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Visceral leishmaniasis: Therapeutic challenges and the potential of microalgae as a source of antileishmanial compounds

Leishmaniose visceral: Desafios terapêuticos e o potencial das microalgas como fonte de compostos anti-Leishmania

Leishmaniasis visceral: Desafíos terapéuticos y el potencial de las microalgas como fuente de compuestos anti-Leishmania

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Abstract
Leishmaniases are diseases caused by protozoa of the *Leishmania* genus, transmitted by sandflies, manifesting as visceral, cutaneous, or mucocutaneous forms. Classified as a neglected tropical disease, it disproportionately affects vulnerable populations, especially in low-income regions. This narrative literature review aimed to assess current knowledge on the therapeutic potential of microalgal extracts and compounds for the treatment of visceral leishmaniasis. The research was conducted using the PubMed, SciELO, and Google Scholar databases, employing the keywords *Leishmania infantum*, *Visceral Leishmaniasis*, *Microalgae*, *Cyanobacteria*, *Treatment*, and *Extracts*, as well as their combinations, and considering publications from 2013 to 2024. Original studies analyzing microalgae and cyanobacteria as sources of bioactive compounds against *Leishmania infantum* were prioritized. Current treatments for human visceral leishmaniasis face severe limitations, including toxicity, parasite resistance, and high costs, while therapeutic options for dogs are largely ineffective. Microalgae and cyanobacteria are emerging as promising sources of bioactive compounds with antiprotozoal activity, showing efficacy comparable to certain drugs used in conventional treatments. Therefore, investigating microalgae and cyanobacteria as sources of antileishmanial compounds is crucial, given the limitations of current therapies. These organisms exhibit significant biotechnological potential but remain underexplored. Investments in bioprospecting may reveal safer, more accessible, and more effective therapeutic alternatives to address this global health challenge.
Keywords: *Leishmania infantum*; Treatment; Bioprospection; Algae; Cyanobacteria.

Resumo
As leishmanioses são doenças causadas por protozoários do gênero *Leishmania*, transmitidas por flebotomíneos, que podem se apresentar nas formas visceral, cutânea ou mucocutânea. Classificada como uma doença tropical negligenciada, afeta populações vulneráveis, especialmente em regiões pobres. Esta revisão narrativa da literatura tem como objetivo avaliar o conhecimento atual sobre o potencial terapêutico de extratos e compostos de microalgas para o tratamento da leishmaniose visceral. A pesquisa foi realizada nas bases PubMed, SciELO e Google Acadêmico, utilizando as palavras-chave *Leishmania infantum*, *Visceral Leishmaniasis*, *Microalgae*, *Cyanobacteria*, *Treatment*, and *Extracts*, bem como suas combinações, considerando publicações de 2013 a 2024. Foram priorizados estudos originais que analisaram microalgas e cianobactérias como fontes de compostos bioativos contra *Leishmania*

infantum. Os tratamentos atuais para leishmaniose visceral humana enfrentam limitações graves, incluindo toxicidade, resistência parasitária e alto custo, enquanto as opções para cães são ineficazes. Microalgas e cianobactérias surgem como fontes promissoras de compostos bioativos com atividade antiprotozoária, apresentando eficácia comparável a alguns fármacos utilizados nos tratamentos convencionais. Assim, investigar as microalgas e cianobactérias como fontes de compostos antileishmaniais é essencial diante das limitações dos tratamentos atuais para leishmaniose. Esses organismos apresentam alto potencial biotecnológico, mas ainda são pouco explorados. Investimentos em bioprospecção podem revelar alternativas terapêuticas mais seguras, acessíveis e eficazes para enfrentar esse desafio global de saúde.
Palavras-chave: *Leishmania infantum*; Tratamento; Bioprospecção; Alga; Cianobactéria.

Resumen
Las leishmaniasis son enfermedades causadas por protozoos del género *Leishmania*, transmitidas por flebótomos, que pueden presentarse en formas visceral, cutánea o mucocutánea. Clasificada como una enfermedad tropical desatendida, afecta a poblaciones vulnerables, especialmente en regiones empobrecidas. Esta revisión narrativa de la literatura tuvo como objetivo evaluar el conocimiento actual sobre el potencial terapéutico de extractos y compuestos de microalgas para el tratamiento de la leishmaniasis visceral. La búsqueda se realizó en las bases de datos PubMed, SciELO y Google Académico, utilizando las palabras clave *Leishmania infantum*, *Visceral Leishmaniasis*, *Microalgae*, *Cyanobacteria*, *Treatment*, and *Extracts*, así como sus combinaciones, considerando publicaciones comprendidas entre 2013 y 2024. Se priorizaron estudios originales que analizaron microalgas y cianobacterias como fuentes de compuestos bioactivos contra *Leishmania infantum*. Los tratamientos disponibles para la leishmaniasis visceral humana presentan limitaciones significativas, como toxicidad, resistencia parasitaria y alto costo, mientras que las opciones terapéuticas para perros son limitadas en eficacia. Las microalgas y cianobacterias destacan como fuentes prometedoras de compuestos bioactivos con actividad antiprotozoaria, mostrando eficacia comparable a algunos fármacos utilizados en tratamientos convencionales. Por lo tanto, investigar las microalgas y cianobacterias como fuentes de compuestos antileishmaniales es esencial frente a las limitaciones de los tratamientos actuales. Estos organismos presentan un alto potencial biotecnológico, aunque aún están poco explorados. La inversión en bioprospección podría revelar alternativas terapéuticas más seguras, accesibles y eficaces para abordar este desafío global de salud.
Palabras clave: *Leishmania infantum*; Tratamiento; Bioprospección; Alga; Cianobacteria.

1. Introduction

Leishmaniasis, a neglected tropical disease transmitted by sandflies, is caused by protozoa of the *Leishmania* genus and can present in three main clinical forms: cutaneous, mucocutaneous, and visceral. Visceral leishmaniasis, the most severe form, is often fatal if untreated and represents a critical public health challenge. The disease affects millions of people worldwide, particularly in tropical and subtropical regions. It is strongly associated with poverty, malnutrition, inadequate housing, and insufficient healthcare systems, perpetuating a cycle of social and economic vulnerability (WHO, 2023; Dias et al., 2024).

Available therapies, such as pentavalent antimonials, amphotericin B, and miltefosine, face significant challenges, including high toxicity, parasite resistance, and invasive administration methods. Additionally, although drugs with fewer side effects exist, their high costs often limit accessibility for vulnerable populations and public health systems. These limitations, combined with the lack of innovation in new treatments, exacerbate the issue and highlight the urgent need for alternative therapeutic options (Santiago et al., 2021).

In this context, microalgae, microscopic aquatic organisms, stand out for their vast biotechnological potential. These organisms produce a wide range of bioactive secondary metabolites, including antimicrobial, antioxidant, and immunomodulatory compounds, which can be leveraged for drug development (Lage et al., 2023). Recent studies have highlighted the potential of these biomolecules in combating parasites, including Leishmania, suggesting that microalgae could serve as a promising resource for innovative, effective, and sustainable therapies (Cerutti et al., 2018; Rodrigues, 2018).

Given the limitations of current therapeutic options for visceral leishmaniasis, this narrative literature review aimed to assess current knowledge on the therapeutic potential of microalgal extracts and compounds for its treatment.

2. Methodology

The bibliographic search was conducted on the PubMed, SciELO, and Google Scholar platforms using the keywords *Leishmania infantum*, *Visceral Leishmaniasis*, *Microalgae*, *Cyanobacteria*, *Treatment*, and *Extracts*, as well as their combinations. The time frame included publications published between 2013 and 2024. The initial selection of articles was based on a review of abstracts and an analysis of keywords to identify studies aligned with the objectives of this review. Subsequently, articles meeting the inclusion criteria were fully analyzed to gather relevant information and develop this narrative literature review. Exclusion criteria included removing articles that did not meet the review's objectives, with priority given to original studies presenting relevant data and appropriate methodologies. Only articles investigating microalgae and cyanobacteria as sources of new bioactive compounds with activity against *Leishmania infantum* were selected, forming the basis of the final analysis.

3. Results and Discussion

Leishmaniasis

Leishmaniases are zoonotic diseases caused by obligate intracellular protozoan parasites of various species within the genus *Leishmania*, which belong to the family *Trypanosomatidae*. Transmission to humans and other mammalian hosts occurs through a complex cycle involving the blood-feeding activity of female sandflies, which act as vectors. These vectors belong to the family *Psychodidae*, subfamily *Phlebotominae*, and are divided into two genera: *Phlebotomus* in the Old World and *Lutzomyia* in the New World. Approximately 70 different species have been involved in transmission, with vector activity primarily occurring during the nighttime hours (Conceição-Silva & Alves, 2014; Galvis-Ovallos et al., 2020; Mann et al., 2021).

Leishmania spp. alternates between two distinct life cycle forms. In the promastigote stage, the extracellular, flagellated parasites reside in the gut of sandflies, where they multiply and differentiate into infective metacyclic forms. During a blood meal, an infected sandfly regurgitate these promastigotes into the skin of the host. Once inside, the parasites are phagocytosed by mononuclear cells and transform into amastigotes in response to altered environmental conditions, such as changes in temperature and pH. These intracellular, non-flagellated forms adapt to life within phagolysosomes, specialized organelles where they successfully multiply (Costa-da-Silva et al., 2022).

Another noteworthy feature of *Leishmania* is its species-specific tissue tropism (Maatallah et al., 2022). However, the clinical outcome of the disease is influenced not only by the *Leishmania* species but also by a complex interplay of factors, including the host's immune response, vector characteristics, and environmental and social conditions (Costa-da-Silva et al., 2022). The disease primarily manifests in three clinical forms: visceral leishmaniasis (VL), cutaneous leishmaniasis (CL), and mucocutaneous leishmaniasis (MCL). Additionally, two rarer forms have been identified: diffuse cutaneous leishmaniasis (DCL) and post-kala-azar dermal leishmaniasis (PKDL) (McGwire & Satoskar, 2014; Sasidharan & Saudagar, 2021; Cecílio et al., 2022).

The World Health Organization (WHO, 2022) estimates that 700,000 to 1 million new cases of leishmaniasis occur annually. The disease is endemic in 99 countries, including 89 where cutaneous leishmaniasis (CL) is endemic, 80 for visceral leishmaniasis (VL), and 71 for both clinical forms. Epidemiological data indicate that leishmaniasis disproportionately affects tropical and subtropical developing countries, leading to its classification as a neglected tropical disease (NTD). NTDs primarily impact the poorest and most marginalized populations, where risk factors such as inadequate sanitation and healthcare services are prevalent (Álvarez-Hernández et al., 2020; Magalhães et al., 2023).

Additionally, global climate change has the potential to significantly alter the epidemiological patterns of leishmaniasis, as sandfly vectors are highly sensitive to environmental factors, particularly temperature. Such changes could result in shifts in the geographical distribution of these vectors, facilitating the disease's spread into previously non-endemic areas (EBioMedicine, 2023; Hlavacova et al., 2013). A recent study analyzed the spatial and temporal distribution of autochthonous leishmaniasis cases caused by *L. infantum* in Europe from 2005 to 2020. Maia et al. (2023) reported no significant increase in incidence. However, other studies suggest that future climatic conditions in Europe may favor the spread of *Phlebotomus* spp., potentially increasing the risk of leishmaniasis on the continent (Fischer et al., 2011; Trájer et al., 2013; Semenza & Suk, 2018). A similar trend is observed in North America, where projections indicate that the risk could expand beyond currently affected areas, moving further north (González et al., 2010). Supporting this, Beasley et al. (2022) documented autochthonous cases in four U.S. states, highlighting how climate change is reshaping disease distribution and posing emerging public health risks.

Globalization and conflicts, including wars that often weaken healthcare systems, are recognized as risk factors for the emergence of leishmaniasis due to their association with migration processes. These factors collectively increase the likelihood of introducing new vector species and, consequently, parasites into previously unaffected regions (Cecílio et al., 2022; Berry & Berrang-Ford, 2016; Pavli & Maltezou, 2010)

Leishmania-HIV coinfection is an additional aggravating factor in managing leishmaniasis. Documented in 42 countries, it shows particularly high prevalence in regions where both infections are endemic. This coinfection complicates clinical management and treatment by increasing the risk of severe disease, poor outcomes, and higher relapse rates. Cutaneous, mucocutaneous, and visceral forms of leishmaniasis each pose distinct challenges for diagnosis, treatment, and prevention, particularly in immunocompromised individuals (WHO, 2023). Understanding the specific characteristics and interactions of these forms is crucial for developing effective strategies to control and manage leishmaniasis in affected populations.

Human Visceral Leishmaniasis

Among the clinical forms of leishmaniasis, visceral leishmaniasis, also known as kala-azar, is the most severe with a mortality rate exceeding 95% in untreated cases. Common symptoms include fever, weight loss, splenomegaly, hepatomegaly, and anemia. According to the World Health Organization (WHO), an estimated 50,000 to 90,000 new cases occur globally each year, although only 25 - 45% are officially reported. This significant underreporting underscores the risk of outbreaks and associated high mortality. VL is most prevalent in four countries, India, Sudan, Brazil, and Kenya, which together account for 68% of global cases. In the Americas, 69,665 new VL cases were reported between 2001 and 2021, with the highest lethality rate, approximately 8%, the highest among continents (Steverding, 2017; WHO, 2023). In Asia and East Africa, VL is primarily caused by *Leishmania donovani*, with humans serving as the principal reservoirs of the pathogen. In contrast, in Latin America and the Mediterranean region, the disease is caused by *Leishmania infantum*, which constitutes a zoonosis where dogs play a critical role as hosts (Scarpini et al., 2022).

The Brazilian Ministry of Health reports that Brazil accounts for 90% of the reported cases in Latin América. Since the first case was identified in 1913 in Boa Esperança, state of Mato Grosso, the disease has spread across various regions of Brazil, shifting its transmission pattern from predominantly rural areas to include urban centers. Annually, around 3,500 cases are reported in the country, with an incidence rate of 2.0 cases per 100,000 inhabitants. Mortality rates have risen from 3.1% in 2000 to 7.1% in 2012. Until August 2024, the Brazilian Ministry of Health had recorded 50,478 new cases and 3,945 deaths, representing a mortality rate of 7.02% (Brasil, 2024).

It is important to note that American visceral leishmaniasis (AVL) is not a contagious disease and cannot be directly transmitted from person to person, between animals, or from animals to humans. The parasite is transmitted exclusively through the bite of infected female sandflies. Among the vector species responsible for transmission, *Lutzomyia longipalpis* is the primary vector. However, *Lutzomyia evansi* plays a significant role in certain Central American countries, including Colombia and Venezuela. Similarly, *Lutzomyia cruzi* acts as a vector in border regions among Bolivia, Brazil and Argentina (WHO, 2024).

In urban environments, domestic dogs (*Canis familiaris*) are the primary carriers, serving as a source of infection for Phlebotomine sandflies. However, wild reservoirs also play a significant role in the transmission cycle of AVL. Examples include foxes, wild canids such as *Cerdocyon thous* and *Lycalopex vetulus*, and opossums of the genus *Didelphis* (Brasil, 2020).

As a neglected tropical disease, visceral leishmaniasis requires early diagnosis to prevent potentially fatal complications. In addition to clinical symptoms, laboratory tests are available to confirm the diagnosis. These include serological tests such as ELISA and indirect immunofluorescence assays, as well as bone marrow aspiration for detecting the parasite (Brustolin, 2022; WHO, 2024). It is critical to intensify efforts in the prevention, timely diagnosis, and effective treatment is essential to protect vulnerable populations and curb the disease's spread. Collaboration among governments, healthcare organizations, professionals, and affected communities is crucial to address this public health challenge effectively. Furthermore, public awareness about symptoms, preventive measures, and the importance of treatment also plays a vital role in combating visceral leishmaniasis (Alvar et al., 2021).

Canine Visceral Leishmaniasis

As previously discussed, dogs play a central role as reservoirs of *L. infantum*, the causative agent of canine visceral leishmaniasis, a multisystemic, and incurable disease that is fatal for symptomatic animals if left untreated. Although largely unfamiliar to veterinarians outside endemic areas, the disease is spreading in the Northern Hemisphere, driven by travel and climate change (Nery, 2017; WHO, 2024).

Infection with *Leishmania* in dogs shares clinical similarities with human infection, including visceral involvement. The disease begins at the vector’s bite site, such as the nose or inner ear margins, triggering a localized inflammatory response. Parasitic forms, neutrophils, lymphocytes, and macrophages aggregate to form nodular lesions known as leishmaniomas. These lesions, ranging from one to three centimeters in diameter, are alopecic, ulcerative, and sometimes crusted, causing minimal pain and no itching. Depending on the immune response (cellular or humoral), leishmaniomas may spontaneously regress or progress to visceral disease (Freitas, 2022).

Due to the neglected nature of leishmaniasis, drug discovery progress has been slow. It is unlikely that the few drugs that reach clinical trials for humans will be made available for canine use. However, several approaches are being developed to support chemotherapy, including next-generation vaccines and novel prevention strategies (WHO, 2024).

Treatment and Challenges

Humans

Currently, the standard treatment for human leishmaniasis relies on five main drugs: pentavalent antimonials (commonly administered as meglumine antimoniate in Brazil), amphotericin B and its liposomal formulation, miltefosine, paromomycin, and pentamidine (Tiwari et al., 2018; Santiago et al., 2021; Silva et al., 2021).

Pentavalent antimonials have served as the first-line treatment for all forms of leishmaniasis for over 70 years (Santiago et al., 2021; Barrett & Croft, 2012). Despite their effectiveness, their use is being discontinued in India due to rising

resistance, although they remain effective in other regions. The need for daily parenteral administration, coupled with high toxicity, side effects, and treatment failures pose challenges to patient adherence and often leads to therapy discontinuation (Silva et al., 2021; Roatt et al., 2020; Silveira et al., 2024).

Amphotericin B (AmpB), a polyene antifungal agent, serves as a second-line treatment with demonstrated efficacy against all forms of *Leishmania* infection (Santiago et al., 2021; Silva et al., 2021), it targets both amastigote and promastigote forms of the parasite. AmpB is administered intravenously and is particularly recommended for visceral leishmaniasis (VL) cases involving resistance to antimonials or adverse effects associated with these drugs (Nascimento, 2023). While the liposomal formulation significantly reduces AmpB's toxicity, its high cost restricts accessibility for low-income populations most affected by the disease and hinders its widespread use in public health systems (Guedes et al., 2018; Santiago et al., 2021; Silva et al., 2021).

Miltefosine is currently the only oral leishmanicidal drug proven to be effective and safe for therapeutic use in leishmaniasis cases (Santiago et al., 2021; Silva et al., 2021). It has been successfully employed in treating VL patients in India, achieving a 95% success rate (Singh et al., 2023). However, its use is hindered by severe side effects, including nephrotoxicity, hepatotoxicity, and teratogenicity. Additionally, there are increasing reports of acquired resistance in the parasite, further complicating its application (Santiago et al., 2021; Singh et al., 2023; Reguera et al., 2019; Schubach, 2024).

Clinical studies on paromomycin monotherapy for VL show that the drug's efficacy varies by region, with an average cure rate of 63.8%, significantly lower than that of pentavalent antimonials. While paromomycin is low-cost and has minimal side effects, its low efficacy in monotherapy limits its application. However, its affordability and safety profile may make it a viable option in combination therapies (Singh et al., 2023; Musa et al., 2010; Bray et al., 2022).

Pentamidine, another second-line drug, is a synthetic amidine derivative with high leishmanicidal activity. However, it presents substantial toxicity risks, including cardiotoxicity, hypotension, and irreversible diabetes mellitus when used to treat VL (Soni et al., 2019; Singh et al., 2023). Although no cases of clinical resistance have been reported, laboratory experiments suggested that *Leishmania* parasites can develop resistance when gradually exposed to higher concentrations of pentamidine (Dukhiyil, 2019; Tiwari et al., 2018).

Despite their effectiveness, these treatments face significant limitations, including toxicity, prolonged treatment durations, and parasite resistance, often leading to therapy discontinuation. As a result, there is an urgent need for novel molecules with antileishmanial properties and new, safer therapies.

Dogs

Treatments for dogs diagnosed with canine visceral leishmaniasis (CanVL) share similarities with human VL therapies, with some differences (Morales-Yuste et al., 2022). Therapeutic choices depend on the disease stage, determined through clinical signs, serological and laboratory findings, and individual prognosis (Solano-Gallego et al., 2011). The disease is classified into four stages: Stage I (asymptomatic to mild disease): Dogs may receive no treatment or only allopurinol. Stage II (moderate disease) and Stage III (severe disease with chronic kidney disease): Combination therapy with allopurinol and antimonials or miltefosine is recommended. Stage IV (very severe disease, including nephrotic syndrome): Only allopurinol is used to minimize further renal damage (Solano-Gallego et al., 2011; Morales-Yuste et al., 2022).

Despite these therapeutic stages, the use of drugs intended for humans or those unlicensed by the Ministry of Agriculture, Livestock, and Supply (MAPA) for CanVL treatment has been prohibited in Brazil since 2008 (Marcondes & Day, 2019; Brasil, 2008). This regulation limits available treatment options and emphasizes the need for veterinary-specific alternatives.

Microalgae and Cyanobacteria as a Source of New Compounds Against *Leishmania infantum*

The fight against neglected diseases, such as leishmaniasis, is complex, involving geographic, environmental, economic, and social challenges. A significant obstacle to eradicating these diseases is the lack of safe, effective, and affordable drugs. Current treatments, however, are limited by toxicity, low efficacy, high costs, and difficulties in administration (Silva et al., 2021; Roatt et al., 2020).

The development of new technologies is, therefore, crucial to improving disease control and potentially achieving eradication. This highlights the importance of research, development, and innovation in addressing these health challenges. Biodiversity-derived compounds, for instance, offer a promising alternative, expanding therapeutic options while also driving innovation and economic development in the medical field (Neto, 2022).

Microalgae and cyanobacteria are particularly promising microorganisms in this regard. Their bioactive compounds have diverse applications across the cosmetic, food, chemical, and pharmaceutical industries. Numerous companies worldwide are producing microalgal biomass on a commercial scale for high-value-added products (Vidotti, 2015). Microalgal biomass is rich in essential compounds, including proteins, carbohydrates, and lipids, necessary for growth and maintenance (Rizwan et al., 2018). Secondary metabolites produced by these organisms include fatty acids, polymers, enzymes, pigments, vitamins, toxins, amino acids, and sterols, which have broad therapeutic potential (Borowitzka, 2018).

Torres et al. (2014) demonstrated that microalgae exhibit a wide range of pharmacological activities, including antitumoral, antiviral, antibacterial, antifungal, wound-healing, and antiprotozoal effects. These findings highlight their significant pharmacological potential, encouraging researchers to further explore their diverse biological activities and potential applications (Cerutti et al., 2018).

Algae, classified within the kingdoms Protista or Plantae depending on the taxonomic system, are incredibly diverse, with over 174,809 species and infraspecific names recorded to date (Guiry, 2024). Found primarily in aquatic environments, algae can also thrive in diverse habitats, showcasing their adaptability and resilience (Levasseur et al., 2020; Chen, 2022). In addition to their ecological importance as primary oxygen producers and a cornerstone of food chains, algae have substantial economic value, with applications spanning multiple sectors, including biotechnology, agriculture, and pharmaceuticals (Simões et al., 2016).

Cyanobacteria, or blue-green algae, are photosynthetic prokaryotes within the phylum *Cyanobacteria*. These microorganisms thrive in various environments, from aquatic and terrestrial ecosystems to extreme conditions such as arid soils and rocks (Whitton & Potts, 2007).

Certain algae and cyanobacteria species exhibit remarkable biological properties, including antileishmanial activity, positioning them as promising candidates for developing novel treatments for parasitic diseases like leishmaniasis. This underscores a largely untapped pharmacological potential (Pereira et al., 2023; Guiry, 2024). Currently, these organisms are attracting growing interest due to their diverse biotechnological applications, including agriculture (e.g., biofertilizers and biostimulants), biofuels, human and animal nutrition, wastewater treatment, and the production of bioactive molecules (Tinoco et al., 2015; Simões et al., 2016; Pereira et al., 2023). In particular, their potential in medicine stands out, as algae are increasingly recognized as valuable sources of novel biologically active molecules for therapeutic development.

These organisms exhibit a remarkable ability to transform simple nutrients into a diverse range of compounds, such as lipids, pigments, polyphenols, and peptides, which are products of both primary and secondary metabolism (Pagels et al., 2022). Many of these compounds have demonstrated significant biological activities, including anticancer, anti-inflammatory, anticoagulant, antiviral, antibacterial, and antifungal properties. These characteristics position algae as excellent candidates for the development of innovative medical, therapeutic, and pharmacological solutions (Basheer et al., 2020; Pooja, 2014).

To fully harness the potential of microalgae and produce pharmacologically relevant molecules in a controlled and scalable way, these organisms can be employed as bioreactors under optimized cultivation conditions to achieve high yields (Pereira et al., 2023). This method provides additional benefits, including the rapid growth rate of microalgae and their contribution to sustainable development by fixing carbon dioxide through photosynthesis, thus reducing environmental impacts (Levasseur et al., 2020).

Despite their high potential as source of biologically active compounds, microalgae have been underexploited in studies against *L. infantum*. Although few studies have investigated the antileishmanial effects of microalgal extracts and compounds, their findings have been encouraging. For instance, Gharbi et al. (2021) identified microalgae species from water bodies in Tunisia and highlighted *Dunaliella sp.* for its promising antileishmanial activity against *L. infantum* and *L. major* (IC_{50} = 151 and 284 µg/mL, respectively). Similarly, Vaitkevicius-Antão (2022) evaluated *Dunaliella tertiolecta* and found that its extracts demonstrated a Selectivity Index (SI) of 4.7, outperforming meglumine antimoniate (SI = 2.1) in tests against *L. infantum*. These findings together demonstrate the potential of bioactive extracts from photosynthetic microorganisms of the genus *Dunaliella* as promising candidates for developing effective leishmaniasis treatments.

Keller et al. (2020) isolated palstimolide A, a complex polyhydroxy macrolide with a 40-membered ring, from the cyanobacteria *Leptolyngbya sp.* Their findings revealed significant antileishmanial activity, with an IC_{50} of 4.67 µM, highlighting the potential of cyanobacteria to produce structurally diverse natural products with biological activity. Similarly, Carneiro et al. (2014) isolated coibacin A, a bioactive compound derived from *Oscillatoria sp.*, which further demonstrated its antileishmanial properties. Moreover, Vaitkevicius-Antão et al. (2022) evaluated extracts from *Arthrospira platensis* against *L. infantum* and reported that *A. platensis* (SI = 3.8) exhibited greater efficacy compared to meglumine antimoniate (SI = 2.1). These findings reinforce the potential of cyanobacteria as a source of novel therapeutic compounds for leishmaniasis treatment.

Beyond their remarkable diversity and wide distribution, certain species of algae and cyanobacteria exhibit extraordinary biological properties, including antileishmanial activity. However, research into their potential remains scarce. This capability underscores their ecological significance and substantial potential in the quest for new therapeutic approaches to parasitic diseases like leishmaniasis, highlighting a vast pharmacological field yet to be explored.

4. Conclusion

Investigating the antimicrobial potential of microalgae extracts against protozoa of the *Leishmania* genus is crucial, given the global health challenge posed by leishmaniasis. Current treatments face significant limitations, including difficulties in dose administration, high costs, and adverse side effects. These challenges highlight the urgent need for research into new compounds and strategies to address these issues. In this context, microalgae and cyanobacteria emerge are promising sources of secondary metabolites with biotechnological potential. However, their role as sources of novel antileishmanial compounds remains underexplored. Greater investment and intensified efforts in bioprospecting could unveil new natural antileishmanial compounds, paving the way for safer, more affordable, and more effective therapeutic alternatives for leishmaniasis.

Future studies should focus on exploring the great biodiversity of microalgae to isolate and characterize specific bioactive compounds from both microalgae and cyanobacteria, aiming to identify their mechanisms of action against *Leishmania* species. Moreover, advancements in cultivation techniques, such as optimizing growth conditions for microalgae biomass production, could enhance the yield of these promising compounds, reducing their production costs. In addition, collaborative efforts between biologists, pharmacologists, and parasitologists are essential to translate these findings into clinical applications. Finally, the exploration of synergistic effects between microalgal compounds and existing antileishmanial drugs could open avenues for combination therapies that reduce drug resistance, minimize side effects, and lower treatment costs.

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Conflict of Interest

There is no conflict of interest to declare.

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