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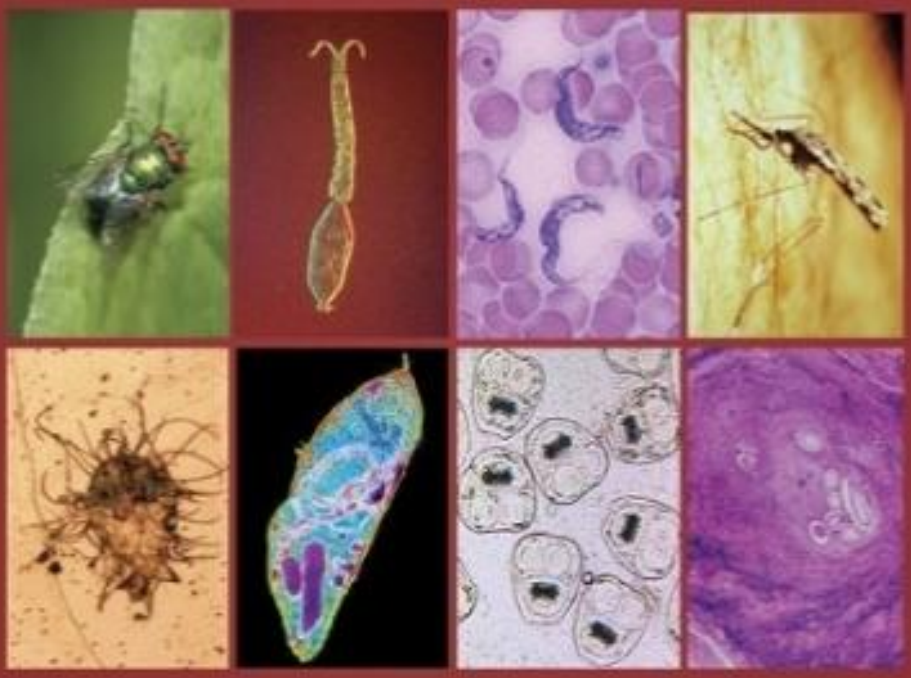

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Effect of *Viscum album* Extract on the Angiogenic Process During the Muscular Phase of Experimental *trichinellosis*

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ABSTRACT

Albendazole is the current treatment for trichinosis; however, there are uncertainties about its efficacy in removing the encapsulated phases. This study explored the effect of *Viscum album* "VA" extract as a possible substitute with and without albendazole, against the muscular phase of trichinellosis. Four groups of infected CD1 Swiss-Albino male mice were used: **G1**: non-treated, **G2**: treated with albendazole, **G3**: treated with VA, and **G4**: treated with VA combined with albendazole. Assessment was conducted by counting the number of larvae, followed by histopathological examination and immunohistochemical quantitative detection of the vascular endothelial growth factor (VEGF) angiogenic marker. The treated group by combined medications signified the lowest number of larvae (64.38±21.3) with the best reduction rate (93%). Immunohistochemical stain reported significantly lower levels of VEGF in treated groups with VA and combined therapy in comparison to infected non-treated groups and infected treated by albendazole monotherapy (3.4 ±0.09, 2.9 ±0.06 and 12.7 ±0.11, 11.9 ±0.12) respectively, reflecting the great anti-angiogenic activity of VA. In addition, the inflammatory response was greatly diminished in VA-treated groups, manifesting its anti-inflammatory effect as well. Our findings suggest that VA is a possible therapeutic agent against the muscular phase of experimental Trichinellosis, especially when combined with albendazole. V A succeeded in affecting the encapsulated phases by depriving them of a nutritional source and positively modulated the inflammatory response in favor of the host. Therefore, aquatic extracts of VA are recommended to be further investigated as a prophylactic or therapeutic agent against a wide range of parasitic infections.

INTRODUCTION

Trichinella spiralis is a well-known nematode parasite, typically transmitted by ingesting the first-stage larvae inhabiting infected meat, basically pork, resulting in trichinosis or trichinellosis (Kang *et al.,* 2011). Although trichinosis is one of the most widespread zoonotic parasitic diseases globally and can lead to life-threatening complications, its incidence is generally low in Muslim countries due to religious prohibitions against pork consumption. However, localized studies have reported relatively high seroprevalence rates among specific populations. For example, in Egypt, the occurrence of trichinosis among individuals presenting with suggestive symptoms was 67.7% in Assiut and 46.7% in Sohag, as confirmed by serological testing (Sayed *et al.,* 2010).

These findings were attributed to the indoor breeding and unsupervised slaughtering of pigs, often without proper meat inspection, which may facilitate disease transmission despite its overall rarity in the broader population.

The larval stages within the infected meat habitually invade the small intestine, circulate to reach the final destination "striated muscles", where they start the growing phase till complete effective occupation over about 20 days. The infected larvae modify the muscle fibers during this phase by inducing major cellular changes, plus the formation of new blood vessels around the transformed muscle cells, resulting in the formation of nurse cells that guarantee long-term habitation for the larvae (Capo *et al.,* 1998).

The creation of new blood vessels, or what is called angiogenesis, is one of the most obvious steps during nurse cell formation, supplying the parasitic stages constantly by nutrients and disposing of waste products. Vascular endothelial growth factor (VEGF) is frequently detected immediately when tested, surrounding the nurse cells (Fong, 2008). Inhibition of the angiogenic process is currently being investigated as a new therapeutic possibility for many medical conditions, including cancer (Elluru *et al.,* 2009). A similar strategy was previously investigated using calcium channel blockers as anti-angiogenic and anti-inflammatory agents and achieved promising results against trichinosis, reaching a 99% larval reduction rate (Fadil *et al.,* 2022).

Viscum album "VA" is a semi-parasitic plant that can grow on apple, pine, poplar, and oak trees (Bonamin *et al.,* 2017). For decades, VA was widely employed in traditional medicine to treat neurological problems (Szurpnicka *et al.,* 2019) and malignancies (Ozpinar et al., 2019). Furthermore, various studies have demonstrated that VA has antibacterial, antifungal, and antiparasitic properties (Hussain *et al.,* 2011; Ozpinar *et al.,* 2019). The extract also exhibits anti-angiogenic and anti-inflammatory properties (Hegde *et al.* 2011).

The current study sought to compare the therapeutic efficacy of VA extract on the muscular phase of experimental trichinosis to the widely utilized Albendazole therapy.

MATERIALS AND METHODS

Experimental Animals:

A total of 32 CD1 Swiss-Albino male mice ranging in age from 6 to 8 weeks and weighing between 20 and 25gm were obtained from Theodor Bilharz Research Institute (TBRI) and divided into four groups of eight mice each: **G1**: infected non-treated, **G2**: infected treated with the reference drug albendazole, **G3**: infected group treated with VA, and **G4**: infected treated with both medications. Animals were housed in specific cages that provided free access to food and water. During our investigation, we handled animals in accordance with the National Institutes of Health (NIH) guidelines for the care and use of laboratory animals. The scientific research ethics committee of the Faculty of Medicine at Fayoum University approved the experiment.

The Parasite and The Infection:

In this experiment, the *T. spiralis* strain was maintained in the muscle fibres of infected mice at the Theodor Bilharz Research Institute in Giza, Egypt. Donor mice for the larvae were slaughtered, skinned, and eviscerated. Gajadhar *et al.* (2019) reported that each mouse's muscle was artificially digested with a pepsin-HCl mixture, and the larvae were collected and studied under a microscope (x40). Oral gavage was used to introduce around 200 larvae per mouse.

Drugs and Dosing:

The treatment programs began on the 35th day post-infection in the chronic phase of infection with oral gavage tubes. Albendazole in syrup form (Bendax, SIGMA Pharmaceutical Industries, Egypt) was administered at a dose of 250 mg/kg for six consecutive days (Li *et al.,* 2012).

Viscum album medicinal preparation was acquired from Sigma-Aldrich Company and diluted in 0.9% NaCl to create an isotonic solution of 5 mg/ml and 10 mg/ml. The solution was endotoxin-free and contained standardized amounts of mistletoe lectins (0.375 ng/ml) and viscotoxins (0.12 ng/ml). The dose was reduced to 100mg/kg and given for six days straight (Hegde *et al.,* 2011).

Mice Euthanasia:

After infection and completion of the experiment, mice in both groups were euthanized (45 days post-infection) via intraperitoneal injection of an anesthetic-anticoagulant solution (500 mg/kg thiopental and 100 units/ml heparin) (Laferriere *et al.,* 2020).

Parasitological, Histopathological and Immunohistochemical Evaluation:

Each mouse's muscle mass was weighed and artificially digested, and the quantity of larvae per gram was estimated for parasitological examination following identification and counting under the microscope. The decrease rates were determined using the methods previously disclosed (Gu *et al.,* 2020). The diaphragm of each mouse in the study was removed and stored in 10% formalin. The tissues were then treated and embedded in paraffin. Three 5 μm-thick sections were cut from each paraffin block. The first section was stained with hematoxylin and eosin (H&E) for histological examination (Slaoui *et al.,* 2011). Inflammatory cellular infiltration was graded as no, minimal, mild, moderate, or severe depending on the percentage of inflammatory cells compared to the control group over five fields of vision (x100) (Lei *et al.,* 2020). The other two sections underwent immunohistochemistry using a number of chemical processes, including staining with Mouse Monoclonal Anti-VEGF Antibody (Sino Biological Inc., Beijing, China). A quantitative examination of the area% of vascular endothelial growth factor (VEGF) positive cells within 5 fields of vision (x100) was performed at the Pathology Department, National Research Centre, Giza, Egypt, using a Leica Qwin500 Image Analyzer (Cambridge, England).

Statistical Analysis of Data:

Quantitative data (mean ± SD) were used to indicate the number of diaphragmatic larvae and local muscle expression of VEGF in each study group, while qualitative data (inflammatory score) were recorded. All analyses were carried out using SPSS software version 28.0 (IBM Corp, Armonk, NY). For various pairwise comparisons between the research groups, a one-way ANOVA test was used, followed by an LSD post hoc test and a chi-square test. A P-value of <.05 was judged statistically significant.

RESULTS

Efficacy of Treatments on Larval Burden Reduction

A quantitative examination of larval burden found a significant reduction in larval counts across all treated groups compared to the infected non-treated group ($p < 0.001$) (Table 1). The infected non-treated group (G1) had the largest mean larval count (439.3 ± 37 larvae), which served as the baseline. Albendazole (G2) treatment reduced larval counts by 69.5%, with an average of 134.4 ± 24. The group treated with VA alone (G3) achieved a 57% decrease (189.1 ± 3.5 larvae), showing modest efficacy. The combination therapy group (G4) had the greatest reduction in larval load, with an average of 34.38 ± 21.3 larvae, representing a 93% reduction and much lower than the other groups. These data indicate that, while both albendazole and VA have antiparasitic properties, their combination provides a synergistic advantage, resulting in the maximum treatment efficacy.

Table 1: The mean larval count and the reduction rates among groups.

Groups	Mean ± SD	Reduction rates	*P* value
G1	439.3 ±37[a]	0 %	
G2	134.4 ±24[b]	69.5%	
G3	189.1 ±3.5[c]	57%	*P* <0.001**
G4	34.38 ±21.3[d]	93%	

Histopathological Assessment of Larval Stages and Inflammatory Response

The histopathological study indicated distinct tissue responses between the experimental groups. In the infected non-treated group (G1), multiple intact larval stages were found surrounded by a significant inflammatory infiltrate, indicating an active infection and a strong host immune response (Fig. 1A). In contrast, the albendazole-treated group (G2) had dead larval stages surrounded by significant inflammation, indicating the drug's parasiticidal impact and the subsequent host response to larval degeneration (Fig. 1B). The VA-treated group (G3) exhibited modest inflammation around reasonably undamaged larvae, indicating partial therapeutic efficacy or immunomodulation (Fig. 1C). Similarly, the combination therapy group (G4) showed a modest inflammatory response around reasonably intact larval stages (Fig. 1D), indicating a potential anti-inflammatory benefit, while complete larvae clearance was not observed histologically.

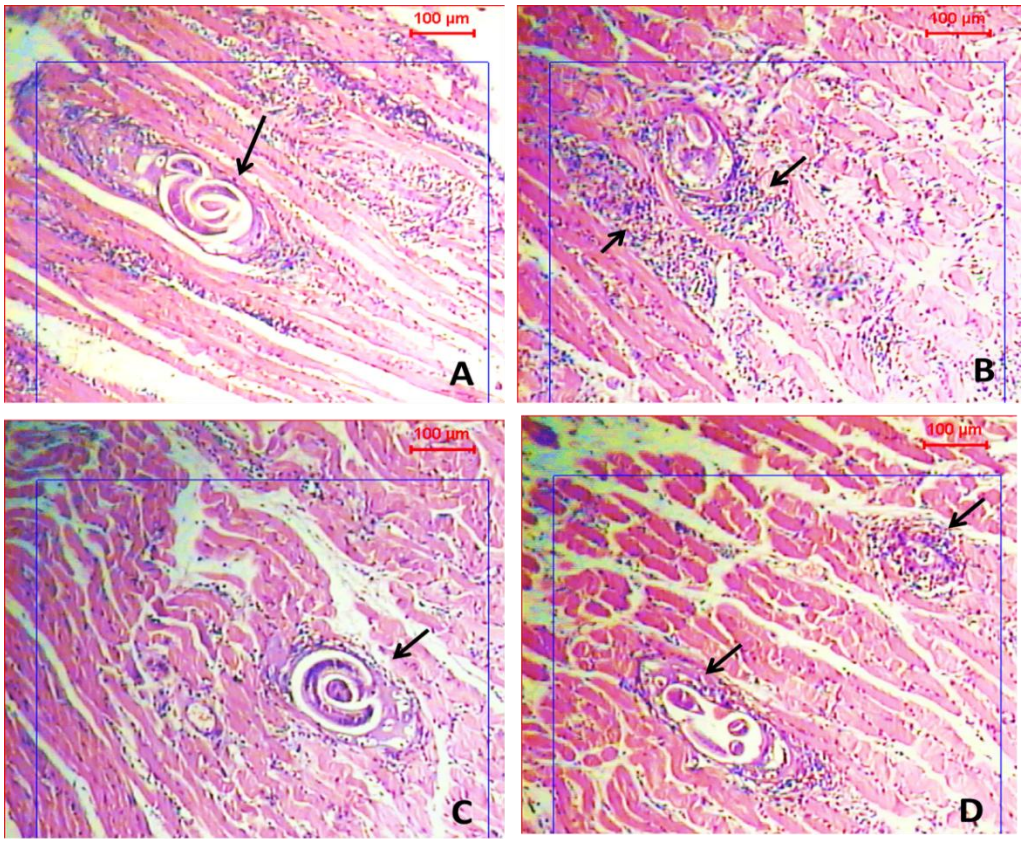

Fig. 1: Histopathological pictures represent features of different groups (indicated by black arrows): A, G1 non-treated showed intact larval stage surrounded by inflammatory response, B, extensive inflammation surrounding dead larvae is seen in G2 treated with albendazole. C; mild inflammation is noticed around the relatively intact larval stage, and D; mild inflammation is observed around the relatively intact larval stage.

Immunohistochemical Evaluation of VEGF Expression:

Immunohistochemical examination revealed that the VA-treated group (G3) and the combined therapy group (G4) had significantly lower vascular endothelial growth factor (VEGF) expression than the infected non-treated group (G1) and the albendazole-treated group (G2). In comparison to G1 and G2, G3 and G4 had significantly lower VEGF levels (3.4 ± 0.09 and 2.9 ± 0.06, respectively) (Figs. 2 and 3). These data indicate that VA, either alone or in combination, may have an anti-angiogenic effect by reducing VEGF expression.

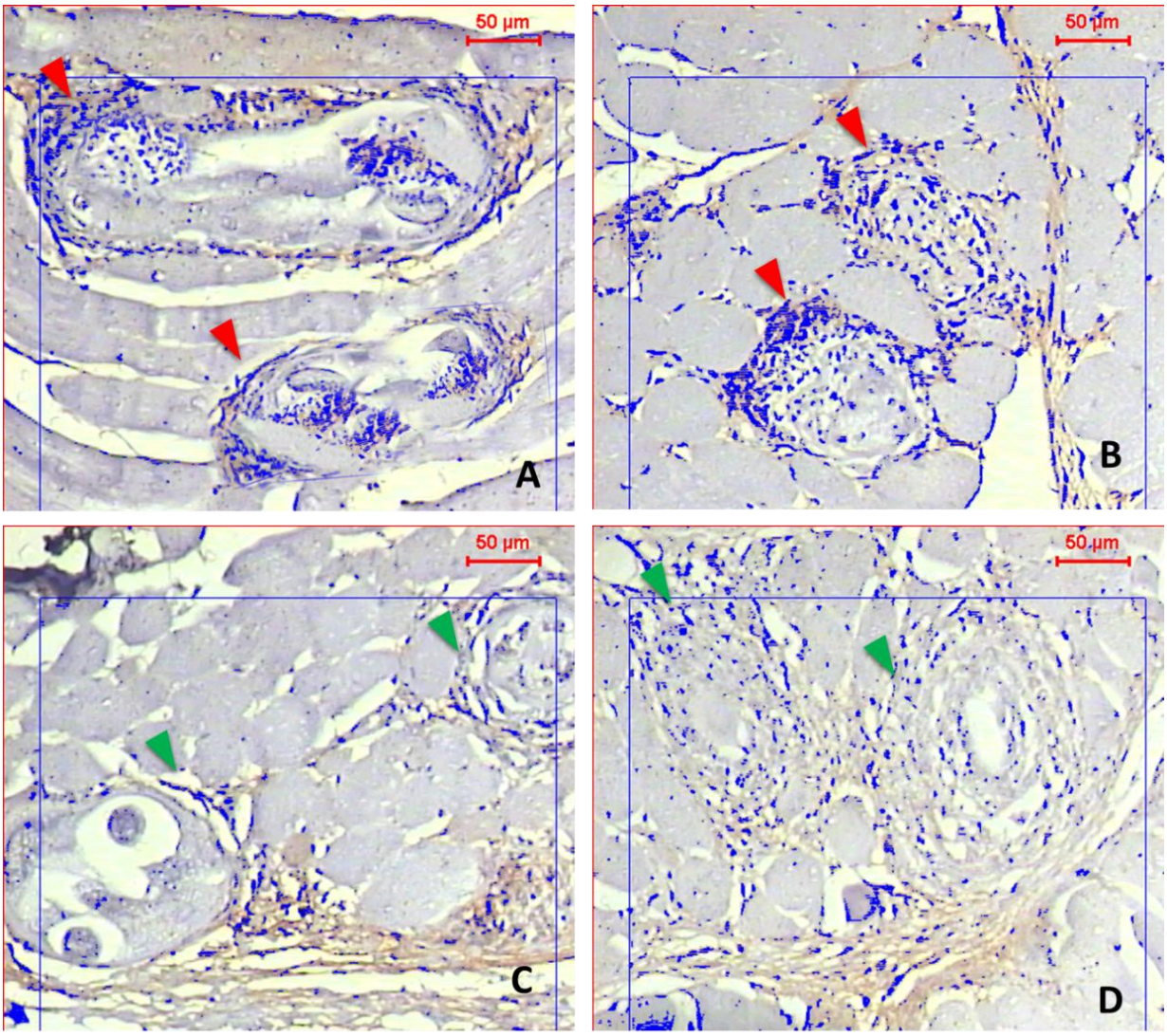

Fig. 2: Immunohistochemical pictures represent levels of VEGF expression in different groups. Moderate expression is seen in G1 and G2 (red arrows), and relatively lower expression is noticed in G3 and G4 (green arrows).

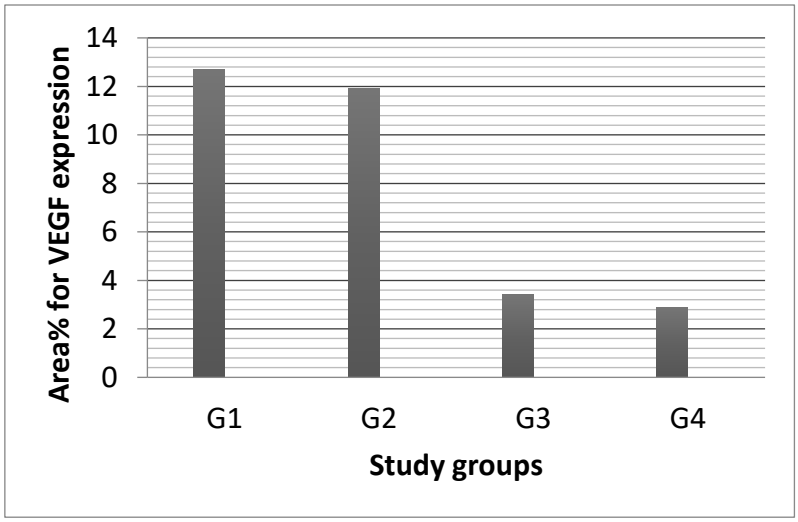

Fig. 3: A bar chart depicts the average VEGF expression levels in each experimental group. Data demonstrate that VA-treated and combined therapy groups had considerably lower levels than the control and albendazole-treated groups.

DISCUSSION

Phytopharmaceuticals are commonly employed as substitutes for synthetic drugs, especially in less economically developed countries (Ozpinar *et al.,* 2019). Mistletoe, a parasite of hundreds of tree species, has assorted bioactive compounds, such as flavonoids, mistletoe lectins, and viscotoxins. The botanical name for mistletoe is *Viscum album* (VA), and it has been utilized for centuries across cultures for medicinal use (Twardziok *et al.,* 2016).

In the present research, VA was investigated as a potential therapeutic approach for the muscular phase of T. spiralis infection, both alone and in association with the standard drug albendazole. Histopathology and immunohistochemistry techniques were employed to establish inflammation and angiogenesis, respectively. In the counting of the larvae, notable reduction rates were established in the group treated with albendazole (69.5%). This is because the drug's mechanism of action includes selective degeneration of cytoplasmic microtubules in larvae and helminths, reduced glucose uptake, and glycogen depletion of the parasites (Lloyd *et al.,* 2014). Another previous study showed comparable findings, wherein *T. spiralis* larval count was significantly decreased by 79.6% in the albendazole-treated group on the 35th day of infection (Fahmy and Diab, 2021). A previously noted reduction of 62.62% is rather conservative (Li *et al.,* 2012). These variations in findings may be the result of variations in experimental design, dose of treatment, or administration schedule timing.

Angiogenesis is a cellular process by which new blood vessels are created. Abnormal cells and microbial agents need a sufficient blood supply and nutrients to sustain their growth, and thus, angiogenesis emerges as a possible therapeutic strategy against such abnormalities, including trichinosis (Elluru *et al.,* 2009). During the muscle phase of infection, *T. spiralis* larvae convert muscle fibers into nurse cells, generating collagen-encysted complexes that require vascularization to continue larval growth. *T. spiralis* has been shown to stimulate angiogenesis through VEGF expression (Ock *et al.,* 2013). Therefore, anti-angiogenic treatment is considered an old method to fight malignant cells, obliterating the oxygen and nutritional sources supplying the cancer (Lopes-Coelho *et al.,* 2021). A similar strategy was previously studied to eradicate the muscular phase of *Trichinella spiralis,* which is

dependent on new blood vessels for its cellular existence.

In the current investigation, infection with *T. spiralis* was linked to positive local expression of VEGF in skeletal muscle tissue of the infected non-treated group. VEGF expression was shown to be lower in albendazole-treated mice than in animals treated with VA alone or with both albendazole and VA. In agreement, Kang *et al.* (2011) reported that VEGF was expressed within muscle fibers of mice infected with *T. spiralis*, facilitating the formation of new blood vessels necessary to feed and support larval stages present in muscle tissue.

The extreme decline in the number of larvae counted in the VA-treated group (G3, 57%) and the greatest percentage of decrease in the combination therapy group (G4, 93%) could be due to the anti-angiogenic activity of VA. These effects are thought to be induced by VA's lectin component, causing endothelial cell apoptosis, thereby blocking blood flow to lactating cells (Elluru *et al.,* 2009). This may explain the increased efficacy of the combination therapy, as VA might be involved in breaking down the parasitic larval structure by attacking the vascular supply mechanism that sustains the nurse cells. In support of our findings, an earlier study using the extract of *Viscum verruscum* in Tswana goats showed a significant reduction in fecal egg count, an indication of an anti-helminthic effect, which is most likely due to the tannin content in the plant (Moncho *et al.,* 2012).

Histopathologically, albendazole-treated groups had significant inflammation around deceased larvae, which could be attributed to antigen exposure after larval degeneration. This is consistent with the suggested mechanism for albendazole and its immunostimulatory effects (Ricken *et al.,* 2017). In contrast, VA-treated groups had significantly lower inflammatory responses, indicating VA's anti-inflammatory properties (Nicoletti *et al.,* 2023).

Numerous factors led to the report of VA's anti-inflammatory action. This plant's constituents were examined for their selective suppression of cytokine-induced cyclooxygenase production, COX-2 inhibition that implicates COX-2 mRNA instability, and mediated PGE2 (Van Huyen *et al.,* 2006; Elluru *et al.,* 2015; Saha *et al.,* 2015). Also, it contains phenols and flavonoids responsible for this activity (Urech & Baumgartner, 2015). Furthermore, VA is found to contain various chemical constituents such as lectins. Mistletoe lectins are type II ribosome-inactivating proteins (RIPS) extracted from *Viscum* plants, which have anti-inflammatory effects that bind to inflammatory proteins (Peumans *et al.,* 1996). RIPs have an impact on immune response, platelet aggregation, and inflammatory pathways in various ways specific to the lectins (Mishra *et al.,* 2004).

Our findings suggest that VA is a possible therapeutic agent against the muscular phase of experimental *Trichinellosis*, especially when combined with albendazole. Therefore, extracts of Viscus Album are recommended to be further investigated as a prophylactic or therapeutic agent against a wide range of parasitic infections. These plant extracts can be a source of new complementary medicines, supporting the treatment of many infectious diseases and preventing or decreasing their complications.

Declarations:

Ethical approval: The clinical research studies were approved by the IRB office of the Ethical Committee of Fayoum University, according to the Declaration of Helsinki https://www.wma.net/policies-post/wma-declaration-of-helsinki/

Competing interests: All authors declare no conflict of interest.

Availability of Data and Materials: All datasets analyzed and described during the present study are available from the corresponding author upon reasonable request.

Authors Contributions:
Goma Desoky Eimam and Asmaa R. Abd-Alghany; Methodology, Software, Formal analysis, Investigation, Resources, Visualization, and Writing- original draft. Marwa Ahmed El-Dardiry and Manal Badawi; Conceptualization, Data curation, Writing—review and editing, and Supervision. All authors have read and agreed to the published version of the manuscript.

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