EGYPTIAN ACADEMIC JOURNAL OF

BIOLOGICAL SCIENCES

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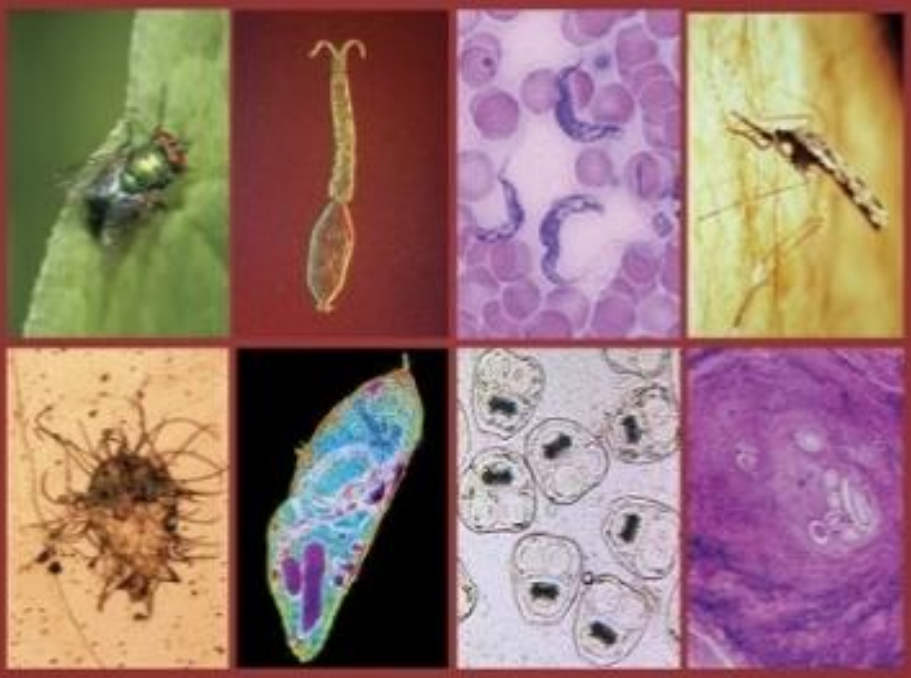
MEDICAL ENTOMOLOGY & PARASITOLOGY



ISSN
2090-0783

WWW.EAJBS.EG.NET

Vol. 17 No. 1 (2025)

Citation: *Egypt. Acad. J. Biolog. Sci. (E-Medical Entom. & Parasitology Vol.17(1) pp **29-38**(2025)*
DOI: 10.21608/EAJBSE.2025.431497

Egypt. Acad. J. Biology. Sci., 17 (1):29 – 38 (2025)

Egyptian Academic Journal of Biological Sciences
E. Medical Entomology & Parasitology

ISSN: 2090–0783
www.eajbse.journals.ekb.eg

Potential Antiparasitic Effects of Ginger Tablets in Experimental Toxoplasmosis and Its Impact on Ensuing Brain Lesions

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ARTICLE INFO
Article History
Received:3/5/2024
Accepted:2/6/2025
Available:9/6/2025

Keywords:
Chronic Toxoplasmosis - Ginger - Brain cysts- IFN-γ - IL8.

ABSTRACT

The intracellular protozoan parasite, *Toxoplasma gondii* (*T. gondii*) can result in serious manifestations in humans, especially pregnant women and immunocompromised persons. Standard drugs for treatment toxoplasmosis have serious side effects. Safe therapeutics are still needed. Our work aimed to ascertain the effectiveness of ginger tablets in treating chronic toxoplasmosis alone and in combination with spiramycin in mice model. Our experiment was conducted on 48 mice divided into 4 equal groups, Group (I) Infected non-treated control, Group (II) Infected treated with spiramycin, Group (III) infected treated with ginger and Group (IV) Infected treated with spiramycin plus ginger. All mice were scarified 60 days after infection. Parasitological measures through counting brain cysts and histopathological measures through using hematoxylin and eosin (H&E) were employed. Also, Sera of different groups were collected to detect levels of proinflammatory cytokines, interleukin 8 (IL-8) and interferon gamma (IFN-γ). Our results showed that ginger tablets are considered promising option for treatment chronic toxoplasmosis.

INTRODUCTION

Toxoplasmosis is one of the parasitic infections that is thought to be widely prevalent and it is caused by the intracellular parasite *Toxoplasma gondii.* Nearly all warm-blooded creatures, including humans can be infected with *T. gondii*, making it a very important parasite affecting public health (Torrey and Yolken, 2013) . Consuming raw meat that contains parasite tissue cysts, oocysts from cat excreta, receiving blood transfusions, organ transplantation and transplacental transmission are all ways to become infected with *T. gondii* (Shiojiri *et al.*, 2019). The lives of the fetus and the infected mothers may be at risk if the parasite is vertically transmitted through the placenta (Sun *et al*., 2013).

Toxoplasmosis, which affects over one-third of people worldwide, is asymptomatic in those who are immunocompetent. However, the infection can be fatal in immunocompromised patients (Montoya and Liesenfeld, 2004). *Toxoplasma gondii* infection results in a potent cellular immune response aiming at controlling infection (Suzuki *et al*., 1988).

A crucial cytokine in innate and acquired immune responses to *T. gondii* infection is (IFN-γ) (Saha *et al*.,2010). IFN-γ triggers a cellular response that activates a variety of effector mechanisms so preventing intracellular infections from growing and surviving (Yap *et al*., 2000 & Lieberman *et al*., 2004).

Currently, pyrimethamine and sulfonamide medications are the first-line medications for toxoplasmosis (Schmidt *et al*., 2006). These drugs induce their effects through inhibiting folic acid metabolism resulting in the suppression of synthesis of DNA and or RNA of the parasite (Choi and Lee, 2018). Pyrimethamine by it self, in high dosages, or in conjunction with macrolide antimicrobials such as azithromycin can be used to treat patients with sulfonamide hypersensitivity (Wei *et al*., 2015).

Unfortunately, these medicines used in treating toxoplasmosis have limitations due to numerous adverse effects, including hypersensitivity reactions, hematological disorders, and bone marrow suppression. In addition, their effectiveness in eliminating tissue cysts is limited. (Furtado *et al*., 2011). Other disadvantages include limited efficacy in parasite purification, pyrimethamine and sulfadiazine toxicity and low spiramycin penetration in embryonic tissues (Franco *et al*., 2011). So, the chronic infection remains unabated because existing treatments only suppress parasites that are actively multiplying and have little effect on bradyzoites found in tissue cysts. (McCabe, 2001). So, it is essential to discover novel and effective treatments. Herbal medicinal extracts are thought to be a promising source for new drugs because they include a wide variety of bioactive compounds (Dias *et al*., 2012).

Zingiber officinale, or ginger is a common dietary spice with various medicinal properties (Nandi *et al*., 2013). It has an antioxidant effect that enhances the immune system, enabling the body to combat illnesses. Ginger can increase digestive fluids, absorb and neutralize toxins, thus helping in parasitic clearance (Abdel-Hafeez *et al*., 2015 & Abouelsoued *et al*., 2020). Moreover, it demonstrated notable anti-parasitic properties against adult *Schistosoma*, intestinal and muscular stages of *Trichinella spiralis*, and hydatid cyst protoscolices. (Sanderson *et al*., 2002, El-Melegy *et al*., 2006 & Moazeni and Nazer 2011). The pharmacological effects of ginger are caused by its active ingredients, which include gingerdoine, gengerdiol, and gingerol (Londhe *et al*., 2011). Therefore, our study was done to assess the possible therapeutic effects of ginger in mice model.

MATERIALS AND METHODS

Animals:

In this study, 48 healthy Swiss Albino mice were used , bred in a laboratory setting and free from parasites. Each mouse weighed approximately 18-20 grams and was sourced from the Theodor Bilharz Research Institute (Giza, Egypt) animal facility. The mice were maintained under controlled laboratory conditions for 6 to 8 weeks before the experiments. The study received ethical approval from the Theodor Bilharz Research Institute's Research Ethics Committee (TBRI-REC) under approval number PT836.

Parasite:

For the infection, *Toxoplasma gondii* (Me49 strain) cysts were isolated from the brains of infected mice. Each brain was suspended in 1 mL of sterile phosphate-buffered saline (PBS) and mechanically homogenized. The resulting homogenates were pooled, and cyst quantification was performed using a hemocytometer. Cysts were microscopically enumerated in a 25 mL aliquot of the brain homogenate (Huskinson-Mark *et al*., 1991).

Infection and Euthanasia:

Mice were infected via intra-oesophageal gavage with 75 *Toxoplasma gondii* (Me49 strain) cysts suspended in 0.2 mL of sterile water (Almurshidi *et al*.,

2023). 60 days post-infection, all animals were euthanized under intraperitoneal anesthesia using a solution containing thiopental (500 mg/kg) and heparin (100 units/mL) for sedation and anticoagulation (Liang *et al*., 1987).

Drugs and Dosing:

Spiramycin was obtained as film-coated tablets (Medical Union Pharmaceuticals). A suspension was prepared by dissolving 704 mg of crushed tablets in 14.5 mL of distilled water. The drug was administered orally via esophageal tube at a dose of 2.5 mg Spiramycin per mouse (0.05 mL suspension), once daily for 10 days starting from day 45 post-infection (El-Kady *et al*., 2022).

Ginger tablets (400 mg per tablet) were obtained from the Arab Company for Pharmaceuticals & Medicinal Plants (MEPACO-MEDIFOOD, Egypt). A daily dose of 250 mg per mouse was prepared by suspending the powdered tablets in distilled water and it was administered orally for 14 consecutive days, beginning 45 days post-infection. Both spiramycin and ginger were delivered via oral gavage as aqueous suspensions (El-Kady *et al*., 2022).

Experimental Design:

Forty-eight mice were randomly divided into four experimental groups, with 12 mice in each group and maintained under standardized conditions for 60 days. The groups were designated as follows:

- **Group I:** *T. gondii*-infected, untreated (the infection control)
- **Group II:** Infected + spiramycin monotherapy
- **Group III:** Infected + ginger monotherapy
- **Group IV:** Infected + combined spiramycin/ginger treatment

No mortality was observed in any group during the study period.

Parasitological Examination:

Following euthanasia, brain tissues were collected from all experimental groups. Each brain sample was homogenized in 1 mL of phosphate-buffered saline (PBS; pH 7.2) to create a uniform suspension. For cyst enumeration, a 10 µL aliquot of each homogenate was examined microscopically (Kaňková *et al.* 2010). The cyst count was determined in 10 high-power fields (HPF) per sample, and the mean cyst burden was calculated for each group.

Histopathological Examination:

All histopathological procedures were performed in the Pathology Department of Theodor Bilharz Research Institute (TBRI). The brain tissue of each mouse was preserved in 10% buffered formalin, processed in graded alcohol concentrations, cleaned with xylol, and then separately embedded in paraffin blocks. Tissue sections with a thickness of 4 µm were stained with H&E. Histopathological assessment was conducted using a Zeiss Scope A1 light microscope (Germany) equipped with an AxioCam MRc5 digital camera system. The slides were examined under a light microscope at magnifications of ×100, ×400, and ×1000 to check for any pathological changes such as necrosis and hemorrhage (Abdallah *et al*., 2022) .

Assessing Levels of Interleukin (IL)-8 & Interferon Gamma (IFN-γ):

Blood samples were taken on the day of sacrifice, from each mouse and allowed to clot at room temperature. The serum was separated by centrifuging the clotted blood at 2500 rpm for 20 minutes. The collected serum was then divided into aliquots and stored at -20°C for future analysis. The levels of IFNγ, IL-8 in mouse serum were measured using commercially available ELISA kits supplied by SUNLONG, China, cat # SL0304Mo and QS0327Mo, respectively. Absorbance at 450 nm was determined by using a microplate reader (Tecan, Switzerland) (Wang *et al*., 2021).

Statistical Analysis:

Results are presented as mean ± SD for quantitative values of the measured parameters. Statistical analysis was performed using one-way ANOVA in SPSS (Statistical Package for the Social Sciences, version 16.0 to ascertain the significance of

differences between the groups under study. At $p<0.05$, all statistical tests were considered significant.

RESULTS

Parasitological Results:

There was significant reduction in the number of brain cysts in all groups expressed as mean ± SD with most significant results in group IV treated with combined therapy (spiramycin and ginger) (Fig. 1a and Fig. 1b).

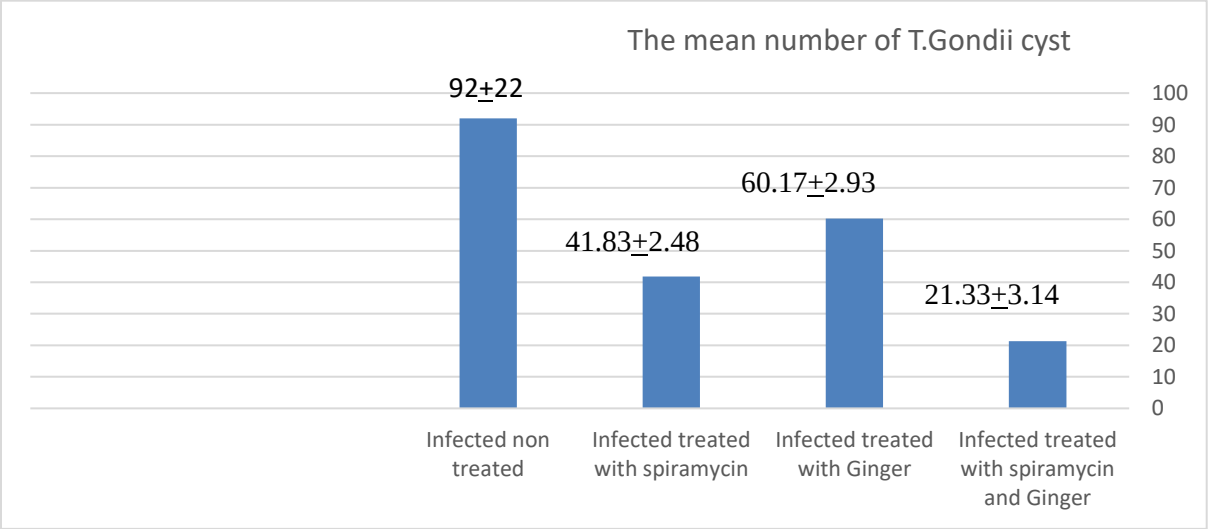

Fig.1a: the mean number of the number of *T. gondii* cysts after treatment in all groups.

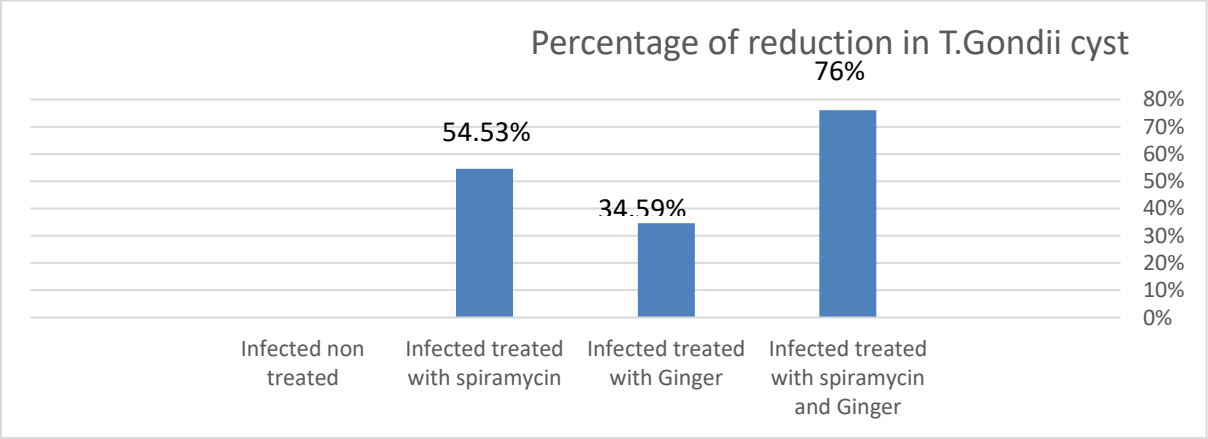

Fig 1b: The percentage of reduction in number of *T. gondii* cysts after treatment in all groups.

Histopathological Results:

Histopathological examination of brain sections of *T. gondii*-infected and untreated mice group (G1) showed large *Toxoplasma* cysts in mouse brain tissue with focal infiltration by lymphocytes. Whereas, brain sections of ginger treated mice group (GIII) showed dense infiltration by lymphocytes. Brain sections of spiramycin treated mice group (GII) showed only mild focal infiltration by lymphocytes. As regard brain sections of (GIV) which received combined treatment of ginger and spiramycin, showed mild focal infiltration by lymphocytes with mild interstitial oedema. (Fig. 2).

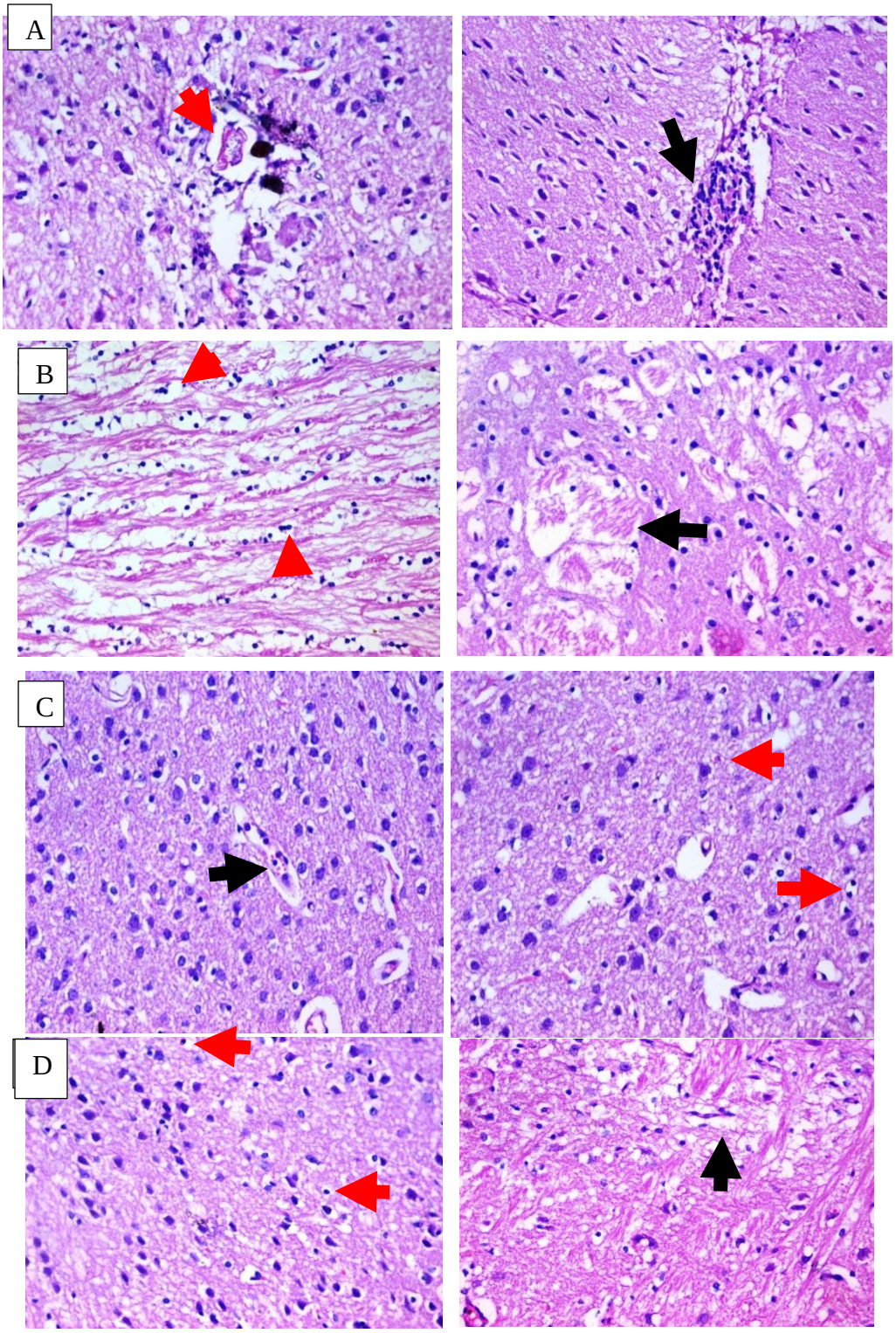

Fig 2: A- Brain Sections of control infected mice (GI) showed *Toxoplasma* cyst (red arrow) with focal infiltration by lymphocytes (black arrow) (H&E stain, X400) B- Brain Sections of ginger treated mice (GIII) showed dense infiltration by lymphocytes (red arrows) with interstitial edema (black arrow) (H&E stain, X400) C- Brain Sections of spiramycin treated mice (GII) showed mild focal infiltration by lymphocytes (red arrows) with nearly normal capillary pattern (black arrow) (H&E stain, X400).D- Brain Sections of mice which received ginger and spiramycin (GIV) showed mild focal infiltration by lymphocytes (red arrows) with mild interstitial edema (black arrow) (H&E stain, X400).

Immunological Assessment:

There was an increase in the level of the measured cytokines (Serum level of IL-8 and IFN-γ) in (GI). In other treated groups, there was reduction in the level of the measured cytokines with the greatest decrease of these cytokines was found in group of mice treated with spiramycin and ginger (GIV) **(**Table 1).

Table (1): The mean number ±SD of IFN-γ and IL8 in pg/ml in all groups

	Infected non-treated (GI)	**Infected treated with spiramycin(GII)**	**Infected treated with Ginger (GIII)**	**Infected treated spiramycin +Ginger (GIV)**
Mean ±SD INF-Y	156.56±0.29	78.51±0.31	136.65±0.4	70.55±0.17
Mean ±SD IL8	128.53±0.3	34.53±0.3	111.56±0.25	33.35±0.22

DISCUSSION

Current therapeutic options for toxoplasmosis primarily target the infection's acute phase (Montazeri *et al*., 2018). However, an ideal anti-*Toxoplasma* agent should demonstrate efficacy against all parasitic stages, particularly the cyst form, while maintaining safety for transplacental passage without fetal toxicity. Existing medications fail to meet these essential requirements (El-Kady *et al*., 2022).

Current treatment protocols for toxoplasmosis primarily involve sulfadiazine and pyrimethamine for acute infection, targeting the proliferative stage of the parasite, while chronic infections are managed with spiramycin, clindamycin, or atovaquone. Even so, serious toxicity problems and new resistance have undermined these medications' efficacy (Al Nasr *et al*., 2016). This increases the urgent need to develop novel therapeutic alternatives for toxoplasmosis management.

The anti-parasitic effects of many medicinal plants were investigated with proved efficacy (AlGabbani *et al*., 2023). Many medicinal plants were studied for the treatment of toxoplasmosis such as *Vernonia colorata* (Benoit-Vical *et al*., 2000), *Sophora flavescens* (Choi *et al*., 2008) and *Curcuma longa* (Al-Zanbagi, 2009). In our study, the therapeutic effect of ginger against chronic toxoplasmosis was assessed using mice model.

The group that received ginger treatment revealed a notable decline in the number of brain cysts. In agreement with our results, Choi *et al* .(2013) found that ginger extract (GE) and ginger-derived fraction GE/F1 significantly suppressed *T. gondii's* growth in C6 cells both in vitro and in vivo. They also found a reduction in inflammatory cytokines in vivo.

Another study used ginger extract alone in treatment of toxoplasmosis and found that throughout the chronic stage of infection, mice with *T. gondii* had a lower parasite burden in their brains. Ginger was found to reverse the pathological alterations in the brain, liver, and lungs brought on by *T. gondii* (El-Kady *et al*.,2022).

As regard our histopathological results of the brain tissues, sections of brains of *group* 1 mice showed extensive histopathological changes with focal infiltration by lymphocytes. These findings are in the same line with El-Temsahy *et al*. (2016) who found *T. gondii* surrounded by inflammatory cells in brain sections of the infected untreated mice. These lesions we found can be explained by the parasite's invasion of brain tissue and the blood-brain barrier disruption (Nishi *et al*., 2020).

The best results were found in the brain sections of GIV which received ginger and spiramycin where mild focal infiltration

by lymphocytes and mild interstitial edema were observed. This in the same line with El-Kady *et al*. (2022) who found that ginger extract treatment significantly reduced the degenerative alterations in the brain brought on by the *T. gondii* infection.

At the site of inflammation, endothelial, epithelial, and macrophage cells release chemical signals called cytokines. These cytokines, such as IL-8 and IFN-γ, are essential for many immunological responses. (Choi *et al*., 2013). We evaluated the changes of IFNγ, IL-8 in the serum of *T. gondii*-infected mice.

In our study, there was an increased cytokines level in the infected untreated group. This aligns with Alajmi *et al*. (2019) and Wakid *et al*. (2023), who stated that *T. gondii*-infection is associated with a significant increase in TNF-α and IFN-γ levels.

There was a reduction in the cytokines level in all treated groups (II, III &IV) with the most significant decrease was noticed in group IV, mice treated with spiramycin and ginger. The reduction in cytokine level in group (III) might be explained by the truth that ginger induces a wide range of bioactivities, such as anti-inflammatory (Grzanna *et al.* 2005) and antimicrobial effects (Ficker *et al*. 2003). Similarly**,** Choi *et al*. (2013) demonstrated that fraction 1 obtained from ginger root extract (GE/F1) inhibited the release of INF-γ and IL-8 effectively and concluded that ginger extract had antiparasitic effects that suppress the release of inflammatory cytokines in vivo. The most significant decrease noticed in group IV can be explained by the synergistic effect of ginger plus spiramycin.

Conclusion

The findings of this study highlight ginger's remarkable potential as a novel therapeutic agent against chronic toxoplasmosis, demonstrating significant cyst reduction and anti-inflammatory effects. Notably, the ginger-spiramycin combination showed superior efficacy, suggesting a powerful synergistic strategy against *T. gondii* infection. These results pave the way for plant-based therapeutics either as monotherapy treatments or drug adjuvants to address the critical limitations of current toxoplasmosis regimens. The role of medicinal plants against parasitic infections is promising as a replacement or synergistic alternative to drugs currently used for treatment of toxoplasmosis.

Declarations:

Ethical Approval: All experiments were conducted following the Clinical and Laboratory standards Institute (CLSI) standards and took the approval of the institution for animal ethics concerning care for animals and proper management of their waste at Theodor Bilharz Research Institute (TBRI) with approval number PT836.

Competing interests: The author declares no competing interests.

Author's Contributions:

R.R.: Conceptualization, data curation, writing, reviewing
S.A.: Methodology, reviewing
Z.H.: Conceptualization, Methodology, reviewing, editing and supervision
E.A.: Conceptualization, Methodology, reviewing
T.A: Methodology, reviewing
S.S: reviewing, editing and supervision
A.R.: Conceptualization, data curation, writing, reviewing

Funding: No financial support was received for this study.

Availability of Data and Materials: All data generated or analyzed in this article are included.

Acknowledgments: The authors gratefully acknowledge Dr Amany A. Abdel-Aal and Dr Marwa A.Elmallawany for accepting reviewing this study.

REFERENCES

Abdallah, K. F., Saleh, M. H., Kishik, S., Barakat, A. M., Ali, B. T., & Elkholy, A. A. (2022). A new approach in treatment of chronic murine models of toxoplasmosis using nitrofurantoin antibiotic.

Zagazig University Medical Journal, 28(5), 1169-1175.

Abdel-Hafeez, E. H., Ahmad, A. K., Kamal, A. M., Abdellatif, M. Z., & Abdelgelil, N. H. (2015). In vivo antiprotozoan effects of garlic (Allium sativum) and ginger (Zingiber officinale) extracts on experimentally infected mice with Blastocystis spp. *Parasitology research*, 114, 3439-3444.

Abouelsoued, D. M., Shaapan, R. M., Elkhateeb, R. M. M., Elnattat, W. S., Hammam, A. M. M. M., & Hammam, A. M. (2020). Therapeutic efficacy of ginger (Zingiber officinale), ginseng (Panax ginseng) and sage (Salvia officinalis) against Cryptosporidium parvum in experimentally infected mice. *Egyptian Journal of Veterinary Sciences*, 51(2), 241-251.

Alajmi, R. A., Al-Megrin, W. A., Metwally, D., Al-Subaie, H., Altamrah, N., Barakat, A. M., ... & El-Khadragy, M. (2019). Anti-Toxoplasma activity of silver nanoparticles green synthesized with Phoenix dactylifera and Ziziphus spina-christi extracts which inhibits inflammation through liver regulation of cytokines in Balb/c mice. *Bioscience Reports*, 39(5), BSR20190379.

AlGabbani, Q., Shater, A. F., Assiri, R., Assiri, G. A., Assiri, A. A., Makhlof, R. T., ... & AlDughaishem, H. (2023). Differential effects of methanolic extracts of clove, ginger, garlic and eucalyptus essential oils on anti-parasitic partitivities of G. lamblia and E. histolytica: an in vitro study. *Rendiconti Lincei. Scienze Fisiche e Naturali*, *34*(3), 853-866.

Almurshidi, B. H., Fahmy, Z., El-Shennawy, A., Selim, E. A., Hammam, O. A., Okasha, H., ... & Abuelenain, G. L. (2023). A multimodality therapeutic application on Toxoplasma gondii encephalitis utilizing Spiramycin and 'de novo'Ferula asafetida in immunodeficient mice. *Parasite Immunology*, 45(12), e13014.

Al Nasr, I., Ahmed, F., Pullishery, F., El-Ashram, S., & Ramaiah, V. V. (2016). Toxoplasmosis and anti-Toxoplasma effects of medicinal plant extracts-A mini-review. *Asian Pacific Journal of Tropical Medicine*, *9*(8), 730-734.

Al-Zanbagi, N. A. (2009). In vivo effect of some home spices extracts on the Toxoplasma gondii tachyzoites. *Journal of Family & Community Medicine*, *16*(2), 59-65

Benoit-Vical, F., Santillana-Hayat, M., Kone-Bamba, D., Mallie, M., & Derouin, F. (2000). Anti-Toxoplasma activity of vegetal extracts used in West African traditional medicine. *Parasite*, 7(1), 3-7.

Choi, K. M., Gang, J., & Yun, J. (2008). Anti-Toxoplasma gondii RH strain activity of herbal extracts used in traditional medicine. *International Journal of Antimicrobial Agents*, *32*(4), 360-362.

Choi, W.H., Jiang, M., & Chu, J. (2013). Antiparasitic effects of Zingiber officinale (Ginger) extract against Toxoplasma gondii. *Journal of Applied Biomedicine*, *11*(1),15-26.

Choi, W. H., & Lee, I. A. (2018). Evaluation of anti-Toxoplasma gondii effect of ursolic acid as a novel toxoplasmosis inhibitor. *Pharmaceuticals*, 11(2), 43

Dias, D. A., Urban, S., & Roessner, U. (2012). A historical overview of natural products in drug discovery. *Metabolites*, 2(2), 303-336.

El-Kady, A. M., Al-Megrin, W. A. I., Abdel-Rahman, I. A., Sayed, E., Alshehri, E. A., Wakid, M. H., ... & Younis, S. S. (2022). Ginger is a potential therapeutic for chronic

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toxoplasmosis. *Pathogens,* 11(7), 798.

El-Melegy, M. A., El-Saify, G. H., & Hassab-El-Nabi, S. E. (2006). Evaluation of therapeutic effect of ginger compared to flubendazole on experimental trichinelosis in mice. Egyptian Journal of Medical Sciences, Egyp J Med Sci, 27(2), 25-48.

El Temsahy, M. M., El Kerdany, E. D., Eissa, M. M., Shalaby, T. I., Talaat, I. M., & Mogahed, N. M. (2016). The effect of chitosan nanospheres on the immunogenicity of Toxoplasma lysate vaccine in mice. *Journal of Parasitic Diseases*, *40*, 611-626.

Ficker, C. E., Arnason, J. T., Vindas, P. S., Alvarez, L. P., Akpagana, K., Gbeassor, M., ... & Smith, M. L. (2003). Inhibition of human pathogenic fungi by ethnobotanically selected plant extracts. *Mycoses,* 46(1-2), 29-37.

Franco, P. S., Gomes, A. D. O., Barbosa, B. D. F., Angeloni, M. B., Silva, N. M., Teixeira-Carvalho, A., ... & Ferro, E. A. V. (2011). Azithromycin and spiramycin induce anti-inflammatory response in human trophoblastic (BeWo) cells infected by Toxoplasma gondii but are able to control infection. *Placenta*, 32(11), 838-844.

Furtado, J. M., Smith, J. R., Belfort Jr, R., Gattey, D., & Winthrop, K. L. (2011). Toxoplasmosis: a global threat. *Journal of Global Infectious Diseases*, 3(3), 281-284.

Grzanna, R., Lindmark, L., & Frondoza, C. G. (2005). Ginger—an herbal medicinal product with broad anti-inflammatory actions. *Journal of Medicinal Food,* 8(2), 125-132.

Huskinson-Mark, J., Araujo, F. G., & Remington, J. S. (1991). Evaluation of the effect of drugs on the cyst form of Toxoplasma gondii. *Journal of Infectious Diseases,* 164(1), 170-177.

Kaňková, Š., Holáň, V., Zajícová, A., Kodym, P., & Flegr, J. (2010). Modulation of immunity in mice with latent toxoplasmosis—the experimental support for the immunosuppression hypothesis of Toxoplasma-induced changes in reproduction of mice and humans. *Parasitology Research,* 107, 1421-1427.

Liang, Y. S., Bruce, J. I., & Boyd, D. A. (1987). Laboratory cultivation of schistosome vector snails and maintenance of schistosome life cycles. In Proceeding of the 1st Sino-American symposium (Vol. 1, pp. 34-48). Stanford Medicine California, USA.

Lieberman, L. A., Banica, M., Reiner, S. L., & Hunter, C. A. (2004). STAT1 plays a critical role in the regulation of antimicrobial effector mechanisms, but not in the development of Th1-type responses during toxoplasmosis. *The Journal of Immunology*, 172(1), 457-463.

Londhe, V. P., Gavasane, A. T., Nipate, S. S., Bandawane, D. D., & Chaudhari, P. D. (2011). Role of garlic (Allium sativum) in various diseases: An overview. *Angiogenesis,* 12(13), 129-134.

McCabe, R. E. (2001). Antitoxoplasma chemotherapy. Toxoplasmosis: a comprehensive clinical guide, 319-359.

Moazeni, M., & Nazer, A. (2011). In vitro lethal effect of Zingiber officinale R. on protoscolices of hydatid cyst from sheep liver. *Microbiology Research,* 2(2), e25.

Montazeri, M., Mehrzadi, S., Sharif, M., Sarvi, S., Shahdin, S., & Daryani, A. (2018). Activities of anti-Toxoplasma drugs and compounds against tissue cysts in the last three decades (1987 to 2017), a

systematic review. *Parasitology research*, 117, 3045-3057.

Montoya, J. G., & Liesenfeld, O. Toxoplasmosis Lancet. 2004; 363: 1965–1976. doi: 10.1016. S0140-6736 (04).

Nandi, S., Rahman, M. Z., Siraj, S., Ahmed, S., Ahsan, M. A., Sultana, N., ... & Roy, S. K. (2013). Quality composition and biological significance of the Bangladeshi and China ginger (Zingiber officinale Rosc.). J*ournal Of Microbiology, Biotechnology And Food Sciences*, 2(5), 2283-2290.

Nishi, L., Santana, P. L., Evangelista, F. F., Beletini, L. F., Souza, A. H., Mantelo, F. M., ... & Falavigna-Guilherme, A. L. (2020). Rosuvastatin reduced brain parasite burden in a chronic toxoplasmosis in vivo model and influenced the neuropathological pattern of ME-49 strain. *Parasitology*, *147*(3), 303-309.

Saha, B., Prasanna, S. J., Chandrasekar, B., & Nandi, D. (2010). Gene modulation and immunoregulatory roles of Interferonγ. *Cytokine*, 50(1), 1-14.

Sanderson, L., Bartlett, A., & Whitfield, P. J. (2002). In vitro and in vivo studies on the bioactivity of a ginger (Zingiber officinale) extract towards adult schistosomes and their egg production. *Journal of Helminthology*, 76(3), 241-247.

Schmidt, D. R., Hogh, B., Andersen, O., Hansen, S. H., Dalhoff, K., & Petersen, E. (2006). Treatment of infants with congenital toxoplasmosis: tolerability and plasma concentrations of sulfadiazine and pyrimethamine. *European Journal of Pediatrics*, 165, 19-25.

Shiojiri, D., Kinai, E., Teruya, K., Kikuchi, Y., & Oka, S. (2019). Combination of clindamycin and azithromycin as alternative treatment for Toxoplasma gondii encephalitis. *Emerging Infectious Diseases*, 25(4), 841-843

Sun, X., Lu, H., Jia, B., Chang, Z., Peng, S., Yin, J., ... & Jiang, N. (2013). A comparative study of Toxoplasma gondii seroprevalence in three healthy Chinese populations detected using native and recombinant antigens. *Parasites & Vectors*, 6, 1-7.

Suzuki, Y., Orellana, M. A., Schreiber, R. D., & Remington, J. S. (1988). Interferon-γ: the major mediator of resistance against Toxoplasma gondii. *Science*, 240(4851), 516-518.

Torrey, E. F., & Yolken, R. H. (2013). Toxoplasma oocysts as a public health problem. *Trends in parasitology*, 29(8), 380-384.

Wakid, M. H., Alsulami, M. N., Farid, M., & El Kholy, W. A. (2023). Potential Anti-Toxoplasmosis Efficiency of Phoenix dactylifera Extracts Loaded on Selenium Nanoparticles. *Infection and Drug Resistance*, 7743-7758.

Wei, H. X., Wei, S. S., Lindsay, D. S., & Peng, H. J. (2015). A systematic review and meta-analysis of the efficacy of anti-Toxoplasma gondii medicines in humans. *PloS one*, 10(9), e0138204.

Yap, G., Pesin, M., & Sher, A. (2000). Cutting edge: IL-12 is required for the maintenance of IFN-γ production in T cells mediating chronic resistance to the intracellular pathogen, Toxoplasma gondii. *The Journal of Immunology*, 165(2), 628-631.

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