International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Helminthic Therapy As Modern Immunotherapy

Dr. Musku Nikhitha Reddy

M.V.Sc, Veterinary Parasitology, Independent Researcher, Hyderabad, Telangana, India

Abstract

Helminthic therapy, the deliberate introduction of benign parasitic worms, has emerged as a novel approach to manage autoimmune and allergic diseases. This concept draws on the *hygiene hypothesis*, which suggests that reduced exposure to parasites and microbes in modern, sanitized societies contributes to rising immune dysregulation. Helminths have co-evolved with humans, acting as natural immunoregulators to maintain balance. Experimental and clinical studies have demonstrated promising outcomes in conditions such as crohn's disease, ulcerative colitis, multiple sclerosis, rheumatoid arthritis, and allergic disorders. Specific species, including *Trichuris suis ova* and *Necator americanus*, are under investigation due to their relatively safe profiles and immunomodulatory effects. Additionally, helminth-derived molecules and related biotherapies, such as medicinal leech therapy, offer complementary treatment options for immune modulation. However, challenges remain regarding safety, standardization, ethical concerns, and patient acceptance. This review highlights the scientific basis, mechanisms, current evidence, and limitations of helminthic therapy, emphasizing its potential as an adjunct in the management of immune-mediated disorders.

Keywords: Parasite, Hygiene hypothesis, Immune modulation, Autoimmune diseases, Microbiome

Introduction

Helminthic therapy, sometimes called worm therapy, is based on the idea of introducing benign, mutualistic worms as eggs or larvae to restore immune balance in patients with autoimmune and allergic diseases (Helmby, 2015). Main reason behind the concept of helminthic therapy is co-evolution. Humans and animals have long hosted helminths as part of their microbiome, resulting in an intertwined superorganism that created a degree of interdependence (Trinh *et al*., 2018). Another reason is the westernization of society. There was a large spike in the incidence of autoimmune and allergic diseases such as multiple sclerosis, crohn's disease, inflammatory bowel disease, asthma etc in the 20th century, which was credited with the development of medical treatment facilities, modern water and sewage treatment facilities, personal hygiene, nuclear families which inturn depleted the microbiome (Broussard and Devkota, 2016).

The concept behind this is the Hygiene Hypothesis also known as Old Friend Hypothesis, which suggests that our immune system was adapted in such a way that it has to be able to protect us against an extensive range of disorders and rely on them for optimal functioning, failing which resulted in immune system breakdown (Okada *et al*., 2010). On a comparison between developed and developing, rural communities, in a developed environment where the family size is small, pathogen exposure is low, the incidence of allergic and autoimmune disorders is found to be quite high whereas in developing, rural communities with large family size and high pathogen exposure, the incidence of disorders is low, proving the theory of hygiene hypothesis (Bloomfield *et al.* 2006).

Historical Background

Initial trials using Trichuris suis ova (TSO) for Crohn's disease around 30 years ago showed encouraging results. For example, Elliott *et al*. (2003) found that helminths could reduce colitis symptoms, while Correale and Farez (2007) performed a five-year study about helminthic colonisation in patients with multiple sclerosis and observed that the patients with helminths in gut revealed less symptoms in comparison. Pritchard (2011) was considered a pioneer in this therapy as he self-infected with *Necator americanus* to treat his autoimmune disorder. Pineda *et al.* (2012) documented that helminthic molecules significantly inhibited the progression of rheumatoid arthritis in mice.

Mechanism of action

Quite a disparity is seen in the immune responses stimulated against bacteria, virus and helminthes. In case of bacteria and virus, the host responses stimulated are of more aggressive in nature and mainly geared towards eliminating them. However, the immune responses stimulated by the host against helminthes are of strongly regulatory in character and of less severe in nature (Maizels and Yazdanbakhsh, 2003). The host recognizes the parasite, neutralizes it, and attempts to destroy it upon its entry. To persist, parasites have evolved a range of immune evasion and modulation tactics that help them stay ahead of the host's defenses. As McKay (2006) describes, an effective parasite extracts what it needs from its host, completes its life cycle successfully, and avoids causing significant harm that could endanger its own survival.

Whenever helminthes or other microbes are eliminated from the microbiome, the holobiont of the living being is altered, which leads to alterations in Th1, Th2 effector cells, which then result in autoimmune and allergic disorders. A number of autoimmune diseases are accompanied by overstimulation of Th1 and Th17 responses. The majority of evidence indicates that these responses are downregulated by a modified Th2 response that is induced by helminth exposure (Smallwood *et al*., 2017).

Within 24 hours of infection, helminths typically trigger a strong Th2-dominant immune response (Maizels and Yazdanbakhsh, 2003). To persist, the parasite counteracts this by several immune evasion strategies: (1) enhancing Treg cell activity to dampen Th1 responses (immunosuppression); (2) acting as a continuous stimulus and driving Th2 cells into a tolerant state (immunotolerance); and (3) promoting cytokines such as IL-4, IL-5, and IL-10, which favour a modified Th2 response (Rajamanickam and Babu, 2013).

Experimental studies

Numerous studies in animal models have demonstrated helminths potential to reduce allergic and autoimmune reactions. For instance, Bashir *et al*. (2002) found reduction in peanut allergy severity in helminth-treated mice, while Cooke *et al*. (1999) reported lower autoimmune incidence in mice exposed to *Schistosoma mansoni* ova. Sewell *et al*. (2003) induced experimental autoimmune encephalomyelitis (EAE) in mice to model multiple sclerosis by subcutaneous injection of specific antigens. Subsequent treatment with *Schistosoma mansoni* ova improved muscle paralysis and reduced inflammatory cell infiltration in nervous tissues. Wang *et al*. (2001) induced allergic lung inflammation in mice and administered two doses of *Strongyloides stercoralis*, which led to a marked reduction in allergen-specific IgE levels.

Criteria for Therapeutic Use of Helminths

For a helminth or helminth-derived product to be considered suitable for therapeutic use, it must meet several essential requirements (Sobotkova *et al*., 2019):

- It should cause no or only minimal pathology in the host during and after treatment.
- Its colonisation should remain confined to the gut, without causing long-term harmful effects.
- It must be safe for use in individuals with weakened or suppressed immunity and should not alter host behaviour.
- It should be easy to administer, store, and transport.
- At therapeutic doses, it must not induce disease and must not mature to a stage that poses risk to the host.

Therapeutic Helminths and Helminthic Molecules

Based on these criteria, few helminths have been selected for clinical trials worldwide:

1. ***Trichuris suis*** **ova (Pig Whipworm):** It is one of the most commonly encountered gastrointestinal nematodes in pigs. The ova are collected from the faeces and purified for the treatment purpose. It is mainly indicated in crohn's disease, multiple sclerosis, ulcerative colitis, food allergies, rheumatoid arthritis etc. on clinician's approval, a dose rate of 2500 ova for every 1.5-2 weeks is being followed (Fleming *et al*., 2011).
2. ***Necator americanus*** **(Human Hookworm):** This is the only hookworm currently used in helminthic therapy, as it consumes about ten times less blood than other hookworm species. It is primarily investigated for skin conditions such as psoriasis, chronic eczema, urticaria, and seasonal allergies. (Giacomin *et al*., 2015).
3. ***Trichuris trichiura*** **ova (Human Whipworm):** This species can survive for up to four years in the human host, longer than *N. americanus*. It is mainly used for autoimmune conditions related to gastrointestinal tract. Current practice recommends 1000–2000 ova per patient under physician guidance, depending on severity (Cheng *et al*., 2015).
4. ***Hymenolepis diminuta*** **cysticercoids (Rat Tapeworm):** For therapeutic use, the intermediate host beetles made to feed on infected rat faeces, and the cysticercoids are then harvested and purified (Edelmen *et al*., 1965). This species has gained interest for its potential benefits in neuropsychiatric and other chronic conditions, including ADHD, PTSD, bipolar disorder, anxiety, migraine and non-migraine headaches, autism, cardiac arrhythmias, gum disease, and haemorrhoids (Cheng *et al*., 2015).

Potential Helminthic molecules

In addition to whole helminths, several helminth-derived molecules have demonstrated immune-modulating effects. For example:

1. Excretory–secretory (ES) products from adult *Nippostrongylus brasiliensis* have been shown to reduce asthma development in a mouse model of ovalbumin-induced hypersensitivity (Marsland *et al*., 2005).
2. ES-62, a product derived from *Acanthocheilonema vitae*, can stimulate dendritic cells to induce a modified Th2 response while suppressing Th1 and Th17 pathways (Jang *et al*., 2011).

Leech Therapy

Also known as Hirudotherapy or Medicinal Leech Therapy (MLT). This therapeutic practice utilizes the bioactive compounds present in leech saliva, with various therapeutic effects, including antipyretic, anaesthetic, anticoagulant, and platelet-inhibitory properties. Medicinal leeches are sourced from certified biofarms, thoroughly cleaned, and applied under sterile conditions. After use, they are safely detached from the patient and disposed of as regulated medical waste. Leech therapy is indicated for joint conditions such as osteoarthritis and epicondylitis, as well as for skin grafting, periorbital haematoma, macroglossia, penile replantation, post-phlebitic syndrome, and lymphadenopathies. However, it is contraindicated during pregnancy, in septic conditions, and in haematological disorders such as haemorrhagic diathesis, leukaemia, or bone marrow suppression (Sig *et al*., 2017).

Challenges

Despite its potential benefits, helminthic therapy faces several challenges and limitations in its development and application:

1. Relapse of disease symptoms can occasionally occur if treatment is discontinued after initial improvement, sometimes leading to abnormal immune responses (Fleming *et al*., 2011).
2. There are ethical concerns, as many patients are hesitant about receiving live worms or ova. Practical risks also exist, such as the possibility of aberrant migration of larval stages (L3, L4), which may cause unexpected pathogenic effects (Maruszweska-Cheruiyot *et al*., 2018).
3. Standardisation of dosage regimens and thorough safety assessments are still required.
4. Patient susceptibility must be carefully considered. For example, experimental infection of mice with *Heligmosomoides polygyrus* increased their susceptibility to *Citrobacter rodentium* infection (Chen *et al*., 2006).
5. Some parasites, including *Schistosoma haematobium, Taenia solium, Taenia taeniformis*, and *Spirometra mansonoides,* have been associated with tumour-promoting activities that could pose oncogenic risks (Herrera and Wegman, 2001).
6. Clear and ethical marketing strategies must be developed to ensure responsible promotion of helminthic therapy.
7. While medicinal leech therapy was approved by the FDA in 2004 and by the CDSCO in India in 2008, helminthic therapy remains under an “Investigational New Drug” status with the FDA.

Conclusion

With the global burden of autoimmune and allergic diseases soaring high, it is increasingly important to re-examine the dual role of parasites, not only as pathogens but also as potential allies in immunomodulation. Although parasitism is traditionally defined as harmful to the host, controlled trials and careful clinical studies suggest that this complicated host–parasite relationship may offer therapeutic opportunities. Continued research into helminthic therapy and parasite-derived molecules as a promising approach could help develop novel, evidence-based treatments that contribute to better healthcare in the future.

REFERENCES

1. Bashir M.E., Andersen P., Fuss I.J., “An enteric helminth infection protects against an allergic response to dietary antigen”, *Journal of Immunology*, 2002, 169, 3284–3292.

2. Bloomfield S.F., Smith R.S., Crevel R.W.R., Pickup J., "Too clean, or not too clean: the hygiene hypothesis and home hygiene", *Clinical and Experimental Allergy*, 2006, 36 (4), 402–425.
3. Brady M.T., O'Neill S.M., Dalton J.P., Mills K.H., "Fasciola hepatica suppresses a protective Th1 response against Bordetella pertussis", *Infection and Immunity*, 1999, 67, 5372–5378.
4. Broussard J.L., Devkota S., "The changing microbial landscape of western society: diet, dwellings and discordance", *Molecular Metabolism*, 2016, 5, 737–742.
5. Chen C.C., Louie S., McCormick B.A., "Helminth-primed dendritic cells alter the host response to enteric bacterial infection", *Journal of Immunology*, 2006, 176, 472–483.
6. Cheng A., Jaint D., Thomas S., Wilson J., Parker W., "Overcoming evolutionary mismatch by self-treatment with helminths: current practices and experience", *Journal of Evolutionary Medicine*, 2015, 3, 1–22.
7. Cooke A., Tonks P., Jones F.M., "Infection with Schistosoma mansoni prevents insulin dependent diabetes mellitus in non-obese diabetic mice", *Parasite Immunology*, 1999, 21, 169–176.
8. Correale J., Farez M., "Association between parasite infection and immune responses in multiple sclerosis", *Annals of Neurology*, 2007, 61, 97–108.
9. Edelman M.H., Spingarn C.L., Nauenberg W.G., Greogory C., "Hymenolepis diminuta (rat tapeworm) infection in man", *American Journal of Medicine*, 1965, 38, 951–953.
10. Elliott D.E., Li J., Blum A., Metwali A., Qadir K., Urban J.F., et al., "Exposure to schistosome eggs protects mice from TNBS-induced colitis", *American Journal of Physiology – Gastrointestinal and Liver Physiology*, 2003, 284, G385–G391.
11. Fleming J.O., Isaak A., Lee J.E., Luzzio C.C., Carrithers M.D., Cook T.D., et al., "Probiotic helminth administration in relapsing-remitting multiple sclerosis: a phase 1 study", *Multiple Sclerosis Journal*, 2011, 17, 743–754.
12. Helmby H., "Human helminth therapy to treat inflammatory disorders—where do we stand?", *BMC Immunology*, 2015, 16, 12.
13. Herrera L., Ostrosky-Wegman P., "Do helminths play a role in carcinogenesis?", *Trends in Parasitology*, 2001, 17 , 172–175.
14. Jang S., Cho M.K., Park M., Kang S., Na B.K., Ahn S.C., et al., "Parasitic helminth cystatin inhibits DSS-induced intestinal inflammation via IL-10 macrophage recruitment", *Korean Journal of Parasitology*, 2011, 49, 245–254.
15. Maizels R., Yazdanbakhsh M., "Immune regulation by helminth parasites: cellular and molecular mechanisms", *Nature Reviews Immunology*, 2003, 3, 733–744.
16. Marsland B., Camberis M., Le Gros G., "Secretory products from infective forms of Nippostrongylus brasiliensis induce a rapid allergic airway inflammatory response", *Immunology and Cell Biology*, 2005, 83, 40–47.
17. Maruszewska-Cheruiyot M., Donskow-Kysoniewska K., Doligalska M., "Helminth therapy: advances in the use of parasitic worms against inflammatory bowel diseases and its challenges", *Helminthologia*, 2018, 55, 1–11.
18. McKay D., "The beneficial helminth parasite?", *Parasitology*, 2006, 132, 1–12.
19. Okada H., Kuhn C., Feillet H., Bach J.F., "The 'hygiene hypothesis' for autoimmune and allergic diseases: an update", *Clinical and Experimental Immunology*, 2010, 160, 1–9.
20. Pineda M.A., McGrath M.A., Smith P.C., Al-Riyami L., Rzepecka J., Gracie J.A., et al., "The parasitic helminth product ES-62 suppresses pathogenesis in collagen-induced arthritis by targeting

the IL-17 producing cellular network at multiple sites", *Arthritis and Rheumatism*, 2012, 64, 3168–3178.

21. Pritchard D., Blount D., Schmid G.P., Till S., "Parasitic worm therapy for allergy: is this incongruous or avant-garde medicine?", *Clinical and Experimental Allergy*, 2011, 42, 505–512.
22. Rajamanickam A., Babu S., "Immunomodulation by filarial parasites", *International Trends in Immunity*, 2013, 1, 12–20.
23. Sewell D., Qing Z., Reinke E., Elliott D., Weinstock J., Sandor M., "Immunomodulation of experimental autoimmune encephalomyelitis by helminth ova immunization", *International Immunology*, 2003, 15, 59–69.
24. Sig A.K., Guney M., Guclu A., Ozmen E., "Medical leech therapy: an overall perspective", *Integrative Medicine Research*, 2017, 6 , 123–129.
25. Smallwood T.B., Giacomin P.R., Loukas A., Mulvenna J.P., Clark R.J., Miles J.J., "Helminth immunomodulation in autoimmune disease", *Frontiers in Immunology*, 2017, 8 (n/a), 453.
26. Sobotková K., Parker W., Levá J., Růžková J., Lukeš J., Jirků P.K., "Helminth therapy—from the parasite perspective", *Trends in Parasitology*, 2019, 35, 503–515.
27. Trinh P., Zaneveld J.R., Safranek S., Rabinowitz P.M., "One health relationships between human, animal and environmental microbiomes: a mini-review", *Frontiers in Public Health*, 2018, 6, 235.
28. Wang C.C., Nolan T.J., Schad G.A., Abraham D., "Infection of mice with the helminth Strongyloides stercoralis suppresses pulmonary allergic responses to ovalbumin", *Clinical and Experimental Allergy*, 2001, 31, 495–503.