Giardiasis: Pathophysiology and Management

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Abstract

Giardia, a common human parasite, can cause significant morbidity; however, natural medicine has great potential to influence the course of Giardia infection. The most beneficial way to treat giardiasis naturally may be through a combination approach, utilizing both nutritional interventions and phytotherapeutic agents. Nutritional intervention aims to reduce the acute symptoms of Giardia and help clear the infection. This can best be achieved by consuming a whole-food based, high-fiber diet that is low in fat, lactose, and refined sugars. Additionally, ingestion of probiotics and wheat germ assists in parasite clearance. Numerous medicinal herbs show promise in the treatment of giardiasis. Berberine-containing herbs, garlic, and the Ayurvedic formulation Pippali rasayana currently have the most clinical evidence supporting their use. Blending the nutritional interventions and phytotherapeutic agents outlined in this article can minimize Giardia symptomatology and aid clearance of the parasite, without significant ill effects. As such, this therapeutic strategy should be considered the first-line approach. Antibiotic use may best be reserved for cases that fail to respond to initial treatment with natural measures.

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Introduction

Giardiasis is caused by the protozoan parasite *Giardia lamblia* (also known as *G. intestinalis* or *G. duodenalis*). Giardiasis is considered the most common protozoal infection in humans; it occurs frequently in both developing and industrialized countries.[1] Worldwide incidence is believed to range between 20-60 percent[2] with 2-7 percent in industrialized nations.[3] *Giardia lamblia* was first described in 1681 after Dutch microscopist Antonie van Leeuwenhoek observed the protozoan in one of his own diarrheic stools: "...wherein I have sometimes also seen animalcules a-moving very prettily...albeit they made a quick motion with their paws, yet for all that they made but slow progress." Van Leeuwenhoek's description is of the Giardia trophozoite.[4]

Giardia can exist in two distinct forms – the cyst (Figure 1) and the trophozoite (Figure 2). Cysts are dormant forms responsible for the transmission of giardiasis. They are excreted from an infected host with the feces, and are exceptionally hardy, being able to tolerate extremes of both pH and temperature.

Transmission to humans usually occurs through the ingestion of cysts in contaminated water or food, or via direct fecal-oral contact.[5] It appears ingestion of a sufficient number of cysts is required to cause infection. Early human research demonstrated ingestion of <10 cysts failed to cause infection, whereas >100 cysts resulted in infection. Signs and symptoms usually begin within 6-15 days of contact with the organism.

Once ingested, cysts pass into the stomach, where they are exposed to gastric acid. The low pH in the stomach and pancreatic proteases

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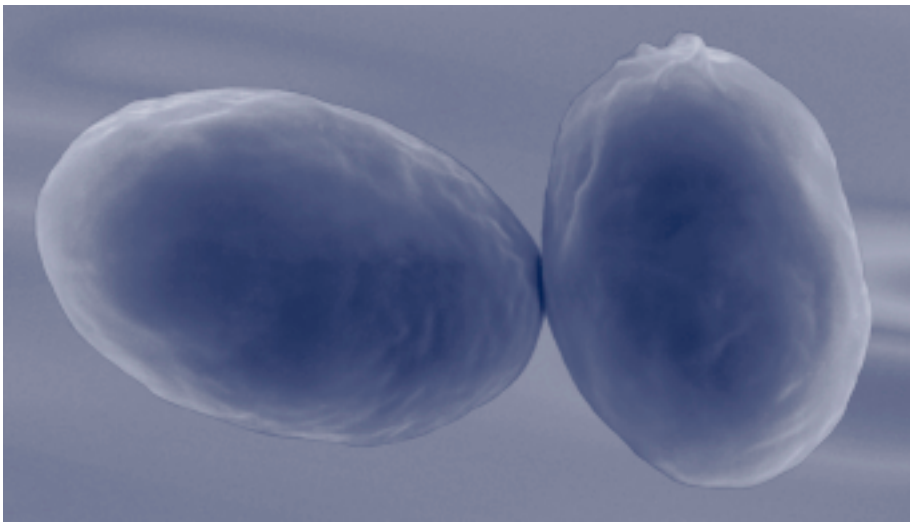
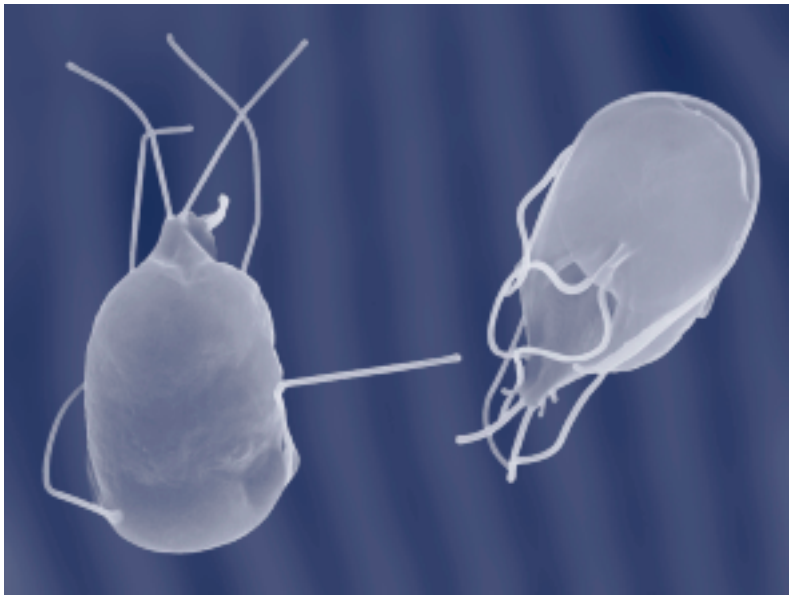
Figure 1. *A Scanning Electron Micrograph of Giardia*



found in the proximal small intestine promote rapid excystation within minutes of reaching the duodenum. Typically, each cyst gives rise to two trophozoites.[6,7]

Figure 2. *Giardia Trophozoites under the View of a Scanning Electron Microscope*



Trophozoites are the vegetative form of Giardia; they are able to colonize and rapidly replicate in the gastrointestinal tract as well as cause gastrointestinal symptoms.[7] Symptoms of Giardia infestation include abdominal pain, nausea, anorexia, diarrhea, vomiting, flatulence, eructation, and fatigue. Signs include weight loss, abdominal distension and tenderness, pale watery stools, malodorous flatulence, and signs of malabsorption (e.g., frothy, foul-smelling stools).[8,9] Less common symptoms include low-grade fever, chills, headaches, urticaria, and polyarthritis. Mucous- and blood-tinged feces are rarely found.[10,11] Symptoms usually range in severity from mild to extreme; however, a significant proportion of infected individuals are completely asymptomatic. In some individuals giardiasis is short-lasting and resolves spontaneously, whereas in others infection can be prolonged and debilitating.[8]

Giardiasis is diagnosed by signs and symptoms, as well as the presence of Giardia cysts and trophozoites in the stool. Stool examination can be unreliable, however, as organisms may be excreted at irregular intervals, which can produce a false negative test result.[10] Hence, definitive diagnosis may require repeated stool examinations, fecal immunoassays, or even sampling of the upper intestinal contents. Two stool examinations will detect 80-90 percent of infections, while three samples detect >90 percent.[12]

Giardiasis can often be distinguished from viral or bacterial gastrointestinal (GI) infections by the longer duration of illness (often 7-10 days by the time of first presentation) and weight loss. In addition, careful history taking may uncover recent travel to tropical or sub-tropical environments, wilderness exposure, or situations involving poor fecal-oral hygiene.[12]

Pathophysiology

Once excystation occurs, Giardia trophozoites use their flagella to "swim" to the microvillus-covered surface of the duodenum and jejunum, where they attach to enterocytes using a special disk located on their ventral surface.[13] In addition, lectins on the surface of Giardia bind to sugars on the surface of enterocytes.[14] The attachment process damages microvilli, which interferes with nutrient absorption. Rapid multiplication of trophozoites eventually creates a physical barrier between the enterocytes and the intestinal lumen, further interfering with nutrient absorption.[13] This process leads to enterocyte damage, villus atrophy, crypt hyperplasia,[15] intestinal hyperpermeability,[16,17] and brush border damage that causes a reduction in disaccharidase enzyme secretion.[18] Recent research also demonstrates the presence of cytopathic substances, such as glycoproteins,[19] proteinases,[20] and lectins[12] that may cause direct damage to the intestinal mucosa. Trophozoites do not usually penetrate the epithelium, invade surrounding tissues, or enter the bloodstream. Thus, infection is generally contained within the intestinal lumen.[13]

Interestingly, the mechanism leading to Giardia-induced diarrhea has not been fully characterized, although one or a combination of the following factors is believed to be involved:

- A glycoprotein located on the surface of *G. lamblia* trophozoites has been demonstrated to induce fluid accumulation in ligated ileal loops in rabbits.[19]
- Giardiasis results in decreased jejunal electrolyte, water, and 3-O-methyl-D-glucose absorption, thus leading to electrolyte, solute, and fluid malabsorption.[15]
- Damage to the intestinal brush border and the corresponding decrease in disaccharidase activity may lead to increased quantities of disaccharides in the intestinal lumen, which can result in osmotic diarrhea.[18]
- Giardia infection in gerbils accelerates intestinal transit time and increases smooth muscle contractility, both of which may play a role in giardial diarrhea.[1]

Giardia trophozoites scavenge nutrients in the intestinal lumen for sustenance and growth. Glucose appears to be the primary energy source, with other sugars appearing not to be utilized. The amino acids alanine, arginine, and aspartate are readily used by Giardia trophozoites for energy production. It appears Giardia lacks the ability to synthesize most amino acids and is thus dependent on scavenging them from the intestinal milieu.[7]

Animal models suggest Giardia is unable to survive in the small bowel in the absence of bile acids. Uptake of bile acids by Giardia may explain the fat malabsorption often seen in giardiasis patients.[6] Chronic giardiasis also results in malabsorption of lactose, vitamin B12, and fat-soluble vitamins, which can result in weight loss, nutritional deficiencies, and failure to thrive in children.[12] Exposure to bile is the primary stimulus for encystation, where trophozoites transform into cysts that pass out with the feces.[7]

Some factors appear to predispose to Giardia infection. Hypogammaglobulinemic patients appear to have higher incidences of giardiasis and more severe sequelae, particularly those patients with decreased immunoglobulin A (IgA) production.[8,13] Common variable immunodeficiency also increases the risk of developing chronic symptomatic giardiasis,[11] while HIV/AIDS does not appear

to increase susceptibility to giardiasis.[13]

Altered GI microflora may also predispose to giardiasis. Singer and Nash observed two genetically identical strains of mice purchased from two different suppliers differed significantly in their susceptibility to Giardia infection. The Giardia-resistant mice were inoculated with a special mix of bacteria (including two species of Lactobacilli) by the original supplier, while the susceptible strain was not.[21] As Lactobacilli can tolerate the acidic conditions in the proximal small bowel, and are one of the most common organisms found in the small intestine,[22] the authors theorized the presence of Lactobacilli in the small bowel was the major factor that increased resistance to Giardia infection. Giving large doses of antibiotics to the Giardia-resistant mice significantly increased their susceptibility to infection, while housing the two strains together for two weeks resulted in decreased rates of infection in the previously susceptible strain.[21]

Microflora-induced resistance to infection has been demonstrated against many bacterial and fungal pathogens.[23,24] The protective role of the microflora may be related to the following: (1) competition for nutritional substrates; (2) specific competition for receptor sites on the intestinal mucosa; (3) production of antimicrobial compounds and metabolic by-products that inhibit the growth of pathogenic microorganisms; and (4) enhancement of the host's immune responses.[5] Differences in normal host flora may partly explain Giardia's ability to produce highly variable sequelae, ranging from asymptomatic infection to severe and protracted disease.[21] Resilient bacterial strains inhabiting the small bowel may effectively prevent Giardia trophozoites from gaining a substantial foothold; whereas, insufficient numbers or weaker bacterial strains may allow Giardia trophozoites to colonize the small intestine in large numbers.

Host Defenses Against Giardia

Host defenses against Giardia infection may be classified into two broad categories – non-immunological responses and immunological responses.

The body has a number of non-immunological mechanisms by which it responds to attempted infection by Giardia trophozoites. Nitric oxide (NO) can inhibit the growth of many pathogenic microorganisms, and enterocytes have been shown to produce and release nitric oxide into the intestinal lumen. NO has been demonstrated to inhibit trophozoite proliferation and differentiation *in vitro*.[8] However, Giardia can prevent the formation of NO by actively taking up and metabolizing arginine from the intestinal lumen, which effectively removes the substrate enterocytes need to produce NO. Addition of extra arginine to the growth media has been shown to restore enterocyte NO production.[1]

Scavenging arginine may also affect mucosal integrity, as NO is involved in the regulation of mucosal barrier integrity.[25] *G. lamblia* inhibits epithelial NO production by consuming arginine before epithelial cells can utilize it. This may partly explain the increase in intestinal permeability associated with Giardia infection. Although not yet researched, supplementation with arginine or the consumption of arginine-rich foods may be able to overcome this impediment and increase mucosal NO production.

Another non-immunological response to Giardia are defensins – small antimicrobial peptides released from intestinal epithelial cells. Paneth cells located within the crypts of the small intestine release α-defensins, while β-defensins are released by enterocytes. Both classes of defensins appear to insert themselves into cell membranes of pathogens, which creates pores in the membrane and leakage of intracellular materials, ultimately resulting in cell lysis.[26] *In vitro* research has demonstrated the ability of α-defensin to kill Giardia trophozoites.[8]

The protective intestinal mucous layer consists mainly of water, immunoglobulins, and mucins – highly complex glycoproteins that give mucous its gel-like nature.[27] The small intestine is coated by a gel-like mucous layer sandwiched between the lumen and the apical epithelial membrane. Diverse carbohydrate structures on mucins create a vast array of potential binding sites for both commensal and pathogenic microorganisms.

Intestinal mucins may protect the intestinal epithelium by binding pathogens such as Giardia, and impeding microbial-epithelial interactions that otherwise could trigger injurious host-cell responses or excessive inflammation. Mucins also restrict microbes to the mucus layer and may assist in their elimination via peristalsis.[26] Both of these actions may be relevant in the case of *G. lamblia*.[28]

As Giardia infections are confined to the lumen, effective immune defenses must act luminally. Both arms of the immune system appear to play a role in the control of Giardia infections, although the exact mechanisms through which the immune system interacts with Giardia trophozoites have yet to be clearly elucidated. Immunoglobulin M, IgG, and IgA-specific antibodies appear to play the major role, but T-cell subsets, neutrophils, macrophages, and complement also contribute.[13] Recent research utilizing gene-targeted mice has demonstrated the importance of Giardia-specific IgA in clearance of infections.[8]

Singer and Nash illustrated the importance of T-cells in the control of giardiasis. Neither Th1 nor Th2 cells were absolutely necessary for the clearance of Giardia infection. This suggests that in the absence of Th1 cells, Th2 cells are sufficient for clearance of the parasite, or that in the absence of Th2 cells, Th1 cells are sufficient. Alternatively, Th3 cells (mucosal T cells) may play the major role. However, in interferon-gamma-deficient animals parasite clearance was delayed when compared to controls, suggesting the Th1 response may be more substantial in controlling Giardia infections. T-cell cytokines may also induce the production and release of antigiardial defensins into the intestinal lumen.[29]

Management of Giardiasis

Giardiasis is potentially successfully managed using a combination of nutritional interventions and phytotherapy. These interventions should be considered the first-line approach. Because of the increased risk of side effects[30,31] and the possible emergence of antibiotic-resistant organisms, metronidazole, tinidazole, or benzimidazole antibiotics may best be reserved for cases in which the primary non-antibiotic treatment program is ineffective. In particular, metronidazole has been associated with recurrence rates as high as 90 percent, and the prevalence of clinical metronidazole-resistance may be as high as 20 percent.[3]

Nutritional Management

Nutritional management of giardiasis consists of foods and supplements that inhibit Giardia growth, replication, and/or attachment to enterocytes; and promote host defense mechanisms against Giardia. In addition, the overall diet should be modified to diminish acute symptomatology.

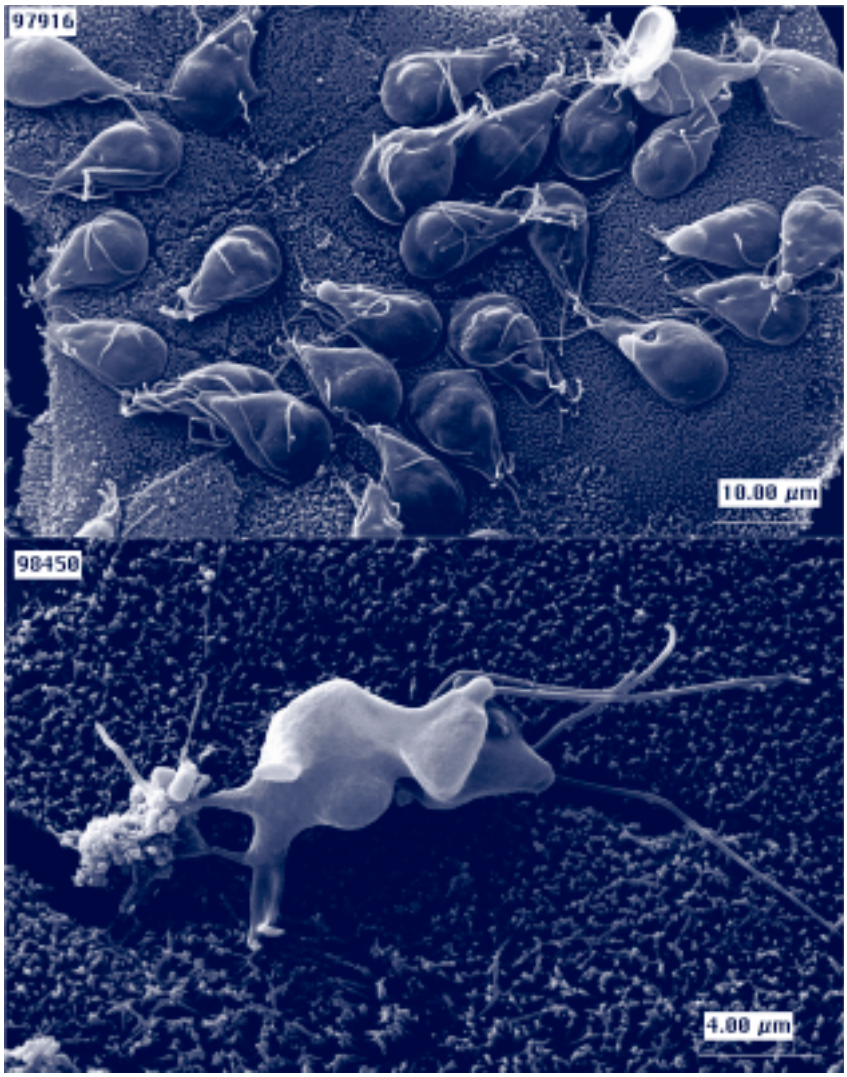
Probiotics

Probiotics may interfere with Giardia infection through a number of mechanisms, including competition for limited adhesion sites;[32] competition for nutrients that would otherwise be utilized by pathogens (e.g., glucose);[33] and stimulation of the immune response.[34] Orally administered probiotics have great potential to affect the microflora of the proximal small intestine as this area is sparsely populated when compared to the colon or distal small bowel.[5,22] Probiotic attachment, subsequent growth, and metabolic activity may have dramatic effects on host immune responses and the local micro-ecology.

Probiotics may also directly inhibit giardial growth and induce innate and immunological antigiardial mechanisms. *Lactobacillus johnsonii* strain La1 has demonstrated the ability to produce substances that inhibit growth of *G. intestinalis in vitro*. Substances found in *L. johnsonii* La1 supernatant impaired the ability of Giardia to replicate and encyst. The La1 extracellular products also caused dramatic alterations in the morphology of Giardia trophozoites (Figure 3).

Administration of *L. johnsonii* strain La1 may help arrest the proliferation of Giardia and prevent encystation, consequently breaking the life cycle of the parasite.[5] Other strains of Lactobacilli may have similar activity against Giardia, but currently only *L. johnsonii* La1 has been shown

Figure 3. *The Effects of* L. johnsonii *La1 Extracellular Factors on* Giardia *Trophozoites*



(TOP) Adhesion of untreated trophozoites of *G. intestinalis* strain WB on intestinal cells. (BOTTOM) Trophozoites preincubated with La1 culture supernatant prior to adhesion essay.
From Perez PF, Minnaard J, Rouvert M, et al. Inhibition of *Giardia intestinalis* by extracellular factors from Lactobacilli: an *in vitro* study. *Applied and Environmental Microbiology* 2001;67(11):5037-5042.[5] Used with permission.

to produce substances that inhibit trophozoite replication and encystation.

Probiotics can also enhance intestinal IgA immune responses and increase intestinal mucin production. *L. johnsonii* La1,[35] *L. acidophilus* strain LA5,[36] and *L. rhamnosus* strain GG[37] have all been shown to enhance IgA immune responses. In addition, *L. rhamnosus* GG has been demonstrated to enhance intestinal mucin production.[38] Both of these actions may enhance intestinal clearance of Giardia.

Some strains of *Lactobacillus plantarum* utilize a mannose-specific adhesion mechanism to attach to intestinal epithelial cells.[39] Giardial attachment to epithelial cells is also partially dependent on a mannose-specific mechanism.[40] Thus, *L. plantarum* may inhibit giardial adhesion to enterocytes, although this process has yet to be researched. *L. plantarum* can be found in large quantities (~10^8 viable bacteria/gram) in traditionally fermented foods such as sauerkraut[41] and kim chi (a Southeast Asian fermented vegetable dish),[42] as well as in specific supplements.

The actions and qualities of probiotics appear to be strain specific.[43] Even closely related bacterial strains within the same species may have significantly different actions.[44] Well-researched probiotic strains should demonstrate gastric acid and bile tolerance, adherence to the intestinal mucosa, and temporary colonization in the intestinal tract – all requisite characteristics for a probiotic strain to have therapeutic effects.[45]

Some brands of yogurt contain sufficient quantities of viable organisms to have a therapeutic effect.[46] The number of viable organisms recovered in feces is greater for some probiotic strains when 10^8 organisms are ingested in dairy foods than when 10^{10} organisms are ingested as encapsulated lyophilized supplements.[47] Yogurt may act as an ideal

transport medium that enhances the survival of bacteria through the upper GI tract.[48]

Dietary Fiber

Dietary fiber may play an important role in the clearance of Giardia infection. Utilizing animal models, Leitch et al demonstrated consumption of a diet high in insoluble fiber significantly protects against Giardia infection. Animals consuming a low-fiber diet were significantly more likely to contract giardiasis when inoculated with Giardia cysts than animals on a high-fiber diet ($p \leq 0.05$). When infected animals on the low-fiber diet were put on the high-fiber diet, trophozoites were cleared from the small bowel. The number of trophozoites attached to the jejunal epithelium decreased, while the number associated with the mucus layer increased. The authors concluded that the fiber induced an increase in mucus secretion and, in combination with the bulk movement of insoluble fiber, reduced trophozoite attachment to the intestinal mucosa and decreased the probability of trophozoites establishing and maintaining mucosal colonization.[28]

Insoluble fiber intake has been demonstrated to markedly increase the relative number of goblet cells along the GI tract and significantly enhance luminal mucin levels in the small bowel.[27] This may partly explain how fiber can prevent and treat Giardia infections. Insoluble fiber may also "sweep" out Giardia trophozoites, as suggested above by Leitch et al.

When ingested, both soluble fibers[49] and lignins[50] have the capacity to bind to bile salts. This may effectively reduce the quantity of bile salts available to Giardia trophozoites, which depend on these salts for continued growth and survival. Hence, consumption of foods high in insoluble and soluble fibers, as well as lignins, may play a significant role in aiding Giardia clearance via multiple mechanisms.

Prebiotics

Prebiotics, such as fructooligosaccharides, may play a minor role in the management of giardiasis, since they primarily affect the large intestine. Prebiotics possess limited ability to alter the small bowel ecosystem and most likely have no effect in the proximal section of the small bowel where Giardia resides.[51] Prebiotic fermentation increases short-chain fatty acid production in the colon, and subsequent increased mucin production in the GI tract,[52] which may enhance giardial clearing.[49] Only minimal dosages of prebiotics can be used (e.g., 2 g twice daily), as symptoms such as abdominal bloating, pain, and flatulence may increase.[53]

Wheat Germ

N-acetyl-D-glucosamine (NAG) residues are major structural components of both Giardia cysts and trophozoites. Wheat germ contains a lectin (wheat germ agglutinin – WGA) that specifically binds to NAG residues.[54] Commercial wheat germ preparations contain between 13-53 μg of WGA per gram.[55] *In vitro* research has demonstrated pre-exposure of Giardia cysts to WGA inhibits excystation by more than 90 percent. Wheat germ agglutinin appears to inhibit excystation by interfering with proteolysis of the cyst wall glycoproteins.[56] In addition, WGA can inhibit the growth of Giardia trophozoites *in vitro*. Wheat germ agglutinin arrests the trophozoite growth cycle in the G2/M phase, thus preventing Giardia growth, replication, and encystation.[57]

Utilizing a mouse model of giardiasis, Ortega-Barria et al found WGA administration reduced the rate of Giardia infection. Mice were fed 100 μg WGA daily for two weeks beginning on the day of, or the day prior to, Giardia inoculation. Wheat germ agglutinin administration resulted in a 50-percent reduction in cyst excretion compared to control animals. Additionally, the number of intestinal trophozoites was decreased by 30 percent. Concomitant *in vitro* experiments demonstrated a dose-dependent response, with maximal activity noted at a concentration of 100 μg/mL. Wheat germ agglutinin did not kill the parasites, but prevented their growth, replication, and attachment.[57]

Grant et al conducted a double-blind, placebo-controlled clinical trial of 63 infected subjects to assess the effectiveness of wheat germ in the treatment of human giardiasis. Twenty-five asymptomatic subjects consumed wheat germ (2 g or ~1 tsp three times daily) or a placebo (cornstarch – 2 g three times daily) for 10 days. Thirty-eight symptomatic subjects received metronidazole (250 mg three times daily) plus either wheat germ or placebo for seven days. In asymptomatic subjects, fecal cyst and trophozoite numbers were reduced by approximately 60 percent in those taking wheat germ compared to placebo ($p<0.01$), with a significant reduction noted within 24 hours. Coproantigen levels also decreased after wheat germ supplementation, although not significantly ($p=0.06$). In symptomatic subjects, cyst passage and coproantigen levels fell precipitously after antibiotic administration, with no significant difference between the placebo and wheat germ groups; however, a trend for quicker resolution of symptoms was noted in the wheat germ group. The wheat germ supplement was well tolerated by both groups.[55] As previous *in vitro* research showed a dose-dependent response, incorporating a higher amount of wheat germ into the diet (e.g., 1-2 Tbl three times daily) may be therapeutic.

General Dietary Recommendations

The main aims of dietary modification in giardiasis should be to reduce the acute symptomatology, promote host defense mechanisms, and inhibit growth and replication of Giardia trophozoites. These aims can be achieved by consuming a whole-food, high-fiber, low simple-carbohydrate, low-fat diet.

This diet will ensure adequate amounts of lignins and insoluble and soluble fibers are consumed, which can increase mucin production in the small bowel, sequester bile acids, and help mechanically sweep trophozoites out of the small intestine. Consuming foods low in simple carbohydrates limits the amount of sugars available in the intestinal lumen, which may lessen the osmotic draw of water into the intestinal lumen, and reduce diarrhea.

Reducing the intake of fat might reduce nausea, steatorrhoea, and diarrhea often associated with giardiasis. Dietary fat is also the main stimulator for the release of bile acids into the intestinal lumen,[58] which Giardia trophozoites depend on for survival in the small bowel.[6]

Studies have shown Giardia infection, whether symptomatic or asymptomatic, can reduce the production of lactase in the small intestine, resulting in lactose malabsorption and its resultant diarrhea.[59] Therefore, minimizing consumption of lactose-containing dairy products may improve diarrhea and the abdominal bloating and pain commonly associated with giardiasis. Studies have shown reducing the consumption of lactose-containing foods to less than 6 g of lactose in a single dose should relieve symptoms.[60] A 100-150 g serving of yogurt (~1/2 cup) contains 3.0-5.3 g of lactose, and thus should be a safe amount to consume.[61]

More specific dietary recommendations include consumption of:

- 2 Tbl wheat germ three times daily;
- 1/2 cup low-fat yogurt containing well-researched probiotic strains (e.g., *Lactobacillus johnsonii* La1, *L. acidophilus* LA5, and/or *L. rhamnosus* GG) with guaranteed levels of viable bacteria (minimum 10^6/mL). Alternatively, a probiotic supplement containing these or other well-researched bacterial strains can be substituted;
- Sauerkraut or kim chi throughout the day.

Following these specific recommendations should aid in the clearance of Giardia from the intestinal tract.

Phytotherapy

Phytotherapeutic agents play a vital role in the natural management of giardiasis. Medicinal herbs can be used to both alleviate the symptoms of giardiasis and clear the infection. Garlic (*Allium sativa*), berberine-containing herbs, Indian long pepper (*Piper longum*), Pippali rasayana, flavonoid-containing herbs, and propolis have all been shown to inhibit Giardia growth and/or replication.

Garlic (*Allium sativa*)

Garlic has traditionally been used as an antiparasitic and antimicrobial agent.[62] Recent research has substantiated its traditional uses and elucidated probable active constituents and possible mechanisms of action. Harris et al demonstrated the antigiardial activity of both whole raw garlic and some of its constituents. Whole garlic extract demonstrated an IC_{50} (the concentration that inhibits growth of parasites by 50%) of 0.3 mg/mL, while the allicin breakdown products diallyl disulfide, diallyl sulfide, and allyl mercaptan demonstrated IC_{50} values of 0.1 mg/mL, 1.3 mg/mL, and 0.037 mg/mL, respectively. Other garlic constituents, such as allyl alcohol and dimethyl disulfide were also strongly inhibitory (with IC_{50} values of 0.007 mg/mL and 0.2 mg/mL, respectively).[63]

Incubation of Giardia trophozoites with whole garlic results in the loss of flagellar movement and cell motility, internalization of flagella, and trophozoite swelling. These events are believed to be caused by the loss of osmoregularity and the collapse of the transmembrane electrochemical potential. Electron microscopy also indicates morphological changes to the ventral disc, which may result in decreased ability to adhere to host cells.[63]

Soffar and Mokhtar performed an open trial investigating the use of garlic in giardiasis. Twenty-six children infected with *G. lamblia* took 5 mL crude extract (fresh garlic blended with distilled water and then centrifuged and filtered to remove the solids) in 100 mL water twice daily or a commercial garlic preparation two capsules (0.6-mg capsules) twice daily for three days. Both preparations were given on an empty stomach two hours before meals. Clinical symptoms subsided in all cases within 36 hours. Parasitic cure (according to stool examinations) occurred within three days of beginning treatment.[64]

Garlic may improve giardiasis via a number of mechanisms. Allicin may inhibit the activity of Giardia's cysteine proteases – excretory/secretory products that may be involved with Giardia-induced mucosal alterations – resulting in a reduction of Giardia-induced gastrointestinal symptoms.[20,65] Garlic may also stimulate mucosal production of nitric oxide synthase (the enzyme that produces NO), thereby increasing the release of NO by enterocytes, which may have direct giardicidal effects.[63]

Berberine-containing Herbs

Berberine is an isoquinoline alkaloid found in a number of medicinal plants. Berberine-containing herbs have a long history of use in Chinese (*Coptis chinensis*), Western (*Berberis vulgaris, Hydrastis canadensis, Berberis aquifolium)*, and Ayurvedic herbal medicine (*Berberis aristata*). Most of these herbs have been used in the treatment of gastrointestinal infections, intestinal parasites, and diarrhea.[66-68]

Berberine salts and extracts have demonstrated *in vitro* inhibitory activity against Giardia trophozoites,[69] and berberine sulfate has been shown to induce morphological damage to trophozoites, including the appearance of irregularly-shaped vacuoles, swollen trophozoites, and the development of glycogen deposits.[70]

In a placebo-controlled clinical trial, 40 subjects received either a vitamin B-complex syrup (as a placebo), berberine hydrochloride (5 mg/kg/d), or metronidazole for six days. Berberine administration resulted in a marked decline in gastrointestinal symptoms (superior to that of metronidazole) and a 68-percent reduction in Giardia-positive stools. Metronidazole-treated patients were 100-percent parasite free, and patients on placebo had a 25-percent reduction in Giardia-positive stools. The authors speculated that an increase in the dose or a longer duration of treatment would increase berberine's treatment efficacy.[71]

In an uncontrolled trial of 137 children ranging from five months to 14 years, berberine was administered in one of four regimens. Group 1 received 5 mg/kg/d for five days, group 2 received 5 mg/kg/d for 10 days, group 3 received 10 mg/kg/d for five days, and group 4 received 10 mg/kg/d for 10 days. The number of individuals with Giardia-negative stool samples was 47 percent in group 1, 55 percent in group 2, 68 percent in group 3, and 90 percent in group 4. The cure rate in group 4 was comparable to that obtained with furazolidone (92%) and metronidazole (95%). A small number of subjects in group 4 and in the metronidazole-treated group experienced a relapse one month after treatment ceased. The authors suggested either re-infection occurred or that a longer duration of treatment or multiple treatment periods may be necessary to improve overall outcomes in some patients.[72]

In vitro research has indicated crude extracts have greater antiprotozoal activity than isolated berberine salts, probably due to a synergistic effect between berberine and the other isoquinoline alkaloids found in these plants.[69] Research further elucidates the presence of compounds (5'-methoxyhydnocarpin-D and pheophorbide α) found in some berberine-containing herbs[73] that inhibit multidrug resistance (MDR) pumps (which are common among protozoa),[74,75] and increase intracellular concentrations of the alkaloid. It has yet to be demonstrated that these compounds potentiate the giardicidal activity of berberine and related isoquinoline alkaloids.

Indian long pepper (*Piper longum*)

Indian long pepper is a traditional Ayurvedic herb that has long been used for its anthelmintic and carminative actions.[76] Recently, Tripathi et al assessed the antigiardial action of Indian long pepper *in vitro*, and found aqueous extracts (250 μg/mL) and ethanol extracts (125 μg/mL) demonstrated 100-percent giardicidal activity (both $p<0.001$). Utilizing a mouse model of giardiasis, *Piper longum* (PL) fruit powder (900 mg/kg), PL aqueous extract (450 mg/kg), and PL ethanolic extract (250 mg/kg) all significantly decreased the live number of trophozoites in jejunal aspirates by approximately 75 percent after five days' administration (all $p<0.001$).[2] The equivalent dose of the ethanolic extract for a 70-kg adult is 17.5 mL of a 1:1 extract per day.

Pippali rasayana

Pippali rasayana is a traditional Ayurvedic formulation consisting of *Piper longum* and *Butea monosperma* (palash). Pippali rasayana (PR) has traditionally been used in the treatment of chronic dysentery and worm infestations. Agarwal et al recently investigated the antigiardial and immunostimulatory effects of PR. In a mouse model of giardiasis, administration of PR at 900 mg/kg body weight, 450 mg/kg, and 225 mg/kg resulted in parasite clearance in 98 percent, 79 percent, and 62 percent of animals, respectively ($p<0.001$). All three doses of PR also significantly increased the macrophage migration index and macrophage phagocytic activity, with the 225 mg/kg dose producing the greatest effects ($p<0.001$). Interestingly, PR had no giardicidal effect on the parasite *in vitro*, suggesting enhancement of the immune response and host clearance mechanisms may be responsible for PR's effectiveness in clearing Giardia infection.[77]

Agarwals' research team conducted a double-blind, placebo-controlled trial with 50 subjects, all of whom had clinical signs and symptoms of giardiasis, as well as Giardia trophozoites and cysts in the stool. Twenty-five subjects received active treatment (1 g PR three times daily), while the others received a placebo. After 15 days of treatment, complete disappearance of *G. lamblia* from the stools was seen in 92 percent of the PR group and 20 percent in the placebo group. Diarrhea and the presence of mucus in the stool were also significantly reduced ($p<0.01$). There was also an improvement in cell-mediated immune status, as assessed by the leukocyte migration inhibition test ($p<0.01$).[78]

The small dosage used in this clinical trial contrasts markedly with that utilized in the *Piper longum* animal study. This suggests either a synergistic effect between the two herbs in PR and/or that PR functions not so much as an anti-giardial agent, but as a stimulator of host defense mechanisms. The latter option appears to be the most

likely explanation, as PR has no antigiardial activity *in vitro*[77] and both human and animal studies have shown it to have immunostimulatory effects.[78]

Flavonoid-containing Herbs

In vitro research found many plant flavonoids display antigiardial activity. Epicatechin, epigallocatechin, kaempferol, quercetin, and apigenin all exhibited substantial antigiardial activity.[79] Interestingly, many herbs used to treat diarrheal diseases contain considerable quantities of some of these flavonoids (e.g., *Quercus robur, Croton lechleri*, and *Hamamelis virginiana*).[80-82]

A recent *in vitro* study also demonstrated the antigiardial activity of many herbs rich in flavonoids and tannins. Oregano (*Origanum vulgare*) and guava leaves (*Psidium guajava*) both demonstrated antigiardial activity superior to tinidazole (an antibiotic commonly used to treat giardiasis). Mango leaves (*Mangifera indica*) and plantain leaves (*Plantago major*) were nearly equal to tinidazole.[83] Many of these herbs have traditionally been used to treat diarrheal disorders.[84-87]

As both isolated flavonoids and flavonoid-containing herbs can inhibit Giardia growth, consumption of flavonoid supplements (e.g., quercetin) and foods high in flavonoids (onions, apples, kale, French beans, parsley, and black currants) may also aid in Giardia clearance.[88,89]

Propolis

Miyares et al investigated the antigiardial activity of propolis in varying concentrations in an open trial in Cuba. Subjects (n=138) with giardiasis (diagnosed via duodenal aspiration) received a five-day regimen of tinidazole or propolis. Children received a 10-percent propolis solution, whereas adults received either a 20-percent or a 30-percent propolis solution (quantities unspecified). Cure rates (as evaluated by duodenal aspiration) were 52 percent in the propolis-treated children, 40 percent in adults taking 20-percent propolis, and 60 percent in those taking 30-percent propolis. In comparison, tinidazole (dosage regimen not stated) produced a 40-percent cure rate. No side effects were noted with propolis treatment.[90]

Conclusion

Giardia is a common human parasite that can cause significant morbidity. Natural medicine has great potential to influence the course of Giardia infection. The most beneficial way to treat giardiasis naturally may be through a combination approach, utilizing both nutritional interventions and phytotherapeutic agents. The main aims of nutritional intervention are to reduce the acute symptomatology of giardiasis, promote host defense mechanisms, and inhibit growth and replication of Giardia trophozoites. These aims can best be achieved by consuming a whole-foods, high-fiber, low-fat, low simple-carbohydrate diet. Additionally, ingestion of wheat germ and probiotics can aid in parasite clearance.

The most promising phytotherapeutic agents in the treatment of giardiasis appear to be the berberine-containing herbs, garlic, and the Ayurvedic combination Pippali rasayana, although other medicinal herbs also show great potential.

Blending nutritional interventions and phytotherapeutic agents should result in minimization of Giardia symptomatology and clearance of the parasite, without significant side effects. As such, this therapeutic strategy should be considered the first-line approach, while antibiotic use should be reserved for cases that fail to respond to management with natural measures.

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