Microorganisms and Trypanosomatid Diseases

Subjects: Parasitology

Contributor: Manuel Jesus Chan-Bacab

Trypanosomatids are the causative agents of leishmaniasis and trypanosomiasis, which affect about 20 million people in the world's poorest countries, leading to 95,000 deaths per year. They are often associated with malnutrition, weak immune systems, low quality housing, and population migration. They are generally recognized as neglected tropical diseases. New drugs against these parasitic protozoa are urgently needed to counteract drug resistance, toxicity, and the high cost of commercially available drugs. Microbial bioprospecting for new molecules may play a crucial role in developing a new generation of antiparasitic drugs.

Keywords: microbial metabolites ; antitrypanosomatid agents ; leishmaniasis ; trypanosomiasis

1. Introduction

Infectious tropical diseases constitute a problem for many human beings that inhabit tropical areas of our planet. Affecting people who live in developing countries, these neglected diseases are caused by viruses, protozoa, helminths, and bacteria, which generate different symptoms and may often lead to death [1]. Parasitic diseases have an overwhelming impact on public health, and their geographical distribution favors climates that allow vector persistence for transmission. Vector control is possible, eradication is probably not possible, and vaccine development has so far been unsuccessful, as parasites are experts at evading or deregulating the human immune system [2][3].

Trypanosomatids are flagellated unicellular protozoan parasites belonging to the order Kinetoplastida, family Trypanosomatidae. They are characterized by a single, large mitochondrion that extends through most of these organisms' bodies, and whose DNA creates a unique and elaborate structure called the kinetoplast, located near the flagellar basal body [4][5]. Several species within the Trypanosomatidae family are responsible for the severe but largely neglected diseases of humans and domestic animals, such as *Leishmania* and *Trypanosoma*, the causative agents of leishmaniasis, American trypanosomiasis (Chagas disease), and Human African trypanosomiasis [6][7].

Although leishmaniasis and trypanosomiasis are targeted for control or eradication by the World Health Organization Division of Control of Tropical Diseases, most available drugs are associated with prolonged treatments, high toxicity, and the emergence of drug resistance or a lack of treatment adherence and, therefore, there is a need for new drugs [8]. In recent years, non-profit research and development organizations, academic and institutional centers, and public–private partnerships with pharmaceutical companies have succeeded in discovering new drugs, which must be evaluated in various clinical phases [9].

The ongoing search for new drugs to treat different diseases has been focused on nature because natural sources have continuously provided humanity with broad and structurally diverse pharmacologically active compounds. These continue to be utilized as highly effective drugs to combat many deadly diseases, or as lead structures to develop novel-synthetically derived compounds. Traditionally, higher plants and, since the discovery of penicillins, terrestrial microorganisms have proven to be the richest sources of natural drugs that are indispensable for treating several diseases [10]. Natural products are a source of antiprotozoal drugs. For example, for malaria treatment, quinine was isolated from *Cinchona* species, and, later, artemisinin was obtained from *Artemisia annua* [11]. Although infrequently mentioned, the leishmanicidal agents, amphotericin B and paromomycin, are produced by the actinobacteria *Streptomyces nodosus* and *S. krestomuceticus*, respectively [12][13].

2. Trypanosomatid Diseases

Leishmaniasis comprises a group of diseases with different clinical manifestations caused by various species of *Leishmania* parasites. Twenty species are known to cause infections and drive the four clinical forms of the disease: cutaneous, diffuse cutaneous, mucocutaneous and visceral leishmaniasis. Cutaneous forms are produced by *L*. *mexicana* or *L*. *braziliensis* complexes in the Americas and *L*. *major*, *L*. *tropica*, or *L*. *aethiopica* in the Old World.

Cutaneous lesions resolve spontaneously after some months but, depending on the *Leishmania* species causing them, they can evolve into diffuse cutaneous and mucocutaneous leishmaniasis [14]. Visceral leishmaniasis is caused by *L. infantum* in Latin America [15], *L. donovani* in Africa and Asia, or *L. infantum* in the Mediterranean basin, which can be fatal if not treated [14].

Current chemotherapy for leishmaniasis has many drawbacks, including low efficacy, severe toxic side effects, and the appearance of drug resistance. The first effective drug, ureastibamine, was developed in India in 1922, but it had severe side effects. Later, the refinement and development of pentavalent antimonials reduced the side effects.These compounds remain crucial in the treatment of all forms of leishmaniasis. However, reports of non-response to pentavalent antimony began in the 1970s, even at higher doses, and several other side effects of this regimen were reported, including pancreatic inflammation, nausea, and abdominal pain, pancytopenia, peripheral neuropathy, and cardiotoxicity. This led to trials with pentamidine and amphotericin B. Pentamidine's reported side effects were myalgia, pain at the injection site, nausea, headache, and, less commonly, an oral metallic taste, a burning sensation, numbness, and hypotension [16][17]. Amphotericin B is highly nephrotoxic and, to minimize these side effects, several formulations of colloids and lipids were prepared. These preparations are comparatively safe but extremely expensive. Later, miltefosine was introduced to the market, but the drug is teratogenic and, thus, the administration is contraindicated during pregnancy and shows severe gastrointestinal side effects. Moreover, its cost is another limiting factor. Finally, other drugs, such as paromomycin, allopurinol, and sitamaquine, have been reported with variable cure rates [17].

American trypanosomiasis (Chagas disease), caused by the protozoan parasite *Trypanosoma cruzi*, is characterized by a generalized infection that clinically courses from an acute form to a chronic phase. The chronic phase of the disease is highly disabling due to cardiac and digestive disorders that can eventually lead to death. This flagellated protozoan parasite is transmitted to humans by a blood-sucking reduviid bug, which deposits its infective feces on the skin at the time of biting. It can also be transmitted directly by infected blood or by congenital transmission [6][18]. The drugs currently used for Chagas disease's etiological treatment are nitroimidazole, benznidazole, and nitrofuran, nifurtimox. The benefits of benznidazole are most significant during the acute stages of the disease in adults and children, and young adults with intermediate Chagas disease [19]. Benznidazole prevents congenital transmission when administered to reproductive-age women, which may be an essential strategy to prevent disease in newborns [20]. Tolerance to benznidazole is satisfactory since no severe side effects have been observed in treated patients. Side effects include allergy, skin disease, nausea, and vomiting. Less common are polyneuropathy and bone marrow depression. Nifurtimox is used as a second-line option for the treatment of this disease. Several clinical studies have shown that this drug, in children and adults, achieved a cure rate of 80–90%. However, its adverse side effects are common and include anorexia, vomiting, gastric pain, insomnia, headache, myalgia, and seizures [21][22].

Following the bite of the tsetse fly of the genus *Glossina*, Human African trypanosomiasis (HAT) can occur in two clinical forms: a chronic form caused by *Trypanosoma brucei gambiense*, found mainly in West and Central Africa, representing more than 98% of recorded cases, and an acute form, caused by *Trypanosoma brucei rhodesiense*, found mainly in Eastern and South-Central Africa. Without treatment, both types of parasites penetrate the blood–brain barrier and invade the CNS, manifesting in complex symptoms that lead to patient death [23]. Drug treatment in the early stage of HAT is effective and less toxic than in the late stage. Pharmacotherapy for *T. b. gambiense* consists of intramuscular or intravenous pentamidine. For late-stage disease, the first-line therapy for *T. b. gambiense* is NECT, a combination of intravenous eflornithine (DFMO), an ornithine decarboxylase inhibitor, and oral nifurtimox [24]. Finally, fexinidazole, a derivative of 5-nitroimidazole, is a DNA synthesis inhibitor developed by Sanofi in collaboration with the Drugs for Neglected Diseases initiative (DNDi) for the treatment of HAT [25]. Fexinidazole is the first oral drug treatment for the disease's early and late stages [26][27].

3. Microbial Diversity as a Source of Antiprotozoal Metabolites

Natural resources are recognized as important sources of potential drugs for treating various infections, and microorganisms are a rich natural source of diverse compounds [28]. The discovery of penicillin from *Penicillium notatum* marked a significant shift from plants to microorganisms as a source of natural products. The early years of antibiotic research discovered streptomycin from *Streptomyces griseus*, cephalosporin C from *Cephalosporium acremonium*, erythromycin from *Saccharopolyspora erythraea*, and vancomycin from *Amycolatopsis orientalis* [29]. Moreover, it is worth noting that two drugs used to treat leishmaniasis, amphotericin B and paromomycin, were isolated from *S. nodosus* and *S. krestomuceticus*, respectively [12][13].

To the best of our knowledge, few reviews are deal with bacterial and fungal metabolites against trypanosomatid parasites [11][30][31][32] since these reviews only briefly mention them.

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