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Review Article

NEGLECTED TROPICAL DISEASES: CURRENT TREATMENT CHALLENGES AND FUTURE THERAPEUTIC POTENTIALS

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ABSTRACT

Neglected tropical diseases (NTDs) predominantly affect developing countries. Human African trypanosomiasis, leishmaniasis, Chagas disease, and malaria are protozoan infections that are endemic in developing countries and for which new drugs are desperately needed. Gaining better control of these diseases requires discovering and developing safe, effective, and affordable new drugs for the populations at risk. Unfortunately, incentives for the research and development of new medicine to combat NTDs are currently insufficient. This paper examines recent efforts to increase R&D investments in the development of new anti-parasitic drugs and provides an overview of the most recent and promising compounds at different development stages for each pathogen. Additionally, information on the development of novel formulations combining existing drugs and delivery systems that can improve therapeutic outcomes as well as recent advances in drug discovery, obstacles to developing new chemical entities (NCEs), and the role of public-private partnerships (PPPs) are discussed. In conclusion, drug discovery for neglected diseases entails a larger challenge of demonstrating translational readiness at an early stage. Classification systems can help identify gaps and focus research and development efforts on candidates with the highest likelihood of becoming clinical options. To overcome funding shortages and reduce the incubation time for promising drug discovery initiatives, it is necessary to harness the power of collaborative networks and use innovative funding models.

KEYWORDS: Neglected tropical diseases; anti-parasitic drugs; protozoan infections; innovative funding models

1. Introduction

Current estimates suggest that the overall burden of Neglected Tropical Diseases (NTDs) is roughly comparable to that of HIV or malaria [1]. Protozoan infections such as human African trypanosomiasis, leishmaniasis, Chagas disease, and malaria are prevalent in developing countries, where the need for new drugs is critical [2]. To better control these diseases, the development of new, safe, effective, and affordable drugs is essential for at-risk populations. Unfortunately, the current incentives for research and development (R&D) of new treatments for NTDs are inadequate [3].

Neglected tropical diseases (NTDs) are a group of communicable diseases that are highly endemic in the tropical and subtropical areas of the world [4]. They affect more than one billion of the world's population, whose ability to work and quality of life are severely impaired, representing a huge economic burden on the world's developing countries [5]. The group of NTDs includes parasitic infections such as Chagas disease, leishmaniasis, lymphatic filariasis, onchocerciasis, schistosomiasis, and others. Currently, the main approach to control these diseases is by mass treatment with one or more of the few available drugs [6]. However, all of the current treatments have several disadvantages, such as low efficacy, high toxicity, the appearance of resistant strains, and limited availability or affordability. The development of new and improved drugs is essential to overcome these problems and help control NTDs in the most vulnerable populations.

In this review, we highlight recent initiatives aimed at increasing R&D investments for anti-parasitic drug development, provide an overview of promising compounds at various stages of development for each pathogen, and explore novel formulations that combine existing drugs and delivery systems to improve therapeutic outcomes. Additionally, we feature the challenges associated with developing new chemical entities (NCEs) and the role of public-private partnerships (PPPs).

2. Methodologies and Drug Discovery

There are multiple methodologies involved in drug discovery. High-throughput screening (HTS) is one of the important processes in drug discovery in which thousands to millions of compound samples can be tested for biological activity [7, 8]. Virtual screening is an alternative way to perform large-scale screening. It is comparatively cheaper and faster [9]. The discovery of drugs against infectious diseases is more challenging than against other diseases because it requires the designing of drugs that act on infectious agents which have evolved to have multifaceted relationships with the host [10].

In the contemporary world, drug discovery is highly dependent on specialized instrumentation and large compound libraries [11]. Several crucial steps are involved in the process of drug discovery. It begins with the identification of a biological target which could be a protein, DNA, RNA or even a whole cell that is responsible for the disease [8]. In the case of infectious diseases, the biological target is usually a protein encoded by the infectious organism such as viruses, bacteria, parasites or fungi [12]. Functional genomics can be used to identify suitable gene targets. Once a target is identified, small molecules, natural products, biomolecules or synthetic peptides can be screened against it [7]. Lead compounds are optimized by chemical modifications [13] and used to interrogate the target in order to verify its identity and involvement in the disease. Then the drug is further optimized for activity and bioavailability. It is finally subjected to clinical trials and if it passes all the criteria, it is released as a marketable drug. The process is lengthy and costly resulting in less availability of safe and effective drugs against NTDs.

NTDs affect millions of people and the current treatments for the majority of these diseases are far from optimal [14]. These diseases, then, constantly threaten those who live in the most abject poverty in the developing countries of Africa, Asia, and the Americas. Remarks on public health motivations for the development of new anti-parasitic drugs were recently provided. The high prices of new chemotherapeutic agents and the relatively low commercial interest are key obstacles to overcoming NTDs. There is also a need for new and accessible treatments for those diseases currently normalized according to the WHO Essential Medicines List [15]. Therefore, the development of new drugs from medicinal plants and the investigation into the bioactivity of their compounds may offer a natural, more affordable alternative to fighting neglected diseases [16]. Several reports indicated the effectiveness of natural products and medicinal plants against NTDs, though these plant-derived pharmaceuticals are yet to undergo further assessment for their bioavailability and specificity against certain parasitic infections [17–20].

3. Key parasitic diseases and current treatment option

The following sections provide an overview of the key parasitic diseases that could be targeted for drug discovery and the current treatment options.

3.1. Malaria

Malaria is one of the most important infectious diseases in the world, causing an estimated 207 million new cases and 627,000 deaths in 2012, the vast majority of which are in children under five years of age in sub-Saharan Africa [21]. The world mortality rate has decreased significantly over the past two decades, with saving lives of about 11.7 million between 2000 and 2021 [22]. 94-95% of all malaria cases were accounted to WHO African Region, with a half a million deaths every year [23]. Unfortunately, the only region where the mortality rate increased between 1990 and 2019 is the region of Central Sub-Saharan Africa [24]. Malaria is caused by *Plasmodium* parasites and is transmitted by the bite of infected *Anopheles* mosquitoes [25]. Although several drugs are available for the treatment and prevention of malaria, resistance has emerged for all currently available anti-malarial drugs, including the first-line treatment artemisinin combination therapies [26].

Plasmodium parasites have a unique biology with several distinct stages in their life cycle, it is this unique biology that has obstructed the development of new drugs to treat malaria. For example, the dormant liver stage of *Plasmodium* parasites can last up to 30 days; the parasite's exo-erythrocytic stage is sequestered in the liver for several days, hidden from the host immune system [27]. Similarly, the *Plasmodium falciparum* blood stage can modify the host red blood cell in order to obtain nutrients and avoid destruction by the spleen [28].

The most commonly used antimalarial drugs are artemisinin derivatives, which are pivotal drugs of Artemisinin-based Combination Therapy (ACT). Their rapid action in reducing the parasite load is due to the generation of reactive oxygen species that damage the membranes and proteins of the parasite [29]. Chloroquine is used as the first line treatment of malaria, it inhibits the heme polymerization, leading to toxic accumulation of heme in the parasite. Unfortunately, it is challenged by the high rate of resistance [30]. Mefloquine and quinine also target the parasite heme detoxification process, yet are less favorable options due to their serious adverse effects [31]. The continuous development of resistance against anti-malarial drugs has further complicated the search for new drugs to treat malaria. Today, resistance has been described against all currently used anti-malarial drugs. In addition to drug resistance, developing a vaccine for malaria has proven to be challenging due to the complex life cycle of the *Plasmodium* parasites. Therefore, there is an urgent need for the development of novel anti-malarial drugs.

3.2. Chagas disease

Chagas disease, also known as American trypanosomiasis, is caused by the protozoan parasite Trypanosoma cruzi [32]. The disease is endemic in 21 countries of the South American continent where it affects 8-10 million people and has considerable public health importance [33]. Chagas disease has two successive stages: acute and chronic. The acute stage is characterized by high parasitemia, and symptoms include cardiac, hepatic, meningoencephalic, dermatological, and febrile abnormalities. The most dreaded symptoms from *T. cruzi* infection are chronic, especially congestive heart failure, for which organ transplantation is the only final treatment. Up to now, only two drugs, nifurtimox and benznidazole, are being used to treat Chagas disease, but both have serious deficiencies [34]. The two drugs show good efficacy in the acute phase while showing minimal effectiveness during the chronic phase [34, 35]. In response to these challenges focusing on managing symptoms, an ongoing search for new drug development has been considered [35], ergosterol synthesis inhibitor (Posaconazole) as an alternative therapeutic option has emerged. Posaconazole is usually used in combination with allopurinol and amiodarone [36]. For managing symptoms, comprehensive care should be provided for cardiovascular and digestive complications [37, 38]. The most important challenges associated with the treatment of Chagas disease are, firstly the adverse drug reactions to the current medications which leads to patient non-adherence. Secondly the lack of new medication development despite ongoing research for effective medications [39]. Thirdly, the disease impact had been exacerbated in non-endemic regions due to underdiagnosis and lack of screening [40].

3.3. Leishmaniasis

Leishmaniasis is a vector-borne disease caused by obligate intracellular protozoa of the genus Leishmania [41]. Approximately 350 million people are at risk, with an estimated prevalence of 12 million cases and an annual incidence of 1-2 million cases [42]. Consequently, 1.6 million DALYs (Disability Adjusted Life Years) are assigned to this disease [43]. Three main clinical forms are known: visceral (VL), cutaneous (CL), and mucocutaneous disease (MCL). The current chemotherapy for leishmaniasis is far from satisfactory, the existing treatments are toxic, expensive, and difficult to administer, and resistance is emerging [44]. Pentavalent antimonial is considered the first-line treatment for leishmaniasis. They act by inhibiting the glycerol-3-phosphate dehydrogenase enzyme in the parasite, thereby affecting the energy metabolism pathway. Unfortunately, they face the challenges of resistance and adverse drug reactions such as cardiotoxicity [45]. Through liposomal Amphotericin B, the drug delivery to macrophages had been enhanced, yet also facing the challenges of the high cost and the reactions associated with the infusion.

4. Emerging Targets in Anti-Drug Development

Although several potential drug targets have been described in the literature, there are relatively few druggable proteins encoded in any protozoan or helminthic genome, according to the criteria of possessing active sites that are susceptible to competitive inhibition, and the presence of a binding site that allows selective inhibition in the parasite versus the host [46–48]. Some candidate targets have gained support by identifying selective inhibitors with activity against parasite growth.

Immune pathology is usually due to the release of parasite antigens, which both stimulate the immune response and poison the host [49]. If the infectious disease syndrome is to be alleviated, preferably without exposing the host to the risk of other diseases, the release of antigens must be prevented. The development of drugs that prevent disease by inhibiting the release and/or degradation of pathogen antigens should be encouraged.

4.1. Drug targets in protozoan disease

Two main strategies are now being used for the development of new anti-parasitic drugs. First is target-based drug discovery, which requires the validation of specific parasite proteins or pathways as drug targets through genetic, biochemical, and/or chemical biology means [50, 51]. Ideally, essential proteins unique to the parasite relative to the host are identified, but even non-essential targets can have therapeutic value if inhibitors show synergy with other anti-infective drugs. Second is pathway-based drug discovery, which identifies and validates entire metabolic or signal transduction pathways in the parasite [52]. The latter approach is especially useful when a drug target may be difficult to work with, for example, essential but elusive parasite proteins with no close orthologs in model organisms [53]. Phenotypic Drug Discovery (PDD) is an empirical approach to studying the effect of drugs *in vivo* or *in vitro* without prior knowledge of the mechanism of action [54]. Structure-based drug design (SBDD) includes designing the drugs based on the three-dimensional structure of the biological targets, which often leads to more targets and effective therapies [54]. Various diseases are implicated by gene expression that is regulated by epigenetic modifications, therefore epigenetic drug discovery (EDD) targeting it [55]. An important approach is drug repurposing which leverages available drugs for new therapeutic uses, this method reduces the time and cost of drug development [56]. In Silico Drug Discovery method utilizes computational tools to predict drug interactions and optimize lead compounds, when integrated with a natural product screening approach can enhance the identification of promising candidates from a natural source [57].

4.2. Drug targets in helminthic parasites

G protein-coupled neurotransmitter receptors are another major family of receptors in helminths that have potential as drug targets [58, 59]. The structures of G protein-coupled receptors are well characterized, with drug-binding domains present in different extracellular regions [60]. As research advances in reversing drug resistance, we could focus on the development of new anti-helminthic drugs with potential drug targets in different pathways, it is better to aim drugs at pathogen receptors that do not harm the host. At present, several molecular techniques are used routinely to discover novel drug targets,

these techniques include the exploration, annotation, and model validation of various new pathways and best-known drug targets that maintain gene expression levels in approved databases [61]. The other crucial drug targets are metabolic enzymes such as Glycolytic Enzymes [62], Rhodoquinone-dependent Metabolism [63] and Checkpoint Reaction [64].

5. Natural products as potential anti-parasitic agents

Natural products have served as sources of new medicines for thousands of years. Several classes of drugs currently used to treat infectious diseases are derived from natural products, such as the antimalarials quinine, artemisinin, and their synthetic derivatives [65]. These compounds are the standards of care, and their natural origins provide support for drug discovery efforts based on the exploration of natural sources.

5.1. Plants and plants derivatives

Herb and herbal derivatives have been utilized for the development of a great number of drugs, and they play a key role in the development of therapies in different cultures [66]. Several compounds isolated or derived from plants have shown some degree of activity against different parasites that cause neglected diseases [67]. The vast diversity of phytochemicals and the variety of their possible interactions at different levels of parasitic organisms make combination therapy using a number of phytochemicals a feasible option [68]. Another advantage of using natural compounds is the fact that parasite resistance to these compounds is less likely to occur [69]. Furthermore, drug development from natural compounds is cost-effective [70, 71]. Despite all the advantages of using natural compounds, there are also a number of drawbacks associated with it. The difficulty in standardizing the composition of complex mixtures of phytochemicals, along with the low bioavailability and stability of some compounds, may limit their use [72, 73].

5.2 Marine organisms

Different groups of marine organisms, such as bacteria, unicellular algae, protozoa, metazoa, and fungi, are studied and evaluated for the presence of biologically active compounds that possess antiparasitic activity [74]. Many of these compounds have shown promising activity and are being further studied and developed in order to become new drugs for neglected diseases. However, despite the fantastic diversity of marine organisms, the development of new drugs for neglected diseases from marine compounds is, at present, at a relatively low exploration level [75]. The example of marine organisms that have promising activity are sponges and molluscs, these invertebrates are rich sources of metabolites with therapeutic activity against parasites [76]. Cyanobacteria and marine bacteria are known sources of unique chemical compounds and they contribute to the efforts of drug discovery [77].

6. Recent advances in drug delivery systems for anti-parasitic drugs

Drug delivery development is an essential aspect to consider in the process of bringing new anti-parasitic drugs to the market. While the research and development of new dosage forms for anti-parasitic drugs has progressed far less than that of drug compounds, the field of drug delivery is rapidly advancing with innovations in formulation design and the development of new technologies. More effort should be invested in collaborating of drug delivery scientists with pharmacologists specializing in anti-parasitic drugs to ensure that the potency of novel therapeutics is maximized with the development of patient-friendly dosage forms. The review concludes with a perspective outlining the future directions of anti-parasitic drug delivery systems.

6.1. Nanotechnology

Solid lipid nanoparticles (SLN) have been used to incorporate anti-infective drugs for a different route of administration [78]. Amphotericin B incorporated into SLN produced a significant reduction of the parasite burden in experimental visceral leishmaniasis after oral administration, and the same route of administration was selected to use pentamidine incorporated into SLN in an experimental infection with *Trypanosoma cruzi* [79, 80]. Other types of nanoparticles, such as hydrogel nanoparticles or dendrimers, have also been used to incorporate and deliver anti-infective drugs [81]. The use of nanotechnology allows us to explore the possibility of multi-drug administration by incorporating different anti-infective drugs into the same nanoparticle (or a combination of nanoparticles). Because different drugs have different physicochemical properties, it is possible to design different types of nanoparticles to best deliver each drug.

6.2 Lipid-based drug delivery

The lipid-based drug delivery (LDD) system is a class of drug carriers that have been developed over the past few decades [82]. The excipients used in LDD systems, such as liposomes, niosomes, SLN, and nanostructured lipid carriers (NLCs), play an important role in the formulation [82]. These LDD carriers can protect the loaded drug from the biological environment, improve the bioavailability of poorly absorbable and/or poorly soluble drugs, and have multiple characteristics such as physical stability, protection, controlled release, and site-specific targeting, leading to improved therapeutic efficacy with minimized side effects of the drug compounds [83]. LDD has been extensively applied to drug delivery. However, there have been few reports describing the use of LDD for the delivery of anti-parasitic drugs, the development of new anti-parasitic drugs, or the treatment of parasitic diseases. Microneedle Patches, Robotic Pills, and Biodegradable polymers represent an innovative advancement in the treatment of NTDs. Microneedle Patches with minimum invasive methods of drug delivery reduce the pain and injection discomfort [84]. This approach also improves the bioavailability of the drug [85], and promotes self-administration which is positively associated with patient compliance [84]. Robotic Pills can provide targeted delivery and real-time monitoring [86]. Biodegradable polymers allow controlled drug release and decrease the environmental impact thereby improving long-term patient safety [87].

7. Challenges and opportunities in anti-parasitic drug development

The challenges facing the identification of novel targets for anti-parasitic drugs can be caused by but are not limited to the complexity of parasite biology, economic factors, and the limitations of the current research methods. Target identification is complicated by the diversity of the parasite's genetics and biochemistry. An important example is the challenging identification of enzymes, structural proteins, or transporters susceptible to drug compounds, ensuring treatment potency and efficacy [88]. From an economic point of view, and due to limited market potential, investment in new anti-parasitic drug development is not attractive for investors [89]. Advancements in omics technologies and bioinformatics can overcome the limitations associated with the traditional methods of drug discovery [90].

In contrast to the challenges, there are several opportunities to facilitate anti-parasitic drug development. The most significant is the availability of multiple funding sources that support different phases of drug development for NTDs [91]. By collaborating and pooling resources, the field realistically progresses bridging the gap between academia, industry, and regulators. The diverse portfolio of potential drug targets and compounds across the major parasitic organisms allows rapid knowledge transfer when a difficult development issue is encountered with a compound in the pipeline [91]. The increasing support and commitment of endemic countries for surveillance, diagnostics, and drug access can be leveraged to facilitate clinical development [92]. With appropriate planning and collaboration, it is possible to address the challenges and capitalize on opportunities to maintain a robust pipeline of anti-parasitic compounds that will ensure the sustainable management of parasitic diseases into the future [93].

8. Conclusions

In conclusion, drug discovery for neglected diseases entails a larger challenge of demonstrating translational readiness at an early stage. Classification systems can help identify gaps and focus research and development efforts on candidates with the highest likelihood of becoming clinical options. To overcome funding shortages and reduce the incubation time for promising drug discovery initiatives, it is necessary to harness the power of collaborative networks and use innovative funding models.

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