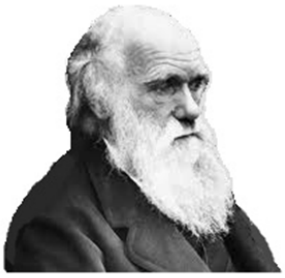
Available online at www.worldnewsnaturalsciences.com



World News of Natural Sciences

An International Scientific Journal

WNOFNS 55 (2024) 231-240 EISSN 2543-5426

Benzimidazole against intestinal parasitic infections

O. O. Akinola[1,2,*], **E. D. Adebayo**[3,4,5]

[1]Phytomedicine Research, Drug Discovery and Development Laboratory, Department of Biochemistry, School of Basic Medical Sciences, Babcock University, Ilishan-Remo, Ogun State, Nigeria

[2] Department of Natural Sciences, British Canadian University, Obudu, Cross-River State, Nigeria

[3] Department of Biochemistry, Covenant University, Ota, Ogun State, Nigeria

[4]Covenant Applied Informatics and Communication Africa Centre of Excellence (CApIC-ACE), Covenant University, Nigeria

[5]Department of Chemical Sciences, Bells University of Technology, Ota, Ogun State, Nigeria

*E-mail address: olusegunakinola49@gmail.com

ABSTRACT

Intestinal parasite infections (IPIs) are still a major hazard to public health worldwide, particularly in nations with subpar sanitary infrastructure. Due to poor hygienic conditions, limited access to sanitation, and a disregard for health education, intestinal parasite infections (IPIs) have continued to occur in developing countries. The two benzimidazole-anthelmintic drugs that are frequently prescribed for Necator Americanus and Ancylostoma Duodenale infections are mebendazole and albendazole. These drugs stop the microtubule polymerization that kills mature worms in invertebrates. Necator Americanus and Ancylostoma Duodenale are similarly vulnerable to benzimidazoles. With a high overall cure rate, hookworm infection can be successfully treated. Despite the lack of rigorous safety trials in children under the age of two, methendazole and albendazole have been used frequently in mass drug administration (MDA) programs to treat entire communities, regardless of the age of the participants. The life cycle and route of transmission of intestinal parasites are similar. The most common method for identifying IPIs is the stool test. Several anti-parasitic medications are used as a kind of treatment. However, effective IPI control depends on taking the right preventive actions.

***Keywords*:** Intestinal parasite infections, albendazole, hookworm infections, medications

(Received 08 June 2024; Accepted 01 July 2024; Date of Publication 03 July 2024)

1. INTRODUCTION

Globally, intestinal parasite infections (IPIs) continue to pose a serious threat to public health, especially in countries with inadequate sanitation infrastructure (1,2). Intestinal parasite infections (IPIs) have persisted in developing nations because of inadequate hygienic conditions, a lack of access to sanitation, and a failure to prioritize health education (3,4,5). Intestinal parasites known as hookworms are a subset of soil-transmitted helminths (STH), a class of nematode diseases that primarily have an effect on people in low- and middle-income nations and affect millions of people globally (6), hookworm infections are linked to the highest worldwide causes of diseases among the group of soil-transmitted helminths, with a projected 2·2 million life years reduced due to disability in 2013. Chronic infections caused by soil-transmitted helminths can affect school-age children's psychometric performance, delayed development of the body, delayed cerebral development, and absenteeism from school (7). Most people with soil-transmitted helminth infections either live in or are displaced from areas with poor access to sanitary conditions, clean water, and hygienic conditions (8,9). STH affects disadvantaged populations more frequently in low- and middle-income countries, but it also affects them in high-income ones (10,11). According to WHO estimates, 875 million children need regular STH therapy in 2010. *S stercoralis*, which may infect up to 100 million people worldwide, is not included in this (9). Data suggest that during the past 10 years, the number of disability adjusted life years (DALYs) associated with soil-transmitted helminths has declined; however, this decline has primarily occurred in upper-middle-income countries, with the disease burden shifting more towards lower- and middle-income countries (12). The disability-adjusted life-years (DALY) associated with soil-transmitted helminths may significantly underestimate the actual illness burden, for instance, by failing to account for hookworm-induced anemia (13).

One of the most prevalent forms of geohelminthic infections in developing nations is hookworm infection (14). Recurrent hookworm infections can result in severe anemia and blood loss. Hookworm disease presents with a variety of symptoms, such as diarrhea, stomach pain, and nausea (15). As a result of the usage of bare hands and feet when playing in the sand, kids are especially susceptible to infection with hookworms (16). Regular anthelminthic treatment, basic healthy learnings, sanitation, and appropriate personal hygiene practices are the main components of a global strategy to eradicate soil-transmitted helminthiasis (17). Yet, studies casting doubt on these tactics have surfaced recently, and there is conflicting data demonstrating these interventions' ability to effectively prevent hookworm infection (18).

2. HOOKWORM INFECTIONS

Hookworms, which include *Ancylostoma duodenale* and *Necator americanus*, are two of the most frequent and persistent parasite illnesses in the world that affect people. These parasites have a detrimental effect on both human health and the socioeconomic advancement of the afflicted areas (19). One of the most prevalent forms of geohelminthic infections in developing nations is hookworm infection (20). Warm, tropical, and subtropical climates are associated with greater rates of hookworm infections (19,21). According to Bouchary et al. (2020), hookworms can cause a variety of health problems and are quite good at evading and modifying the immune system. Grown parasites that live in the host's small intestine typically

induce anemia by consuming blood, degrading erythrocytes, causing persistent intestinal disturbances, depleting the host's blood supply, and lowering hemoglobin levels by attaching themselves to the intestinal wall (18,22,23).

2. 1. Clinical Symptoms of Hookworm Infections

Many times, hookworm infections show no symptoms at all. The symptoms are usually associated with the diseased host and the proliferation of the parasite (22). When skin penetration occurs, it shows up as a localized erythema (24). Accordingly, a moderate or severe infection may result in headaches, fatigue, palpitations, and epigastric pain, while a modest hookworm burden may not cause any symptoms (25). Even though mild anemia may not cause any symptoms, it can nevertheless result in tachycardia, weakness, shortness of breath, and low consciousness (26). The two primary species of human hookworms, Ancylostoma duodenale and Necator americanus, can have high worm burdens that result in anemia, diarrhea, weight loss, nausea, and stomach pain (27, 28). It is important to note that individuals with the infection will develop hemoptysis, bronchitis, sneezing, coughing, and eosinophilic pneumonia at the pulmonary stage (22).

2. 2. Diagnosis Techniques of Hookworm Infections

Fecal testing, whether microscopic or molecular, is necessary to detect hookworm infection (29). Although stool microscopy is a valuable analytical tool, it has many drawbacks. It facilitates the counting and sorting of hookworm eggs. Hospital laboratories employ egg concentration procedures, and there are readily available simple assays such the Kato-Katz techniques. These methods are employed in epidemiological studies because they offer an imprecise estimation of the worm load (30,31). Since hookworms are digestive tract parasites, a recent fecal sample must be examined for the diagnosis.

Examinable during this procedure include hookworm eggs, larvae, and whole or partial parasites. Actually, feces needs to be refrigerated or treated within 24 hours after collection to stop the eggs from developing into larvae. The most important thing to keep in mind is that egg production varies depending on the nutritional status of the host. Moreover, fecal consistency may have an impact on the quantity of eggs per gram in feces, making this method unsuitable for calculating the number of worms in the gut (21).

The McMaster, Formol-Ether Concentration, Kato-Katz, Direct Wet Mount Microscopy, and Test Tube Flotation procedures are a few of the methods utilized in microscopic research. Furthermore, although it can reveal parasites, capsule endoscopy is rarely utilized to diagnose infection. There are still intriguing questions regarding the use of computer-assisted capsule endoscopy imaging for hookworm identification. In this field, automatic discovery models are ultimately intended to be used for analysis, which is more accurate than skilled endoscopists (21,31,32).

2. 3. Treatment Approaches of Hookworm Infections

Mebendazole and albendazole are the two commonly used benzimidazole-anthelmintic medications for *Necator Americanus* and *Ancylostoma Duodenale* infections. These medications prevent invertebrates' microtubule polymerization, which kills adult worms. *Ancylostoma Duodenale* and *Necator Americanus* are equally susceptible to benzimidazoles. The treatment of hookworm infection can effectively cure the infection with an overall cure

rate of 72% for a single dosage of albendazole and 15% for a single dose of mebendazole (33). The results of the other trial, which had 1,845 students, also indicated that an albendazole single dose had an overall cure rate of 87.8%. It is important to note that this rate differs greatly between age groups, nations, and infection severity (34). It is less appropriate for mass treatment movements even if three consecutive daily doses of each medication approve egg decrease rates and improved treatment. The therapeutic efficacy of benzimidazole medications can vary. Astonishingly high rates of single dose medication failure are observed for both mebendazole and albendazole (35). Single dose oral albendazole, mebendazole, and pyrantel pamoate were found to be 72%, 15%, and 31% effective against hookworm infections (36).
Putting in place water, sanitation, and hygiene (WASH) programs is another way to combat hookworms. These programs usually try to stop the spread of hookworms using a variety of techniques. First, by constructing latrines (and/or other sanitation systems), handling human waste, and dissuading ground defecation with health information, these interventions can prevent fecal eggs from entering the soil (37, 38). Second, by encouraging handwashing and improving access to clean water, WASH interventions can prevent human fecal-oral intake of hookworm eggs, which is necessary for *A. duodenale* alone (37,38).

3. BENZIMIDAZOLE

Benzimidazole is also known by the names 1,3-diazaindene, azindole, 3-azaindole, benziminazole, benzoglyoxaline, and 3-benzodiazole. It is a white crystal with melting point of 170–172 °C. Numerous naturally occurring and pharmacologically active compounds have the significant structural motif benzomidazole (39). With applications ranging from HIV-RT inhibitors to anticancer, antimicrobial, antihistamine, antihelmintic, antioxidant, antihypertensive, antiviral, anticoagulant, and antiulcer activity, the benzimidazole moiety is an important pharmacophore in the modern era and has been used as privileged scaffolds to create specific drugs (40). Every member of this class has a structure based on the fusion of the imidazole and benzene rings to form a bicyclic ring structure.

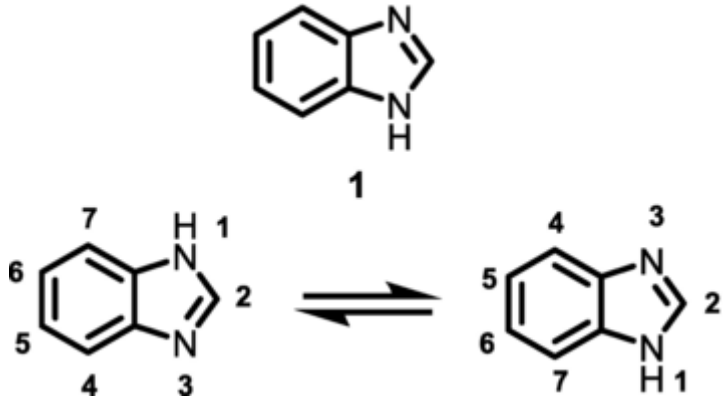


Figure 1. Benzimidazole (compound 1) with its tautomeric forms

The independent discovery that thiabendazole is deactivated by hydroxylation of the benzene ring and that activity is improved by adding a 2-methylcarbamate moiety to the

imidazole ring led to the development of metronidazole and albendazole. Except for triclabendazole, the main way that the benzimidazoles (and other antiparasitic agents) work against parasites is by selectively binding to the tubulin of nematodes (36). This prevents the tubulin from polymerizing into microtubules, which disrupts cell division and energy pathways. Additionally, the interference with similar vital processes leads to the death of the parasite. Additionally, this tubulin-related action stops helminth egg hatching (41). Treatment for parasite infections involves the use of broad-spectrum benzimidazole anthelmintics such as mebendazole and albendazole. These medications are known to impair the uptake and transport of glucose and ultimately cause cell death by blocking the microtubule systems of parasites and mammalian cells. Albendazole and mebendazole are the most often prescribed medications for intestinal nematode infections, which include ascariasis, hookworm infections, trichuriasis, strongyloidiasis, and enterobiasis. Additionally, intestinal tapeworm infections (taeniases and hymenolepiasis) can be treated with these medications.

In 1982, the medicine albendazole, methyl [5-(propylthio)-1*H*-benzimidazol-2-yl] carbamate, was licenced for use as a broad-spectrum anthelmintic in humans. It has been widely applied to combat a variety of protozoa and parasitic worms. When taken orally, albendazole quickly breaks down into albendazole sulfoxide and albendazole sulfone.

Figure 2. Structure of Albendazole (42)

In 1971, mebendazole, also known as methyl 5-benzoyl-1H-benzimidazol-2-yl-carbamate, was administered to humans for the first time as a broad-spectrum anthelmintic. Mebendazole is a benzimidazole anthelmintic that functions similarly to albendazole and thiabendazole in terms of structure and mode of action. Mebendazole is intended for the treatment of common parasitic worm infections and was licenced for usage in the US in 1974. Chewable tablets containing mebendazole in dosages of 100 mg and 500 mg are marketed both generically and under the trade names Emverm and Vermox. Depending on the indication, the standard dosage for pinworm is 100 or 500 mg once, or different amounts for three days for infections with whipworm, hookworm, and roundworm, or other doses for longer periods of time.

While temporary stomach discomfort, diarrhoea, nausea, dizziness, and headaches are possible side effects, both albendazole and mebendazole have good safety ratings when taken to treat hookworm infection. Concerns have been raised concerning the usage of benzimidazoles in pregnant women and children under the age of one due to their embryotoxic and teratogenic effects in pregnant rats and rabbits. There has not been any evidence of

teratogenicity in humans to date, and aresearch including over 800 women receiving albendazole during the second and third trimesters showed no negative side effects. Nonetheless, it is not advised to use albendazole during the first trimester. In a comparable way, mebendazole and albendazole have been used extensively in mass drug administration (MDA) programmes to treat entire communities, regardless of the age of the persons, despite the lack of formal safety studies in children under the age of two.

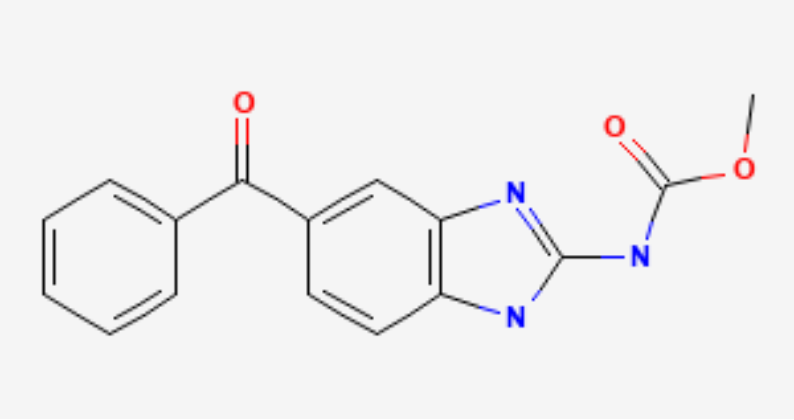


Figure 3. Structure of mebendazole (National Center for Biotechnology Information, 2024).

4. CONCLUSION

For the purpose of implementing therapeutic interventions and preventive measures in these vulnerable preschool-age groups, it is critical to comprehend the prevalence and consequences of infection. The current findings require further proof, and aspects such as geography, seasonality, socioeconomic status, behavior, and deworming programs should be included in future studies.

References

[1] Haghighi, A., Riahi, S.M. and Taghipour, A. (2018) Amoebiasis in Iran: A systematic review and meta-analysis. *Epidemiology Infection*, 146(15): 1880–90.

[2] Chelkeba, L., Mekonnen, Z. and Alemu, Y. (2020) Epidemiology of intestinal parasitic infections in preschool and school-aged Ethiopian children: A systematic review and meta-analysis. *BMC Public Health*, 20(1): 1–16.

[3] Taghipour, A., Tabarsi, P. and Sohrabi, M.R. (2019). Frequency, associated factors and clinical symptoms of intestinal parasites among tuberculosis and non-tuberculosis groups in Iran: a comparative cross-sectional study. *Transactions of The Royal Society of Tropical Medicine and Hygiee*, 113(5): 234–41.

[4] Eslahi, A.V., Badri, M. and Nahavandi, K.H. (2021) Prevalence of strongyloidiasis in the general population of the world: A systematic review and metaanalysis. *Pathogens Global Health*, 115(1): 7–20.

[5] Taghipour, A., Bahadory, S. and Badri, M. (2022) A systematic review and meta-analysis on the co-infection of Helicobacter pylori with intestinal parasites: Public health issue or neglected correlation? *International Journal of Environmental Health Research*, 32(4):808–18.

[6] Murray, C.J., Barber, R.M. and Foreman, K.J. (2015). Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990–2013: quantifying the epidemiological transition. *Lancet*, 386: 2145–91.

[7] Pabalan, N., Singian, E., Tabangay, L., Jarjanazi, H., Boivin, M.J. and Ezeamama, A.E.J. (2014) Soil-transmitted helminth infection, loss of education and cognitive impairment in school-aged children: A systematic review. *PLoS Negl Trop Dis* 2018 Jan 12;12(1): e0005523

[8] Strunz, E.C., Addiss, D.G., Stocks, M.E., Ogden, S., Utzinger, J. and Freeman, M.C. (2014) Water, sanitation, hygiene, and soil-transmitted helminth infection: a systematic review and meta-analysis. *PLoS Medicine*, 11: 1001620.

[9] WHO. (2015) Water, sanitation and hygiene for accelerating and sustaining progress on neglected tropical diseases. A global strategy 2015–2020. Geneva: World Health Organization.

[10] Hotez, P.J., Alvarado, M. and Basanez, M.G. (2014) The global burden of disease study 2010: interpretation and implications for the neglected tropical diseases. PLoS Neglected Tropical Disease, 8: 2865.

[11] Starr, M.C. and Montgomery, S.P. (2011) Soil-transmitted helminthiasis in the United States: a systematic review 1940–2010. *American Journal of Tropical Medicine and Hygiene*, 85:

[12] Stolk, W.A., Kulik, M.C. and le Rutte, E.A. (2016) Between-country inequalities in the neglected tropical disease burden in 1990 and 2010, with projections for 2020. *PLoS Neglected Tropical Diseases*, 10: 0004560.680–84.

[13] King, C.H. and Bertino, A.M. (2008) Asymmetries of poverty: why global burden of disease valuations underestimate the burden of neglected tropical diseases. *PLoS Neglected Tropical Diseases*, 2: 209.

[14] Tadege, B. and Shimelis, T. (2017) Infections with Schistosoma mansoni and geohelminths among school children dwelling along the shore of the Lake Hawassa, southern Ethiopia. *PLoS One*. 12(7):0181547. doi: 10.1371/journal.pone.0181547.

[15] Loukas, A., Hotez, P.J., Diemert, D., Yazdanbakhsh, M., McCarthy, J.S., Correa-Oliveira, R., Croese, J. and Bethony, J.M. (2016) Hookworm infection. *Nature Reviews Diseases Primers*, 8;2:16088. doi: 10.1038/nrdp.2016.88. PMID: 27929101.

[16] World Health Organisation (2023) Soil-transmitted helminth infections fact sheet.

[17] World Health Organization, “2030 targets for soil-transmitted helminthiasis control programmes,” World Health Organization, 2020, https://www.who.int/intestinal_worms/resources/ 9789240000315/e.

[18] Haldeman, M.S., Nolan, M.S. and Ng'habi, K.R. (2020) Human hookworm infection: Is effective control possible? A review of hookworm control efforts and future directions. *Acta tropica*, 201:105214.

[19] Ghodeif, A.O. and Jain, H. (2023) Hookworm. National Library of Medicine: StatPearls Publishing; 2023.

[20] Tadege, B. and Shimelis, T. (2017) Infections with Schistosoma mansoni and geohelminths among school children dwelling along the shore of the Lake Hawassa, southern Ethiopia. *PLoS One*. 12(7):0181547. doi: 10.1371/journal.pone.0181547

[21] Loukas, A., Maizels, R.M. and Hotez, P.J. (2021) The yin and yang of human soil-transmitted helminth infections. *International Journal of Parasitology*, 51(13-14):1243–53. https://doi.org/10.1016/j.ijpara.2021.11.001.

[22] Zeleke, A.J., Addisu, A., Derso, A., Tegegne, Y., Birhanie, M. and Sisay, T. (2021) Evaluation of Hookworm Diagnosis Techniques from Patients in Debre Elias and Sanja Districts of the Amhara Region, Ethiopia. *Journal of Parasitology Research*. 2021; 2021.

[23] Hotez, P.J., Alvarado, M. and Basanez, M.G. (2014) The global burden of disease study 2010: interpretation and implications for the neglected tropical diseases. *PLoS Neglected Tropical Disease*, 8: 2865.

[24] Lenk, E.J., Redekop, W.K., Luyendijk, M., Rijnsburger, A.J. and Severens, J.L. (2016) Productivity loss related to neglected tropical diseases eligible for preventive chemotherapy: a systematic literature review. *PLoS neglected tropical diseases*.10(2):0004397.

[25] Majid, M.F., Kang, S.J. and Hotez, P.J. (2019) Resolving" worm wars": An extended comparison review of findings from key economics and epidemiological studies. *PLoS neglected tropical diseases*, 13 (3): 0006940.

[26] Vercruysse, J., Behnke, J.M., Albonico, M., Ame, S.M., Angebault, C. and Bethony, J.M. (2011) Assessment of the anthelmintic efficacy of albendazole in school children in seven countries where soil-transmitted helminths are endemic. *PLoS Neglected Tropical Diseases*, 5(3):948.

[27] Brooker, S., Bethony, J. and Hotez, P.J. (2004) Human hookworm infection in the 21st century. *Advances in Parasitology*, 58:197.

[28] Jourdan, P.M., Lamberton, P.H., Fenwick, A. and Addiss, D.G. (2018) Soil-transmitted helminth infections. *The Lancet*, 391(10117): 252-65.

[29] Keiser, J. and Utzinger, J. (2008) Efficacy of current drugs against soil-transmitted helminth infections: systematic review and meta-analysis. *Jama*, 299(16):1937-48.

[30] Vercruysse, J., Behnke, J.M., Albonico, M., Ame, S.M., Angebault, C. and Bethony, J.M. (2011) Assessment of the anthelmintic efficacy of albendazole in school children in seven countries where soil-transmitted helminths are endemic. *PLoS Neglected Tropical Diseases*, 5(3):948.

[31] Soukhathammavong, P.A., Sayasone, S., Phongluxa, K., Xayaseng, V., Utzinger, J., and Vounatsou, P. (2012) Low efficacy of single-dose albendazole and mebendazole against

hookworm and effect on concomitant helminth infection in Lao PDR. *PLoS Neglected Tropical Diseases*, 6(1):1417.

[32] Haldeman, M.S., Nolan, M.S. and Ng'habi, K.R. (2020) Human hookworm infection: Is effective control possible? A review of hookworm control efforts and future directions. *Acta tropica*, 201:105214.

[33] Asaolu, S.O. and Ofoezie, I.E. (2003) The role of health education and sanitation in the control of helminth infections. *Acta Tropica*, 86, 283–294. https://doi.org/10.1016/S0001-706X(03)00060-3.

[34] Haldeman, M.S., Nolan, M.S. and Ng'habi, K.R. (2020) Human hookworm infection: Is effective control possible? A review of hookworm control efforts and future directions. *Acta tropica*, 201:105214.

[35] Gibson, S. B., Ness-Cohn, E., & Andersen, E. C. (2022). Benzimidazoles cause lethality by inhibiting the function of Caenorhabditis elegans neuronal beta-tubulin. *International journal for parasitology. Drugs and drug resistance*, 20, 89–96. https://doi.org/10.1016/j.ijpddr.2022.10.004.

[36] James S. McCarthy, Thomas A. Moore. Drugs for Helminths, Editor(s): John E. Bennett, Raphael Dolin, Martin J. Blaser, Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases (Eighth Edition), W.B. Saunders, 2015, Pages 519-527.e3. https://doi.org/10.1016/B978-1-4557-4801-3.00042-4.

[37] Hofmann, D., Brussee, J. M., Schulz, J. D., Coulibaly, J. T., Pfister, M., & Keiser, J. (2022). Pharmacokinetic modelling and simulation to optimize albendazole dosing in hookworm- or Trichuris trichiura-infected infants to adults. *The Journal of antimicrobial chemotherapy*, 77(4), 1082–1093. https://doi.org/10.1093/jac/dkac020.

[38] Tahlan, S., Kumar, S., Kakkar, S., & Narasimhan, B. (2019). Benzimidazole scaffolds as promising antiproliferative agents: a review. *BMC chemistry*, 13(1), 66. https://doi.org/10.1186/s13065-019-0579-6.

[39] Vasava, M. S., Bhoi, M. N., Rathwa, S. K., Jethava, D. J., Acharya, P. T., Patel, D. B., & Patel, H. D. (2020). Benzimidazole: A Milestone in the Field of Medicinal Chemistry. *Mini reviews in medicinal chemistry*, 20(7), 532–565. https://doi.org/10.2174/1389557519666191122125453.

[40] Loukas, A., Hotez, P. J., Diemert, D., Yazdanbakhsh, M., McCarthy, J. S., Correa-Oliveira, R., Croese, J., & Bethony, J. M. (2016). Hookworm infection. *Nature reviews. Disease primers*, *2*, 16088. https://doi.org/10.1038/nrdp.2016.88.

[41] LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Mebendazole. [Updated 2021 Sep 18]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK547885/

[42] Chai, J. Y., Jung, B. K., & Hong, S. J. (2021). Albendazole and Mebendazole as Anti-Parasitic and Anti-Cancer Agents: an Update. *The Korean journal of parasitology*, 59(3), 189–225. https://doi.org/10.3347/kjp.2021.59.3.189

[43] National Center for Biotechnology Information (2024). PubChem Compound Summary for CID 4030, Mebendazole. Retrieved June 19, 2024 from https://pubchem.ncbi.nlm.nih.gov/compound/Mebendazole