Experts warn about the need for seeking novel treatments for parasitic worm diseases

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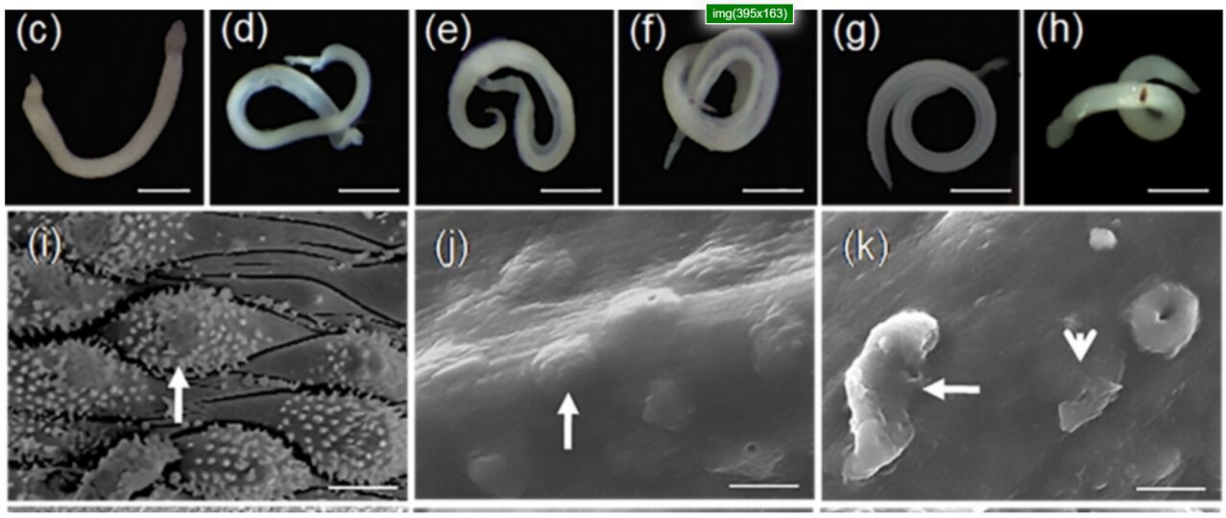

Worms of the species Schistosoma mansoni submitted to different compounds. Credit: NPDN/Universidade Guarulhos

Advances in biology and medicinal chemistry, in conjunction with rising investment in research, have led to the development of promising new candidate treatments for some of the main neglected tropical diseases (NTDs) in recent years.

However, scant progress has been made on parasitic worm diseases, which affect more people worldwide than other NTDs in absolute numbers, in terms of moving on from in vitro studies to clinical and pre-

clinical trials.

This is one of the conclusions of a study published in the journal *Drug Discovery Today* by researchers affiliated with the University of São Paulo (USP) and Universidade Guarulhos (UnG) in Brazil.

"Over a billion people in the world are affected by helminth [parasitic worm] diseases, but these are the NTDs with the least treatment of all. Some 250 million people have schistosomiasis, for which there's only one drug, while more funding is allocated to the other NTDs for the pursuit of treatment options," said Josué de Moraes, one of the three co-authors of the article. Moraes is a researcher at UnG supported by FAPESP and leads the university's Center for Research on Neglected Diseases (NPDN).

In 2021, the World Health Organization (WHO) issued an action plan to eradicate or control 20 diseases that affect one in five people worldwide and kill some 500,000 per year by 2030. The vast majority of the people who suffer from these diseases are poor. The goals include development of novel medications, given the lack of effective treatments and vaccines for the diseases in question.

In the study just published, the researchers note that despite a longstanding lack of innovation in drugs for these diseases, partnerships between public, private and nonprofit entities have funded and accelerated the discovery of possible novel medications using advanced medicinal chemistry strategies.

"Drug development strategies have undergone deep-seated changes in recent years. In the past, researchers performed random screening and testing of compounds on infectious agents by trial and error. With the advance of medicinal chemistry, as well as enhanced experimental and computational tools, we can now conduct more rational screening before

embarking on laboratory trials," said Adriano Andricopulo, also a co-author of the study. Andricopulo is a professor at the São Carlos Institute of Physics (IFSC-USP) and a researcher at the Center for Innovation in Biodiversity and Drug Discovery (CIBFar).

CIBFar is one of the Research, Innovation and Dissemination Centers (RIDCs) supported by FAPESP.

Silent diseases

As the researchers show in the article, major progress has been made in developing candidate treatments for leishmaniasis, Chagas disease and African human trypanosomiasis (AHT), also known as sleeping sickness. The same is not true of schistosomiasis and other helminth diseases.

Several compounds for leishmaniasis are currently being tested in clinical trials. Studies on Chagas disease, in contrast, face difficulties in progressing from the drug discovery stage to the pre-clinical stage. The complex biology of the parasite that causes the disease, Trypanosoma cruzi, and its interaction with different types of human tissue continue to represent a daunting challenge for scientists.

"Most parasitic diseases are silent and chronic. In the case of Chagas, when a patient is diagnosed, it's typically because they already have heart failure, and the parasite has infected cardiac tissue. The challenge is how to have the medication reach T. cruzi without harming the patient," Moraes said.

The authors add, however, that recent studies have pointed to novel molecular targets and parasite signaling pathways, which could contribute to the development of new treatments.

In the case of AHT, which is caused by T. brucei, the approval of

fexinidazole in 2021 was a major advance, representing the first all-oral therapy for the disease.

Drug discovery for diseases caused by worms such as those of the genus Schistosoma is lagging well behind, with no compounds at an advanced stage of development. Drug repositioning is considered promising for helminth diseases, as in the case of miltefosine, known since the 1980s as a cancer drug and currently used to treat leishmaniasis. The group led by Moraes recently reported that an anti-inflammatory drug reduced parasite load by more than 80% in mice infected with Schistosoma mansoni. Research on basic biological aspects of the worm has revealed novel molecular targets, and studies involving a compound that acts against both adult and young parasites are also promising.

Nevertheless, the authors consider these efforts insufficient, given the high global prevalence of helminth diseases, advocating a strengthening of multidisciplinary and collaborative drug discovery efforts that focus on these diseases.

"One of the difficulties involved in research on helminth diseases is culturing the parasites in the laboratory. While trypanosomes and plasmodia [which cause malaria] can be maintained more easily, for worms we need rodents and snails as intermediate and definitive hosts. Research on other parasites therefore advances much faster," Moraes explained.

Owing to this and other difficulties, eradicating these diseases requires not just drug development but also public health measures such as diagnosis, control of transmission vectors and universal basic sanitation. "Multiple measures are needed. We won't be able to get rid of these diseases using medication alone," he said.

More information: Leonardo L.G. Ferreira et al, Approaches to advance drug discovery for neglected tropical diseases, *Drug Discovery Today* (2022). DOI: 10.1016/j.drudis.2022.04.004

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