Research & Reviews

Research and Reviews: Journal of Zoological Sciences

# Helminthic Therapy: A Review

Sasmita Biswal*

Department of Pharmacology, SCB Medical College and Hospital, Cuttack, Odisha, India.

## Review Article

Received: 02/02/2013
Revised: 16/03/2013
Accepted: 19/04/2013

***For Correspondence:**

Department of Pharmacology, SCB Medical College and Hospital, Cuttack, Odisha, India.

**Keywords:** helminthes, immunomodulation, autoimmune disorders

**ABSTRACT**

Autoimmune and inflammatory diseases represent a significant health burden, especially in affluent societies and that no cure exists for majority of these diseases. Medication can slow the disease's progression, but many of the drugs on the market have unpleasant side effects. Current research on parasitic worms (helminthes) has demonstrated a great potential for whole worms, their eggs or their excretory/secretory proteins in down regulating the immune system and hence the associated inflammatory responses both in vitro and in vivo, in various animal models of diseases and in some clinical trials. The helminthes are thought to modulate and down regulate the T helper cell 1 (Th1) and T helper cell 2 (Th2) axis. Helminthic therapy is hence a novel attempt to restore some of the organisms that we have co evolved with, that can modulate our immune system thereby leading to remission or cure from certain incurable inflammatory and auto immune diseases.

## INTRODUCTION

The rapid rise in prevalence of immune mediated diseases, like inflammatory bowel disease, multiple sclerosis and asthma in highly developed industrialized countries, as populations adopt modern hygienic practices, suggests an existence of a strong correlation between improved sanitation and hygiene and a drastic increase in atopic, autoimmune, and inflammatory diseases [1].

Some epidemiologic studies too suggest that people who carry helminthes have less immune mediated diseases as compared to others. This also explains some observational studies, where some allergic diseases like hay fever and eczema, were found to be less common in children from larger families, who presumably were supposed to have more infectious agents acquired through their siblings, in comparison to children from families who had only one child. [2] Similarly researchers have shown that, mice colonized with helminthes were protected from disease manifestations in experimental models of colitis, encephalitis, Type 1 diabetes and asthma [3, 4]. Some clinical trials have also shown that exposure to helminthes reduced the disease activity in patients of Crohn's disease, where 29 patients were advised to ingest 2,500 pig whipworm eggs every three weeks for a period of six months. Amongst all these patients, 23 patients (79.3 %) had significant improvement while 21 of them (72.4 %) had remissions [5, 6].

All these studies suggest that since the human immune system has evolved with helminthes / microorganisms for a long time and that both of them have become mutually symbiotic over such a period of time, the absence of the later due to improved hygiene, immunization or drugs, could result in an increase in the incidence of certain autoimmune diseases and immunological disorders [7]. This is the basis of the origin of a theory called the "hygiene hypothesis" [8]. This theory postulates that the normal immune response is modulated by the inhabiting microorganisms and parasites which forms a balanced ecosystem with the human body. Thus when such parasites are excluded from the ecosystem there is a triggering of exaggerated immune responses which ultimately results in various inflammatory or autoimmune diseases. Certain epidemiological studies have also established the missing link between parasitic infestation and their protective role in prevention of autoimmune diseases, thereby proving the hygiene hypothesis [15].

## The Normal Immune Response

The T helper cells (Th) have critical functions in regulating adaptive immune responses in the human body. Amongst the two types of T helper cells, the T helper 1(Th1) cells are critical for cell mediated immunity while the T helper 2 (Th2) cells are important for immune mediated responses. Th1 cell-mediated response in response to a pathogen, such a virus, intracellular bacterium, fungus, a protozoan, or a cancer cell produces pro-inflammatory cytokines. So persistent Th1 mediated inflammation can be linked with Crohn's disease, rheumatoid arthritis, systemic lupus erythemaosus, and other autoimmune conditions.

On the other hand, the T helper 2 (Th2) cells are important for immune responses against extracellular parasites and involved in the development of asthma and other allergic diseases. By secreting a variety of cytokines, Th2 cells activate B cells, macrophages, mast cells and recruit eosinophils to the inflammatory site. Th2 cells also produce IL-10, IL-21 and IL-25, which are also involved in regulating the magnitude of Th2 responses. A characteristic feature of helminthes induced infection is a Th2-dominated immune response, Excessive Th1 inflammatory response can be regulated by Th2 cytokines. Thus the Th2 cells induce an immune response that targets parasites, toxins, and allergens. Thus the infesting parasites could dampen the excessive Th1 inflammatory immune response that is often implicated in autoimmune diseases.

In atopic disorders there is exposure to an allergen and the body responds to such allergens by producing IgE antibodies against them. The cells that favor the production of IgE are known as Th2 cells, which proliferate, secrete interleukins like IL-4, IL-5 and IL-13 and trigger an inflammatory response. This in turn results in activation of the B cells, development and recruitment of eosinophils, smooth muscle proliferation and increased mucus production. Thus there is a high level of IgE, eosinophils and mast cells which leads to degranulation of eosinophils and mast cells (via IgE linking) which are responsible for most of the clinical manifestations of such diseases [9].

## Immune Responses in Helminth Infestations

Helminthes are parasitic, multicellular metazoan organisms with a potential to cause significant tissue injury as they mature, migrate and feed within the host. Since they live inside the human body, they have evolved many ways to turn down the host immune systems to prevent their self destruction by the host by effective immune evasion strategies by secreting various immuno down regulatory molecules that have profound impacts on the functioning of the host immune system. One of these is a protease inhibitor, cystain which causes changes in the antigen processing and interleukin expression by the host macrophages. Hence chronic parasitic infestation causes T-cell hypo responsiveness and the resultant poor T- cell responses thereby reduces both the allergic responses and the intestinal inflammatory responses to the infested helminthes which helps to maintain their parasitism for a prolonged period [10]. Thus the immune system of a person infected with intestinal parasites is down regulated, for there is production of fewer pro inflammatory components, along with more anti inflammatory components. This immunomodulatory hyporesponsiveness of the immune system induced by helminthes is thought to spill over to other unrelated antigens of autoimmune disorders. Helminthic infestations suppress T-helper Type 1 (Th1) cells while inducing T-helper Type 2 (Th2) immunoresponses, leading to high levels of IgE, eosinophil and mast cells. Hence such high levels are seen in both helminth infestations as well as in atopic disorders like asthma and seasonal rhinitis. Saturation of mast cells by these high circulating levels of IgE can prevent further inflammatory reactions which can be explained by the IgE blocking hypothesis [11]. This suggests that the high IgE levels seen in parasitic infestations can hence paradoxically prevent the development of atopic diseases in parasitic infested individuals as these subjects are somehow protected from mast cell degranulation and inflammation by other allergens due to their high IgE levels.

Eradication of such parasitic worms (helminthes) through increased hygienic practices, may be one such imbalances that has led to increased prevalence of autoimmune diseases, indicating a probable connection between a reduction in parasitic worms in industrialized societies to a significant and sustained increase in such diseases. [12] Besides the chemicals that we are ingesting along with our food, on a daily basis are killing the commensal microorganisms inside our body, which regulate and maintain our immune system, thereby misbalancing the ecosystem in the human body. Infestations with helminthes could thus be beneficial because of their unique capacity to decrease hyper reactive immune responses [13, 14]. Helminthes, like any organism that lives in or on us, has to prevent their destruction by our immune system, and have evolved ways to turn our immune systems down.

## Proposed Theory behind Helminthic Infestation

It has been thus proposed that infections with helminthes can protect one from the development of allergic diseases .Hence helminthic therapy is a novel, emerging, experimental but as yet unapproved treatment for autoimmune diseases, various inflammatory conditions and allergies which involves deliberate infestation with helminthes or their ova into an individual. Theoretically such process can alter the immune responses, against the dysregulated inflammation and thus such helminthes host immune interactions can have potentially important implications for the treatment of many immune mediated diseases. Certain parasitic worms are able to have a beneficial effect because they modulate the T helper cell 1 (Th1) and T helper cell 2 (Th2) axis.

The worms are so modulated, that when used during treatment, they cannot reproduce, and would simply pass out in feces after termination of their life cycle, which is usually 5 years. During their life span in a host, they would blunt the exaggerated immune response, leading to treatment of many incurable immune mediated diseases. Such artificially infested patient cannot infect anyone else and that the treatment can be terminated at any time by use of anthelmintics. It may be suggested that some of the intestinal worms may be probiotic, meaning the parasite is beneficial to its host.

So the immune system of a person infected with hookworm or whipworm appears to be better regulated, produce fewer pro inflammatory components, and more anti inflammatory components.

**What is Helminthic Therapy ?**

Helminthic therapy, a type of immunotherapy, is the treatment of autoimmune diseases and immune disorders by means of deliberate infestation with a helminth or with the ova of a helminthes. Helminthic therapy is currently being studied as a treatment for several (non-viral) auto-immune diseases including celiac disease, Crohn's disease, multiple sclerosis, asthma, and ulcerative colitis. Autoimmune liver disease has also been demonstrated to be modulated by active helminth infections.

Helminthic therapy consists of the inoculation of the patient with specific parasitic intestinal nematodes (helminths). There are currently three closely related treatments available. Inoculation with *Necator americanus*, commonly known as hookworms, or *Trichuris suis* ova (TSO), commonly known as pig whipworm eggs, or inoculation with *Trichuris trichiura* ova, commonly referred to as human whipworm eggs [15] .

Current research and available therapy are targeted at, or available for, the treatment of Crohn's disease, ulcerative colitis,inflammatory bowel disease (IBD), multiple sclerosis, asthma, eczema, dermatitis, hay fever and food allergies.

**For use as a therapeutic agent, the specific helminth should meet all the following minimum requirements:** [16]

- should not have the potential to cause disease in man at therapeutic doses
- should not be able to reproduce in a host, thus allowing control of dose
- should not be a potential vector for other parasites, viruses, or bacteria
- should not be easily transmissible from the host to other people
- should be compatible with a patient's existing medication
- should have a significant period of residence in the host
- must be easily eradicated from the host, if required

Both *Necator americanus* (hookworm) and *Trichuris trichiura* (human whipworm) ova meet these requirements. Neither is known to cause any specific disease in man except some allergic reactions. *N. americanus*, the species of hookworm used therapeutically, takes on average 0.03 ml (less than one drop) of blood per day from the host, so anemia is only observed in malnourished individuals with very large numbers of hookworms;

**Status of Helminthic Therapy**

The concept of helminthic therapy, is quite new and still emerging and thus Helminthic Therapy somewhat unique in emerging medical therapies.There are only a few contraindications, such as very severe anemia, malignancy, blooding disorders and pregnancy, the possible side effects of the worms, which include diarrhea, fatigue, gas and an itch at the inoculation site for hookworm.

Helminthic therapy with both hookworm and TSO has been investigated in research published by the University of Nottingham and University of Iowa.[17]

Helminthic therapy is currently being studied as a treatment for several (non-viral) auto-immune diseases including celiac disease,[18] Crohn's disease, multiple sclerosis, and ulcerative colitis [15, 16,17,18] .

Celiac disease is a very common autoimmune-like disease (1% of Americans are affected although only a minority are aware they have the condition). In this condition, an individual becomes reactive to gluten, a protein in foods derived from wheat, barley, oats and rye.

Hookworms have been found to reduce the risk of developing asthma, while *Ascaris lumbricoides* (roundworm infection) was associated with an increased risk of asthma[3].

### Ethical Aspects

Although the therapy has not yet been approved by the Food and Drug Administration, the FDA has classified helminthes as a drug in November of 2009. So it is an experimental therapy that has not been approved by any governmental body for the treatment or prevention of disease.

## CONCLUSION

Helminths and helminth-derived products are very attractive new targets for drug development. Extensive research shows that parasitic worms have the ability to deactivate certain immune system cells, leading to a gentler immune response. However still, there is much experimentation and research to be completed before such results can be considered conclusive. Helminthic therapy is just one step in restoring the natural environment in our bodies. There is ongoing research in the United States, the United Kingdom and Australia, as well as several other countries

This paper has been compiled for a broad understanding of such innovative and novel therapies. There are no conflicts of interest.

## REFERENCES


1. Summers R, Elliott D, Weinstock J. *Trichuris Suis* In The Therapy Of Inflammatory Bowel Disease: Summary of Two Clinical Studies Conducted in The Center for Digestive Diseases at the University of Iowa. University of Iowa Health Care 2004:1-6.
2. Jung RC, Beaver PC. Clinical observations on *Trichocephalus trichiurus* (whipworm) infestation in children. Pediatrics. 1951; 18: 548-557.
3. Elliott DE, Li J, Crawford C, Blum AM, Metwali A, et al. Exposure to helminthic parasites protect mice from intestinal inflammation. Gastroenterol. 1999; 116: G3072.
4. Khan WI, Blennerhasset PA, Varghese AK, et al. Intestinal nematode infection ameliorates experimental colitis in mice. Infect Immun 2002; 70:5931-7.
5. Niv Y, Torten D, Tamir A, Epstein L. Incidence and prevalence of ulcerative colitis in the upper Galilee. Northern Israel 1967-1986. Am J Gastroenterol. 1990;85:1580-1583.
6. R W Summers, D E Elliott, J F Urban Jr, R Thompson, J V Weinstock. *Trichuris suis* therapy in Crohn's disease. Gut. 2005; 54:87-90.
7. Schnoeller C, Rausch S, Pillai S, Avagyan A, Wittig BM, Loddenkemper C, Hamann A, Hamelmann E, Lucius R, Hartmann S. A helminth immunomodulator reduces allergic and inflammatory responses by induction of IL-10-producing macrophages. J Immunol. 2008; 180: 4265 – 4272.
8. Elliott DE, JJ Urban, CK Argo, JV Weinstock. Does the failure to acquire helminthic parasites predispose to Crohn's disease?. FASEB J. 2000; 14: 1848-1855.
9. Romagnani S. The role of lymphocytes in allergic disease. J Allergy Clin Immunol. 2000; 105: 399.
10. VanRiet E, Hartgers FC, Yazdanbakhsh M. Chronic Helminth Infections Induce Immunomodulation: Consequences and Mechanisms. Immunobiol. 2007; 212 (6):475-490.
11. Johansson SGO. Raised levels of a new immunoglobulin class (IgND) in asthma. Lancet. 1967; 2: 951 – 3.
12. Elliott DE, Summers RW, Weinstock JV. Helminths and the Modulation of Mucosal Inflammation. Curr Opi Gastroenterol. 2005; 21(1):51-58.
13. Sabin EA, Araujo MI, Carvalho EM, Pearce EJ. Impairment of tetanus toxoid specific Th1-like immune responses in humans infected with Schistosoma mansoni. J Infect Dis. 1996; 173:269-272.
14. Borkow G, Leng Q, Weisman Z, Stein M, Galai N, Kalinkovich A, et al. Chronic immune activation associated with intestinal helminth infections results in impaired signal transduction and anergy. J Clin Invest. 2000; 106:1053-1060.
15. Leonardi-Bee J, Pritchard D, Britton J. Asthma and current intestinal parasite infection: systematic review and meta-analysis. Am J Resp Crit Care Med. 2006; 174 (5): 514-523
16. David E Elliott, Robert W Summers, Joel V Weinstock. Helminths as governors of immune-mediated inflammation. Int J Parasitol. 2007; 37 ,457-464.
17. Mortimer K, Brown A, Feary J, et al. Dose - ranging study for trials of therapeutic infection with Necator americanus in humans. Am J Trop Med Hyg. 2006; 75(5): 914-20.
18. Inoculating Celiac Disease Patients With the Human Hookworm Necator Americanus: Evaluating Immunity and Gluten-Sensitivity - Full Text View - ClinicalTrials.gov . Retrieved 2/9/12