Journal of the Egyptian Society of Parasitology, Vol.50, No.1, April 2020
J. Egypt. Soc. Parasitol. (JESP), 50(1), 2020: 160 - 166

TREATMENT POTENTIAL OF *ALOE VERA* GEL IN *GAIRDIA INTESTINALIS* INFECTED ALBINO RATS

By

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Abstract

Aloe vera has been used as a traditional medicine in many cultures, especially Egypt, and known for its therapeutical effects with dermatitis, ulcer and burns. It has many beneficial properties as it is a powerful antioxidant, anti-inflammatory and antimicrobial agent. *G. intestinalis* is a waterborne parasite that causes human giardiasis. In Egypt, outbreaks commonly occur in areas where water treatment is insufficient leading to infection rates of 50% of the total population. The current treatment against *G. intestinalis* involves metronidazole, known as flagyl, which can induce many side effects as headache, vertigo, nausea, and a metallic taste in the mouth. Previous studies showed that high doses of metronidazole, over long periods, have mutagenic and carcinogenic effects in experimental animals. The study aims to evaluate the effect of *Aloe vera* in treatment of *G. intestinalis* in male albino rats in comparison to metronidazole. Our results showed that *Aloe vera* cleared the infection and reduced inflammatory cytokines in treated groups. Thus it can be used instead of metronidazole in treatment of *G. intestinalis* due to its anti-inflammatory properties and to avoid the undesired side effect of the metronidazole.

Key words: *G. intestinalis*, IFN-γ, IL-10, IgA

Introduction

G. intestinalis (synonyms: *G. duodenalis* or *G. lamblia*) is a common intestinal protozoan in Egypt (Adam, 2001; Adam *et al,* 2016). In Egypt, the prevalence of giardiasis accounted up to 48%; as a hyperendemic country (Fahmy *et al,* 2015). But, a parasitological examination of drinking water showed a high prevalence of the parasite (Hamdy *et al,* 2019). Parasite can affect all ages; but, commonly in children and infection causes acute diarrhea leading to malabsorption and malnutrition (Nematian *et al,* 2008; Puebla *et al,* 2014; Tsourdi *et al,* 2014).

Therapy includes diverse pharmaceutical agents as metronidazole, quinacrine and furazolidone (Gardner and Hill, 2001; Harris *et al,* 2001). But, many evidences pointed to an increasing resistance to treatment with these drugs (Brasseur and Favennec, 1995). Metronidazole, marketed under commercial name Flagyl®, is the most commonly used one to treat giardiasis (Abdel-Fattah and Nada, 2007). Hill (2000) showed that metronidazole acquired potential carcinogenicity and mutagenic effect in rats. Parasite resistance and drugs side effects highlight the need for other alternatives as medicinal plants. WHO reported that medicinal plants as the best source for so many drugs (Santos *et al,* 1995). Egyptian medicinal plants have several potential effective agents against helminthes, snail hosts and protozoa (Massound *et al,* 2007).

Generally, *Aloe vera* (El-Sabar) is a succulent plant of the genus *Aloe* that belongs to family Aloeaceae (Sahu *et al,* 2013). For millennia, the plant has been used as a medicinal plant for many purposes in China, Egypt, Greece and Japan (Marshall, 1990). The first known written reports on the nourishing juice of the aloe vera plant reach as far back as 6,000 years ago in ancient Egypt. Aloe was regarded as a sacred plant the "blood" of which held the secrets to beauty, health and immortality. Both Queen Cleopatra and Queen Nefertiti greatly valued the nourishing juice and used it as a part of their daily skin and beauty care (Myskja, 2003).

Generally speaking, *Aloe vera* leaves contain many vitamins, minerals, amino acids, natural sugars and other bioactive components possessing anti-inflammatory, anti-oxidant, anti-helminthic, antiprotozoa and antifungal effects on health (WHO, 2008).

The present study aimed to evaluate the efficacy of *Aloe vera* in treatment of giardiasis infected Albino rats as compared to metronidazole. The anti-inflammatory properties of *A. vera* were evaluated by measuring inflammatory cytokines (IFN-γ, IL-4 & IL-6), cytokine (IL-10) and IgA & IgG.

Materials and Methods

Drug**s:** Tru-Alo 99% *Aloe vera* drinking gel (*Aloe barbadensis* Miller folium succus), Aloin content < 40 ppm; produced by Hi Tech *Aloe vera* Pty Ltd, Bundaberg, Australia. Animals were given with *Aloe vera*, in daily doses of 150µl in drinking water, for 7 successive days post-infection. Infection was proved by examination of stained stool smears Metronidazole was supplied by Rhone Opulence Rorer Co, as suspension. Dose given to each rat was 120µg/kg twice daily for 7 successive days.

Parasite: *Giardia intestinalis* cysts were obtained from heavily infected fresh patients' stool without other parasites. Each rat was orally infected with 10,000 cysts of *G. intestinalis* suspended in 1 ml normal saline. Animals stool were examined daily, from 3rd day post infection, to evaluate the time of maximal cyst excretion.

Animals: Twenty parasite free male Albino rats 4-5 weeks old, weighing 170- 200 gm. They were purchased from Theodore Bilharz Research Institute (TBRI) and maintained in the animal house, Faculty of Science, Cairo University. Animals were divided into 4 groups (5 for each): GI: healthy control rats, GII: *G. intestinalis* infected untreated rats, GIII: *G. intestinalis* infected rats treated with metronidazole, and GIV: G. *intestinalis* infected rat treated with *Aloe vera*. All the experimental procedures were performed according to the international care and use of laboratory animals' guidelines.

Stool analysis was done by direct examination of fresh stool by merthiolate iodine formaldehyde concentration (MIFC) technique (Blagg *et al,* 1955). Rats were sacrificed on 10th days post treatment and intestinal contents were examined for trophozoites & counted.

ELISA plates were coated with 50µl/well (Iµg/ml) of capture antibody (IFN-γ, IL-4, IL-10, & IL-6) (Beckton Dickenson & Co.) and incubated at 4°C overnight. Plates were washed in phosphate buffered saline (PBS) / Tween 20, blocked with 200µl/well of skimmed milk and washed again. 50µl of serum samples were added followed by incubation for an hour at 37°C. Then, plates were washed and biotin labeled anti-monoclonal antibody (lµg/ml) was added followed by an hour incubation at room temperature. 100µ/well of avidin-alkaline phosphatase were added to plates followed by 30 minutes incubation at room temperature. The reaction was visualized by addition of 100µl/well of pnitrophenyl phosphate (pNpp) substrate solution. Reaction was stopped by adding 50µl/well of 8 N H2SO4 and plates read at 405nm using ELISA microplate reader (Bio Rad).

Histopathological examination: Small intestine were fixed in 10% formaline, embedded in paraffin and stained with hematoxylin/eosin (Bancroft and Stevens, 1975).

Statistical analysis: Data were analyzed using SPSS for Windows (version 11) computer program. All data were expressed as mean± standard deviation (SD). Significance of differences between groups was calculated using Student's t-test. Data were considered significant if $P<0.05$.

Results

Rats of GIII, treated with 120µg/kg metronidazole twice daily for 7 successive days showed a significant reduction in cyst count (356.02±0.14) when compared with infected untreated GII (5621.56±1.23). A significant reduction was in GIII (9.61±3.51) in comparison to GII (49.41±2.56). GIV, treated with *Aloe vera* showed a significant reduction in both cyst and trophozoites count (259.03±4.16 & 10.68±3.67, respectively) when compared to GII (Tab 1). No significant differences were observed in cyst or trophozoites numbers between GIII & GIV.

Details were given in tables (1, 2, & 3).

Table 1: *G. intestinalis* cyst count in stool and trophozoites count in intestinal wash in groups.

Group	Cyst count in stool		Trophozoites count in intestinal wash	
	m±SD	% PR	m±SD	% PR
Group II	5621.56±1.23	0	49.41±2.56	0
Group III	356.02±0.14[a]	93.66	9.61±3.51[a]	80.55
Group IV	259.03±4.16[a]	95.39	10.68±3.67[a]	78.38

[a=] significance compared with the corresponding *G. intestinalis* untreated infected GII (P<0.05), GII: *G. intestinalis* infected untreated, G: *G. intestinalis* infected treated with metronidazole, GIV: G. *intestinalis* infected treated with *Aloe vera.*

GII, infected untreated rats showed a significant elevation in cytokine measurements (751.54, 82.48, 483.14 & 571.25 for IFN-γ, IL-4, IL-10 & IL-6 respectively) when compared with healthy control GI (Tab. 2). GIII, treated with metronidazole showed a significant reduction in cytokines levels as compared to infect untreated GII (G: 270.54, 34.26, 132.87 & 199.54 vs. GII: 751.54, 82.48, 483.14 & 571.25 for IFN-γ, IL-4, IL-10 & IL-6 respectively). In GIII, cytokines levels were significantly high than those of healthy control GI. Cytokines levels in GIV, treated with *A. vera*, showed no significant differences with corresponding in healthy control GI.

Table 2: Cytokines secretion (pg/dl) in different experimental groups.

Group	IFN-γ	IL-4	IL-10	IL-6
Group I	172.02±6.41	16.47±8.91	87.25±10.71	148.91±3.44
Group II	751.54±3.16[a]	82.48±7.40[a]	483.14±5.13[a]	571.25±7.54[a]
Group III	270.54±2.77[a,b]	34.26±5.42[a,b]	132.87±0.45[a,b]	199.54±3.33[a,b]
Group IV	198.41±11.21[b]	21.41±14.04[b]	99.10±7.12[b]	191.47±7.13[b]

[a=] significance compared with healthy control & [b=] significance compared with *G. intestinalis* untreated infected GII (P<0.05).

GII showed a strong increase in immunoglobulin levels (132.47 & 345.41 for IgA & IgG, respectively) as a result of infection with *G. intestinalis*. Both metronidazole and *A. vera* decreased immunoglobulins levels, in GIII & GIV, when compared to infected untreated GII (Tab. 3). However, immunoglobulins levels in *Aloe vera* treated infected GIV showed no significant changes with corresponding in GI (GIV: 61.20 and 191.41 vs GI: 53.14 & 170.46 for IgA and IgG, respectively).

Table 3: Immunoglobulin secretion (mg/dl) in different groups.

Group	IgA	IgG
Group I	53.14±1.24	170.46±4.12
Group II	132.47±2.71[a]	345.41±1.13[a]
Group III	82.41±5.01[a,b]	213.87±2.71[a,b]
Group IV	61.20±4.52[b]	191.41±2.14[b]

[a]=significance compared with healthy control GI and [b]=significance compared with the *G. intestinalis* untreated infected GII (P<0.05).

Histopathological results: *G. intestinalis* untreated GII showed short broad villi with marked intra-villous edema, inflammatory infiltrate and dilated blood vessels. GIII and GIV showed few broad villi with average sized submucosa with moderate inflammatory infiltrate.

Discussion

G. intestinalis is a flagellated protozoan that has a direct life cycle in the upper part of the small intestine (Meyer and Jarroll, 1980). The host became infected by ingesting the infective stage, cysts, with contaminated water or food. After ingestion, in the duodenum, the trophozoites emerge from the cysts and attach to the mucosa of small intestinal. Some cysts undergo mitotic division and the others are encysted to be eliminated in host feces (Keystone *et al,* 1978). The symptoms, develops 7-10 days after infection, include greasy and foul smelling diarrhea that is accompanied by abdominal cramps and nausea (Robertson *et al,* 2010). Chronic disease is characterized by malabsorption of nutrients, weight loss and fatigue (Barry *et al,* 2013).

The infection led to reduced expression of brush border enzymes, villi morphological changes and elevation in intestinal permeability. The trophozoites were not usually penetrate the epithelium, invade surrounding tissues, or enter the bloodstream. Thus, the

infection was generally contained within the intestinal lumen (Faubert, 2000). The attachment process of trophozoites to intestinal wall damages the microvilli that result in interfering with nutrient absorption. Rapid multiplication of trophozoites, eventually, created the physical barrier between the enterocytes and the intestinal lumen and further interfering with nutrient absorption (Cotton *et al,* 2011). This process led to enterocyte damage, villus atrophy and crypt hyperplasia (Buret, 2008), intestinal hyperpermeability (Chin, 2002; Dagci, 2002) and brush border damage caused a reduction in disaccharides enzyme secretion (Nain, 1991).

The present study showed that intestinal sections of *G. intestinalis* untreated GII rats had short broad villi with marked intravillous edema, inflammatory infiltrate and dilated blood vessels. The histopathological examinations coincided with the parasitological outcome, where these rats had the highest cysts and trophozoites counts (5621.56 & 49.41, respectively). Besides, *G. intestinalis* infection caused a significant elevation in cytokines (IFN-γ, IL-4, IL-10 & IL-6) and immunoglobulins (IgA & IgG) secretion in GII. The present results agreed with those of Singer and Nash (2000) who reported that the impor- tance of T cells in the control of giardiasis. Several studies explained the immune mechanism by which host control infection. Both humoral and cell-mediated immune responses were involved in human giardiasis (Adam, 2001). Human and animals experiments confirmed that parasite-host relationship was affected by T lymphocytes (Heyworth *et al,* 1987; Hill, 1990; Djamiatun and Faubert, 1998; Singer and Nash, 2000; Scott *et al,* 2004), high secretion of IgA (Heyworth and Vergara, 1994; Langford *et al,* 2002) and cytokines (Venkatesan *et al,* 1996; Scott *et al,* 2000; Jimenez *et al,* 2009). Di Prisco *et al.* (1998) reported that giardiasis infection increased the production of total and specific IgE antibodies. Jiménez *et al.* (2004) found that the immunized mice with the excretory-secretory antigens of *G. intestinalis* showed a strong specific antibody responses. Jiménez *et al.* (2014) added that mice infected with *G. intestinalis* trophozoites produced high levels of circulating IgG1a, IgG2a, IgA, & IgE antibodies.

The metronidazole [1-(b-hydroxyethyl)-2-methyl-5-nitroimidazole; Flagyl] was discovered in late of 1950s and used to treat *Trichomonas vaginalis* and *Entamoeba histolytica* (Durel *et al,* 1960), and to treat giardiasis (Darbon *et al,* 1962). After oral administration, metronidazole is completely and quickly absorbed then penetrates body tissues and secretions (Tracy and Webster, 1996). It is metabolized in liver then excreted in urine (Lau *et al.,* 1992). The drug has many side effects as headache, vertigo, nausea, and a metallic taste in the mouth. Many studies reported that high doses of metronidazole, over long periods, have a mutagenic effect in bacteria and carcinogenic effects in rats and mice (Lindmark and Muller, 1976; Voogd, 1981; Tracy and Webster, 1996).

Mothana and Linclequist (2005) reported that 20% of worldwide plants have been subjected to biological or pharmacological tests; and several antibiotics are extracted from natural resources. Genus *Aloe*, belongs to family *Alliaceae*, is a succulent herb. It is 80-100cm height, matures in 4-6 years and survived for nearly 50 years especially under favorable conditions (Joshi, 1997). The plant leaf has three layers: 1- The outermost thick protective layer that synthesize proteins and carbohydrates (Brown, 1980), 2- Middle layers that contains anthraquinones and glycosides, 3- Innermost gel layer that contains 99% water with amino acids, sterols, vitamins, lipids and glaucomannans (Reynolds and Dweck, 1999). Also, elements Al, B, Ba, Ca, Fe, Mg, Na, P, Si were found in *Aloe vera* gel (Choi *et al,* 2001).

The present study used *Aloe vera* drinking gel for treatment of *G. intestinalis* in experimentally infected rats. *Aloe vera* anti-parasitic effect was compared to that of metronidazole. The parasitological results revealed that both of metronidazole and *Aloe vera*

cleared infection. *Aloe vera* returned cytokines and immunoglobulins levels to normal levels more than did metronidazole.

Aloe vera gel, found in the inner part of leaf, contains more than 75 compounds as polysaccharides, amino acids, steroids, organic acids, enzymes and antibiotic agents. It is a traditional therapy used for many purposes without any side effects. Sehgal *et al.* (2013) reported that a commercial aloe gel, consumed as a beverage, was neither genotoxic nor toxic in mice. Talmadge *et al.* (2004) reported that *Aloe vera* gel have been used to treat sunburn and wound ulcers. And added that, it possess antimicrobial and anti-inflammatory properties. Abdulrahman *et al.* (2019) studied the effect of water extracts of *Aloe vera* and *Hyptis suaveolens* plants singly and in combinations on *G. lamblia* and *Salmonella* species *in vitro*, they found that *A. vera* extracts exhibited a good zone of inhibitions on *Salmonella* species and a better activites on *Giardia lamblia*.

Haller (1990) showed that *A. vera* gel possesses sterols, campesterol, *β*-sitosterol, lupeol, and cholesterol, with both anti-inflammatory and analgesic activity. Davis *et al,* (1991) found that 5.0% of leaf homogenate reduced inflammation in arthritic induced inflammatory rat model by 48% Madan *et al.* (2008) reported that the plant with aspirin-like compound responded for antimicrobial and anti-inflammatory effects.

Conclusion

The outcome data proved that *Aloe vera* to be effective treatment for *G. intestinalis* infected rats without side effects, as it significantly reduced both cysts and trophozoites.

Also, its anti-inflammatory effect was obvious in the reduction of inflammatory cytokines (IFN-γ, IL-4 & IL-6) reflected on IL-10 level in a direct way. *Aloe vera* can replace metronidazole in *G. intestinalis* treatment due to its anti-inflammatory properties and to avoid drug undesired side effects.

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Explanation of figures

Fig. 1: Haematoxylin and eosin intestinal sections of rat showed (X200), **a-** GI, average mucosal thickness with average villi (black arrow), average submucosa (red arrow), and average musculosa (green arrow), **b-** GII, broad blunted villi (black arrow) and others with tapered necrotic tops (blue arrow), mild intra-villous inflammatory infiltrate (red arrow), **c-** GIII, few broad villi with partially necrotic tops (black arrow), mild intra-villous inflammatory infiltrate (blue arrow), average submucosa (red arrow), **d-** GIV, few broad villi with partially necrotic tops (black arrow), mild intra-villous inflammatory infiltrate (blue arrow), and average submucosa (red arrow).