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MINI-REVIEW

Medicinal fungi: a source of antiparasitic secondary metabolites

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Abstract

Regions with a tropical climate are frequently affected by endemic diseases caused by pathogenic parasites. More than one billion people worldwide are exposed directly to tropical parasites. The literature cites several antiparasitic metabolites obtained from medicinal plants or via synthetic pathways. However, fungi produce a diversity of metabolites that play important biological roles in human well-being. Thus, they are considered a potential source of novel natural agents for exploitation in the pharmaceutical industry. In this brief review article, we will provide an overview of the current situation regarding antiparasitic molecules derived from filamentous fungi, in particular, those which are effective against protozoan parasites, such as *Plasmodium*, *Trypanosoma*, and *Leishmania*, vectors of some neglected tropical diseases. Diseases and parasitic agents are described and classified, and the antiparasitic properties of natural compounds produced by the fungi of the phyla *Basidiomycota* and *Ascomycota* are reviewed herein, in order to explore a topic only sparsely addressed in the scientific literature.

Keywords Macrofungi · Protozoa · Natural products · Antiparasitic molecules

Introduction

Neglected tropical diseases (NTDs) are a diverse group of infectious diseases caused by bacteria, parasites, or viruses which prevail especially in tropical and subtropical regions. Populations lacking sanitation, living in poverty and in contact with animals, are the most affected. NTDs are common and sometimes fatal, and they regularly infect humans in over 150 countries. According to reports published by World Health Organization (WHO), the major diseases of concern are malaria, visceral leishmaniasis, and Chagas disease. Published data to the World Malaria Report (WHO 2017b), in 2016, there were as estimated 216 million cases of malaria. With regard to the visceral leishmaniasis (VL) in 2015, 90% of global VL cases were reported from seven countries: Brazil, Ethiopia, India, Kenya, Somalia, South Sudan, and Sudan (Global Health Observatory (GHO)). In addition, Chagas disease affects about six million to seven million people worldwide, mostly in Latin America (WHO 2017a). All of these diseases are caused by parasites.

Parasites can be classified into two categories: endoparasites and ectoparasites. The endoparasites colonize internal parts of the human body, such as blood, digestive tract, muscle cells, and many other parts. The ectoparasites live outside of the human body, e.g., on hair, skin, and nails. Parasites do not usually kill their hosts, although they can cause severe discomfort. However, many infections parasitic can be deadly, such as malaria, leishmaniosis, giardiosis, and Chagas disease (Wink 2012). Parasitic diseases are generally more severe in the tropical areas, where the climate is more favorable to the reproduction of the parasites and vectors. Parasites can have different life cycles: simple or complex. Simple life cycle parasites complete their life cycles in only one host, while for complex life cycle parasites, different hosts and vectors may be required to spread the infection (Auld and Tinsley

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2015). Most of these diseases can be controlled, but not eradicated. The high cost and long periods associated with treatment adversely affect the poor communities living in tropical areas. Some of these diseases do not have appropriate treatment, and the number of studies aimed at finding new antiparasitic drugs is low (Torgerson 2013).

There is no vaccination for most of these diseases, and the drugs used in treatments were generally developed a long time ago. Some of these drugs are no longer effective, and the parasites may have gained resistance to them (Croft et al. 2006). Moreover, the most drugs used in the disease treatment are synthetic and have strong side effects which, associated with the long-term treatment, leads to people giving up on treatment (Silva-Jardim et al. 2014). These untreated people still host the parasite, thus acting as a reservoir of the infection and helping to spread the disease (Beaumier et al. 2013). In addition, many of these neglected diseases are zoonoses, where wild animals and even pets can be reservoirs of the diseases (Dawit et al. 2013).

Many organisms produce various bioactive constituents with different types of biological activity that can be used to treat several diseases. The traditional medicine systems employ several thousands of medicinal plants, some of which have known antiparasitic properties. Nevertheless, medicinal fungi also offer a unique opportunity for obtaining natural products that could be used to treat parasitic infections. However, they are still not well known as antiparasitic agents. Like plants (Bertin et al. 2014; Siebert et al. 2014; Tenfen et al. 2017), the fungi synthesize distinct natural compounds for therapeutic use (Costa et al. 2016). With the advance of biotechnological processes, it is possible to obtain a variety of natural molecules through microbial metabolism (Vieira et al. 2008; Borderes et al. 2011; Chicatto et al. 2014; Pedri et al. 2015) and thus reducing the exploitation of natural resources. There are many studies showing the antiparasitic action of secondary metabolites obtained from plants (Wink 2012). However, microorganisms can also produce several secondary metabolites, among them the drug ivermectin, produced by *Streptomyces avermitilis* and used as an antiparasitic drug against infections caused by some parasites (Patra 2010).

With the use of microorganisms and their application in biotechnology, besides minimizing the use of endangered plant species, it is possible to obtain a better yield in short time (Chen et al. 2016; Stierle and Stierle 2015). This brief review aims to highlight parasites related to neglected tropical diseases and conventional treatments for their control. Furthermore, a discussion on the natural chemical products (secondary metabolites) produced by fungi, which are also molecules of plant origin, with antiparasitic properties is presented. Finally, some biological applications of natural chemical products in the causative agents of neglected diseases are described.

Major parasites and conventional treatment

Plasmodium spp.

The protozoan parasite *Plasmodium* spp. is the causing agent of malaria, a deadly disease that affects millions of people worldwide every year. It causes a febrile disease that disappears usually after some days. However, young children and immunocompromised people are particularly susceptible to severe malaria, which can cause death.

There are five species of *Plasmodium* that can cause human malaria. *Plasmodium falciparum* is the most common, but *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale*, and *Plasmodium knowlesi* can also cause the disease. Infection can be caused by one parasite or a combination of *Plasmodium* species (Krishna et al. 2015). Early treatments with the synthetic drugs chloroquine and sulfadoxine pyrimethamine have become ineffective due to parasite resistance. Subsequently, in the early 1970s, the isolation of the molecule artemisinin from the plant *Artemisia annua* resulted in a new treatment, which is used nowadays (Miller et al. 2013). However, many studies have been conducted on the resistance of the parasite to treatment with artemisin, and the resistance is spreading (Ashley et al. 2014).

Leishmania spp.

There are around 20 species of *Leishmania* (*Trypanosomatidae*) which can cause three variations of the leishmaniasis disease: cutaneous, mucocutaneous, or visceral leishmaniasis (Dawit et al. 2013). Cutaneous leishmaniasis causes skin lesions, which can persist for months, sometimes years. The lesions are usually painless and can evolve into ulcers. The clinical manifestations of mucocutaneous leishmaniasis can vary between erythema, edema, crusting of lips and nose, perforation of the cartilage, and even cause permanent damage to the larynx and pharynx (Downing et al. 2014). Visceral leishmaniasis can vary in severity and manifestation. The incubation period generally ranges from weeks to months, but it can be longer. The visceral manifestation of the disease is usually caused by *Leishmania donovani* and *Leishmania infantum*, and it can affect internal body organs. It is also popularly known as kala-azar and can be fatal in severe cases (Clem 2010).

There is no vaccine to control the disease (Dewitt et al. 2013). The current therapy consists of pentavalent antimonials, such as sodium stibugluconate (Pentosam®), meglumine antimonate (Glucantime®), and also miltefosine, amphotericin B, and paromomycin. The first drugs used for treatment were the antimonials. However, in the 1970s, the parasites started to show resistance to pentavalent sodium antimony gluconate, even at high doses, and as a result, these drugs were mostly abandoned. Miltefosine has replaced

antimonials as a treatment in cases of SSG resistance. However, it has also been associated with increasing resistance. Treatment with amphotericin B is effective, but it has highly nephrotoxic effects. The treatment can also be inhibited by cost, access, and difficulties in obtaining oral formulations of the drug (Hefnawy et al. 2017).

Giardia spp.

Giardiasis is a disease caused by the parasite *Giardia lamblia*, also known as *Giardia duodenalis* and *Giardia intestinalis*. The parasite exists as a trophozoite form which causes the clinical disease, and as a cyst form, responsible for the transmission of infection (Lebwohl et al. 2003). It is a zoonotic disease, meaning that the disease can pass through humans and animals (Durigan et al. 2017). The cysts can be found in contaminated water and food. They can survive for long periods in the environment besides being resistant to water and sewage treatment (Ryan and Caccio 2013; Lebwohl et al. 2003). Less than 10 cysts are required to cause an infection. The main symptoms are acute or chronic diarrhea, abdominal pain, nausea, vomiting, and weight loss (Ryan and Caccio 2013).

The treatment of giardiasis can encompass several medications, being effective the drugs from the class of nitroimidazoles, such as metronidazole, secnidazole, and tinidazole. Nevertheless, they present strong side effects and have mutagenic capacity. The drug metronidazole has not shown efficacy against cysts and was only effective against trophozoites. Another drug class, benzimidazoles, such as albendazole and mebendazole, have less severe side effects but are not as effective as metronidazole (Rossignol 2010).

Toxoplasma gondii

Toxoplasma gondii is an intracellular protozoal parasite witch induces the toxoplasmosis. This parasite can infect a wide range of warm-blooded animals, and it is estimated that 30–50% of the world population is infected. Adults present symptoms such as fever, malaise, and lymphadenopathy that resolve spontaneously. This infection can also be asymptomatic, which causes a delay in the diagnosis and treatment (Flegr et al. 2014). *T. gondii* infection in a pregnant woman can cause severe damage; it can be transmitted to the fetus and may cause a series of problems like mental retardation, blindness, epilepsy, and death. In immunesuppressive persons, it can cause severe encephalitis via acute infection or reactivation of latent infection (Dubey 2008).

Soroprevalence of anti-Toxoplasma antibodies varies in a range from 1 to 100%, depending on the country, environmental conditions, eating habits, and level of hygiene. In European countries, there is a prevalence ranging between 10 and 60%. Central and South American countries also show a great prevalence, ranging between 38 and 77% in women in childbearing age (Flegr et al. 2014).

Traditionally, pyrimethamine (5-(4-chlorophenyl)-6-ethyl-2,4-pyrimidinediamine) and sulfadiazine (4-amino-*N*-pyrimidin-2-ylbenzenesulfonamide) are used in the treatment against toxoplasmosis. However, although effective, these drugs are highly toxic to human cells, and therefore, folinic acid is often added to reduce the suppression of the bone marrow (Maldonado and Read 2017). In patients with hypersensitivity to sulfadiazine, a combination of pyrimethamine with the antibiotic clindamycin can be used alternatively. In HIV patients, it is usually used the drug combination co-trimoxazole, consisting of trimethoprim (5-[(3,4,5-trimethoxybenzyl]-2,4-pyrimidinediamine) and sulfamethoxazole ((4-amino-*N*-(5-methyl-1,2-oxazol-3-yl) benzenesulfonamide). In case of severe side effects, dapsone (diamino-diphenylsulfone) and pyrimethamine or atovaquone (hydroxy-1,4-naphtoquinone) can be used alternatively as a treatment. The drug atovaquone is a naphtoquinone analog of the protozoan ubiquinone, which affects the functions of the *T. gondii* cytochrome bc1 without affecting human cells. However, it has low bioavailability which compromises the effectiveness of the drug (Antczak et al. 2016).

Trypanosoma cruzi

The parasite *Trypanosoma cruzi* causes the Chagas disease, and it is transmitted by *triatominians* vectors such as *Triatoma* spp., *Rodnius* spp., and *Panstrongylus* spp. This disease has a high mortality index. However, the number of deaths has been decreasing in recent years. The initial phase of the disease is asymptomatic, which can take years to manifest, hindering the diagnosis. The main symptoms after the manifestation of the disease are cardiomegaly, hepatomegaly, cardiopathy, and problems in the digestive tract. These problems can evolve into mega-colon, mega-esophagus, cardiac hypertrophy, fibrosis, and cardiac failure (Guedes et al. 2011).

The conventional treatment is based on benzimidazole (Bayer Health Care—Lampit®) and nifurtimox (Roche—Rochagan® or Radanil®), which were developed over 30 years ago. Both drugs have strong side effects, such as appetite loss, vomiting, polyneuropathy, and dermopathy. The long-term treatment required combined with the strong side effects contributes to frequent desistence (Guedes et al. 2011). Additionally, benzimidazole and nifurtimox are mostly effective for the blood forms in the acute phase and not so effective against the intracellular forms in the chronic phase (Muelas-Serrano et al. 2002).

Helminths

Helminths are worms generally transmitted by soil or food contaminated with their eggs. Some species spend part of their

life cycle in the ground. People are infected when they ingest their eggs in contaminated water or food. Infection by these parasites can be controlled with appropriate sanitation and hygiene practices. However, some populations do not have access to treated water and sewage treatment systems, so it is very hard to control the diseases. Also, autoinfection occurs very frequently in these cases (Ziegelbauer et al. 2012).

Many drugs are toxic, and their indiscriminate use can present a risk to human health. The drugs which are most commonly used to treat infection by these parasites are albendazole, mebendazole, and praziquantel. Paraherquamide and macfortine A are drugs used to treat infestations with *Caenorhabditis elegans*. These drugs are isolated from the fungi *Penicillium paraherquei* and *Penicillium roqueforti*, respectively. Ivermectin, a semi-synthetic drug derived from avermectin, produced by *Streptomyces avermitilis*, is a drug used to treat infestations by helminths (Yadav and Singh 2011).

Natural products obtained from fungi as important sources of antiparasitic molecules

The role of natural products in the discovery of new therapeutic agents can be demonstrated by an analysis of the number and sources of bioactive agents. Plants have been used for thousands of years to treat a huge diversity of diseases, and they can be very effective. However, not only plants have proven to be a source of bioactive natural products since fungi also have novel structural entities. Many efforts have been made in order to estimate the fungal diversity. There are some data estimating the fungal diversity among 500,000 to 9,900,000 species (Bass and Richards 2011). However, according to the Dictionary of Fungi (Kirk et al. 2008) approximately 99,000 species of fungi have been described. Macrofungi and microfungi have been used in different process, mainly as a food (mushrooms), in preparation of alcoholic beverages (yeasts), and in medicine (Hibbett et al. 2014; Choi et al. 2017). The macrofungi are a large group of wood-rotting fungi of the phyla *Basidiomycota* (basidiomycetes) and *Ascomycota*, which are a major source of pharmacologically active substances (Blackwell 2011).

Fungi can produce a wide range of secondary metabolites (Costa et al. 2016) such as peptides, alkaloids, terpenes, polyketides, quinones, sterols, and coumarins. These metabolites can be used to treat a diversity of diseases (Keller et al. 2005) including neglected tropical diseases caused by protozoa parasites. The potential for obtaining new antiparasite drugs from macrofungi has been underestimated. Widely studied medicinal basidiomycetes like *Ganoderma lucidum* are used to treat several health conditions. However, its antiplasmodial activity against *P. falciparum* has been largely overlooked (Adams et al. 2010). In the same context, *Autraeus hygrometricus* is an Indian mushroom used to treat leishmaniosis, and although popular in traditional communities of India, it is not known in the rest of the world (Lai et al. 2012; Mallick et al. 2015). *Pycnoporus sanguineus*, a pantropical white rot fungus, also showed powerful leishmanicidal activity. Correa et al. (2006) reported the possible action of ergosterol endoperoxide, which could involve reactions that cause the disruption of the *Leishmania panamensis* membrane. *Trametes versicolor* (*Polyporaceae*) is another basidiomycete that has antileishmanial activity against promastigotes and intracellular amastigotes of *Leishmania amazonensis* (Leliebre-Lara et al. 2016). Table 1 summarizes the antiparasitic molecules obtained from fungi, and the number for each compound corresponds to the structures illustrated in Fig. 1, as discussed below.

Terpenes

Terpenes are widely distributed in the plant and fungi kingdoms. They are known for their biological activity and have been showing to be very active against many parasites. Mushrooms can present a wide variety of terpenoids with several biological activities, such as antioxidant, antimicrobial, antitumoral, antibacterial, antifungal, anti-inflammatory, antiplasmodial, antimalarial, antiviral, and cytotoxic action (Duru and Çayan 2015). The antiparasitic activity of sesquiterpenes [a], diterpenes [b], triterpenes [c], and meroterpenes [d] are described below.

[a]. Sesquiterpenes are widely produced by plants and fungi and are very effective against parasitemia, presenting fast action (Kayser et al. 2003). Artemisin, a sesquiterpene endoperoxide lactone, is widely used to treat several parasitic diseases. It is a natural compound found in the leaves of *Artemisia annua*, and studies have verified its effectiveness in vitro and in vivo against the parasites *Leishmania major*, *L. donovani*, *L. infantum*, *T. cruzi*, *Trypanosoma brucei*, *T. gondii*, *Neospora caninum*, *Eimeria tenella*, and *Acanthamoeba castellanii* (Loo et al. 2017). Several sesquiterpenic molecules produced by fungi show effect against these species and other parasites. Sesquiterpenic lactones produced by *Acanthospermum hispidum* showed in vivo and in vitro antiparasitic effects against *P. falciparum*, *Leishmania mexicanum*, and *T. brucei* (Ganfon et al. 2012).

Isaka et al. (2011) extracted terpene molecules from the ethyl acetate extract of the basidiomycete *Stereum ostrea*, among them, the sesquiterpene sterostrein A [1], which presented antiplasmodial activity with an (IC_{50}) value of 2.3 μg/mL. Other antiplasmodial sesquiterpenoids, aurisin A and aurisin K [2], extracted from the luminescent basidiomycete *Neonothopanus nambi*, showed activity

Table 1 Fungal compounds with antiparasitic action

No.	Compound	Fungi	Parasite	References
Terpenes				
1	Sterostrein A	*Stereum ostrea*	*Plasmodium falciparum*	Isaka et al. (2011)
2	Aurisin A, G, K	*Neonothopanus nambi* *Anthracophyllum* sp.	*P. falciparum*	Kanokmedhakul et al. (2012) Intaraudom et al. (2013)
3	Hypnophilin	*Lentinus strigosus*	*T. cruzi*	Cota et al. (2008)
4	Dihydrohypnophilin	*Lentinus connatus*	*P. falciparum*	Rukachaisirikul et al. (2005)
5	Panepoxydone	*L. connatus*	*P. falciparum*	Rukachaisirikul et al. (2005)
6	Panepoxydione	*L. connatus*	*P. falciparum*	Rukachaisirikul et al. (2005)
7	Astrakurkurone	*Astraeus hygrometricus*	*Leishmania donovani*	Lai et al. (2012), Mallick et al. (2015)
8	Ganoderic acid TR Ganoderic acid TR 1 Ganoderic aldehyde TR Ganoderic acid S	*Ganoderma lucidum*	*P. falciparum*	Adams et al. (2010)
9	Ganodermanondiol	*G. lucidum*	*P. falciparum*	Adams et al. (2010)
10	23-Hydroxyganoderic acid S	*G. lucidum*	*P. falciparum*	Adams et al. (2010)
11	C3 epimer of ganoderic acid T	*Ganoderma orbiforme*	*P. falciparum*	Isaka et al. (2013)
12	Ganoboninketal A	*Ganoderma boninense*	*P. falciparum*	Ma et al. (2014)
13	Ganoboninketal B	*G. boninense*	*P. falciparum*	Ma et al. (2014)
14	Ganoboninketal C	*G. boninense*	*P. falciparum*	Ma et al. (2014)
15	Trametenolic acid B	*Trametes versicolor*	*Leishmania amazonensis*	Leliebre-Lara et al. (2016)
16	Austraeusin M	*Astraeus asiaticus*	*P. falciparum*	Isaka et al. (2017)
17	Ascofuranone	*Ascochyta visiae*	*Trypanosoma vivax*	Yabu et al. (2006)
18	Chevalone D	*Eurotium chevalieri*	*P. falciparum*	Kanokmedhakul et al. (2011)
19	Porialbocin A	*Poria albocincta*	*P. falciparum*	Isaka et al. (2014)
Steroids				
20	5α,8α-Epidioxy-22*E*-ergosta-6,22-dien-3β-ol	*Trametes versicolor*	*L. amazonensis*	Leliebre-Lara et al. (2016)
21	5α,8α-Epidioxy-22*E*-ergosta-6,22-dien-3β-ol	*Pleurotus ostreatus*	*T. cruzi*	Ramos-Ligonio et al. (2012)
22	Ergosterol 5,8-endoperoxide	*Pycnoporus sanguineus*	*Leishmania panamensis*	Correa et al. (2006)
Alkaloids				
23	(6-*S*)-3-(1,3-dihydroxypropyl)-6-(2-methylpropyl)piperazine-2,5-dione	*Trichosporum* sp.	*L. donovani*	Metwaly et al. (2015)
24	(6-*R*)-3-(1,3-dihydroxypropyl)-6-(2-methylpropyl)piperazine-2,5-dione	*Trichosporum* sp.	*L.donovani*	Metwaly et al. (2015)
25	Eurochevalierine	*Eurotium chevalieri*	*P. falciparum*	Kanokmedhakul et al. (2011)
26	Hirsutellone F	*Trichoderma* sp.	*P. falciparum*	Isaka et al. (2006)
27	Ascosalipyrrolidinone A	*Ascochyta salicorniae*	*P. falciparum*	Osterhage et al. (2000)

Table 1 (continued)

No.	Compound	Fungi	Parasite	References
Coumarins				
28	7-Butyl-6,8-dihydroxy-3(*R*)-pent-11-enylisochroman-1-one	*Geotrichum* sp.	*P. falciparum*	Kongsaeree et al. (2003)
29	7-Butyl-6,8-dihydroxy-3(*R*)-pentylisochroman-1-one	*Geotrichum* sp.	*P. falciparum*	Kongsaeree et al. (2003)
Proteins and peptides				
30	Apicidin	*Fusarium* sp.	*Plasmodium berghei* *Eimeria tenella; Toxoplasma gondii* *Besnoitia jellisoni* *N. caninum* *Caryospora bigenetica* *P. falciparum;Cryptosporidium parvum*	Darkin-Rattray et al. (1996)
31	Beauvericin Beauvericin A	*Paecilomyces tenuipes*	*P. falciparum*	Nilanonta et al. (2000)
32	Cardinalisamide A	*Cordyceps cardinalis*	*Trypanosoma brucei brucei*	Umeyama et al. (2014)
33	Cardinalisamide B	*C. cardinalis*	*T. brucei brucei*	Umeyama et al. (2014)
34	Cardinalisamide C	*C. cardinalis*	*T. brucei brucei*	Umeyama et al. (2014)
35	Paecilodepsipeptide A	*Paecilomyces cinnamomeus*	*P. falciparum*	Isaka et al. (2007a)
36	Hirsutellic acid A	*Hisutella* sp	*P. falciparum*	Thongtan et al. (2006)
37	Pullularin A	*Pullularia* sp.	*P. falciparum*	Isaka et al. (2007b)
Quinones				
38	Cercosporin	*Mycosphaerella* sp.	*L. donovani*; *T.cruzi*; *P.falciparum*	Moreno et al. (2011)
39	3,5,8-Trihydroxy-6-methoxy-2-(5-oxohexa-1,3-dienyl)-1,4-naphthoquinone	*Cordyceps unilateralis*	*P. falciparum*	Kittakoop et al. (1999)
Other compounds				
40	Preussomerin EG1	*Edenia* sp.	*L. donovani*	Martínez-Luis et al. (2008)
41	Palmarumycin CP2 Palmarumycin CP17	*Edenia* sp.	*L. donovani*	Martínez-Luis et al. (2008)
42	Palmarumycin CP18	*Edenia* sp.	*L. donovani*	Martínez-Luis et al. (2008)
43	CJ-12,371	*Edenia* sp.	*L. donovani*	Martínez-Luis et al. (2008)
44	Agrocybin	*Agrocybe perfecta*	*T. cruzi*	Rosa et al. (2006)
45	Mollicellin C Mollicellin E	*Chaetomium brasiliense*	*P. falciparum*	Khumkomkhet et al. (2009)
46	Mollicellin K Mollicellin L	*C. brasiliense*	*P. falciparum*	Khumkomkhet et al. (2009)
47	Mollicellin M Mollicellin B	*C. brasiliense*	*P. falciparum*	Khumkomkhet et al. (2009)
48	Mollicellin J	*C. brasiliense*	*P. falciparum*	Khumkomkhet et al. (2009)

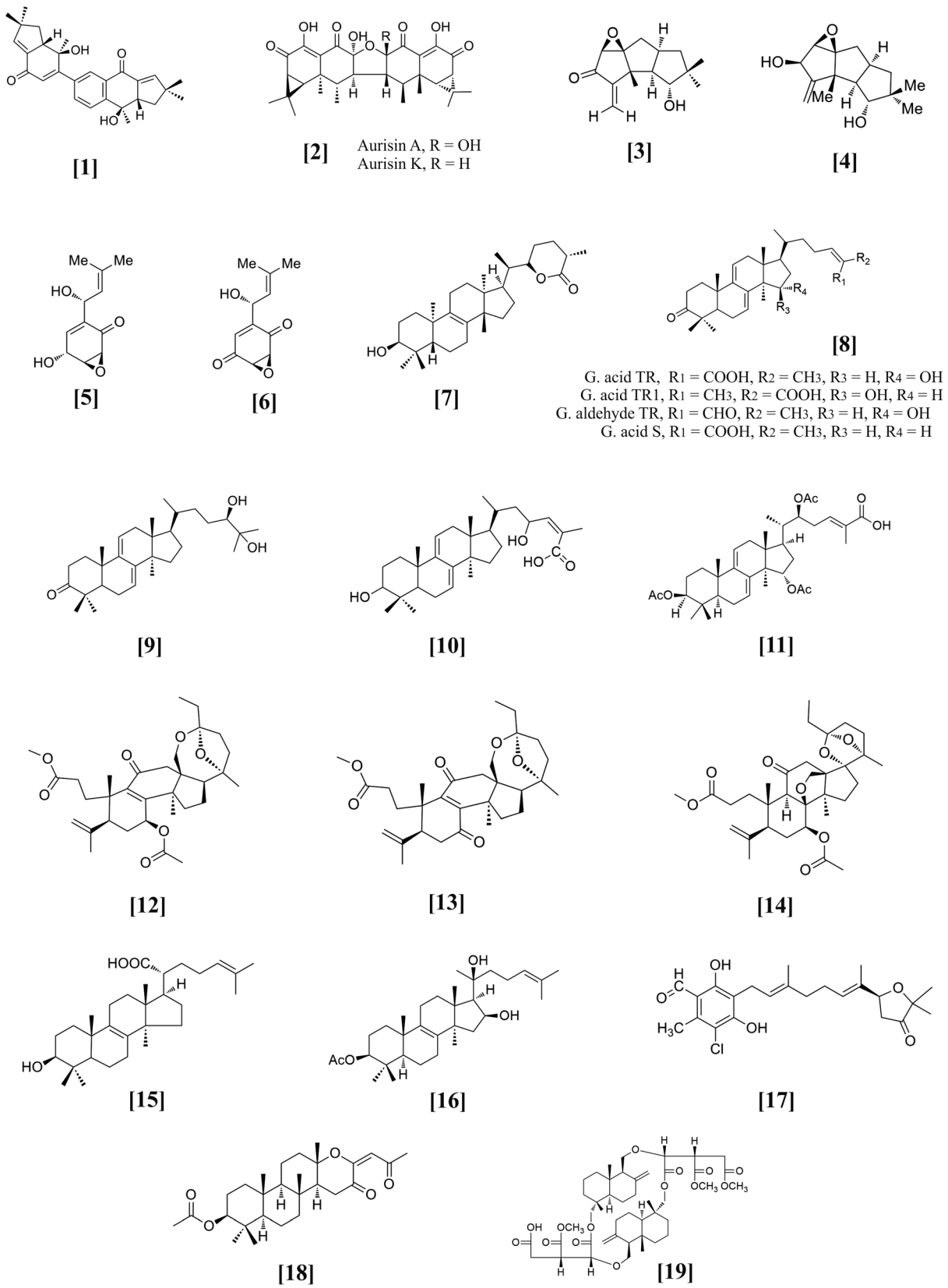
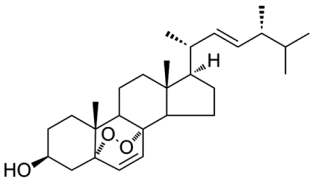


Fig. 1 Structures of fungal compounds with antiparasitic action

Steroids



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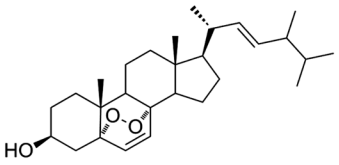

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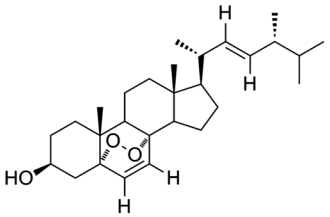

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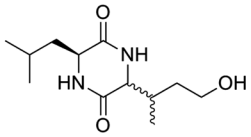
Alkaloids



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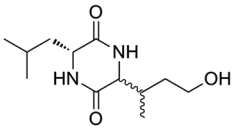

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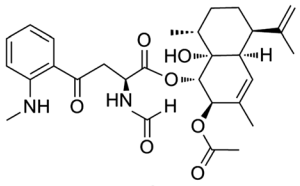

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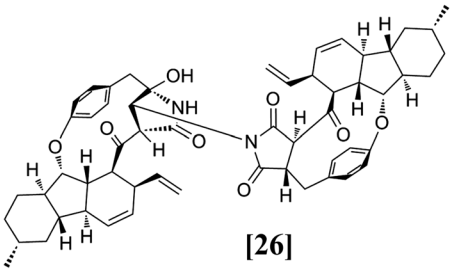

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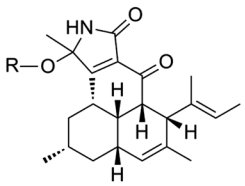
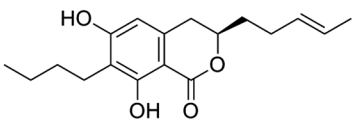


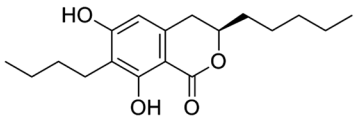
R = - $CH_2CH_2CH_2CH_3$ (C-24 to C-27)

[27]

Coumarins

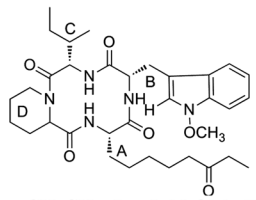


[28]



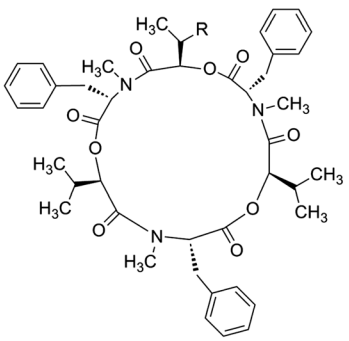
[29]

Proteins and peptides



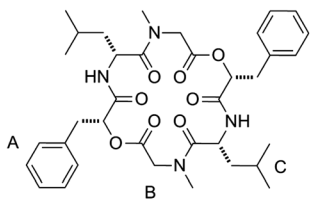
A = CH_2CH_3; B = L-N-OMe-Trp;
C = L-Ile; D = D-Pip

[30]



Beauvericin, R = CH_3
Beauvericin A, R = CH_2CH_3

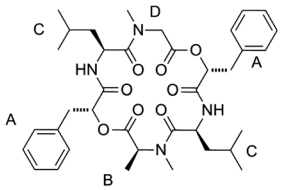
[31]



A = D-Pla; B = NMe-Gly; C = D-Leu

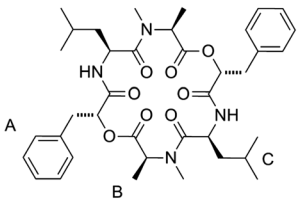
[32]

Fig. 1 (continued)



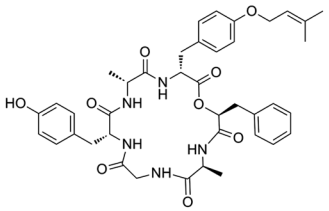
A = D-Pla; B = L-NMe-Ala;
C = L-Leu; D = NMe-Gly

[33]

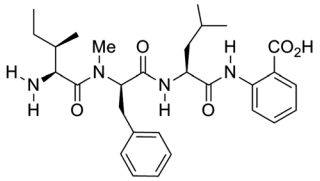


A = D-Pla; B = L-NMe-Ala; C = L-Leu

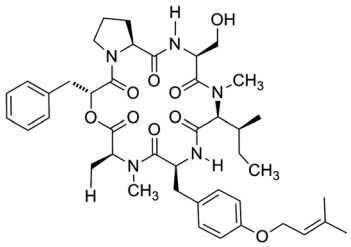
[34]



[35]

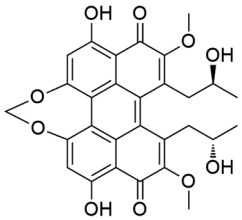


[36]

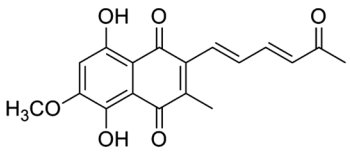


[37]

Quinones

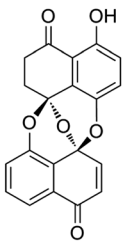


[38]

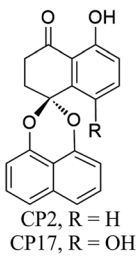


[39]

Other compounds

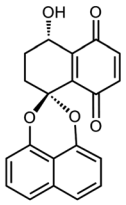


[40]

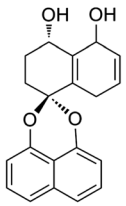


CP2, R = H
CP17, R = OH

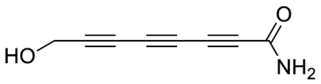
[41]



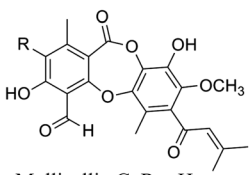
[42]



[43]

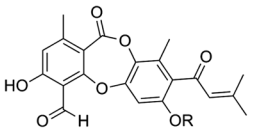


[44]



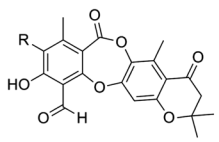
Mollicellin C, R = H
Mollicellin E, R = Cl

[45]



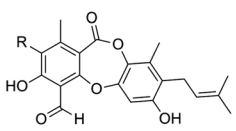
Mollicellin K, R = H
Mollicellin L, R = CH_3

[46]



Mollicellin M, R = Cl
Mollicellin B, R = H

[47]



Mollicellin J, R = Cl

[48]

Fig. 1 (continued)

against *P. falciparum* with IC_{50} values of 0.80 and 0.61 μg/mL, respectively, and also showed cytotoxicity against NCI-H187 cancer cell lines and cholangiocarcinoma cell lines (Kanokmedhakul et al. 2012). These compounds, besides aurisin G [2], have also been isolated from *Anthracophyllum* sp. They have demonstrated antimalarial activity against *P. falciparum*, with IC_{50} values of 1.43, 0.69, and 0.27 μM for aurisin A, K, and G [2], respectively (Intaraudom et al. 2013).

Lentinus species can produce a high diversity of sesquiterpenes. The ethyl acetate extract of the *Lentinus strigosus* inhibited 100% of trypanothione reductase (TR) at 20 μg/mL. From this extract, the sesquiterpene hypnophilin [3] was isolated, with high antiparasitic activity against *T. cruzi* and inhibition of the TR enzyme (IC_{50} 0.8 μM). This enzyme is a molecular target as it is essential to the metabolism of *Trypanosoma* and *Leishmania* species, so the inhibition of this enzyme leads the parasite to death. The molecule tested against amastigotes forms showed an IC_{50} value of 2.5 μM, indicating that it represents a good antiparasitic agent. The author also speculates on the structure-activity relationship regarding the mechanism of inhibition of TR, where conjugated carbonyls may suffer nucleophilic attack by the thyol group present at the active site of TR (Cota et al. 2008). The research of Souza-Fagundes et al. (2010) corroborates with this result, showing the inhibition of the TR enzyme by hypnophilin [3] extracted from *L. strigosus*. The author also tested the molecule panepoxydone [5], also extracted from *L. strigosus*, which showed slightly lower results than hypnophilin [3] (IC_{50} values of 47.6 and 40.3 μM, respectively). When panepoxydone [5] and hypnophilin [3] were tested against amastigote forms of *T. cruzi* and amastigote-like forms of *L. amazonensis*, hypnophilin [3] showed greater inhibition against *T. cruzi* amastigotes than panepoxydone [5] (EC_{50} values of 0.66 and 1.79 μg/mL, respectively). On the other hand, panepoxydone [5] showed better results than hypnophilin [3] for the *L. amazonensis* amastigote-like form (EC_{50} values of 0.84 and 3.99 μg/mL, respectively). Panepoxydone [5] was also found to inhibit PBMC cell proliferation, indicating that the molecule has cytotoxic activity. Based on these studies, the molecule hypnophilin [3] shows promising results for *T. cruzi* inhibition, which makes it a good candidate for the treatment of Chagas disease. Rukachaisirikul et al. (2005) isolated several sesquiterpenes from the fungus *Lentinus connatus*. The ethyl acetate extract showed antiplasmodial activity against *P. falciparum* with an IC_{50} value of 3.1 μg/mL, while the most active compounds were panepoxydone [5], panepoxydione [6], and dihydrohypnophilin [4] with (IC_{50}) values of 3.4, 2.1, and 3.1 μg/mL, respectively. Dihydrohypnophilin [4] is the dihydro derivative of the molecule hypnophilin [3] found in *L. strigosus*. These results indicate that hypnophilin [3] and its derivatives are good sources of antiparasitic drugs.

[b]. Antiparasitic diterpenes produced by plants have been extensively studied and reported in the literature. Fungi also produce diterpenes. However, no research on the application of diterpenes produced by fungi as antiparasitic agents could be found. The fungus *Gibberella fujikuroi* cultivated in mineral medium produces the diterpene kaurenoic acid (Jennings et al. 1993). In an extract of the marine fungus *Chromocleista* sp., the diterpene agathic acid has been identified (Park et al. 2006). Kaurenoic acid and agathic acid show antiparasitic activity against *T. cruzi* (Izumi et al. 2012) when extracted from the leaves of *Copaifera oleoresins*. An extract of *Pestalotiopsis adusta*, an endophytic fungus, provided the diterpene uncinatone. Tests performed with material from the plant *Clerodendrum eriophyllum* containing uncinatone presented antiparasitic activity against *L. donovani* and *P. falciparum* (Xu et al. 2016).

[c]. Basidiomycete fungi can produce a wide variety of triterpenes. Most of them are of the type lanostane, with many different forms of biological activity including anticancer and antiparasitic. Triterpenoids are very common antiparasitic agents. Nyongbela et al. (2013) isolated the triterpenoid estersaponin from the plant *Pittosporum mannii*, which presented antiparasitic activity against *P. falciparum* and *L. donovani*. These molecules are also found in *Cornus florida*, which is used popularly to treat malaria. However, in one study, the terpenes extracted from the bark presented a more potent action against *Leishmania tarentolae*. The most active molecules were the triterpenes ursolic acid, 3β-O-acetyl betulinic acid, 3-epideoxyflindissol, and 3β-O-trans-coumaroyl betulinic acid (Graziose et al. 2012).

The Indian mushroom *Astraeus hygrometricus* produces astrakurkurone [7] (Mallick et al. 2014), a triterpene which presents antileishmanial activity against *L. donovani* (Lai et al. 2012). The hypothesis proposed is that the molecule induces the production of reactive oxygen species (ROS), which leads to mitochondrial dysfunction causing the death of the parasite. Moreover, astrakurkurone [7] causes intracellular lipid accumulation that can cause alterations in the metabolism and plasma membrane of the parasite (Lai et al. 2012; Mallick et al. 2015). *Ganoderma* species are white rot basidiomycetes that present several medicinal uses, including antiparasitic activity. Adams et al. (2010) found that *Ganoderma lucidum* produces triterpene lanostanes that are active against *P. falciparum*. The ethyl acetate extract showed antiplasmodial activity, with 79% inhibition at 4.9 μg/mL. In this extract were identified seven lanostanes [compounds 8, 9, 10], being the most active the compound 3, named by the authors as ganoderic aldehyde TR [8], with an IC_{50} value of 6 μM. It was followed by compound 4, named ganoderic acid

S [8], and by compound 7, named 23-hydroxyganoderic acid S [10], both with IC_{50} values of 11 μM. The C3 epimer of ganoderic acid T [11] from *Ganoderma orbiforme* presented antiplasmodial activity against *P. falciparum* K1 (IC_{50} = 4.6 μM) (Isaka et al. 2013). The medicinal mushroom *Ganoderma boninense* produces three nortriterpenes ganoboninketals A [12], B [13], and C [14], which were tested against *P. falciparum*, showing IC_{50} values of 4.0, 7.9, and 1.7 μM, respectively (Ma et al. 2014). These compounds were evaluated for their cytotoxicity toward A549 and HeLa cells. Ganoboninketals A [12] and C [14] showed low cytotoxicity toward the A549 cell line, while ganoboninketal B [13] showed low cytotoxicity against HeLa cells (Ma et al. 2014). It is important to understand that an antiparasitic compound should show low cytotoxicity toward human cells, as the aim is to damage the parasite cells and not the host cells.

Different basidiomycetes can produce the lanostane triterpene. Leliebre-Lara et al. (2016) isolated the compound trametenolic acid B [15] from the *n*-hexane extract of the mushroom *T. versicolor*. The activity of trametenolic acid B [15] against *L. amazonensis* promastigotes and amastigotes showed IC_{50} values of 2.9 and 1.6 μM for promastigotes and amastigotes, respectively, with a low cytotoxicity toward peritoneal macrophages from BALB/c mice. The molecule was found to be more potent against amastigote forms when compared to the positive drug control, pentamidine (IC_{50} 3.8 μM). The author suggested that the compound acts by interfering in steroid composition and biosynthesis in the plasma membrane of the parasite, leading to parasite death. A new triterpene with the lanostane skeleton, austraeusin M [16], isolated from *Astraeus asiaticus*, a very popular edible mushroom in Thailand and other Asian countries, showed antimalarial activity against *P. falciparum* K1, with IC_{50} value of 3.0 μg/mL (Isaka et al. 2017).

[d]. Meroterpenoids are hybrid molecules that partially originate from the terpenoid pathway. Fungi are able to synthesize a wide variety of biologically active meroterpenoids with the most diverse uses (Matsuda and Abe 2016). Ascofuranone [17] is a meroterpenoid produced by several species of ascomycetes. Originally used as an antitumor agent, this molecule isolated from *Ascochyta visiae* showed trypanocidal activity in *Trypanosoma vivax*-infected mice without the use of glycerol. Ascofuranone [17] works by inhibiting the ubiquinol oxidase of the respiratory chain of the parasite, and a single dose of 50 mg/kg was able to cure the infected mice (Yabu et al. 2006). Ascofuranone [17] is also effective against the African trypanosomiasis caused by *T. brucei*. Mice infected with the parasite were cured after day 4 of treatment with intraperitoneal doses of 100 mg/kg (Yabu et al. 2003). The meroterpenoid chevalone D [18] isolated from the fungus *Eurotium chevalieri* showed antiplasmodial activity against *P. falciparum*, with an IC_{50} value of 3.1 μg/mL (Kanokmedhakul et al. 2011).

The terpene porialbocin A [19], derived from cryptoporic acid, does not fall within the above classification. This molecule was obtained from the mycelial extract of the fungus *Poria albocincta* and was fractionated by column chromatography and preparative HPLC. The compound was tested for antimalarial activity against *P. falciparum* K1 and cytotoxic action against cancer cell lines and nonmalignant Vero cells. Porialbocin A [19] showed antiplasmodial activity (IC_{50} 6.3 μg/mL) and cytotoxic activity of the same magnitude (IC_{50} 5.3 μg/mL) (Isaka et al. 2014).

Steroids

All organisms produce steroids, and they are an important source of biologically active compounds for drug research, as they have the ability to penetrate cell membranes and bind to nuclear and membrane receptors. It is reported that they can have strong antitumoral activity against several types of cancer (Gupta et al. 2013) as well as anti-inflammatory, antimicrobial (Correa et al. 2014), and antiviral (Shamsabadipour et al. 2013) action.

Ergosterol is the major sterol in the membranes of the parasite *T. cruzi*. Fungi also produce ergosterol which can cause a disruption in the plasma membrane steroid metabolism of the parasite. Ergosterol was extracted from the fungus *Pleurotus salmoneostramineus* and tested in *T. cruzi*, showing an IC_{50} value of 51.3 μg/mL against trypomastigotes with no hemolysis and no cytotoxicity toward BALB/c peritoneal macrophages at the maximum concentration (200 μg/mL) (Alexandre et al. 2017). Besides ergosterol, the ergosterol peroxide is widely produced by fungi and has many biological properties, among them immune-suppressive, antimycrobial, antiviral, anti-inflammatory, and antitumoral action (Krzyczkowski et al. 2009). The ergostane 5α,8α-epidioxy-22*E*-ergosta-6,22-dien-3β-ol [20] extracted from the *n*-hexane extract of the fungus *T. versicolor* was tested against promastigotes and amastigotes of *L. amazonensis* (Leliebre-Lara et al. 2016). The molecule [20] (IC_{50} for promastigotes of 13.9 μM and IC_{50} for amastigotes of 4 μM) showed a slightly lower potency than the control drug pentamidine (IC_{50} for promastigotes of 1.2 μM and IC_{50} for amastigotes of 3.8 μM). Leliebre-Lara et al. (2016) explored the ability of steroids to penetrate and interfere with cell membranes, where the molecule would act by interfering in steroid composition and biosynthesis in the plasma membrane of the parasite, leading to parasite death. The ergostane 5α,8α-epidioxy-22*E*-ergosta-6,22-dien-3β-ol [21] is also produced by the fungus *Pleurotus ostreatus*, and it was tested against the parasite *T. cruzi* (Ramos-Ligonio et al. 2012). The molecule showed

an IC_{50} value of 6.74 μg/mL and caused disruption in the parasite plasma membrane without causing hemolysis, and the molecule did not show cytotoxicity toward HeLa cells. Ergosterol peroxide is very similar to the ergosterol present in the plasma membrane of the parasite, and when the peroxide bond is broken, it can cause the production of reactive oxygen species in the cytoplasm, which can lead to the disruption of the plasma membrane of the parasite.

The fungus *P. sanguineus* also produces antiparasitic ergosterols. The molecule ergosterol 5,8-endoperoxide [22] was isolated from the acetone extract of fresh fruiting bodies of the fungus and evaluated regarding its antiparasitic action against *L. panamensis*. The hexane and acetone extracts were tested to determine their antiparasitic and cytotoxic activity. The isolated compound showed better activity (EC_{50} 4.1 μg/mL) than the drug Glucantime® control (EC_{50} 6.7 μg/mL). Although effective against the parasite, the hexane and acetone extracts were more cytotoxic when compared to the isolated molecule [22]. The acetone extract showed higher antiparasitic activity than the isolated molecule [22], which suggests that there are other antiparasitic molecules in the extract (Correa et al. 2006).

Alkaloids

There is a huge diversity of alkaloids, which provide innumerous drugs for human use. They are secondary metabolites produced by a high diversity of plants and fungi, and have several medicinal uses. Alkaloids have shown effective antiparasitic action in studies with plant extracts (Mishra et al. 2009). It is known that alkaloids produced by fungi show antimicrobial, insecticidal, cytotoxic, and anticancer activities (Dembitsky 2014). However, little research has been carried out on antiparasitic alkaloids produced by fungi. In a study by Samoylenko et al. (2009), the methanolic extract of the plant *Albizia schimperiana* was obtained four alkaloids with antiplasmodial activity (IC_{50} of 120–160 ng/mL). Two of these alkaloids showed no cytotoxicity against mammalian kidney fibroblasts. It has been suggested that a hydroxyl substitution of the side chain of the budmunchiamines reduced the cytotoxicity without decreasing the antiplasmodial activity of these compounds. *Citropsis articulata* is a plant which also shows antiplasmodial activity. Lacroix et al. (2011) tested the EtOAc extract of the root bark against *P. falciparum*, and it showed 70% growth inhibition at a concentration of 10 μg/mL. Among the 11 compounds isolated from this extract, the compound 5-hydroxynoracronycine and 1,5-dihydroxy-2,3-dimethoxy-10-methyl-9-acridone showed the best results in the antiplasmodial assay, with IC_{50} values of 0.9 and 3.0 μg/mL, respectively. These compounds also provided the lowest cytotoxicity values (9.3 and 30.5 μg/mL, respectively), and thus, they are promising antiplasmodial alkaloids, especially the compound 5-hydroxynoracronycine, when compared with the positive control (IC_{50} 0.1 μg/mL).

Fungi can produce a high diversity of alkaloids. Diketopiperazine alkaloids produced by fungi have several biological uses (Lu et al. 2014). The endophytic fungus *Trichosporum* sp. is able to synthesize antileishmanial diketopiperazine alkaloids. Diketopiperazine alkaloids also show antiparasitic activity against *L. donovani*. According to Metwaly et al. (2015), the diketopiperazine alkaloid isomers identified as (1,3-dihydroxypropyl)-6-(2-methylpropyl)piperazine-2,5-dione; 6S [23] and 6R [24], have antileishmanial activity, and showed IC_{50} values of 96.3 and 82.5 μg/mL, respectively.

The sesquiterpenoid alkaloid eurochevalierine [25] was isolated from the fungus *Eurotium chevalieri* after 40 days of cultivation. The isolate showed antiplasmodial activity against *P. falciparum* with an IC_{50} value of 3.4 μg/mL (Kanokmedhakul et al. 2011). *Trichoderma* species can also synthesize antiplasmodial alkaloids. Hirsutellone F [26], besides its antitubercular activity, exhibited moderate activity against *P. falciparum* with an IC_{50} value of 4.2 μg/mL (Isaka et al. 2006). Ascosalipyrrolidinone A [27] is an alkaloid isolated from the marine fungus *Ascochyta salicorniae*, and this molecule has shown activity against K1 and NF54 strains of *P. falciparum*, with IC_{50} values of 736 and 378 ng/mL, respectively. It also presented activity against *T. brucei rhodesiense* and *T. cruzi*, with IC_{50} values of 30 and 1.1 μg/mL, respectively (Osterhage et al. 2000).

Coumarins

Coumarins are widely produced by plants and fungi. They show several types of biological activity including antioxidant, antibacterial, antiviral, anti-inflammatory, antinociceptive, antidepressant, antitumor, antiasthmatic, hepatoprotective, antiallergic, and antifungal action as well as the inhibition of serine protease and HIV (Costa et al. 2016). Coumarins derived from fungi have been the subject of only sparse research with regard to their antiparasitic activity. However, antiparasitic coumarins derived from plants have been extensively studied. Coumarins isolated from the aerial parts of *Ferulago angulate* and fruits of *Prangos asperula* showed activity against *L. major*. Osthol, the coumarin extracted from fruit, showed the best result with an IC_{50} value of 14.4 μg/mL. Suberosin epoxide and suberosin extracted from *F. angulate* showed low leishmanicidal activity. After 48 h, suberosin showed better activity than suberosin epoxide, which may be due to the prenyl substituent located at C-8 (Sajjadi et al. 2016). Prenylation seems to increase the antiparasitic power of compounds, since isoprenylated coumarins extracted from the stem bark of *Mesua bornensis* showed antiparasitic activity against *P. falciparum*. Three coumarins, mammea A/BA, mammea A/AA cyclo D, and mesuol,

provided IC_{50} values of 3.72, 1.02, and 8.81 μg/mL, respectively. Mammea A/AA cyclo D was found to be as potent as the control drug chloroquine (IC_{50} 1.03 μg/mL), indicating its potential as an antiparasitic drug. The *n*-hexane and ethyl acetate extracts were also tested, and only the ethyl acetate extract presented activity, with an IC_{50} value of 23.56 μg/mL.

Kongsaeree et al. (2003) studied the antimalarial activity of coumarins produced by fungi. Three new dihydroisocoumarins were isolated from the endophytic fungus *Geotrichum* sp. and tested against multidrug-resistant *P. falciparum*. Two out of the three molecules, 7-butyl-6,8-dihydroxy-3(R)-pent-11-enylisochroman-1-one [28] and 7-butyl-6,8-dihydroxy-3(*R*)-pentylisochroman-1-one [29], presented activity against the parasite, with IC_{50} values of 4.4 and 2.6 μg/mL, while 7-but-15-enyl-6,8-dihydroxy-3(*R*)-pent-11-enylisochroman-1-one did not show antiparasitic activity. Compound [28] also showed antimicrobial activity against *Mycobacterium tuberculosis* and *Candida albicans*, while compound [29] showed activity against *C. albicans*. The crude extract of the fungus was also active, with an IC_{50} value of 0.63 μg/mL, which is higher than the values obtained for the isolated molecules. A slight change in the carbon bonds can make a considerable difference in terms of the antiparasitic action. The only difference between compounds 7-but-15-enyl-6,8-dihydroxy-3(*R*)-pent-11-enylisochroman-1-one and 7-butyl-6,8-dihydroxy-3(*R*)-pentylisochroman-1-one [29] are the two double bonds present in the prenyl groups of 7-but-15-enyl-6,8-dihydroxy-3(*R*)-pent-11-enylisochroman-1-one, which leads to the activity of compound [29] and total lack of activity of 7-but-15-enyl-6,8-dihydroxy-3(*R*)-pent-11-enylisochroman-1-one.

Proteins and peptides

Proteins and peptides have a wide range of biological functions and display several types of activity. Marr et al. (2017) propose peptides as new drug candidates for antileishmanial treatment. The tetrapeptide apidicin [30] exhibits in vitro and in vivo antiprotozoal activity against drug-resistant *Plasmodium berghei* (Darkin-Rattray et al. 1996). It is also effective in vitro against the parasites *E. tenella*, *T. gondii*, *Besnoitia jellisoni*, *N. caninum*, *Caryospora bigenetica*, *P. falciparum* (chloroquine-resistant strain), and *Cryptosporidium parvum*. This molecule [30] is a product of the metabolism of the fungus *Fusarium* spp., and it is postulated that it inhibits histone deacetylase in the parasite, which induces the hyperacetylation of histones, impairing the transcription of DNA and, consequently, the reproduction of the parasite (Darkin-Rattray et al. 1996).

The fungi *Tolypocladium niveum*, *Emericellopsis salmosynnemata*, and *Emericellopsis poonensis* produce the antibiotic peptides efrapeptins, zervamicins, and antiamoebin, respectively. These peptides were studied with regard to their effect against *P. falciparum*, and IC_{50} values of 4.72, 1.21, and 0.45 μM were obtained for antiamoebin, efrapeptins, and zervamicins, respectively. Efrapeptins are known to be inhibitors of mitochondrial F0F1 ATPase, bacterial ATP synthases, and photophosphorylation in plants, while zervamicins and antiamoebins are known to act as uncouplers of mitochondrial oxidative phosphorylation. The three peptides can act as channel-forming ionophores. Therefore, these molecules could cause death to the parasite through the dissipation of the mitochondrial membrane potential (Nagaraj et al. 2001).

Beauvericin [31] is an insecticide isolated from many fungal species including *Beauveria bassiana*, *Paecilomyces fumosoroseus*, *Polyporus sulphureus*, and *Fusarium* sp. In studies by Nilanonta et al. (2000), the cyclodepsipeptides beauvericin [31] and beauvericin A [31] (which is similar to beauvericin) were extracted from the fungus *Paecilomyces tenuipes*. Both molecules showed activity against the *M. tuberculosis* and moderate in vitro activity against the parasite *P. falciparum* with EC_{50} values of 1.6 and 12 μg/mL, respectively. Cyclodepsipeptides also show activity against *T. brucei brucei*. In studies by Umeyama et al. (2014), the cyclodepsipeptides cardinalisamides A [32], B [33], and C [34] were extracted from the fungus *Cordyceps cardinalis* using methanol as the solvent. The molecules showed antitrypanosomal activity with IC_{50} values of 8.56, 8.65, and 8.63 μg/mL, respectively. Paecilodepsipeptide A [35] is a cyclodepsipeptide isolated from the fungus *Paecilomyces cinnamomeus* (Isaka et al. 2007a). This molecule exhibited antiplasmodial activity against a multidrug-resistant strain of *P. falciparum*, with an IC_{50} value of 4.9 μM. It was also active against KB and BC cancer cell lines; however, it showed no action against Vero cells (Isaka et al. 2007a). The cyclodepsipeptide pullularin A [37], one of the five molecules extracted from the endophytic fungus *Pullularia* sp., showed the best antiparasitic activity against *P. falciparum*, with an IC_{50} value of 3.6 μg/mL (Isaka et al. 2007b). This molecule [37] also showed antiviral activity against the herpes simplex virus-type I (HSV-1) and presented low cytotoxicity toward noncancer Vero cells and no activity against KB, BC, and NCI-H187 cancer cell lines. Given its low cytotoxicity, pullularin A [37] is a promising drug candidate, since most of the drugs used to treat malaria are highly cytotoxic (Isaka et al. 2007b). The mechanism involved in the inhibition of the parasite by cyclodepsipeptides is still unknown, and thus, further studies need to be conducted on these promising molecules.

Hirsutellic acid A [36] is a linear tetrapeptide extracted from the fungus *Hisutella* sp. This molecule [36] shows activity against a chloroquine-resistant strain of *P. falciparum* (IC_{50} 8.0 μM) and no cytotoxic toward Vero cells. Hirsutellic acid A [36] is also inactive against KB, BC, and NCI-H187 cancer cell lines (Thongtan et al. 2006). Amaurocine is a 12 kDa protein produced by the basidiomycete *Amauroderma*

camerarium with 39 peptide sequences that was tested against *Trichomonas vaginalis* from three isolates. The minimal inhibitory concentration (MIC) values were 2.6 μM against the strain ATCC isolate 30236 and 5.2 μM against the fresh clinical isolates TV-LACH1 and TV-LACM2. Furthermore, this protein was tested with regard to its cytotoxicity toward neutrophils, and it showed slight cytotoxicity and stimulated nitric oxide release from the neutrophils. Duarte et al. (2016) suggests that the mechanism of inhibition is similar to that of the ATP-dependent RNA helicase MAK5 found in *Amauroderma dermatitidis*, which is similar to amaurocine. The helicase molecule is involved in post-transcriptional and translational processes and may work by disrupting these processes in the parasite (Duarte et al. 2016).

Quinones

Quinones are a functional group of molecules commonly used as dyes, despite their biological diversity. Cercosporin [38] is a perylenequinone, a natural product present in endophytic fungal species. Martinez-Luiz et al. (2011) isolated cercosporin [38] from *Edenia* sp. and tested its action against *P. falciparum*, *L. donovani*, and *T. cruzi*. Cercosporin [38] was found to be active against these parasites, with IC_{50} values of 1.03, 0.46, and 1.08 μM, respectively. The molecule [38] also presented cytotoxicity toward the breast cancer cell line MCF-7 (IC_{50} 4.68 μM). Moreno et al. (2011) isolated cercosporin [38] and other five compounds from the endophytic fungus *Mycosphaerella* sp. The authors tested it against *P. falciparum*, *L. donovani*, *T. cruzi*, and the breast cancer cell line MCF-7 and obtained IC_{50} values of 1.03, 0.46, 1.08, and 4.68 μM, respectively. The cercosporin [38] also showed high cytotoxicity toward Vero cells. To improve these results, in both studies, cercosporin [38] was acetylated and the effect of this modification on the assays was investigated. However, the modification slightly improved the antiparasitic activity only in the case of *T. cruzi* and only slightly decreased the cytotoxicity in both studies. Therefore, it is necessary to study other modifications in the molecule structure in order to produce a molecule with high antiparasitic activity and low cytotoxicity.

Kittakoop et al. (1999) isolated six naphtoquinones: erythrostominone (A), deoxyerythrostominone (B), 4-*O*-methyl erythrostominone (C), epierythrostominol (D), deoxyerythrostominol (E), and erythrostominone 1 (F) from the fungus *Cordyceps unilateralis*. All of these compounds presented activity against *P. falciparum* with EC_{50} values of 4.0, 7.5, 10.1, 7.0, 8.5, and 2.5 μg/mL, respectively. Compounds A–E exhibited cytotoxicity against BC, KB, and Vero cell lines. However, the compound 3,5,8-trihydroxy-6-methoxy-2-(5-oxohexa-1,3-dienyl)-1,4-naphthoquinone [39] did not present cytotoxicity against these cell lines. The absence of cytotoxicity and the antiplasmodial activity makes the molecule [39] a good candidate for the treatment of malaria.

β-Glucans

β-Glucans is the name given to a group of heterogeneous polysaccharides formed by long chains of polymers of (1–3)-β-linked glucose, which are naturally present in bacteria, algae, fungi, and plants. Their remarkable range of biological activities provides several health benefits, such as hypocholesterolemic, hypoglycemic, antitumoral, and immunomodulator (Barsanti et al. 2011).

It has been demonstrated that β-glucans protect against infection and protozoa in several experimental models. Research realized by Goldman and Jaffe (1991) indicated that β-glucan from *Saccharomyces cerevisiae* were effective in the lesion reduction caused by *L. major* in genetically susceptible BALB/c mice. The injection of 50 μg of β-glucans showed a substantial effect in the treatment of the lesions. When 400 μg of β-glucans were used, it prevents the initial stages of lesion formation (Goldman and Jaffe 1991). The protective effect of β-glucans was observed in cases of experimental infection with *T. gondii*, *P. berghei*, and *T. cruzi* (Novak and Vetvicka 2009).

Other compounds

Fungi produce a diversity of molecules that have the potential to be used medicinally. The naphthalene-derivative molecules preussomerin EG1 [40], palmarumycin CP2 [41], palmarumycin CP17 [41], palmarumycin CP18 [42], and CJ-12,371 [43], extracted from the endophytic fungus *Edenia* sp., were tested against *L. donovani*, *P. falciparum*, and *T. cruzi* (Martínez-Luis et al. 2008). All of these molecules showed antiparasitic activity against *L. donovani* with IC_{50} values of 0.12, 3.93, 1.34, 0.62, and 8.40 μM, respectively. Although preussomerin EG1 [40] showed the best antiparasitic activity against *L. donovani* and *P. falciparum* (IC_{50} 16.5 μM), it also showed a high cytotoxicity toward Vero cells (IC_{50} 9 μM). The molecule palmarumycin CP18 [42] was also effective against *L. donovani* and showed lower cytotoxicity toward Vero cells (IC_{50} 152 μM). These findings suggest that this molecule [42] is a good candidate for future drugs against *L. donovani*.

Rodrigues et al. (2014) discovered a new function for the molecule kojic acid, a secondary metabolite extracted from the fungus *Aspergillus* sp. and traditionally used in cosmetics for skin whitening. Kojic acid was tested in vitro and in vivo against *L. amazonensis* and proved to be effective in vitro against promastigotes and amastigotes of *L. amazonensis*, with IC_{50} values of 34 and 27.84 μg/mL, respectively. Studies performed in vitro showed that the kojic acid was able to cause structural alterations and reverse the inhibition of

superoxide anions (O_2^-) promoted by the parasite. In in vitro studies, kojic acid stimulated the healing process through the production of collagen fibers at the infection site and decreased the parasite burden.

Agrocybin [44] is a polyacetylene metabolite produced by the basidiomycete fungus *Agrocybe perfecta* (Rosa et al. 2006). The molecule was tested with regard to its effect on trypanothione reductase from *T. cruzi* and showed an IC_{50} value of 2 μM. Although effective against the enzyme, agrocybin [44] caused the death of only 60% of the trypomastigote form of *T. cruzi*, even at high doses. These authors suggest that this low activity could be due to the low temperature used to mimic banked blood or due to its inactivation by the blood (Rosa et al. 2006).

From the fungus, *Chaetomium brasiliense* were isolated 10 depsidone molecules, which were tested against *P. falciparum.* Mollicellins K [46], L [46], M [47], B [47], C [45], E [45], and J [48] were active with IC_{50} values of 1.2, 3.4, 2.9, 4.7, 9.1, 3.2, and 4.9 μg/mL, respectively (Khumkomkhet et al. 2009). These molecules were evaluated against KB, BC1, and NCI-H187 cancer cell lines. Mollicellin K [46] provided the best antiplasmodial result, but it also had a high cytotoxicity toward the three cancer cell lines. Mollicellin L [46] showed no cytotoxicity toward KB and BC1 cell lines, and thus, it is the best candidate for further research (Khumkomkhet et al. 2009).

Crude extracts

There are many molecules with antiparasitic activity produced by fungi. However, in some cases, it is not possible to isolate the active molecule or there is more than one active molecule, which may act synergistically. Rosa et al. (2009) studied the action of basidiomycete fungi, collected in the Atlantic forest, against *T. cruzi* and *L. amazonensis*. The majority of the fungi studied showed in vitro activity against the parasites. The fungi with antiparasitic activity above 60% were considered active. *Gymnopilus areolatus*, *Irpex lacteus*, *L. strigosus*, *Nothopanus hygrophanus*, and *Pleurotus flabellatus* showed activity against *L. amazonensis*, *Agaricus nigrecentulus*, *Agaricus trinitatensis*, *Agrocybe perfecta*, *Coprinus* sp., *G. areolatus*, *Gymnopilus aureobrunneus*, *Lepiota* sp., *Leucoagaricus cinereus*, *Pluteus cubensis*, *Marasmius cladophyllus*, *Nothopanus hygrophanus*, *Cymatoderma dendriticum*, *Climacodon pulcherrimus*, *Gloeoporus* sp., *Merulius corium*, *L. strigosus*, *L. villosus*, *Lentinus zeyheri*, *P. sanguineus*, *Tyromyces* sp., *Phellinus gilvus*, *I. lacteus*, *Peniophora cinerea*, and *Pleurotus flabellatus* showed activity against *T. cruzi*. These findings are notable due to the high number of fungi that showed antiparasitic activity, which suggests the existence of many more fungi species presenting this type of activity, opening considerable areas for further research.

Pleurotus sajor-caju is rich in compounds with previously reported bioactivity, such as triterpenes, sterols, alkaloids, flavonoids, tannins, proteins, vitamins, minerals, and fatty acids. The aqueous extract of *P. sajor-caju* was used to treat *Trypanosoma congolense*-infected mice for 5 days. The dosages used were 100, 150, 200, and 250 mg/kg. The mice treated with 100 and 150 mg/kg died before day 60 post-treatment. However, mice treated with 200 and 250 mg/kg showed 50 and 100% cure rates, respectively, and remained aparasitemic until day 68 post-infection (Ademola and Odeniram 2017). Martinez-Luis et al. (2011) tested extracts of 25 isolates of Panamanian endophytic fungi against *L. donovani*, *P. falciparum*, and *T. cruzi*. The fungi *Stenocarpella maydis*, *Edenia gomezpompae*, *Xylaria* sp., *Penicillium paxilli*, *Aspergillus* sp., *Diaporthe* sp., *Diaporthe phaseolorum*, *Nectria mauritiicola*, *Mycosphaerella stromatosa*, and *Edenia gomezpompae* showed activity against *L. donovani*. *Stenocarpella maydis*, *P. paxilli*, *Phomopsis* sp., *Trametes maxima*, *Mycosphaerella stromatosa*, and *Ochrocladosporium elatum* showed activity against *P. falciparum*. *Stenocarpella maydis*, *P. paxilli*, *Diaporthe* sp., *Nectria mauritiicola*, *Mycosphaerella stromatosa*, and *Ochrocladosporium elatum* showed activity against *T. cruzi*. The extracts were considered to be active with at least 60% of inhibition of the growth of the parasite. Of the active isolates, *Edenia* sp., *Xylaria* sp., *Aspergillus* sp., *Mycoleptodiscus* sp., *Phomopsis* sp., *Pycnoporus* sp., and *Diaporthe* sp. showed the most promising results based on their antiparasitic activity and lack of toxicity in the assays. The endophytic fungi isolated from the plant *Caesalpinia echinata*, popularly known as Brazilwood, were tested against *L. amazonensis* and *T. cruzi*. The isolates from *Fusarium* sp., *Nectria mauritiicola*, and *Xylaria* sp. were able to inhibit *L. amazonensis* growth, and the isolate from *Fusarium* sp. was able to inhibit *T. cruzi* growth. *Fusarium* sp. showed the most promising result by inhibiting 92% of *T. cruzi* growth. The extract of *Fusarium* sp. was subjected to fractionation, which revealed beauvericin [31] as the active compound (Campos et al. 2015).

Many fungi are used medicinally in communities. However, there is a lack of research confirming their action. Mallick et al. (2014) collected basidiomycete fungi traditionally used in communities in India to treat leishmaniosis. In in vitro experiments, extracts from 18 fungi were tested against amastigotes and promastigotes of *L. donovani*. Of these, six species showed activity: *Russula albonigra*, *Russula laurocerasi*, *Russula delica*, *Termitomyces eurhizus*, *Tricholoma giganteum*, and *Astraeus hygrometricus*. Many edible fungi can be therapeutic, as in the case of the basidiomycete *Agricus blazei*. The aqueous extract of this fungus has shown activity in vitro and in vivo against many species of *Leishmania*. The infected mice were treated 20 days after infection and showed lower levels of infection in the liver,

spleen, and lymph nodes (Valadares et al. 2011; Valadares et al. 2012). Another edible mushroom *Pleurotus highking* is cultivated in India and used against the helminth *Pheretima posthuma*. The methanolic extract of the fungus showed antiparasitic activity against *P. posthuma* in all concentrations tested (10, 20, 40, and 80 mg/mL). However, the concentration with the best result (80 mg/mL) caused parasite death in 21.3 min. This result is comparable with the standard drug albendazole, which causes parasite death in 15.9 min at the same concentration (Haque et al. 2015).

Conclusions

Neglected diseases caused by protozoan parasites are increasing, especially in countries with a tropical climate. It is apparent that few studies have been carried out to develop novel antiparasitic drugs which are effective in treating these diseases but less aggressive to the host. In this review paper, we have focused on six of the major protozoans responsible for the proliferation of neglected diseases and the use of fungi as an alternative approach to the production of effective compounds for the inhibition of parasites. Different compounds with antiparasitic action produced by fungi have been the object of research around the world. However, their number is lower than studies involving the extraction of compounds of plant origin. For medicinal macrofungi, the number of studies is even lower. It is known that terpenes, steroids, alkaloids, coumarins, and quinones are among the compounds known to be effective in combating protozoan parasites, as observed in this review article. Many of these molecular structures are difficult to reproduce via chemical synthesis, but the plant extraction process also poses a challenge. Many fungi have shown the potential to produce these molecules for use as antiparasitic agents in studies conducted in vitro and in vivo. With the development of microbiology and genetic biology, it is possible to advance the synthesis of these structures in order to make them even more effective than conventional medicines. However, little is known about the mechanism involved in the action of fungal molecules on parasites and the synthesis process.

Many research groups have obtained interesting results in studies conducted to investigate edible and medicinal macrofungi as antiparasitic agents. The investigation of the potential for the consumption of these fungi to enhance human immunity against these parasites is an important and interesting theme for future studies. Although the in vitro and in vivo effects of extracts have been identified and compounds obtained from fungal sources which are effective against parasitic diseases have been identified, as cited herein, greater research efforts are required to verify the efficacy of fungi as antiparasitic agents in humans.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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