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Present status with impacts and roles of miRNA on Soil Transmitted Helminthiasis control: A review

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ABSTRACT

Soil-Transmitted Helminthiasis (STH) is one of the most widespread Neglected Tropical Diseases (NTDs), and almost 1.5 billion of the global population is affected, mostly in the indigent, countryside sectors of tropics/subtropics. STH, commonly caused by various nematodes, adversely affects the hosts' growth, cognitive development, and immunity. Albendazole is most commonly used against STH (Soil-Transmitted Helminths) but resistance has already been reported in different countries. To date, no effective vaccine is present against STH. miRNAs are a unique class of small non-coding RNA, regulating various biological activities including host immune responses in host-pathogen interaction of STH. Dysregulation of miRNAs are being considered as one of the most important aspect of host-parasite interactions. Thus, it is the prime importance to identify and characterize parasite-specific as well as host-derived miRNAs to understand the STH infection at the molecular level. Systematic bibliometric analysis reveals a huge knowledge gap in understanding the disease by using both host and parasitic miRNAs as a potential biomarker. In this study, we addressed the present status of the STH prevalence, and therapy under the light of miRNAs. This would further help in designing new inhibitors and therapeutic strategies to control STH.

1. Introduction

Neglected tropical diseases (NTDs) are the particular category of infectious diseases that mostly influence indigent, countryside sectors of the tropical as well as subtropical areas of our world. Among these, Soil-Transmitted helminthiasis (STH) is one of the most widespread forms of NTD. The nematodes like hookworms (*Ancylostoma duodenale*, *Necator americanus*), *Ascaris lumbricoides*, whipworms (*Trichuris trichiura*) and threadworms (*Strongyloides stercoralis*), are considered as STH. There are around 1.5 billion individuals affected worldwide by STH (Moser et al., 2017; Anisuzzaman and Tsuji, 2020, Anisuzzaman et al. 2023), in which India alone comes up with approximately 25% of the total cases. The World Health Organization (WHO) announced that in India around 220 million school-going kids, aged between 1 and 14 years are massively threatened by STH infection (WHO, 2012). They can adversely affect growth, rational development as well as immunity against other diseases (Raj et al., 1997). Albendazole is the most common medicine, given to the kids to prevent STH. Although it is reported to be a safe drug, but

several cases of side effects have been reported to the people after Mass Drug Administration (MDA) (Gupta., 2017).

One of the key strategies to counter helminthic infection and probable drug resistance is to identify the roles of miRNA in modulating STH. Parasite miRNAs can utilize host miRNAs for their survival. miRNAs have a definite role in parasitic development in different modes of environmental changes in the host body (Arora et al., 2017). In the genome, the clustering of miRNAs is an interesting phenomenon that is very species-specific, and shows functional linkage (Britton et al., 2014). Comparative analysis of helminth genomes has revealed that few miRNAs are conserved whereas others are helminth specific. Many conserved miRNAs show similar sequences that are very identical to mammalian miRNAs that are considered as regulators in the immune system. Several soluble proteins or glycans are secreted from parasitic helminths that can suppress the differentiation process of M1 macrophages present in the host body (Tran et al., 2021).

In this present study, we are focusing on documenting the present status of STH infection globally. Also, through bibliometric study of the

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Oyebamiji et al., 2018; Sacolo-Gwebu et al., 2019; Sanchez et al., 2013; Tekaligi et al., 2019). In different districts of Bihar state, India, 95% children are habituated to defecating in openly manner and 60% of them are not using soap to clean their hands (Greenland et al., 2015). In India, helminth infections are also prevalent in all the parts of the country like tea plantation areas of Darjeeling (Das et al., 2019), South Bengal (Mukherjee et al., 2013), North-East India (Ganguly et al., 2019), Uttar Pradesh (Ganguly et al., 2017) and rural parts of south India (Kaliappan et al., 2022; Mahapatra et al., 2020).

4. Transmission strategies adopted by helminths

Eggs, larvae, and adults are the three major life cycle phases of these worms. Adult worms generally infect the definitive host in which sexual reproduction and egg production occur while larval forms of STH are free-living. Mainly two routes of transmission – feco-oral as well as transdermal are being utilized by the parasites. People typically become infected with whipworms by ingesting food and/or water containing viable infective stage (eggs containing first larval stage) (Else et al., 2020). Like whipworm, pinworm infection is transmitted through the feco-oral route. Initially, the eggs appear in the perianal regions. After that, they can prevail for up to 21 days in nature and develops to the infective eggs (eggs containing L3). It may be consumed via contaminated water, food and even inhaled from contaminated bed and cloths. *Ascaris lumbricoides* may enter our body by ingesting infective eggs (eggs containing L2). Children usually put their contaminated dirty fingers or hands into their mouth while playing in the field. *Ascaris* may also be transmitted by consuming raw vegetables, and fruits that are not cooked or washed properly. In the case of hookworm, the eggs hatch and go through two times of moulting in soil and then the 3rd stage larval form infects the human host by dermal penetration while walking barefoot on contaminated soil. After that, they further migrate to the lungs and finally establish themselves in the human intestines (Bharti et al., 2018).

5. Effect STH infection on nutrition and health

While most of the infections are asymptomatic and mild, moderate to severe worm infestations may delay growth, compromise nutrition and develop poor academic skills among children. Malnutrition may be developed by deficiency of micro and macronutrients. The loss of appetite and gastric enteropathy further worsen nutritional deficiencies (Stephenson et al., 2000; de Silva et al., 2003; Albonico et al., 2008).

Several studies have reported that STH infections bring about morbidity by hampering nutritional conditions along with weakening logical operations, particularly among school going children (Brito et al., 2006; Crompton and Nesheim, 2002; Curtale et al., 1999; de Silva et al., 2003; Ostan et al., 2007). In several studies, it has been stated that hemoglobin levels are elevated in infected children of two-year-old due to anthelmintic medication (Stoltzfus et al. 1998, 2004), indicating STH is associated with blood loss and anemia.

6. Prevention strategies against STH transmission

In India, albendazole is considered to be a highly efficient deworming drug for hookworm and *Ascaris* infections but shows limited effect in the case of whipworm infections (Veracruz et al., 2011). In February 2015, the Indian government initiated the National Deworming Day program to deworm every child between 1 and 19 yrs old twice a year. It is considered as special biggest governmental public health plan over the world (NHP, India, 2021). According to WHO, where the frequency of STH infection is more than 20% medication is recommended annually and when exceeds 50% then it should be twice in a year (WHO, 2012). In India, Swachh Bharat Abhiyan activity is especially focusing on the abolishment of open defecation practice to decrease the rate of STH infection. It has been suggested that, at the time of family counselling, and the major hygienic protocols need to be discussed, and more

emphasis to be given on hand cleaning with disinfectant soap after bowel movement, nail cutting, use of cloths, undergarments, toys, bedding, and kitchen utensils after washing and sun drying. And, children must be counselled not to roam around barefoot in the soil. Precautionary therapy should administer to other members of family to inhibit immediate transmission (Dalal et al., 2020)

7. Present status of vaccines against STH

One of the key challenges to encounter and control STH, is to develop a vaccine against different helminthic strains distributed globally. Vaccines could play a vital tool to break the transmission cycle of worms. To date, effective vaccine against STH hasn't been found and no such component has reached up to human clinical trial against *Ascariasis* or any other helminths (Gazzinelli-Guimaraes et al., 2021). Adjuvant selection is another major problem in anti-ascariasis vaccine production because it may cause an allergic reaction in the host. So another priority is to discover functional adjuvants to design adjuvant recombinant vaccines against ascariasis. Reports suggest, a very small number of vaccine candidates against hookworm and schistosomiasis have been brought to the human trial so far. A schistosomiasis vaccine named Bilhvac has just finished phase 3 trial. Other anthelmintic vaccines like Na-APR-1, Na-GST-1, Na-ASP-2 against HW, as well as Sm-TSP-1/SmTSP-2, Sm28GST/Sh28GST, Sm14 and Sm-p80 against schistosomiasis also have been lined up for the clinical trials (Anisuzzaman and Tsuji, 2020).

Helminths always try to adopt defensive mechanisms and secrete considerable amounts of bioactive molecules (BAMs) like inhibitors as well as enzymes to counter host defences and effects of anthelmintics used. These molecules can control their survivability and reproduction. (Anisuzzaman and Tsuji, 2020). Unfortunately, very few studies have been done so far to understand the host-helminth interactions. Recent studies show that all living organisms secrete miRNAs, which play critical roles in the modulation of host-parasite interactions.

8. Overview of miRNA in transmission of helminthic disease

miRNAs (MicroRNAs) are a category of small non-coding RNAs that have appeared as chief regulatory component that can control the gene expression of metazoans, being involved in many different biological processes, including development. miRNAs are endogenous RNAs (~23 nt-long) that combine with target mRNAs to repress their post-transcriptional events. In the nucleus, RNA polymerase II transcribes miRNAs into pri-miRNAs (primary miRNAs) that are further processed by Drosha (an enzyme ribonuclease III) generating a small hairpin-like structure named pre-miRNA (precursor miRNA). Precursor miRNA has been transported into the cytoplasm from nucleus with the help of Exportin 5 protein. The cytoplasm of the cells contain a hairpin loop structure of precursor miRNA is then cleaved by Dicer (an RNase III enzyme) into miRNA duplex (miRNA-miRNA*). Helicase breaks the duplex into a single-strand miRNA and is incorporated into RISC (miRNA-induced silencing complex) which is made up of a major RNA-binding protein belonging to the Argonaute family (AGO). The mature miRISC finally suppresses parasitic growth and development (Chamnanchanunt et al., 2020). It can affect gene stability and regulate gene expression after transcription through such interactions with the 3' UTR (3' untranslated regions) of target mRNAs. Generally, miRNAs can interfere in autophagy, cell signaling, cell death, cell metabolism, cell proliferation as well as differentiation during the commencement of pathogenic infection to generate inflammatory and immune responses. Different kind of miRNAs that has been identified from helminth, are also found in the plasma or serum of a helminth-infected person (Pockar et al., 2019). miRNAs that are present in the helminthes usually helps in the development of the organism from larval stages to the adult, sex determination and regulating metabolic activities (Gazzinelli-Guimaraes and Nutman, 2018). These parasitic miRNAs modulate host immune

Table 3
List of miRNAs identified in various helminthic infection in human.

Type of Helminth	Name of the miRNAs	Role of miRNAs	Reference
<i>Schistosoma mansoni</i>	Bantam, miR-2c-3p, miR-3488 and miR-2a-5p	Development and sex determination of parasitic helminth	(Sotillo et al., 2020)
<i>Schistosoma mansoni</i>	miR-10 and other extracellular vesicle -enclosed miRNAs.	Targets MAP3K7 and consequently downmodulates NF-κB activity to decline type 2 helper T-cell (Th2) immune response	(Meningher et al., 2020; Samoil et al., 2018)
<i>Schistosoma japonicum</i>	sj-miR-125b, sj-miR-190, sj-bantam, sj-miR-36, sj-miR-124, sj-miR-36 miR-155, miR-146a/b, miR-122, miR-21, miR-34a miRNA-33	Parasitic miRNAs help in development morphogenesis and reproduction Human miRNAs help to Suppress the role of Toll-like receptor and cytokine signaling this novel miRNA from egg-derived exosomes of <i>S. japonicum</i> can promote liver fibrosis in the host in a cross-species manner, and the degree of fibrosis can be decreased by inhibiting the expression of this miRNA.	(Arora et al., 2017) (Wang et al., 2022)
<i>Schistosoma japonicum</i>	sj-let-7	Stimulate larva to grow in the human liver	(Unnasch et al., 2018)
<i>Schistosoma japonicum</i>	sj-miR-7	Regulate cercariae development	(Hao et al., 2010)
<i>Schistosoma japonicum</i>	sj-miR-223	Stimulate development of the parasite in the Kupffer cells	(He et al., 2013)
<i>Schistosoma japonicum</i>	miR-2c-3p miR-3488	Regulate cercariae development	(Meningher et al., 2017)
<i>Fasciola hepatica</i>	fhe-mir-71a, fhemir190, fhe-mir-1, fhe-mir-125a (in parasite) fhe-miR-71-P1b, fhe-miR-71-P2, fhe-miR-1-P1, fhe-miR-1-P2, fhe-miR-96 and fhe-miR-7-P1)	Regulate helminth infection in human might be regulating the formation and release of vesicles.	(N.Arora et al., 2017) (Fontenla et al., 2021)
<i>Ascaris suum</i>	asu-miR-391, asu-miR-404	Immune modulation	(Arora et al., 2017)
<i>Taenia solium</i>	miR-12071, miR- 2b, miR-7a, miR-3479b miRs, bantam-3p, let-7-5p, miR-10-5p, miR-71-5p, and miR- 4989-3p miR-10-5p and let-7-5p	Regulate helminth infection by decreasing IL6 decrease the expression of interleukin 16 (<i>Il6</i>), tumor necrosis factor (TNF) and IL-12 secretion.	(Basika et al., 2016; Landa et al., 2019) (Landa et al., 2019)
<i>Echinococcus multilocularis</i>	emu-miR-10, emu-miR-227, miRNAs, miR-71-5p & miR-4989-3p mmu-miR-155-5p	Regulate gene expression downregulate the expression of <i>IKBKE</i> , to elicit immunoregulatory effect on macrophages	(Guo and Zheng, 2020; Ancarola et al., 2020) (Guo and Zheng, 2020)
<i>Ascaris lumbricoides</i>	alu-miR-novel-053, alu-miR-novel-021, alu-miR-novel-064	Change and regulate parasitic environment	(Guo and Zheng, 2020; Ancarola et al., 2020)
<i>Necator americanus</i>	nam-miR-8308, nam-miR-1175-3p nam-miR-25	Regulate protein translation of parasite, maintain cell architecture as well as worm development	(Guo and Zheng, 2020; Ancarola et al., 2020)
<i>Strongyloides stercoralis</i>	STR-MIR-34A-3P, STR-MIR-8397-3P, STR-MIR-34B-3P, STR-MIR-34C-3P, STR-MIR-7880H-5P & STR-MIR-7880M-5P	Involve in metabolic and enzymatic transition of different stages.	(Pomari et al., 2022)
<i>Enterobius vermicularis</i>	let-7	Temporal development of the parasite	(Bracht et al., 2004)

Among patients with NTDs, the miRNAs test could be used as a monitoring tool, but there is some barrier due to limited knowledge regarding clinical application (Chamnanchanunt et al., 2020). Roles of few miRNAs in regulating STH in human have been identified, but still a lot of research need to be done in this aspect, which could provide strong platform to discover newer drug targets and markers for STH diagnosis. A number of miRNAs involved in the STH infection have been listed in Table 3.

10. miRNA based antihelminthic therapy and vaccines

For, mant decades, two different classes of antihelminthic drugs are being used to control STH based on their mode of action: A) Beta tubulin binders, which includes benzimidazole class. Mebendazole and albendazole are widely used drugs in this group. In nematodes, it generally binds to the beta tubulin and hinders microtubule formation, and ruptures the cytoskeleton. It also influences poor glucose uptake in the intestine of worms accelerating starvation. Remarkably, albendazole has both larvicidal along with ovicidal effects in human ascariasis. B) Spastic paralytic agents. levamisole and pyrantel pamoate belong to this class, which initiate physiological responses after binding to the acetylcholine receptors. C) Flaccid paralytic agents including piperazine drug, which reversibly hampers transmission in neuromuscular junction and acts as GABA agonist. It is administered along with some laxatives that can facilitate the exclusion of living paralyzed worms by the peristaltic

movement of the human gut (Gonzalez-Moreno et al., 2011). But, few recent evidences suggested that use of benzimidazole over a prolonged period could give rise to new multi-drug resistance in different species of helminths (Dunn et al., 2019; Kitchen et al., 2019; Orr et al., 2019). Although researchers were unable to find SNPs (Single Nucleotide Polymorphism) related to benzimidazole resistance in adult of *T. trichiura* and *A. lumbricoides*, but they never eliminated the chance of its occurrence (Matamoros et al., 2019). A study revealed that there more chances of benzimidazole resistance that would be terrible for mankind, so systematic monitoring and further analysis are required for chemotherapy programs (Kruken et al., 2017). To date, the specific role of miRNAs and the mechanism of its reduced level after antihelminthic administration in STH are not very clear (Paul et al., 2020). In 2014 Shao et al. identified 97 miRNAs in feces of individuals infected with *A. lumbricoides* infection. Among them alu-miR-novel-021, alu-miR-novel-053, and alu-miR-novel-064 are some candidate miRNAs found to be associated with the survival of parasites by maintaining parasite NADH dehydrogenase and electron carrier functions (Shao et al., 2014). So, drugs or inhibitory molecules that specifically inhibit or decrease the activity of the above mentioned parasitic enzymes could used as potential antihelminthic. In 2016 Kulkarni and Mittal noted that miRNAs like nam-miR-1175-3p, nam-miR-8308, and nam-miR-254 are over-expressed in *Necator americana* helping in their survival in the host (Kulkarni and Mittal, 2016). So, they proposed that these miRNAs could be targeted as potential drug trargets against hookworms. A significant

correlation was also found between miR-2c-3p and praziquantel dose in the case of parasite eradication (Meninger et al., 2017). One specific report has been published stating that some miRNAs in schistosomes interfere in sex-biased gene expression that can be used as novel vaccine targets to develop new vaccines (Cai et al., 2016b). So, more research need to be conducted to discover new miRNA based antihelminthic drugs and vaccines.

11. Conclusion

This study highlights the potential of microRNAs (miRNAs) as molecular tools and biomarkers for Soil-Transmitted Helminthiasis (STH). STH present significant challenges in terms of treatment and control, particularly in Africa, South America, China and in Indian subcontinents etc. The unrelenting and erratic nature of these diseases, along with genetic variations in pathogens and the emergence of drug-resistant strains, necessitate the urge of developing of new drugs against these diseases. Early disease monitoring is crucial, and the detection of miRNAs presents a promising avenue (Hao et al., 2010; Unnasch et al., 2018). Studies have demonstrated the use of candidate miRNAs in predicting treatment outcomes in diseases like *C. trachomatis*. WHO (World Health Organization) recognizes the importance of innovative tools in addressing various neglected tropical diseases including STH, which includes understanding the underlying molecular mechanistic pathway of poor health and early detection (Ackley et al., 2021). miRNAs are attractive candidates for biomarkers as they are stable molecules found in various body fluids. They exhibit disease-specific expression profiles and have specific biological functions. However, a very few studies were conducted on patient samples, and more ground works are necessary to establish reliability and applicability in real-world settings. Overall, miRNAs hold promise as molecular tools for the diagnosis, monitoring, and treatment of neglected parasitic diseases. Continued research, development, and investment in this field are essential to advance our understanding and improve future interventions for STHs.

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Imon Mitra: Methodology, Writing – original draft, Revision. **Arijit Bhattacharya:** Methodology, Writing – review & editing, revision. **Joydeep Paul:** Methodology, Conceptualization, Writing – original draft, revision, Writing – review & editing. **Anisuzzaman:** Methodology, Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

- Anisuzzaman, Tsuji, N., 2020. Schistosomiasis and hookworm infection in humans: disease burden, pathobiology and anthelmintic vaccines. *Parasitol. Int.* 75, 102051 <https://doi.org/10.1016/j.parint.2020.102051>.
- Arora, N., Tripathi, S., Singh, A.K., Mondal, P., Mishra, A., Prasad, A., 2017. Micromanagement of immune system: role of miRNAs in helminthic infections. *Front. Microbiol.* 8, 586. <https://doi.org/10.3389/fmicb.2017.00586>.
- Basika, T., Macchiaroli, N., Cucher, M., Espinola, S., Kamenetzky, L., Zaha, A., Rosenzvit, M., Ferreira, H.B., 2016. Identification and profiling of microRNAs in two developmental stages of the model cestode parasite *Mesocostoides corti*. *Mol. Biochem. Parasitol.* 210 (1-2), 37–49. <https://doi.org/10.1016/j.molbiopara.2016.08.004>.
- Bharti, B., Bharti, S., Khurana, S., 2018. Worm infestation: diagnosis, treatment and prevention. *Indian J. Pediatr.* 85 (11), 1017–1024. <https://doi.org/10.1007/s12098-017-2505-z>.
- Bracht, J., Hunter, S., Eachus, R., Weeks, P., Pasquinelli, A.E., 2004. Trans-splicing and polyadenylation of let-7 microRNA primary transcripts. *RNA* 10 (10), 1586–1594. <https://doi.org/10.1261/rna.7122604>.
- Brito, L.L., Barreto, M.L., Silva Rde, C., Assis, A.M., Reis, M.G., Parraga, I.M., Blanton, R.E., 2006. Moderate- and low-intensity co-infections by intestinal helminths and *Schistosoma mansoni*, dietary iron intake, and anemia in Brazilian children. *Am. J. Trop. Med. Hyg.* 75 (5), 939–944.
- Britton, C., Winter, A.D., Gillan, V., Devaney, E., 2014. microRNAs of parasitic helminths - identification, characterization and potential as drug targets. *Int J Parasitol Drugs Drug Resist* 4 (2), 85–94. <https://doi.org/10.1016/j.ijpddr.2014.03.001>.
- Cai, P., Gobert, G.N., McManus, D.P., 2016a. MicroRNAs in parasitic helminthiasis: current status and future perspectives. *Trends Parasitol.* 32 (1), 71–86. <https://doi.org/10.1016/j.pt.2015.09.003>.
- Cai, P., Hou, N., Piao, X., Liu, S., Liu, H., Yang, F., Wang, J., Jin, Q., Wang, H., Chen, Q., 2011. Profiles of small non-coding RNAs in *Schistosoma japonicum* during development. *PLoS Neglected Trop. Dis.* 5 (8), e1256 <https://doi.org/10.1371/journal.pntd.0001256>.
- Cai, P., Liu, S., Piao, X., Hou, N., Gobert, G.N., McManus, D.P., Chen, Q., 2016b. Comprehensive transcriptome analysis of sex-biased expressed genes reveals discrete biological and physiological features of male and female *Schistosoma japonicum*. *PLoS Neglected Trop. Dis.* 10 (4), e0004684 <https://doi.org/10.1371/journal.pntd.0004684>.
- Cai, P., Piao, X., Hao, L., Liu, S., Hou, N., Wang, H., Chen, Q., 2013. A deep analysis of the small non-coding RNA population in *Schistosoma japonicum* eggs. *PLoS One* 8 (5), e64003. <https://doi.org/10.1371/journal.pone.0064003>.
- Chamnanchanunt, S., Svasti, S., Fucharoen, S., Umemura, T., 2020. Neglected tropical diseases: the potential application of microRNAs for monitoring NTDs in the real world. *MicroRNA* 9 (1), 41–48. <https://doi.org/10.2174/2211536608666190620104308>.
- Crompton, D.W., Nesheim, M.C., 2002. Nutritional impact of intestinal helminthiasis during the human life cycle. *Annu. Rev. Nutr.* 22, 35–59. <https://doi.org/10.1146/annurev.nutr.22.120501.134539>.
- Cucher, M., Macchiaroli, N., Kamenetzky, L., Maldonado, L., Brehm, K., Rosenzvit, M.C., 2015. High-throughput characterization of *Echinococcus* spp. metacystode miRNomes. *Int. J. Parasitol.* 45 (4), 253–267. <https://doi.org/10.1016/j.ijpara.2014.12.003>.
- Curtale, F., Pezzotti, P., Saad, Y.S., Aloi, A., 1999. An analysis of individual, household, and environmental risk factors for intestinal helminth infection among children in Qena Governorate, Upper Egypt. *J. Trop. Pediatr.* 45 (1), 14–17. <https://doi.org/10.1093/tropej/45.1.14>.
- Das, S., Mukherjee, A., Mallick, S., Bhattacharjee, S., Chakraborty, S., Dasgupta, S., 2019. Prevalence of soil-transmitted helminth infestations among children attending Integrated Child Development Service centers in a tea garden area in Darjeeling. *Tropenmed. Parasitol.* 9 (1), 23–29. <https://doi.org/10.4103/tp.TP.55.17>.
- de Silva, N.R., Brooker, S., Hotez, P.J., Montresor, A., Engels, D., Savioli, L., 2003. Soil-transmitted helminth infections: updating the global picture. *Trends Parasitol.* 19 (12), 547–551. <https://doi.org/10.1016/j.pt.2003.10.002>.
- Dunn, J.C., Bettis, A.A., Wyine, N.Y., Lwin, A.M.M., Tun, A., Maung, N.S., Anderson, R.M., 2019. Soil-transmitted helminth reinfection four and six months after mass drug administration: results from the delta region of Myanmar. *PLoS Neglected Trop. Dis.* 13 (2), e0006591 <https://doi.org/10.1371/journal.pntd.0006591>.
- Else, K.J., Keiser, J., Holland, C.V., Grenis, R.K., Sattelle, D.B., Fujiwara, R.T., Bueno, L.L., Asaolu, S.O., Sowemimo, O.A., Cooper, P.J., 2020. Whipworm and roundworm infections. *Nat. Rev. Dis. Prim.* 6 (1), 44. <https://doi.org/10.1038/s41572-020-0171-3>.
- Fontenla, S., Langleib, M., de la Torre-Escudero, E., Dominguez, M.F., Robinson, M.W., Tort, J., 2021. Role of fasciola hepatica small RNAs in the interaction with the mammalian host. *Front. Cell. Infect. Microbiol.* 11, 812141 <https://doi.org/10.3389/fcimb.2021.812141>.
- Ganguly, S., Barkataki, S., Karmakar, S., Sanga, P., Boopathi, K., Kanagasabai, K., Kamaraj, P., Chowdhury, P., Sarkar, R., Raj, D., James, L., Dutta, S., Sehgal, R., Jha, P., Murhekar, M., 2017. High prevalence of soil-transmitted helminth infections among primary school children, Uttar Pradesh, India, 2015. *Infect Dis Poverty* 6 (1), 139. <https://doi.org/10.1186/s40249-017-0354-7>.
- Gazzinelli-Guimaraes, P.H., Nutman, T.B., 2018. Helminth parasites and immune regulation. *F1000Res* 7. <https://doi.org/10.12688/f1000research.15596.1>.
- Ghalehnoei, H., Bagheri, A., Fakhar, M., Mishan, M.A., 2020. Circulatory microRNAs: promising non-invasive prognostic and diagnostic biomarkers for parasitic infections. *Eur. J. Clin. Microbiol. Infect. Dis.* 39 (3), 395–402. <https://doi.org/10.1007/s10096-019-03715-8>.

- Ghedini, E., Wang, S., Spiro, D., Caler, E., Zhao, Q., Crabtree, J., Allen, J.E., Delcher, A.L., Guiliano, D.B., Miranda-Saavedra, D., Angiuoli, S.V., Creasy, T., Amedeo, P., Haas, B., El-Sayed, N.M., Wortman, J.R., Feldblum, T., Tallon, L., Schatz, M., Shumway, M., Koo, H., Salzberg, S.L., Schobel, S., Perlea, M., Pop, M., White, O., Barton, G.J., Carlow, C.K., Crawford, M.J., Daub, J., Dimmic, M.W., Estes, C.F., Foster, J.M., Ganatra, M., Gregory, W.F., Johnson, N.M., Jin, J., Komuniecki, R., Korf, I., Kumar, S., Laney, S., Li, B.W., Li, W., Lindblom, T.H., Lustigman, S., Ma, D., Maina, C.V., Martin, D.M., McCarter, J.P., McReynolds, L., Mitreva, M., Nutman, T. B., Parkinson, J., Peregrin-Alvarez, J.M., Poole, C., Ren, Q., Saunders, L., Sluder, A. E., Smith, K., Stanke, M., Unnasch, T.R., Ware, J., Wei, A.D., Weil, G., Williams, D.J., Zhang, Y., Williams, S.A., Fraser-Liggett, C., Slatko, B., Blaxter, M.L., Scott, A.L., 2007. Draft genome of the filarial nematode parasite *Brugia malayi*. *Science* 317 (5845), 1756–1760. <https://doi.org/10.1126/science.1145406>.
- Greenland, K., Dixon, R., Khan, S.A., Gunawardena, K., Kihara, J.H., Smith, J.L., Drake, L., Makkar, P., Raman, S., Singh, S., Kumar, S., 2015. The epidemiology of soil-transmitted helminths in Bihar State, India. *PLoS Neglected Trop. Dis.* 9 (5), e0003790 <https://doi.org/10.1371/journal.pntd.0003790>.
- Guo, X., Zheng, Y., 2020. Profiling of miRNAs in mouse peritoneal macrophages responding to echinococcus multilocularis infection. *Front. Cell. Infect. Microbiol.* 10, 132. <https://doi.org/10.3389/fcimb.2020.00132>.
- Hao, L., Cai, P., Jiang, N., Wang, H., Chen, Q., 2010. Identification and characterization of microRNAs and endogenous siRNAs in *Schistosoma japonicum*. *BMC Genom.* 11, 55. <https://doi.org/10.1186/1471-2164-11-55>.
- He, X., Sai, X., Chen, C., Zhang, Y., Xu, X., Zhang, D., Pan, W., 2013. Host serum miR-223 is a potential new biomarker for *Schistosoma japonicum* infection and the response to chemotherapy. *Parasites Vectors* 6, 272. <https://doi.org/10.1186/1756-3305-6-272>.
- International Helminth Genomes, C., 2019. Comparative genomics of the major parasitic worms. *Nat. Genet.* 51 (1), 163–174. <https://doi.org/10.1038/s41588-018-0262-1>.
- Jia, T.W., Melville, S., Utzinger, J., King, C.H., Zhou, X.N., 2012. Soil-transmitted helminth reinfection after drug treatment: a systematic review and meta-analysis. *PLoS Neglected Trop. Dis.* 6 (5), e1621 <https://doi.org/10.1371/journal.pntd.0001621>.
- Kaliappan, S., Ramanujam, K., Manuel, M., Farzana, J., Janagaraj, V., Laxmanan, S., Muliylil, J., Sarkar, R., Kang, G., Walson, J., Ajampur, S., 2022. Soil-transmitted helminth infections after mass drug administration for lymphatic filariasis in rural southern India. *Trop. Med. Int. Health* 27 (1), 81–91. <https://doi.org/10.1111/tmi.13697>.
- Kitchen, S., Ratnappan, R., Han, S., Leasure, C., Grill, E., Iqbal, Z., Granger, O., O'Halloran, D.M., Hawdon, J.M., 2019. Isolation and characterization of a naturally occurring multidrug-resistant strain of the canine hookworm, *Ancylostoma caninum*. *Int. J. Parasitol.* 49 (5), 397–406. <https://doi.org/10.1016/j.ijpara.2018.12.004>.
- Kulkarni, A.P., Mittal, S.P., 2016. Sequence data mining in search of hookworm (*Necator americanus*) microRNAs. *Gene* 590 (2), 317–323. <https://doi.org/10.1016/j.gene.2016.05.039>.
- Landa, A., Navarro, L., Ochoa-Sanchez, A., Jimenez, L., 2019. *Taenia solium* and *Taenia crassiceps*: miRNomes of the larvae and effects of miR-10-5p and let-7-5p on murine peritoneal macrophages. *Biosci. Rep.* 39 (11) <https://doi.org/10.1042/BSR20190152>.
- Mahapatra, A., Mohanty, N., Behera, B.K., Dhal, S., Praharaj, A.K., 2020. Soil transmitted helminth infections among school going age children of slums from Bhubaneswar, Odisha. *Tropenmed. Parasitol.* 10 (1), 34–38. <https://doi.org/10.4103/tp.TP.30.19>.
- Matamoros, G., Rueda, M.M., Rodriguez, C., Gabriele, J.A., Canales, M., Fontecha, G., Sanchez, A., 2019. High endemicity of soil-transmitted helminths in a population frequently exposed to albendazole but No evidence of antiparasitic resistance. *Trop Med Infect Dis* 4 (2). <https://doi.org/10.3390/tropicalmed4020073>.
- Meningher, T., Barsheshet, Y., Ofir-Birin, Y., Gold, D., Brant, B., Dekel, E., Sidi, Y., Schwartz, E., Regev-Rudzi, N., Avni, O., Avni, D., 2020. Schistosomal extracellular vesicle-enclosed miRNAs modulate host T helper cell differentiation. *EMBO Rep.* 21 (1), e47882 <https://doi.org/10.15252/embr.201947882>.
- Meningher, T., Lerman, G., Regev-Rudzi, N., Gold, D., Ben-Dov, I.Z., Sidi, Y., Avni, D., Schwartz, E., 2017. Schistosomal microRNAs isolated from extracellular vesicles in sera of infected patients: a new tool for diagnosis and follow-up of human schistosomiasis. *J. Infect. Dis.* 215 (3), 378–386. <https://doi.org/10.1093/infdis/jiw539>.
- Midzi, N., Mtapuri-Zinyowera, S., Mappingure, M.P., Paul, N.H., Sangweme, D., Hlerema, G., Mutsaka, M.J., Tongogara, F., Makware, G., Chadukura, V., Brouwer, K. C., Mutapi, F., Kumar, N., Mdlulza, T., 2011. Knowledge attitudes and practices of grade three primary schoolchildren in relation to schistosomiasis, soil transmitted helminthiasis and malaria in Zimbabwe. *BMC Infect. Dis.* 11, 169. <https://doi.org/10.1186/1471-2334-11-169>.
- Moser, W., Labhardt, N.D., Cheleboi, M., Muhairwe, J., Keiser, J., 2017. Unexpected low soil-transmitted helminth prevalence in the Buthe-Buthe district in Lesotho, results from a cross-sectional survey. *Parasites Vectors* 10 (1), 72. <https://doi.org/10.1186/s13071-017-1995-x>.
- Mu, Y., McManus, D.P., Gordon, C.A., Cai, P., 2021. Parasitic helminth-derived microRNAs and extracellular vesicle Cargos as biomarkers for helminthic infections. *Front. Cell. Infect. Microbiol.* 11, 708952 <https://doi.org/10.3389/fcimb.2021.708952>.
- Narkkul, U., Na-Ek, P., Kaewkungwal, J., Punsawad, C., 2022. Knowledge, attitudes, and practices regarding soil-transmitted helminthiasis among village health volunteers in Nakhon Si Thammarat province, Thailand: a cross-sectional study. *Trop Med Infect Dis* 7 (2). <https://doi.org/10.3390/tropicalmed7020033>.
- Okorie, P.N., Bockarie, M.J., Molyneux, D.H., Kelly-Hope, L.A., 2014. Neglected tropical diseases: a systematic evaluation of research capacity in Nigeria. *PLoS Neglected Trop. Dis.* 8 (8), e3078 <https://doi.org/10.1371/journal.pntd.0003078>.
- Orr, A.R., Quagrain, J.E., Suwondo, P., George, S., Harrison, L.M., Dornas, F.P., Evans, B., Caccone, A., Humphries, D., Wilson, M.D., Cappello, M., 2019. Genetic markers of benzimidazole resistance among human hookworms (*Necator americanus*) in Kintampo North municipality, Ghana. *Am. J. Trop. Med. Hyg.* 100 (2), 351–356. <https://doi.org/10.4269/ajtmh.18-0727>.
- Ostan, L., Kilimcioglu, A.A., Girginkardesler, N., Ozyurt, B.C., Limoncu, M.E., Ok, U.Z., 2007. Health inequities: lower socio-economic conditions and higher incidences of intestinal parasites. *BMC Publ. Health* 7, 342. <https://doi.org/10.1186/1471-2458-7-342>.
- Oyebamiji, D.A., Ebisike, A.N., Egede, J.O., Hassan, A.A., 2018. Knowledge, attitude and practice with respect to soil contamination by Soil-Transmitted Helminths in Ibadan, Southwestern Nigeria. *Parasite Epidemiol Control* 3 (4), e00075. <https://doi.org/10.1016/j.parepi.2018.e00075>.
- Parikh, D.S., Totanes, F.I., Tuliao, A.H., Ciro, R.N., Macatangay, B.J., Belizario, V.Y., 2013. Knowledge, attitudes and practices among parents and teachers about soil-transmitted helminthiasis control programs for school children in Guimaras, Philippines. *Southeast Asian J. Trop. Med. Publ. Health* 44 (5), 744–752.
- Paul, S., Ruiz-Manriquez, L.M., Serrano-Cano, F.I., Estrada-Meza, C., Solorio-Diaz, K.A., Srivastava, A., 2020. Human microRNAs in host-parasite interaction: a review. *3 Biotech* 10 (12), 510. <https://doi.org/10.1007/s13205-020-02498-6>.
- Pockar, S., Globocnik Petrovic, M., Peterlin, B., Vidovic Valentincic, N., 2019. miRNA as biomarker for urethritis - a systematic review of the literature. *Gene* 696, 162–175. <https://doi.org/10.1016/j.gene.2019.02.004>.
- Pomari, E., Malerba, G., Veschetti, L., Franceschi, A., Moron Dalla Tor, L., Deiana, M., Degani, M., Mistretta, M., Patuzzo, C., Ragusa, A., Mori, A., Bisoffi, Z., Buonfrate, D., 2022. Identification of miRNAs of *Strongyloides stercoralis* L1 and IL3 larvae isolated from human stool. *Sci. Rep.* 12 (1), 9957. <https://doi.org/10.1038/s41598-022-14185-y>.
- Raj, S.M., Sein, K.T., Anuar, A.K., Mustaffa, B.E., 1997. Effect of intestinal helminthiasis on school attendance by early primary schoolchildren. *Trans. R. Soc. Trop. Med. Hyg.* 91 (2), 131–132. [https://doi.org/10.1016/s0035-9203\(97\)90196-6](https://doi.org/10.1016/s0035-9203(97)90196-6).
- Sacolo-Gwebu, H., Kabuyaya, M., Chimbari, M., 2019. Knowledge, attitudes and practices on schistosomiasis and soil-transmitted helminths among caregivers in Ingwavuma area in uMkhanyakude district, South Africa. *BMC Infect. Dis.* 19 (1), 734. <https://doi.org/10.1186/s12879-019-4253-3>.
- Samoil, V., Dagenais, M., Ganapathy, V., Aldridge, J., Glebov, A., Jardim, A., Ribeiro, P., 2018. Vesicle-based secretion in schistosomes: analysis of protein and microRNA (miRNA) content of exosome-like vesicles derived from *Schistosoma mansoni*. *Sci. Rep.* 8 (1), 3286. <https://doi.org/10.1038/s41598-018-21587-4>.
- Sanchez, A.L., Gabriele, J.A., Usuanlele, M.T., Rueda, M.M., Canales, M., Gyorkos, T.W., 2013. Soil-transmitted helminth infections and nutritional status in school-age children from rural communities in Honduras. *PLoS Neglected Trop. Dis.* 7 (8), e2378 <https://doi.org/10.1371/journal.pntd.0002378>.
- Schistosoma japonicum* Genome S, Functional analysis C, 2009. The *Schistosoma japonicum* genome reveals features of host-parasite interplay. *Nature* 460 (7253), 345–351. <https://doi.org/10.1038/nature08140>.
- Shao, C.C., Xu, M.J., Alasaad, S., Song, H.Q., Peng, L., Tao, J.P., Zhu, X.Q., 2014. Comparative analysis of microRNA profiles between adult *Ascaris lumbricoides* and *Ascaris suum*. *BMC Vet. Res.* 10, 99. <https://doi.org/10.1186/1746-6148-10-99>.
- Sotillo, J., Robinson, M.W., Kimber, M.J., Cucher, M., Ancarola, M.E., Nejsum, P., Marcilla, A., Eichenberger, R.M., Tritten, L., 2020. The protein and microRNA cargo of extracellular vesicles from parasitic helminths - current status and research priorities. *Int. J. Parasitol.* 50 (9), 635–645. <https://doi.org/10.1016/j.ijpara.2020.04.010>.
- Stoltzfus, R.J., Albonico, M., Chwaya, H.M., Tielsch, J.M., Schulze, K.J., Savioli, L., 1998. Effects of the Zanzibar school-based deworming program on iron status of children. *Am. J. Clin. Nutr.* 68 (1), 179–186. <https://doi.org/10.1093/ajcn/68.1.179>.
- Stoltzfus, R.J., Chway, H.M., Montresor, A., Tielsch, J.M., Jape, J.K., Albonico, M., Savioli, L., 2004. Low dose daily iron supplementation improves iron status and appetite but not anemia, whereas quarterly anthelmintic treatment improves growth, appetite and anemia in Zanzibari preschool children. *J. Nutr.* 134 (2), 348–356. <https://doi.org/10.1093/jn/134.2.348>.
- Tekalign, E., Bajiro, M., Ayana, M., Tiruneh, A., Belay, T., 2019. Prevalence and intensity of soil-transmitted helminth infection among rural community of southwest Ethiopia: a community-based study. *BioMed Res. Int.* 2019, 3687873 <https://doi.org/10.1155/2019/3687873>.
- Tran, N., Ricafrente, A., To, J., Lund, M., Marques, T.M., Gama-Carvalho, M., Cwiklinski, K., Dalton, J.P., Donnelly, S., 2021. Fasciola hepatica hijacks host macrophage miRNA machinery to modulate early innate immune responses. *Sci. Rep.* 11 (1), 6712. <https://doi.org/10.1038/s41598-021-86125-1>.
- Unnasch, T.R., Golden, A., Cama, V., Cante, P.T., 2018. Diagnostics for onchocerciasis in the era of elimination. *Int Health* 10 (suppl_1), i20–i26. <https://doi.org/10.1093/inthealth/ihx047>.
- Vercruyse, J., Behnke, J.M., Albonico, M., Ame, S.M., Angebault, C., Bethony, J.M., Engels, D., Guillard, B., Nguyen, T.V., Kang, G., Kattula, D., Kotze, A.C., McCarthy, J. S., Mekonnen, Z., Montresor, A., Periago, M.V., Sumo, L., Tchuente, L.A., Dang, T.C., Zeynudin, A., Levecke, B., 2011. Assessment of the anthelmintic efficacy of albendazole in school children in seven countries where soil-transmitted helminths are endemic. *PLoS Neglected Trop. Dis.* 5 (3), e948. <https://doi.org/10.1371/journal.pntd.0000948>.
- Wang, Y., Gong, W., Zhou, H., Hu, Y., Wang, L., Shen, Y., Yu, G., Cao, J., 2022. A novel miRNA from egg-derived exosomes of *Schistosoma japonicum* promotes liver fibrosis

- in murine schistosomiasis. *Front. Immunol.* 13, 860807 <https://doi.org/10.3389/fimmu.2022.860807>.
- Zakeri, A., Hansen, E.P., Andersen, S.D., Williams, A.R., Nejsum, P., 2018. Immunomodulation by helminths: intracellular pathways and extracellular vesicles. *Front. Immunol.* 9, 2349. <https://doi.org/10.3389/fimmu.2018.02349>.
- Zheng, H., Zhang, W., Zhang, L., Zhang, Z., Li, J., Lu, G., Zhu, Y., Wang, Y., Huang, Y., Liu, J., Kang, H., Chen, J., Wang, L., Chen, A., Yu, S., Gao, Z., Jin, L., Gu, W., Wang, Z., Zhao, L., Shi, B., Wen, H., Lin, R., Jones, M.K., Brejova, B., Vinar, T., Zhao, G., McManus, D.P., Chen, Z., Zhou, Y., Wang, S., 2013. The genome of the hydatid tapeworm *Echinococcus granulosus*. *Nat. Genet.* 45 (10), 1168–1175. <https://doi.org/10.1038/ng.2757>.