites *ex vivo*, and reduced worm burden and egg production in early and chronic *S. mansoni* infection	315
(−)-6,6′-Dinitrohinokinin	Helminths	*Piper cubeba*	IC_{50} was 103.9 μM at 24 h against adult worms *in vitro*. It also displayed moderate activity against the juvenile liver parasite, (LC_{50} 179.5 μM at 72 h) by reducing the number of egg	316
4-Nerolidylcatechol	Helminths	*Pothomorphe umbellata*	The compound presented *in vitro* activity with EC_{50} of 2.9 μM (0.91 μg mL^{-1}) and SI of 68 against Vero cells. In *S. mansoni* infection, the oral treatment decreased worm burden and egg production in 52.1% and 52.3%, respectively	317
Hydroalcoholic extract	Helminths	*Arctium lappa*	The extract (400, 200, and 100 μg mL^{-1}) caused 100% mortality and reduction on motor activity of all adult worms of *S. mansoni*	318
Ethyl acetate extract	Helminths	*Dichapetalum*	The ethyl acetate extract presented *in vitro* antischistosomal activity against clinical isolates of *S. hematobium* with IC_{50} of 248.6 μg mL^{-1}	204
2-Methylcardol diene	Helminths	*Anacardium occidentale*	It was active against *S. mansoni* adult worms *in vitro*, with LC_{50} values of 14.5 μM and SI of 21.2	317
Usnic acid potassium salt	Helminths	—	It presented schistosomicidal property against couples of adult worms of *S. mansoni*, changed in motility and mortality of schistosomules and young worms	319
Nerolidol	Helminths	—	It at concentrations of 31.2 and 62.5 μM reduced the worm motor activity and caused the death of male and female schistosomes, respectively	320
Gomphoside monoacetate and uscharin	Helminths	—	They (10 mg kg^{-1}) showed suitable therapeutic indices *in vivo* against a chronic *S. mansoni* infection mice	321
Methanol extract of *Aegle marmelos* leaves	*H. bispinosa*; *R.(B.) microplus*	Aeglemarmelosine, alkaloids, coumarins	It caused 100% mortality against two ticks at 2 mg mL^{-1} at 24 h	221
Methanol extract of *Andrographis paniculata* leaves	*H. bispinosa; R.(B.) microplus*	Tannins, flavonoids, carbohydrates	It caused 100% mortality against *H. bispinosa* at 3 mg mL^{-1} and larvicidal activity against *R. (B.) microplus* at 2 mg mL^{-1}, respectively, at 24 h	222
Acetone and methanol extract of *Anisomeles*	*H. bispinosa*	Alkaloids, saponins, protein, gum, mucilage	Two extracts caused 100% acaricidal activity against this ticks at 3 mg mL^{-1} at 24 h	223
Hexane extract of *Calea serrata* aerial parts	*R. (B.) microplus*, *R. sanguineus*	Eupatoriochromene, precocene II	It at 6.25 mg mL^{-1} caused 100% larvicidal mortality rate of both tick species at 48 h post treatment	224
Hexane extract of *Piper tuberculatum* flower	*R. (B.) microplus*	Piplartine, dihydropiplartine, 3,4,5-trimethoxydihydrocinnamic acid	It (0.12 mg mL^{-1}) showed 100% larvicidal mortality at 24 h post treatment, 100% oviposition reduction and acaricidal efficiency	225

Table 6 (*Contd.*)

Extracts or compounds	Parasitic	Species or major compositions	Activity	Ref.
Water extract of *Solanum trilobatum* leaves	*Hyalomma anatolicum (a.) anatolicum*	Carbohydrates, saponins, phytosterols, tannins	It caused 100% larvicidal mortality rate at 10 mg L^{-1}	226
Artemisia herbaalba essential oils	*Ixodes ricinus*	Piperitone (26%)	It has 84.2% repellence rate at 0.015 mg cm^{-2}	227
Calendula officinalis essential oils	*Ixodes ricinus*	α-Cadinol (21%), carvone (18%)	It has 82.0% repellence rate at 0.015 mg cm^{-2}	227
Amyris balsamifera essential oils	*Ixodes ricinus*, *Amblyomma americanum*	—	EC_{50} were 0.003 and 0.009 mg cm^{-2}, respectively, at 15 min	228
Conyza dioscoridis essential oils	*Ixodes ricinus*	α-Cadinol (10%), hexadecanoic acid (10%)	It has 94% repellence rate at 0.015 mg cm^{-2}	227
Mentha spicata essential oils	*Ixodes ricinus*	Carvone (55%), pulegone (14%)	It has 93.2% and 59.4% repellence at 0.015 and 0.0075 mg cm^{-2}, respectively	229
Origanum onites essential oils	*Ixodes ricinus*	4-Terpineol (55.6%)	It has 84.3% repellence rate at 0.015 mg cm^{-2}	229
Tagetes minuta essential oils	*Amblyomma americanum*	*cis*-Ocimene, dihydrotagetone, piperitenone	EC_{50} was 0.002 mg cm^{-2}	230
Rosmarinus officinalis essential oils	*Ixodes ricinus*	1,8-Cineole, borneol	It has 100.0% repellence rate at 0.015 mg cm^{-2}	227
Carvacrol	*Ixodes ricinus*	—	It has more than 89.9% repellence rate at 0.1% at 5 min	231
Linalool	*R. appendiculatus*	—	It has more than 85.0% repellence rate at 0.1% at 5 min	231
m-Cymene	*R. appendiculatus*	—	It has more than 90.0% repellence rate at 0.1% at 5 min	231
Methyl salicylate	*R. appendiculatus*	—	It has more than 87.7% repellence rate at 0.1% at 5 min	231
Nerol and nerolidol	*R. appendiculatus*	—	It has more than 90.0% and 100% repellence rate at 0.1% at 5 min, respectively	231
Phenyl acetonitrile and phenyl acetaldehyde	*R. appendiculatus*	—	It has more than 84.9% and 87.9% repellence rate at 0.1% at 5 min, respectively	231
trans-Geraniol and *trans*-geranyl acetone	*R. appendiculatus*	—	It has more than 90.0 and 90.0% repellence rate at 0.1% at 5 min, respectively	231

most promising antipromastigote activity *in vitro* against *L. tropica* and *L. infantum*, with IC_{50} values of 0.04 μM and 0.042 μM, respectively (Fig. 10A). Quinazoline alkaloids are important natural sources for antileishmanial agents, and their derivatives present good activity. In 2022, Seifu *et al.*[175] reported that 3-aryl-2-styryl substituted-4(3*H*)-quinazolinone derivatives (**66**) displayed the most promising antileishmanial activity against *L. donovani* promastigotes (IC_{50} 0.0212 μM), which was 2 and 150 times more potent than the reference drugs amphotericin B deoxycholate (IC_{50} 0.0460 μM) and miltefosine (IC_{50} 3.1911 μM) (Fig. 10B).

Besides the antileishmanial activity, indole alkaloids such as 2,7-dibromocryptolepine (**60**) have a strong activity against the *T. brucei* bloodstream form (IC_{50} 0.0029 μM) with an exceptional SI value of 2083 and inhibited parasitemia by oral, im, and iv administration.[176,177] Two pyridoacridone alkaloid derivatives (**61–62**) presented a stronger trypanocidal activity than that of the parent compound ascididemin, with IC_{50} values of 0.007 and 0.018 μM, respectively; in contrast, the IC_{50} value for melarsoprol (positive control) was 0.003 μM, and the mechanisms of action involved DNA intercalation and DNA oxidative damage[178] (Fig. 9C). The tetrahydrofuran lignan scaffold derivatives (**67**) presented strong and synergistic effects in combination with benznidazole[132] (Fig. 10C).

Alkaloids and their derivatives presented anti-*T. gondii* activity (Fig. 9D). A quinoline-related compound, PPQ-8 (**63**), presented an anti-*T. gondii* effect in a mouse model of acute and chronic toxoplasmosis.[179] It reduced the parasite load of the liver and spleen and improved the pathology of the liver and spleen in acute infection. In chronic toxoplasmosis, PPQ-8 caused degeneration and reduction of brain cysts without stimulating a devastating inflammatory response within the brain, thereby prolonging the survival of mice.[180] In addition, from a series of tetrahydroquinolone derivatives, JAG21 (**64**) significantly reduced *T. gondii* tachyzoites and encysted bradyzoites in primary and chronic murine infections. After oral administration of JAG21 at 2.5 mg kg^{-1} or 3 days of treatment at a reduced dose (0.625 mg per kg per day), causal prophylaxis and radical cure were achieved after *P. berghei* sporozoite infection. The drug could eliminate parasitemia and lead to

100% survival. Hence, it could be used as a preclinical candidate for controlling toxoplasmosis and malaria.[181]

Alkaloid NPs are a class of compounds with diverse structures and a large variety. We have found that alkaloid NPs with rigid skeletal structures such as quinoline, isoquinoline, quinazoline, and indole seem to exhibit good biological activity against parasites, while the anti-parasitic activity of other alkaloid NPs appears to be generally weaker. In general,

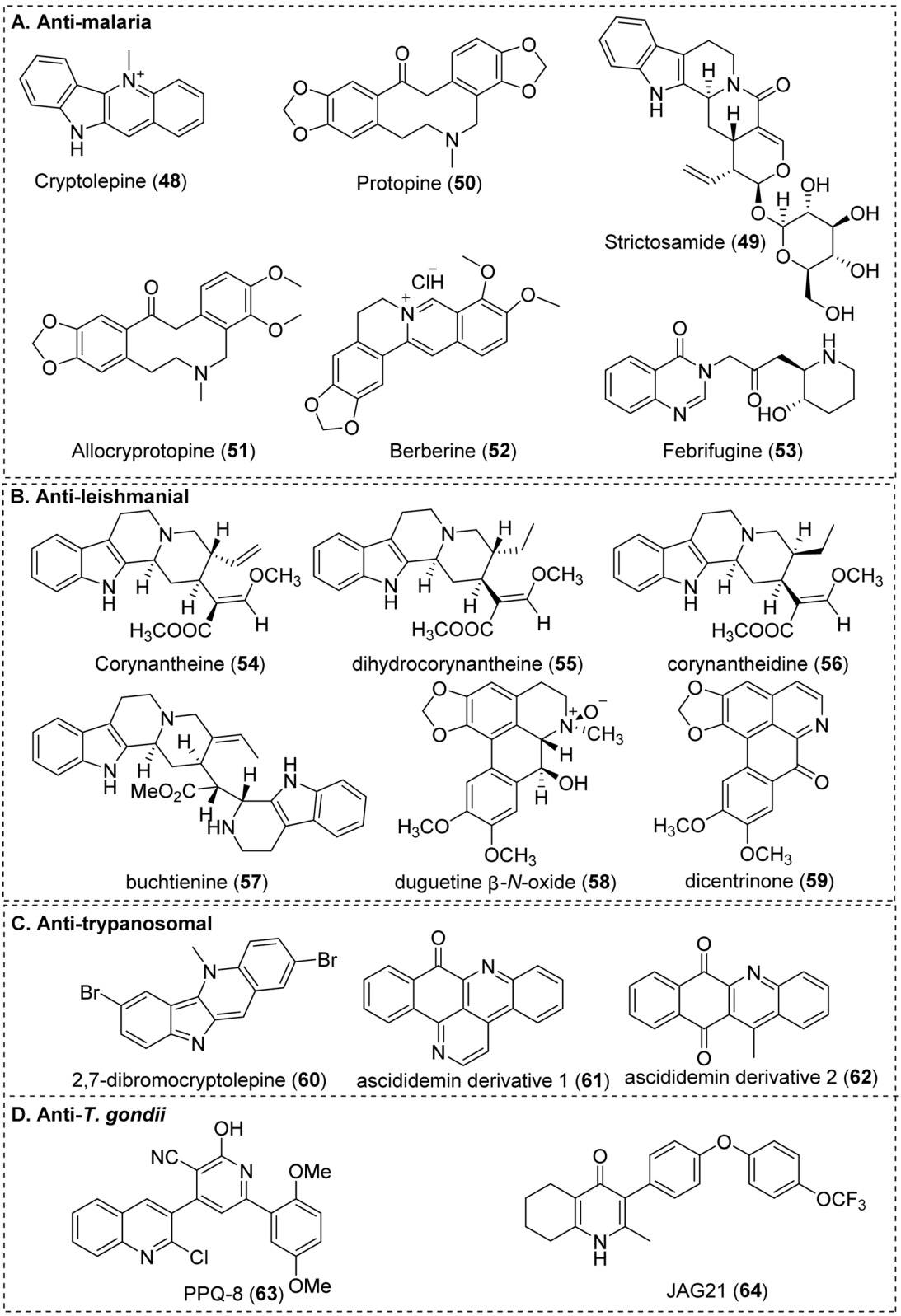

Fig. 9 Promising active alkaloids and their analogs (A–D).

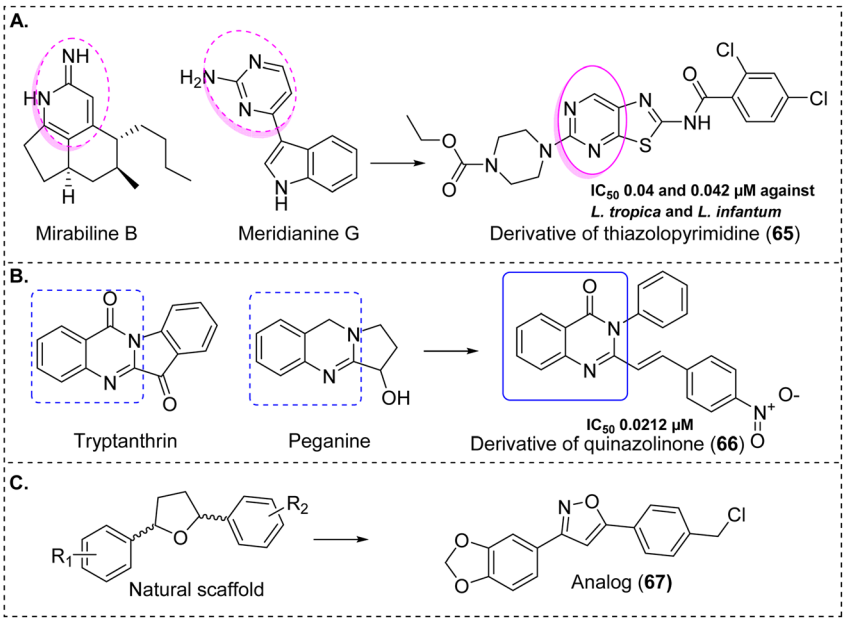

Fig. 10 Structural optimization routes of some specific compounds (A–C).

molecules with rigid structures can better maintain their three-dimensional shapes, thereby enhancing the binding affinity with target proteins. The specificity of this binding can reduce the off-target effects of drugs and decrease side effects, which may be one of the reasons for the differences in the anti-parasitic activities of alkaloid NPs with different structures.[182,183] In addition, it is unclear whether the "proton sponge effect", which is one of the mechanisms of action of chloroquine, is a contributing factor to this result. However, due to numerous contradictory reports to date, the scientific community has not reached a consensus on the validity of this hypothesis, and there is also a lack of corresponding experimental evidence.[184] Therefore, it is necessary to conduct further in-depth studies on the anti-parasitic mechanisms of action of alkaloid NPs to summarize and explain this phenomenon, which has important scientific value for the research and development of anti-parasitic drugs.

4.1.2 Quinones. Quinones are considered to be privileged structures in medicinal chemistry and exist in various families of plants or folk medicine worldwide, such as *Juglans regia* and *Rheum* sp.[185,186] Most compounds and their synthetics present antiparasitic activities by perturbing the electron transport chain (ETC) in the respiratory function and disturbing the energy metabolism, leading to the death of parasites; as a result, many quinone-derived compounds have been developed and have gained considerable interest in the past decades.[187,188] The antimalarial activities of semisynthetic or synthetic derivatives of quinones (naphtho-/benzoquinone, anthraquinones, and thiazinoquinones) and quinone-based hybrids (**69–75**) were explored *in vitro* and *in vivo*, and some of them presented promising activities at the nanomolar level (Fig. 11). The discovery of the naphthoquinone compound lapachol (**68**) as an active ingredient in the tree bark for the treatment of malaria laid the foundation for the discovery of atovaquone (**69**), the active ingredient in Malarone® (Fig. 11A). This drug is still a mainstay of malaria prophylaxis[189] and widely used in combination with proguanil for the treatment of acute, uncomplicated malaria caused by *P. falciparum* by inhibiting Cytbc1 activity.[190] Dimmer *et al.*[191] considered that quinones presented therapy for CL by mediating antimicrobial photodynamic therapy. In addition, Winter *et al.*[192] found that rufigallol (**70**) exhibited potent activity (IC_{50} 35 nM) against wild-type and drug-resistant strains (Fig. 11B).

Fournet *et al.*[193] found that plumbagin (**76**) and 2-methyl-5-(3′-methyl-but-2′-enyloxy)-[1,4]naphthoquinone (**77**) isolated from *Plumbago* species presented activity against amastigotes of *L. donovani* and *L. amazonensis* with EC_{50} values of 2.24 and 1.9 μM, and 3.46 and 5.87 μM *in vitro*, respectively, which were better than the positive control miltefosine. Moreover, at doses of 2.5 and 5 mg per kg per day plumbagin also showed *in vivo* activity. For *L. major*, burmanin A (**78**), identified from *Diospyros burmanica*, presented stronger activity with an IC_{50} of 0.053 μM.[194] In addition, seven anthraquinone-2-carbaldehydes (**79–85**) from *Morinda lucida* distributed in certain West African countries presented promising activity against promastigotes of *L. major*, and chloroquine-susceptible (3D7) and chloroquine-resistant (Dd2) strains of *P. falciparum in vitro*. These results indicated that anthraquinones have remarkable inhibitory effects on *Leishmania* parasites, and an aldehyde group at C-2 and a phenolic hydroxy group at C-3 could be beneficial for this activity, as revealed by structure–activity relationship (SAR) analysis[195] (Fig. 12).

To find promising quinones, Stoppani, Cruz and Docampo studied the effect of lapachol (**68**), β-lapachone (**86**) and their derivatives on *T. cruzi*. Although no active natural compounds were found, the derivative (CG9-442)[196] (**87**) presented inhibitory activity against epimastigote proliferation, and then caused damage to the mitochondrion, chromatin and cellular

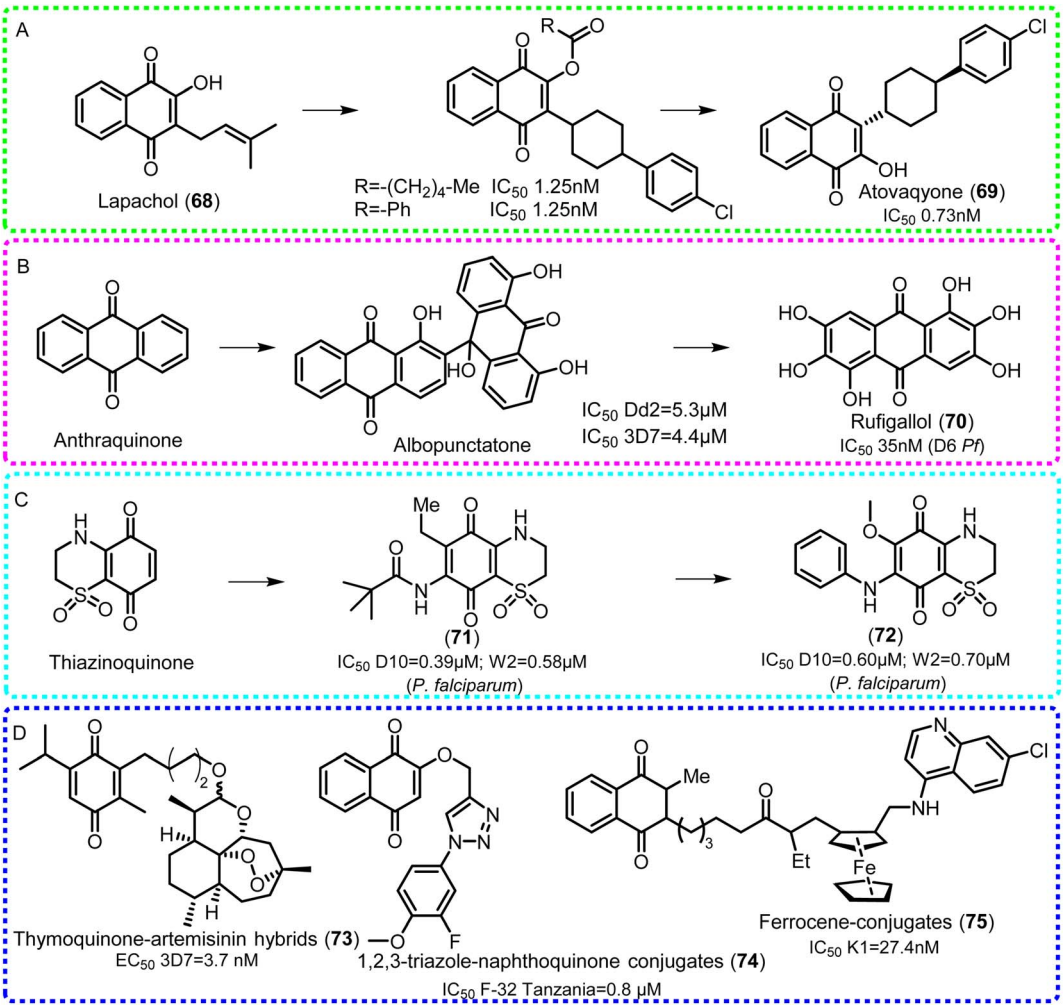

Fig. 11 Structural optimization of benzoquinone and naphthoquinone (A), anthraquinone (B), thiazinoquinone (C) and some hybrids and conjugates of compounds (D) against *Plasmodium* sp.

membranes[197] (Fig. 12). Dhananjeyan *et al.* reported[198] that the anthraquinone analog anthraquinone K (**88**) at 0.0185 μM showed 100% mortality within 1, 5, and 3 days against microfilarial and adult worms of *B. malayi* by affecting intrauterine embryos (Fig. 12).

4.1.3 Terpenes. In China, qinghao (*Artemisia annua* L.) can be used to alleviate malaria symptoms based on Ge Hong's A Handbook of Prescriptions for Emergencies (AD 284–364).[199] According to the historical records and clinical clues, Tu Youyou isolated artemisinin in 1971, and for this achievement, she was awarded the Nobel Prize in Physiology or Medicine in 2015. Then, its derivative, dihydroartemisinin was developed. Compared with artemisinin, it is 10 times effective with a more stable structure and less disease recurrence.[200,201] Currently, artemether and artesunate are used as prodrugs converted to the active form of dihydroartemisinin for the treatment of complex and uncomplicated falciparum malaria.[202] In 2015, the WHO changed its strategy and began using artemisinin combination therapy (ACT) due to its antigametocyte activity; this treatment is widely used to save many lives, mostly those of children in Africa. Further studies have resulted in a very unusual endoperoxide group that provides the basis for a series of fully synthetic, long-acting molecules currently being developed in clinical development. The hydroxyl groups on the molecules provide additional opportunities for the development of new artemisinin derivatives by esterification[203] (Fig. 1B). In 2016, inspired by the discovery of artemisinin, Yue *et al.* isolated a series of lindenane sesquiterpenoid dimers from the medicinal plant of the *Chloranthus* genus, which has been traditionally used in Chinese medicine for the treatment of malaria. Among them, the dimers (**89–91**) exhibited *in vitro* antiplasmodial IC_{50} values ranging from 1 to 7 nM, comparable to that of artemisinin, and also demonstrated significant activity against chloroquine-resistant *Plasmodium falciparum* strains, with a selectivity index (SI) greater than 500 for mammalian cells. Due to their unique skeletal structures, which differ from all currently known antimalarial drugs, they are likely to act through a novel mechanism of action, representing a promising class of new antimalarial lead compounds[204] (Fig. 13).

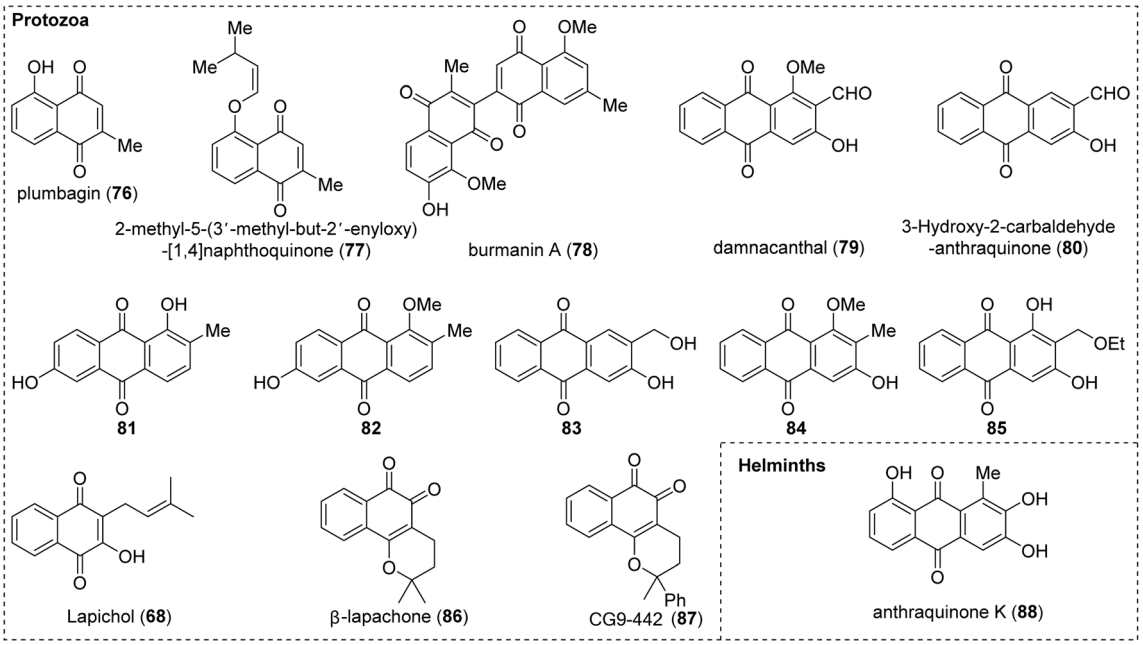

Fig. 12 Promising active quinones and their analogs from natural sources.

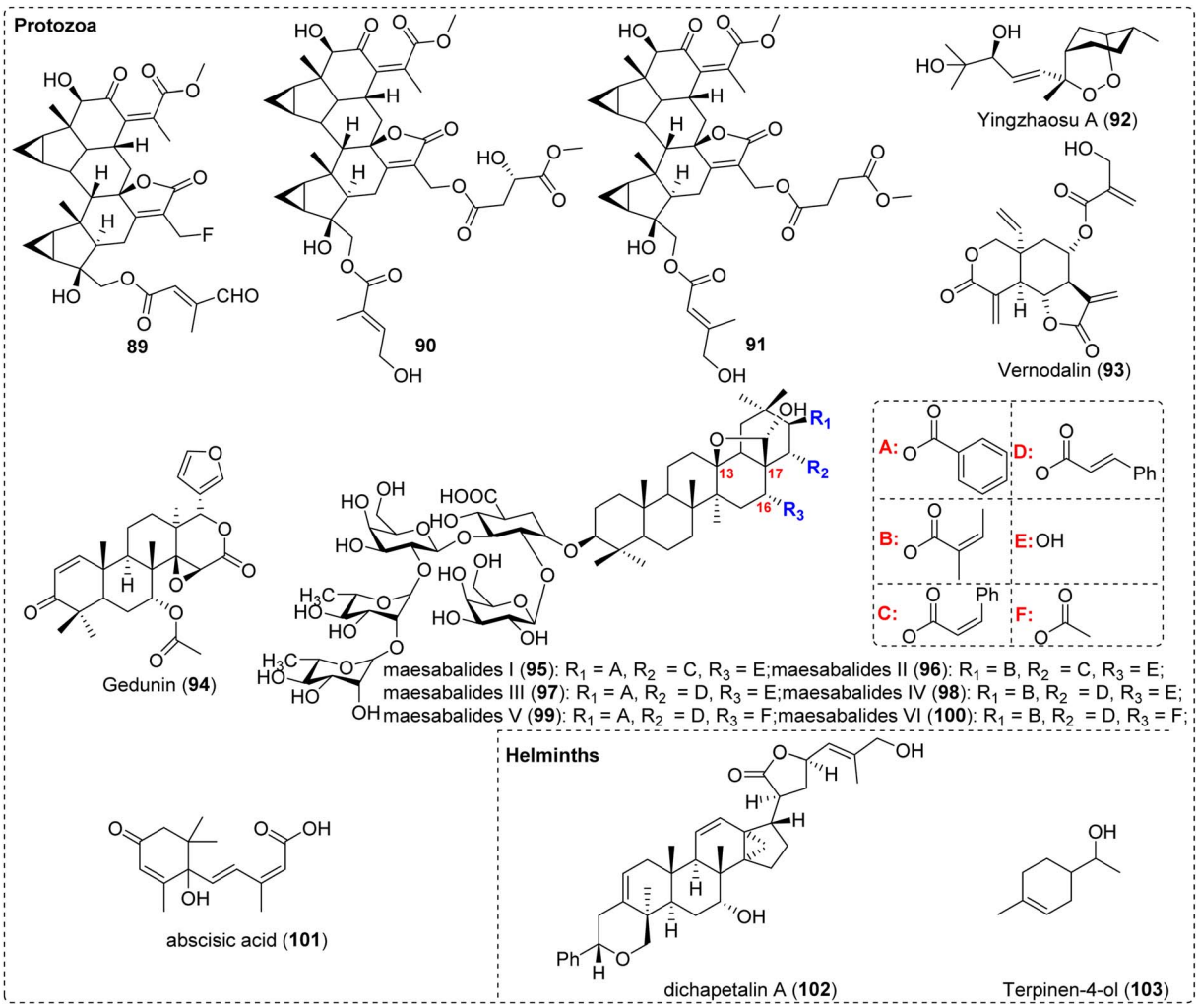

Fig. 13 Promising active terpenes from natural sources.

In addition, some terpenoid compounds have the potential to be developed into anti-malarial drugs by targeting gametocytes, such as yingzhaosu A (**92**) from *Artabotrys uncinatus*,[205] vernodalin (**93**) from *Vernonia amygdalina*,[206] and gedunin (**94**) from *Azadirachta indica*,[207] which presented antimalarial effects in preclinical or clinical tests (Fig. 13).

From the leaves of the Vietnamese medicinal plant *Maesa balansae*, six triterpenoid saponins with potent and specific antileishmanial activity, namely maesabalides I–VI (**95–100**), were isolated and identified, exhibiting *in vitro* IC_{50} values ranging from 0.0046 nM to 0.029 nM (Fig. 13). Among them, maesabalide III (**97**) was the most active compound, demonstrating remarkable *in vivo* efficacy as well, with a single subcutaneous injection of 0.2 mg kg^{-1} reducing the liver amastigote burden by over 90%. Through the construction of natural product derivatives, a preliminary structure–activity relationship analysis was performed, revealing that both the ester moiety and the sugar moiety of the compound molecules are essential for activity. The hydroxyl group at the C-16 position has a more pronounced effect on the activity, and the oxygen bridge between C-13 and C-17 may also play a crucial role in the activity.[208] Besides, abscisic acid (**101**) can control calcium-dependent egress and development in *T. gondii*.[209]

Artemisinin and its derivatives not only presented antimalarial activity but also demonstrated efficacy against *Schistosoma* species. The administration of artemisinin (500 mg kg^{-1}) to mice with 30-day *Schistosoma mansoni* infection elicited distinct morphological alterations in the parasites, including tegumental erosion and desquamation, ultrastructural damage to sensory tubercles, and the formation of membrane-bound vesicles.[210] To prove the clinical efficacy of artemisinin derivatives in *S. japonicum* infection for a patent, 24 randomized controlled trials (RCTs) were performed. After administrating artesunate (6 mg kg^{-1}, p.o.) at 1 week intervals in 5 trials and at 2 week intervals for up to 13 doses in 11 trials, the protective efficiencies were 96% and 85%, respectively. When artemether was administrated once every 2 weeks for up to 12 doses in other 8 trials, the efficacy was up to 86%.[211]

Recently, from the stems and roots of *D. crassifolium*, unique tetracyclic and pentacyclic triterpenoids were separated and discovered, exhibiting promising antiparasitic activity. Especially, dammarane-type tetracyclic triterpenoid dichapetalin A (**102**), which can currently only be separated from the roots of *D. crassifolium*, showed *in vitro* antischistosomal activity (IC_{50}) of 0.26 μM. In contrast, the activity of the currently clinically used standard drug praziquantel is 0.05 μM. This provides new lead compounds for the search in combating various neglected tropical diseases caused by parasitic pathogens.[212] Besides, terpinen-4-ol (**103**) exhibited potential antitrypanosomal activity with the IC_{50} and SI values of 0.13 μM and 1000 (ref. 213) (Fig. 13).

4.1.4 Flavonoids. Flavonoid is among the most common classes of NPs. Most flavonoids have shown a moderate activity in various Trypanosome parasite species. For example, as a promising flavone derivative, 7,8-dihydroxyflavone (**104**) presented inhibitory activity against *T. b. rhodesiense* bloodstream form with EC_{50} and SI values of 0.27 μM and 116, respectively;[214] this compound, as well as quercetagetin (**105**), selectively showed trypanocidal activity with IC_{50} values of 0.16 μM and 0.8 μM, respectively, and the SI values were 1019 and 571.[215] Although there are no clear SAR for this type of compound, colleagues considered that compared with their flavone counterparts, flavonols lack the hydroxyl substituent on C3, which are more trypanocidal. A chalcone-flavone dimer, cissampeloflavone (**106**), from *Cissampelos pareira* exhibits activity against *T. b. rhodesiense* bloodstream forms (IC_{50} 1 μM) and an SI of 173 compared to that of KB cells[216] (Fig. 14).

As described above, the incorporation of natural bioactive components into synthetic drugs is a novel aspect that should be explored from the perspective of medicinal chemistry. Reports have shown that natural chalcones such as licochalcone A (**107**) and dihydrochalcone derivatives (**108**) display good antileishmanial activity.[217] When these types of compounds were optimized (Fig. 14), a promising synthesized scaffold compound (**109**) emerged as the lead derivative with an IC_{50} value of 0.03 μM.[218]

Considering that unique enzymes act as signaling molecules in metabolic pathways and are essential for survival, more herbal-based target inhibitors were found along with the introduction of HTS against molecular targets.[219] As topoisomerase II inhibitors, luteolin[220] (**110**) alter the topology of DNA with an IC_{50} value of 45.5 μM, against promastigote; genistein (**111**) would inhibit the RTK pathway to kill *Leishmania*[221] (Fig. 14). Although there is a large gap between these inhibitors and commercial drugs, the timeline from hit NP identification to hit-to-lead development and drug discovery is shortened rapidly.

In recent decades, our group and other international groups have found a series of active compounds for controlling *T. gondii via* different mechanisms (Fig. 14). Wu *et al.* discovered some chalcone derivatives (**112–114**), which also showed better anti-*T. gondii* effects than acetylspiramycin (**https://pubchem.ncbi.nlm.nih.gov/compound/acetylspiramycin**) *in vivo*, with proliferation inhibition rates of more than 82.2% at a dose of 20 mg kg^{-1}, as well as liver-protecting effects, and the Michael acceptor is very important for their activity.[222] Abugri *et al.*[223] found that combining taxifolin (**115**) from fructus *Polygoni orientalis* with pyrimethamine (**28**) may offer a promising tool for toxoplasmosis treatment with an IC_{50p} of 0.0046 μM, which presented activity by inhibiting the calcium-dependent protein kinase activity of parasites.

4.1.5 Essential oils. Essential oils (EOs) extracted from aromatic plants exhibit anti-schistosomiasis activity because they can penetrate parasite membranes or blood–brain barriers and then increase NO levels in infected hosts and balance the oxidative stress in parasites; finally, the growth of schistosomiasis was affected.[224] According to the criterion provided by Oliveira *et al.*,[225] oils of *Citrus limonia*, *Piper marginatum* and *Tetradenia riparia* at 50 μg mL^{-1}, which caused 100% mortality of adult *S. mansoni* worms after 72 h, 120 h and 120 h, were very active, *Baccharis dracunculifolia* (10 μg mL^{-1}) led to 100% mortality,[226] and *Dysphania ambrosioides* (12.5 μg mL^{-1}) 100% mortality after 72 h with an LC_{50} value of 3.65 μg mL^{-1} (ref. 227) (Table 6). In addition, propolis and wheat germ oil could be

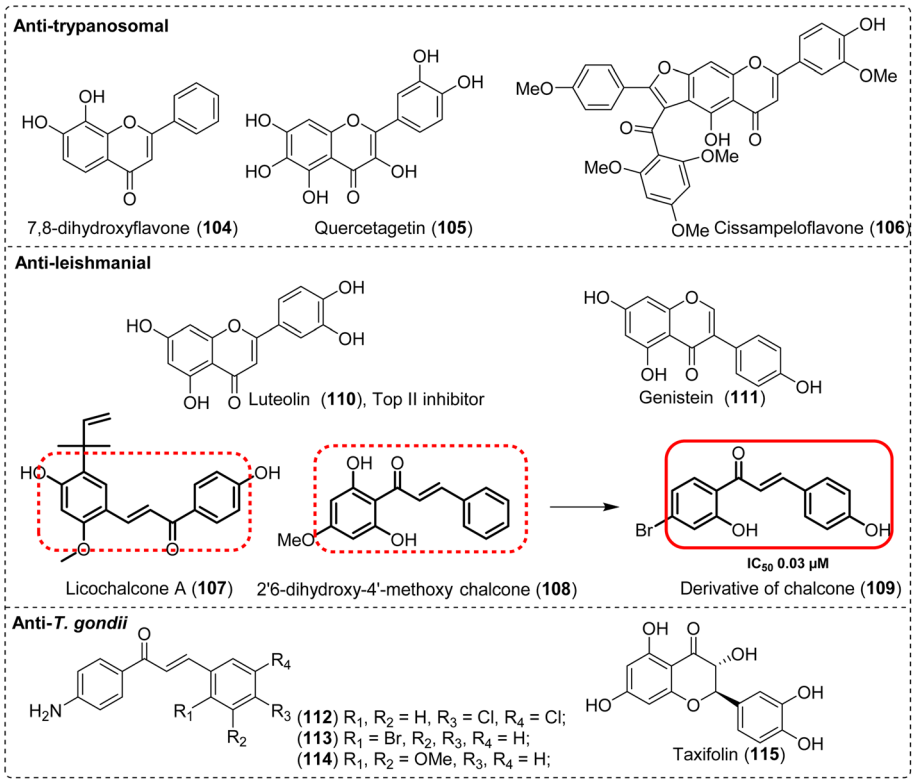

Fig. 14 Promising active flavonoids against parasites from natural sources.

used to treat chronic toxoplasmosis and help overcome the side effects caused by chemical drugs in experimentally infected mice.[228]

In recent decades, many plant extracts and essential oils have been demonstrated to be efficient against ticks,[229–240] and some commercial formulations based on essential oils such as MyggA® Natural, and Citriodiol® have been used to control ticks in some countries.[241] At high concentrations, nicotine-rich extracts (Tobacco) presented the promising anti-tick activity by killing all ticks, regardless of what stage ticks are at.[242] Fang *et al.*[243] studied and compared the efficacy of ten oils against scabies; clove oils were best, followed by oils from tea tree, lavender, geranium, bitter orange, palmarosa, Japanese cedar, and others. In Australia, tea tree oil extracted from *Melaleuca alternifolia* has shown higher activity than ivermectin in killing mites, and has been used by the Royal Darwin Hospital as an adjunct to scabies.[244]

4.1.6 Others. In addition, some plants or foods, including aloe, walnuts, henna plant, garlic, thyme, mimosa, shallots, yarrow, periwinkle, savory, medlar, black beans, and yeah, are effective against parasites and could be prepared as drugs or ointments to heal wounds.[245] *Arnica montana* tincture has been registered to a randomized clinical trial (NCT05094908) and is investigated for a topical treatment of uncomplicated CL in Colombia (**https://clinicaltrials.gov/ct2/show/NCT05094908?term=leishmaniasis+natural+product&draw=2&rank=1**).

Plant-, animal-, algae-, and fungus-based extracts and their metabolites have been reported to be promising sources of anti-*T. gondii* agents. Plant extracts and their metabolites have also been reported to be promising sources of anti-*T. gondii* agents. In 2008, the activities of 15 traditional medicine methanolic extracts against anti-*Toxoplasma* were investigated by Choi *et al.*[246] Of these extracts, *Zingiber officinale* (EC_{50} 0.18 mg mL^{-1}) and *Sophora flavescens* (EC_{50} 0.20 mg mL^{-1}) exhibited significant activity, respectively. Moreover, *Torilis japonica* ethanol extracts (156 ng mL^{-1}) would inhibit its proliferation by 99.3%.[247] Sharma *et al.*[248] reported that *Trametes versicolor* (Turkey tail) methanol extract, as a noncytotoxic and promising source, presented anti-*T. gondii* activity by affecting phytosterols, bioactive sphingolipids, peptides, phenolic acids, and lactones. TAF355 and TAF401, two *Eurycoma longifolia* root extracts, possessed anti-*Toxoplasma* activity, the IC_{50} values of which were 1.125 mg mL^{-1} and 1.375 mg mL^{-1}, respectively.[249]

From 2013 to now, some new extracts or agents were found, but only a small number of them presented promising activity (Table 6). de Castro *et al.*[250] found that many NPs including extracts presented activity against *Schistosoma* species *in vivo* and *in vitro*. However, according to the criteria involving hit activity against helminths (100% inhibition of motility in *S. mansoni* adults at 5 μg mL^{-1}), most NPs fail. Among 346 plant methanol extracts, only three extracts presented strong *in vitro* schistosomicidal activity, including extracts of *Agave lophantha* (LC_{50} of 8.2 μg mL^{-1}), *Furcraea selloa* (LC_{50} of 7.10 μg mL^{-1}), and *Solanum elaeagnifolium* (LC_{50} of 6.0 μg mL^{-1}),[251] and the acetonitrile extract of *Jatropha curcas* had an LC_{90} value of 6.0 μg mL^{-1}.[252] In an *in vivo* study, *Balanites aegyptiaca* fruit aqueous

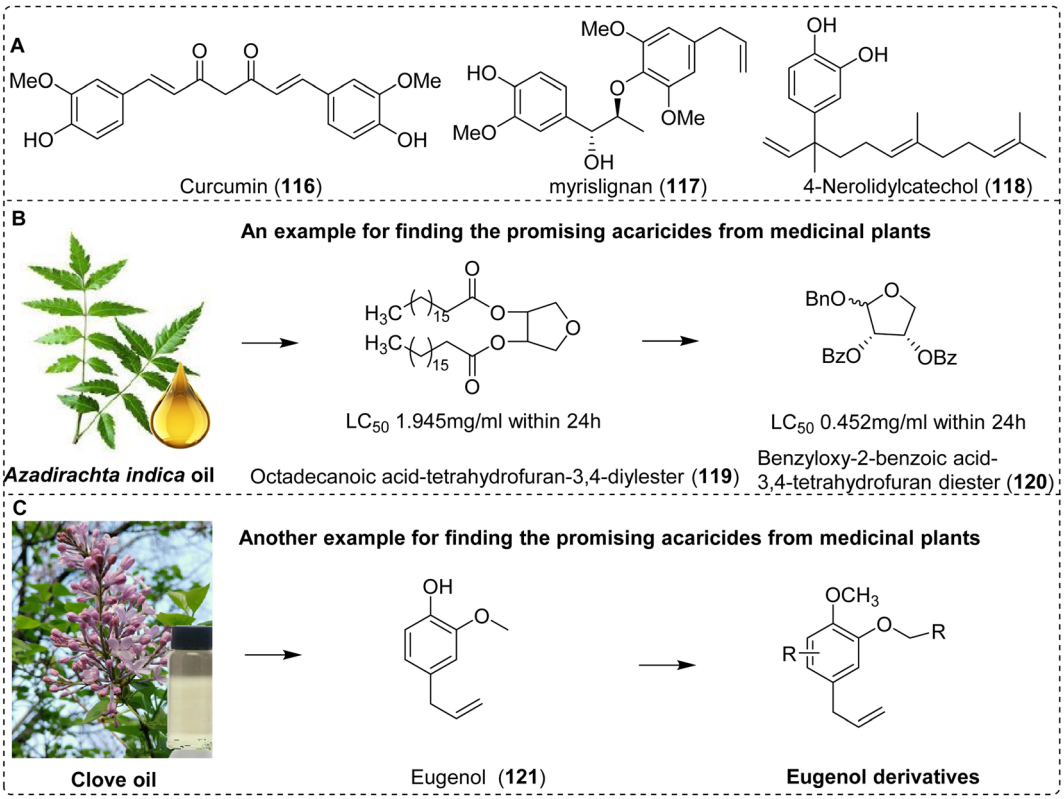

Fig. 15 Other promising active NPs (A), and the two examples of promising acaricidals from medicinal plants ((B) for *Azadirachta indica* oil and (C) for clove oil).

extract (200 mg kg^{-1}),[253] *Chenopodium ambrosioides* hydroalcoholic extract (50 mg kg^{-1}),[254] *Baccharis trimera* (200–400 mg kg^{-1}),[255] and blue green algae (200 mg kg^{-1})[256] presented anthelmintic activity by killing immature and adult worms of *S. mansoni* and exhibited immunomodulatory, hepatoprotective and antioxidant activities.

Moreover, some phenolic compounds, lignans, coumarins, and other NPs and their derivatives also exhibit good antiparasitic activity. For example, curcumin (**116**) from *Curcuma longa*[159] presented antimalarial effects in preclinical or clinical tests; myrislignan (**117**) induces oxidation–reduction to lead to autophagy in *T. gondii*;[257] 4-nerolidylcatechol (**118**) presented significant *in vitro* schistosomicidal activity with an EC_{50} value of 0.0029 μM and SI of 68 against Vero cells, and oral treatment decreased worm burden and egg production by 52.1% and 52.3%, respectively[258] (Fig. 15A).

Ying and her group found that octadecanoic acid-tetrahydrofuran-3,4-diylester (**119**) isolated from *Azadirachta indica* essential oil presented acaricidal activity against *S. scabiei* var. *cuniculi* larvae with an LC_{50} value of 3.06 μM *in vitro*; however, after optimizing the chemical structure, benzyloxy-2-benzoic acid-3,4-tetrahydrofuran diester (**120**) was obtained with an LC_{50} value of 1.08 μM[259,260] (Fig. 15B). The main component of clove oil, eugenol (**121**), as well as its analogs acetyleugenol and isoeugenol, presented a strong acaricidal activity within an hour of contact[261] (Fig. 15C). Our group found that it inhibited complex I activity in the mitochondrial respiratory chain by binding to NADH dehydrogenase chain 2 (MTND2) and then resulted in the death of mites,[262] and for a 1 : 1 mixture of eugenol and ivermectin, the LC_{50} value against mites will decrease 23 times compared with ivermectin only *in vitro* (unpublished data). 4-Methoxycoumarin with significant acaricidal activity were also found.[263] In a single-blind RCT test, after four weeks of treatment with *Tinospora cordifolia* lotion, significant mean global evaluation scores were achieved, and the clinical cure rates were similar to those of permethrin.[264]

The research into extracting NPs from plants has seen significant advancements, uncovering numerous compounds with therapeutic promise and offering key insights for the development of novel pharmaceuticals. In particular, NPs have made a crucial impact in the realm of treating parasitic infections. A comprehensive review reveals that the most extensive research has been conducted on protozoa, such as Plasmodium, Leishmania, and Trypanosome, with significant drug potential identified in NPs ranging from alkaloids and quinones to terpenes and flavonoids. Illustrations of this include the transformative discovery and use of quinine and artemisinin in malaria treatment, as well as the broader application of derivatives such as atovaquone and ivermectin in antiparasitic therapies. However, research on helminths, such as schistosomes, and ectoparasites, including scabies mites and ticks, remains relatively underexplored. Tropical diseases such as

schistosomiasis, scabies, lymphatic filariasis, and onchocerciasis, categorized as NTDs continue to face a shortage of effective and safe treatments. These diseases predominantly affect populations in impoverished regions, yet the lack of research investment and limited market returns have hindered the depth of basic research and the progress of drug development, leaving the actual needs unmet. Consequently, there is an urgent call to intensify research efforts directed at these parasitic diseases.

More importantly, the analysis of biological outcomes for flavonoids and polyphenols should also be conducted with great caution, with attention to screening for Pan-assay interference compounds (PAINS). These compounds do not operate by binding to specific biological targets, but interfere with assay methods *via* various non-specific mechanisms, leading to false-positive results,[265] such as the widely bioactive natural product curcumin.[266] Therefore, identifying and excluding PAINS is crucial for drug discovery, as they not only lead to the wastage of time and resources but may also result in erroneous judgments about potential drugs. Although publicly available filters can help identify potential PAINS, these filters cannot provide a comprehensive conclusion as to whether these suspect compounds are "bad" or innocent.[267] They may inappropriately flag effective compounds as PAINS. Chen *et al.* believe that employing a "fair testing strategy" to identify interesting molecules among PAINS suspect compounds can provide certain structural-functional insights for the development of multi-target-directed ligands (MTDLs).[268]

Of course, this problem is not exclusive to flavonoid and polyphenolic NPs. Similar possibilities may also exist in other NPs.[269] It is necessary to pay special attention to this possibility when screening anti-parasitic NPs.[270] Although PAINS can cause interference, not all compounds with PAINS characteristics are necessarily harmful. Some compounds may indeed possess activity, but it is necessary to carefully evaluate their mechanisms of action to rule out the possibility of detection interference. Moreover, modifying the compounds may eliminate their PAINS properties while retaining or enhancing their activity.[271]

For essential oils and crude extracts in NPs, they may not be sufficient to be developed as anti-parasitic drugs. However, they may have unique advantages in the adjuvant treatment of parasitic diseases. Promoting research in this area can not only extend the lifespan of existing clinical drugs but also achieve more desirable therapeutic effects when treating parasitic diseases clinically.

4.2 Microorganisms and animal

4.2.1 Microorganisms. Since 1974, avermectin has been isolated from the *Streptomyces avermectinius* strain by Õmura and MSD laboratories and presented potent anthelmintic

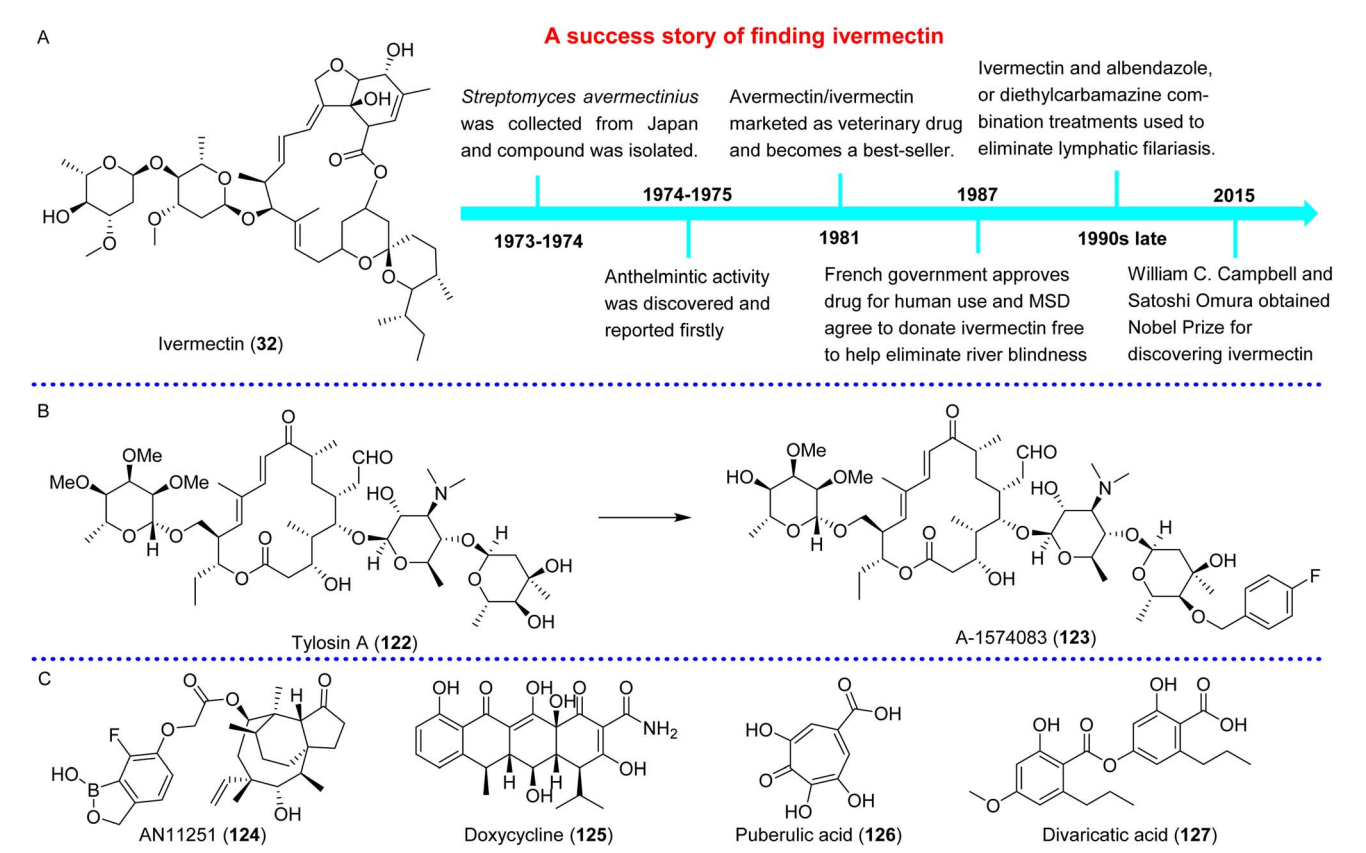

Fig. 16 Development history of ivermectin (A), the structural optimization of tylosin A for lymphatic filariasis and onchocerciasis (B), as well as other anti-parasitic natural products and their derivatives derived from microorganisms (C).

activity and unique mechanisms. Further study showed that it exhibited biocidal activity against a variety of nematodes, insects and arachnids with little or no toxicity. In 1979, the first paper on avermectin and its derivatives was published. Then, an interdisciplinary team at MSD, headed by William Campbell, found that the derivative of avermectin, ivermectin (**32**), has better activity, and in 1981, it was introduced to the market as a veterinary antiparasitic drug. In the past thirty years, ivermectin has proven to be one of the most successful drugs in public health and veterinary medicine.[272] This new concept alerted people worldwide to ivermectin (Fig. 16A). In 2015, the Nobel Prize in Physiology or Medicine was awarded to Prof. William C. Campbell and Satoshi Õmura for their discoveries of a new drug derived from NPs, avermectin. Its derivative, ivermectin, not only dramatically reduced the incidence of blindness and lymphatic filariasis, but also showed good therapeutic efficacy against other growing parasitic diseases, including scabies.[273]

The compound boron-pleuromutilin AN11251 (**124**) (50 mg kg^{-1}) reduced Wolbachia by >99% in a *Litomosides sigmodontis* mouse model, and thus, it was considered as a lead candidate. In addition, good pharmacokinetic and physicochemical properties were also proved.[274] In 2005, Taylor and colleagues reported[275] that doxycycline (**125**) administered orally at 200 mg per day for 8 weeks shows potential anti-*Wolbachia* activity. The drug is readily available, inexpensive and safe to use in adult nonpregnant patients (Fig. 16C). Then, this group found a promising macrolide veterinary antibiotic tylosin A (**122**) analog, A-1574083 (**123**), that presented remarkable anti-*Wolbachia macrolide* activity with high safety profile as a short-term oral drug course for treating lymphatic filariasis and onchocerciasis. A 1 or 2 week course of oral administration of this compound would provide >90% Wolbachia depletion from nematodes in infected animals[276] (Fig. 16B).

Puberulic acid (**126**), a compound isolated from the culture broth of *Penicillium* FKI-4410, exhibits potent anti-malarial activity (Fig. 16C). The *in vitro* IC_{50} values against both chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum* were 0.05 nM, and it showed weak cytotoxicity with an IC_{50} value of 0.29 μM against human MRC-5 cells. Compared with currently used anti-malarial drugs, puberulic acid demonstrated significant therapeutic effects *in vivo*. Moreover, the hydroxyl group at the C-7 position of puberulic acid seems to be an important part of its anti-malarial activity, while the carboxyl group at the C-4 position appears to be important for selectivity. This provided an important reference for subsequent structural optimization and the development of new anti-malarial drugs.[277]

Divaricatic acid (**127**), a depside class natural product isolated from *Canoparmelia texana*, was capable of killing *Schistosoma mansoni* by altering motor capacity and causing ultrastructural damage, with an *in vitro* IC_{50} value of 100.6 μM. Moreover, it exhibited no cytotoxicity to human peripheral blood mononuclear cells at effective concentrations (Fig. 16C).[278]

4.2.2 Animal. Peptides from animal venom have been isolated as promising candidates that exert anti-*T. gondii* activity in small doses; some examples include longicin P4 from *Haemaphysalis longicornis*,[279] HWVM from *Ornitoctonus huwena*[280] and neuwiedase from *Bothrops neuwiedi*.[281] These peptides significantly inhibit the invasion and proliferation of *T. gondii* and exhibit immunomodulatory properties to enhance host immune response and intracellular clearance of parasites.[282]

4.3 Marine organisms

Marine microorganisms provide vast biodiversity as well as significant chemical diversity, and some NPs with significant anti-leishmaniasis property have been identified and show great promise (Fig. 17). For example, a peroxide (**128**) produced by the sponge *Plakortis angulospiculatus* is active against *L. mexicana* by causing lysis of the cell membrane with an LD_{50} value of 0.97 nM, and the positive ketoconazole was 0.11 nM.[283] From *Streptomyces sanyensis*, 7-oxostaurosporine (**129**), 4′-demethylamine-4′-oxostaurosporine (**130**), staurosporine (**131**), and streptocarbazole B (**132**) were isolated, all of which presented significant activity against *L. amanzonensis* promastigotes, *L. donovani* promastigotes, and *L. amanzonensis* amastigotes.[284] Avarol (**133**) from *Dysidea avara* has activity against *L. infantum* promastigotes, *L. tropica* promastigotes, and *L. infantum* amastigotes, with IC_{50} values of 7.42, 7.08 and 3.19 μM, respectively.[285] Renieramycin A (**134**) from *Neopetrosia* species showed antileishmanial activity against *L. amazonensis* with an IC_{50} value of 0.35 μM.[286]

In 2013, Lam *et al.*[234] found that ascidiathiazone A (**135**) from the tunicate *Aplidium* sp. presented activity against the *T. b. rhodesiense* bloodstream form *via* generating reactive oxygen species (ROS) and inhibiting mitochondrial function, and the EC_{50} and SI values were 3.1 μM and 50 against L6 cells, respectively.[287] The endoperoxide motif exemplifies the diverse three-dimensional structural nature of bioactive NPs. Manadoperoxide B (**136**) and 12-isomanadoperoxide B (**137**), all isolated from the sponge *Plakortis* cf. *lita* (EC_{50} 0.0088 μM and 0.032 μM, respectively), exhibited anti-*T. b. rhodesiense* bloodstream form activity, with SI values >3000 and >350 compared with HMEC cells and L6 cells, respectively.[288,289] 11,12-Dehydro-13-oxo-plakortide Q (**138**) and manadoperoxide I (**139**) significantly inhibited *T. b. brucei* and *T. b. rhodesiense* bloodstream form parasites.[290] A cyclic peptide, valinomycin (**140**), presented potential property with an EC_{50} value of 0.0032 μM and high selectivity with an SI value of 3500 (ref. 291) (Fig. 17). In addition, an unusual tetramic acid metabolite ascosalipyrrolidinone A (**141**) from the marine fungus *Ascochyta salicorniae* showed activity against *T. cruzi* (EC_{50} 1.1 μg mL^{-1}), whereas the positive drug benznidazole was 0.12 μM.[292] As mentioned above, the chemical scaffold of NPs can retain the biological activity of the parent NPs, which is very important for the development of lead compounds with better activity and drugability. After chemical optimization, a derivative (**143**) of convolutamine I (**142**), against *Trypanosoma brucei* natural product isolated from the bryozoan *Amathia tortusa*,

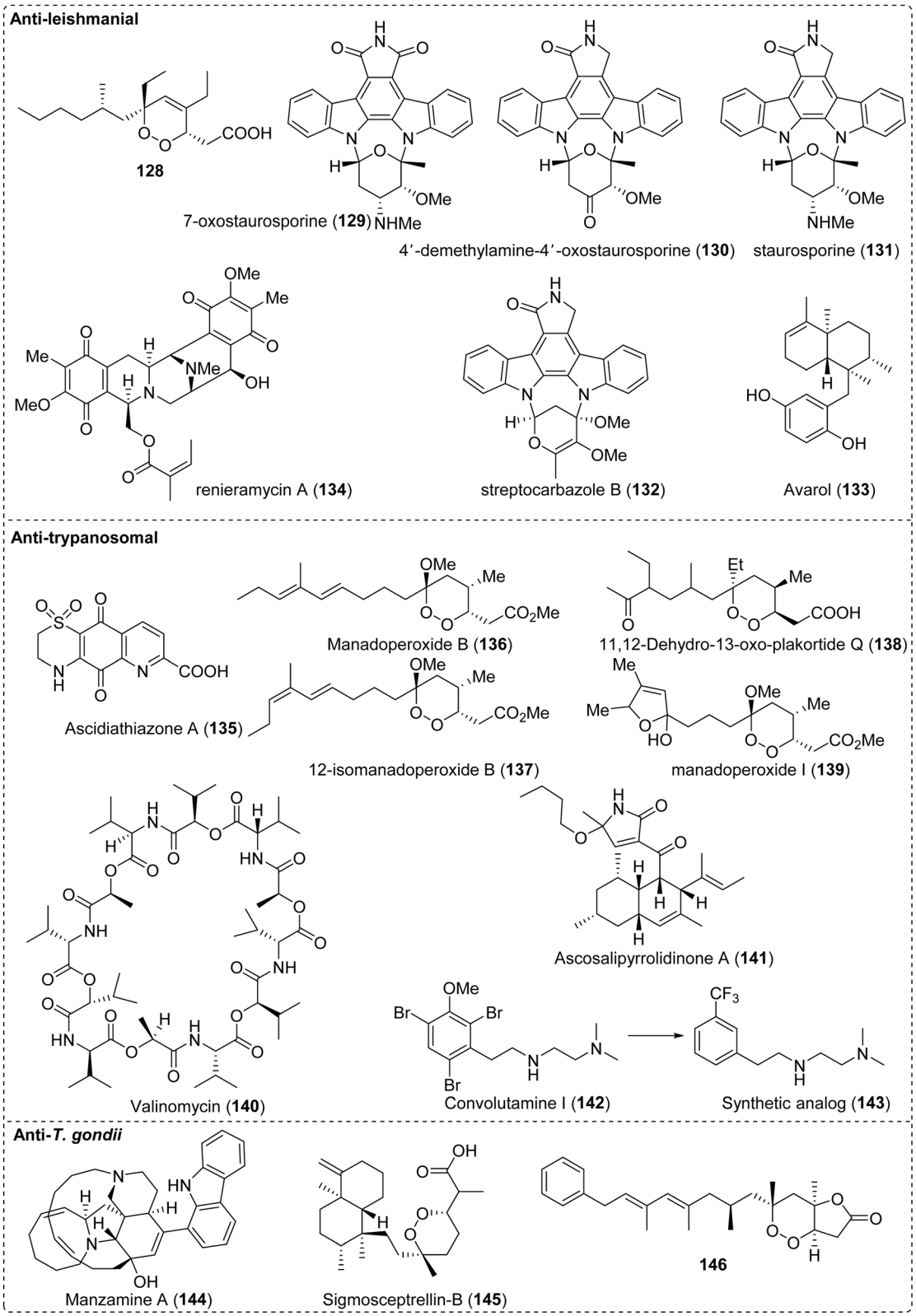

Fig. 17 Promising active NPs from marine organisms.

showed better efficacy than the prototype, with an EC_{50} value of 0.5 μM, and its pharmacokinetic properties were also significantly improved.[293]

Some active alkaloids identified from marine sponges presented remarkable activity against *T. gondii*. Manzamines with a unique group of polycyclic alkaloids presented anti-*T. gondii*

activity, which were isolated from the Okinawan sponge genus *Haliclona* in 1986.[294] Manzamine A (**144**) (0.098 nM) achieved 70% inhibition of the *T. gondii* parasite without causing cell toxic effects and prolonged the survival of Swiss Webster mice to 20 days after the administration of 8 mg kg^{-1} for 8 consecutive days (i.p.) compared to the 16 days observed with untreated controls.[295] Sigmosceptrellin-B (**145**) (0.099 nM) from *Diacarnus erythraeanus* exhibits potent activity against *T. gondii* in human diploid fibroblasts with inhibition rates of 84–99%.[296] Plakortolide (**146**) with a cyclic peroxylactone from the sponge *Plakinastrella onkodes* exhibited activity against *T. gondii* with an IC_{50} value of 64 nM *in vitro*.[297]

5 Advantages and limitations of NPs in the drug development process

As the main resource for drugs, NPs not only exhibit advantages but also pose challenges during the drug discovery process (Fig. 18):

(i) Traditional medicinal plants contain a large number of secondary metabolites with diverse chemical structures and various functions. These bioactive compounds such as alkaloids, flavonoids, and terpenoids after a long period of evolutionary screening often possess unique pharmacological activities and relatively low toxic and side effects.[298] Moreover, traditional medical systems such as Traditional Chinese Medicine and Indian Ayurvedic medicine have accumulated thousands of years of medicinal experience, documenting extensive knowledge about the therapeutic properties and clinical applications of various plants.[299] These traditional knowledge systems provide invaluable clues for modern drug discovery, which can significantly enhance the success rate of translating NPs into viable pharmaceutical agents. By further exploring and organizing traditional medical knowledge and establishing a complete database and knowledge base, it is possible to provide a more reliable basis for drug discovery.[300,301] Meanwhile, strengthening cooperation with traditional medicine practitioners and jointly conducting research and development on medicinal plants can also improve the success rate of drug research and development. Of course, with the rapid development of multi-omics technologies such as genomics, proteomics, and metabolomics, as well as technologies such as CADD, high-throughput screening (HTS), and high-content screening (HCS), researchers are now able to gain a deeper understanding of the gene expression, metabolic pathways, and bioactive components of medicinal plants. This accelerates the screening and optimization process of lead compounds and provides new strategies for drug discovery based on traditional medicinal plants.[302]

(ii) NPs are the result of the evolution of organisms in nature, and they exhibit great diversity in terms of chemical structure and biological activity.[303,304] Moreover, due to factors such as environmental adaptation and species interaction, organisms in different geographical environments will produce NPs with different biological functions, even if they belong to similar taxonomic categories.[305] With the continuous progress of synthetic biology and computational biology, as well as the ongoing development of technologies such as gene editing and multi-omics, it has become possible to regulate the evolution of plants and microorganisms.[306,307] Through means such as metabolic engineering transformation, combinatorial biosynthesis, and environmental regulation, we can not only obtain NPs with potential medicinal value more efficiently but also discover NPs with new biological functions, providing more diverse raw materials for drug discovery.[308–312]

(iii) Recently, along with the development of AI and reasonable molecular design technologies, targets were considered to be the "source power" to discover new drugs. For example, the *Plasmodium* genome contains about 5000 genes, and it has been estimated that about 200 (4%) might encode suitable drug targets. About 30 genes could be used as potential targets for drug discovery, which were not similar to any human genes.[313]

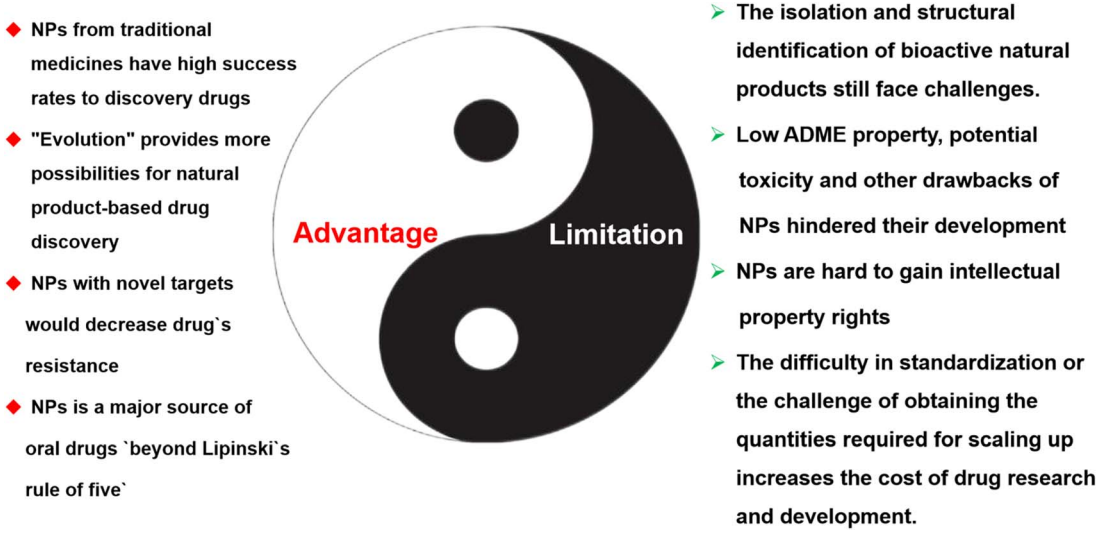

Fig. 18 Advantages and limitations of NPs in the drug development process.

Moreover, due to the complexity and diversity of chemical structures, as molecular probes, some modified NPs were adopted to capture their targets, and then, they were identified by mass spectrometry or selectively isolated, such as using photoaffinity labeling chemistry technology FoF1-ATP synthase.[314] NPs with novel targets may present synergistic effects with conventional drugs to combat diseases by decreasing resistance and increasing efficacy.

(iv) In recent years, an increasing number of orally administered drugs defying Lipinski's Rule of Five have gained regulatory approval.[315] By virtue of their distinctive structural complexity and bioactive profiles, NPs demonstrate high binding affinity and selectivity toward target proteins, have emerged as a critical source for developing novel oral therapeutics, and exhibit unique advantages in transcending conventional pharmaceutical guidelines.[316,317] NPs can further serve as lead compounds that undergo structural modification through chemical synthesis or biosynthetic engineering, thereby optimizing their physicochemical properties and pharmacokinetic profiles to enhance compatibility with oral administration criteria. The rapid development of drug delivery systems has also provided new strategies for the oral administration of NPs. For example, solid lipid nanoparticles (SLNs) can be used to encapsulate NPs, improve their stability and bioavailability, and achieve targeted delivery.[318] Other delivery systems such as microparticles, liposomes, and polymer micelles have also been widely studied for the purpose of enhancing the oral absorption of NPs.

However, NPs still involve limitations:

(i) The isolation and identification of bioactive compounds from natural resources remain challenges.[316] Traditional methods for the isolation of NPs still rely on techniques such as solvent extraction combined with chromatography, mass spectrometry, and membrane separation. The complicated operations and low efficiency limit the discovery of bioactive compounds, and the extensive use of organic reagents may also have a negative impact on the environment.[319] Although high-efficiency green extraction and separation technologies such as deep eutectic extraction have been studied,[319,320] there is still a significant gap between laboratory research and practical application, and these technologies have not been widely applied so far. By combining various technical strategies such as natural product databases, liquid chromatography-mass spectrometry (LC-MS) and nuclear magnetic resonance (NMR), efficient natural product dereplication methods have significantly reduced the waste of time and resources. Moreover, with the continuous development of analytical techniques and computational resources, the efficiency and accuracy of natural product dereplication will keep improving.[321,322] However, due to the fact that the content of NPs in living organisms is usually low, it is still a very difficult task to isolate and purify a single active ingredient and clearly elucidate its complex chemical structure.

(ii) From 1981 to 2019, although approximately 45% of FDA-approved drugs were derived from NPs, only 3.8% of prototypes were used directly as drugs, and more chemicals should be optimized comprehensively. Low ADME properties, potential toxicity and several other drawbacks of NPs have led pharmaceutical companies to reduce drug discovery programs, especially antiparasitic agents, and the difficult total synthesis of active compounds also seriously affects the development prospects. For example, to find new hits or lead compounds for fighting this disease, researchers have focused on medicinal plants and NPs over the past three decades. Approximately 400 species belonging to almost 100 families have been evaluated for activity, especially for Anacardiaceae, Annonaceae, Asteraceae, Euphorbiaceae, Fabaceae, Lamiaceae, Malpighiaceae, and Phytolaccaceae, and more than 200 compounds with antitrypanosomatid activity were found.[34,323] However, according to the guide of the Drugs for Neglected Diseases initiative (DNDi),[22] a small portion of compounds are promising to develop further.

(iii) Gaining intellectual property (IP) rights for NPs exhibiting relevant bioactivities is hard, since naturally occurring compounds in their original form may not always be patented.[324] An additional layer of complexity results from regulations that define the need to share with countries where the biological material originated, framed in the Convention on Biological Diversity of UN approved in 1992 and the Nagoya Protocol in 2014,[325] as well as recent developments concerning benefit sharing linked to the use of marine resources.

(iv) The inherent challenges in isolating and characterizing bioactive compounds, compounded by the potential low natural abundance and structural complexity of active NPs, have engendered significant obstacles in achieving standardized and scalable manufacturing processes for NP-based drug development. Particularly, the intricate molecular architectures characteristic of bioactive NPs often render synthetic modification technically demanding, thereby constraining pharmaceutical development and optimization endeavors (Fig. 18).

Drug discovery and development are long and complex processes that need experts from multiple disciplines to work closely from the beginning to develop sound strategies that guide the entire process, such as physicists, chemists, biologists, computer scientists and pharmacists. The identification and validation of target is an ideal beginning for the drug discovery. Recently, progress has been achieved to increase knowledge on parasite-specific drug targets, especially after using the CRISPR/Cas system and other technologies for structural and functional studies, and more targets have been found. Based on novel targets, computer-aided predictions and design and high-throughput drug screening will help us find promising hits against parasites.[326,327]

6 Prospective analysis

Parasitic diseases seriously threaten human and animal health and have a negative impact on public health security and socioeconomic development. In history, approximately US 300–500 million is needed for research expenditure to develop and release a new product to the market.[2,92] Because these diseases are mainly prevalent in low-income regions, market forces are enough to drive the discovery and development of new agents, and the number of global organizations and investment in

antiparasitic drug discovery are all lower than those for other common diseases. However, there have been good opportunities in the past few years, and several welcome developments have provided new impetus. The WHO, European Union, China, US National Institute of Health, Canadian Institute for Health Research and Health Sector in the African Region paid more attention to parasitic diseases. The establishment of PPP that focuses on tropical diseases, at least to some extent, stimulated the enthusiasm of many pharmaceutical companies to become involved in antiparasitic drug discovery, including the DNDi, the Medicines for Malaria Venture (MMV), and the Institute for One World Health (IOWH). These PPPs disease-specific knowledge and experience of public health care organizations to discovery and develop drug will increase the success rate of candidate drugs in clinical trials.[24,328] The WHO Special Programme for Research and Training in Tropical Diseases (TDR), the World Bank, and the United Nations Education of Scientific and Cultural Organization (UNESCO) promote the development of antiparasitic drugs. More funds were injected into the area of antiparasitic research and provided a large impact, such as the Wellcome Trust and the Bill and Melinda Gates Foundation.

In the past hundreds, people have focused more on exploring NPs from plants for (i) the validation of traditional NPs use in endemic populations and (ii) the use of NPs as sources of new potential antiparasitic compounds. According to the ClinicalTrials.gov (**http://ClinicalTrials.gov**) database, nearly 15% of the drug interventions are derived from plants, with 60% drugs isolated from only 10 taxonomic families.[329,330] Most plant species have not been studied comprehensively for discovering novel drugs. During their long evolutionary process, plants have developed a series of complex defense mechanisms to resist various biological stresses, including parasitic invasions. These mechanisms have led to the production of a diverse array of secondary metabolites responsible for the survival of the organisms, as well as for defending against competitors and invaders.[331,332] Therefore, for a long time, NPs have been an important source of new drugs for parasitic diseases. Due to their remarkable chemical diversity, biochemical specificity, and other molecular characteristics, NPs are favorable lead structures for drug discovery. Especially with the establishment of natural product (NP) libraries and the development and application of new technologies such as high-throughput screening (HTS), the time required for drug discovery will be significantly shortened, which has already promoted the progress of drug research and development for parasitic diseases such as malaria and cryptosporidiosis.[333]

In the past 40 years, more than 12 000 novel chemicals, with hundreds of new compounds still being discovered from non-traditional sources of marine bacteria and cyanobacteria every year, provide a diverse array of NPs, primarily from invertebrates (*e.g.* sponges and tunicates). More than 32 000 compounds are listed in the database of marine NPs.[119] About 30 compounds belong to the marine pharmaceutical clinical pipeline, which comprises 7 FDA-approved drugs and 22 drug candidates for the development of drugs.[334,335] Some of them presented antiparasitic and drug-resistant parasitic activities and have been selected as promising leads for extended preclinical assessment. For example, haliclonacyclamine A from the marine sponge *Haliclona* spp. presented promising activity against chloroquine-sensitive and -resistant strains of *P. falciparum*.[159] Considering that the world's oceans have played an important role in controlling the global infectious disease burden,[336] the identification of more novel drug leads and even drugs from ocean resources will be realized.

Drug discovery remains a high-risk process. The drug development is still a challenge and is hindered by high fail rates, high costs and economic pressures, multidisciplinary collaboration, drug's accessibility and IP constraints. Although this process is time-consuming and requires a significant amount of work, a rational selection of research strategies, along with active NPs that always possess favorable suboptimal pharmacological effects or ADMET characteristics, provides more possibilities and a higher success rate for the development from "hits" to "leads," and ultimately to new drugs. Of course, chemical modification may be needed for most of the NPs, and total chemical synthesis, semisynthesis and active fragment assembly will play a more important role in this condition. Moreover, with breakthroughs in various emerging technologies, drug development has progressed from relying solely on phenotype-based drug discovery to developing new strategies based on target-based drug discovery.[337] For NPs, the phenotypic drug discovery strategy remains crucial at present, as it enables the discovery of drugs with complex mechanisms of action. Recently, the "evolution"-based drug discovery strategy has also attracted the attention of researchers.[338] In addition, as we have previously proposed, drug repositioning is a strategy that can significantly shorten drug development time and reduce costs, as the safety data of approved drugs are usually known. Similarly, exploring the potential of NPs in the adjunctive treatment of parasitic diseases can provide new breakthroughs in clinical treatment efficacy and regimens.

The development and application of various technologies have led to a renewed emphasis on natural product-based drug screening in the field of drug discovery. Nowadays, data science and artificial intelligence (AI) are increasingly becoming key forces driving its vigorous development, as their ability to process complex data offers tremendous assistance in the discovery of new drugs.[339–341] AI can predict which proteins may serve as drug targets by analyzing a large amount of genetic data. After combining with the analysis of a vast amount of bioactivity data, it is also capable of predicting the interactions between NPs and target proteins, thus accelerating the screening process of NPs. Wang *et al.*[342] described a large-scale RNAi screen in adult *S. mansoni* that examined the function of 2216 genes. Among them, TAO and STK25 have the potential, which could change the muscle-specific messenger RNA transcription, and then loss of either of these kinases results in paralysis and worm death. Alkaloids, such as tryptamines, protoberberines and aporphines, also presented potential activity *via* regulating Sm.5HTRL.[343] Moreover, advanced machine learning techniques can obtain models through multi-dimensional data learning that are capable of predicting the potential activities of untested chemical structures.

Additionally, these techniques can design natural product analogs that may possess specific biological activities, which is helpful for expanding the molecular space of drug development and discovering entirely new drug lead compounds.[341,344] Although AI methods have opened up new possibilities for the design, synthesis, and biological analysis of existing and new small molecules, at the core of these methods are public databases of bioactivity data for a large number of (protein) targets and chemical structures.[345] However, the existing natural product data are multimodal, imbalanced, unstandardized, and scattered across many data repositories. This makes it difficult to use natural product data together with existing deep learning architectures, as these architectures require fairly standardized, and usually non-relational, data. This also hinders models from learning the overall patterns in natural product science.[341] Therefore, data science technologies for constructing and managing large-scale natural product databases still require further research.[346] For example, the TCMs-CFA platform integrates traditional Chinese medicine knowledge bases, chemomics data, and high-content screening data, and is used to predict active compounds and their potential mechanisms.[301]

Currently, factors limiting the discovery of antiparasitic drugs include not only the identification of active compounds but also the capability to establish animal models, which is a significant constraint. Parasite animal infection models play a crucial role in the research and development of antiparasitic drugs. They serve as a key bridge between *in vitro* experiments and clinical trials, enabling the assessment of a drug's efficacy, toxicity, and pharmacokinetic properties.[347] However, due to the diverse and highly complex life cycles and parasitic states of parasites, most diseases require testing in several animal models at different stages. These animal models do not always replicate the human infection process and disease pathology. Compared with the primary model related to the acute stage, more important and complex chronic or resistant models are needed for screening the active compounds. Such compounds presenting the efficacy against Chagas disease in both primary model and secondary infection model were considered as lead compounds. Furthermore, there are still many parasites for which predictive preclinical models are lacking, such as *P. vivax* malaria, Chagas disease, and cryptosporidiosis. This has become a research gap that the scientific community urgently needs to address in order to advance the development of antiparasitic drugs.[333]

Drug discovery and development are essentially multidisciplinary areas where chemists, pharmacists, physicists, biologists, computer scientists, and so on must work together even from the beginning, delineating the rationale that will guide the whole process.

7 Conclusion

In summary, the high attrition rates, accessibility, sustainable supply, IP constraints and some problems still hinder the development of NPs; however, based on quinine, artemisinin, ivermectin and other approved antiparasitic drugs derived from NPs, NPs remain a promising pool with high structural diversity and remarkable activities and NPs are the center of attention for the scientific community and exploration of novel antiparasitic drugs. In combination with the recent development and application of revolutionized technologies, NPs will provide a stronger basis for drug discovery and will continue to provide major contributions to human and veterinary health.

8 Conflicts of interest

The authors declare no competing financial interests.

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