

Microencapsulated oxfendazole modulates neuroinflammation in experimental *Taenia crassiceps* neurocysticercosis

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ABSTRACT

Neurocysticercosis (NCC), caused by the larval stage of *Taenia solium*, is the leading cause of acquired epilepsy in developing countries and an increasing public health concern in developed regions. Albendazole (ABZ) and praziquantel are the mainstays of current treatment, but their effectiveness is constrained by their poor absorption in the central nervous system and the worsening of inflammatory reactions after parasite degeneration. This neuroinflammation brought on by the medication poses a serious safety risk. Thus, this study aimed to evaluate the immunomodulatory and histopathological effects of oxfendazole microparticles (OXF-MICRO) in a murine model of *Taenia crassiceps* NCC. BALB/c mice intracranially infected with cysticerci were treated 30 days post-infection with a single oral dose of ABZ (40 mg/kg), conventional oxfendazole (OXF, 30 mg/kg), or OXF-MICRO (30 mg/kg). Brain cytokine levels were quantified 24 h post-treatment using cytometric bead array, and histopathological analyses were performed. All treatments induced cyst degeneration and significantly reduced TNF- α , IL-17, and IL-10 levels, indicating disruption of parasite-induced immune tolerance. Distinct immune profiles were observed: OXF promoted a Th1-type response (increased IFN- γ and IL-2), whereas OXF-MICRO and ABZ induced a Th2-skewed response (elevated IL-4). Notably, only OXF-MICRO significantly reduced polymorphonuclear cell infiltration in brain tissue ($p = 0.029$). These findings demonstrate that OXF-MICRO preserves antiparasitic efficacy while attenuating acute inflammatory infiltration, suggesting an improved safety profile. Collectively, these results support microencapsulation as a promising strategy to enhance therapeutic outcomes in NCC.

1. Introduction

Neurocysticercosis (NCC) is a parasitic disease affecting the central nervous system (CNS), caused by *Taenia solium* cysticerci from ingesting helminth eggs. It is the most common helminthic infection of the CNS globally, particularly endemic in areas of South America, Central America, Sub-Saharan Africa, and parts of Asia (Del Brutto, 2022;

Newton and Garcia, 2012; Pineda-Reyes and White, 2022). Clinical manifestations can vary from asymptomatic to severe neurological issues like chronic headaches and seizures, influenced by lesion characteristics and the host's immune response (Prodjinotho et al., 2020).

The intensity of CNS inflammation plays a central role in determining disease progression and parasite survival, as *T. solium* exhibits sophisticated immune evasion mechanisms (Del Brutto, 2022;

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Prodjinotho et al., 2020; Toledo et al., 2018). As a result, diagnosis and treatment are still difficult and frequently need a mix of anti-inflammatory medications, antiparasitic treatments, and, occasionally, surgery. The developmental stage of the cysticercus is correlated with cytokine expression, and disease progression is intimately linked to dynamic changes in host immunity. Early CNS invasion induces a Th1-type response, driven by the IL-12/STAT4 axis and characterized by IFN- γ production and macrophage activation (Cardona et al., 1999; Cardona and Teale, 2002; Rodríguez-Sosa et al., 2004). In the viable cyst stage, a Th2-dominant response prevails, characterized by high IL-4 and IL-10 levels that encourage immune tolerance via M2 macrophages and regulatory T cells (Adalid-Peralta et al., 2021; Reyes et al., 2009; Terrazas, 2008). As degeneration commences, this regulatory environment disintegrates, resulting in a mixed Th1/Th2 response, followed by a Th1 resurgence that ultimately clears the parasite (Prodjinotho et al., 2020).

Cytokine profiling aids in understanding systemic immune responses, while histopathological analysis is crucial for detailing local tissue changes and the host–parasite dynamics in the CNS. Inflammatory cell infiltrates, including lymphocytes, macrophages, and eosinophils, accumulate around the cysticercus in a manner that is dependent on the parasite developmental stage (Prodjinotho et al., 2020). Adjacent brain tissue frequently exhibits edema, gliosis and neuronal damage, largely determined by parasite burden and the magnitude of the inflammatory response (Del Brutto, 2022). Integrating cytokine data with histopathological findings allows a comprehensive evaluation of disease progression and therapeutic effects.

Albendazole (ABZ) and praziquantel are the primary treatments for NCC, often used with corticosteroids to reduce inflammation. These treatments face challenges, such as the need for long-term use, high rates of adverse effects linked to heightened inflammation, potential neurological complications, and difficulties in attaining complete cures, especially in extraparenchymal cases or those with multiple cysts (Del Brutto, 2022; Garcia et al., 1997; Monk et al., 2021; Pineda-Reyes and White, 2022; White et al., 2018). New chemotherapeutic alternatives are urgently needed, particularly Oxfendazole (OXF), a benzimidazole anthelmintic utilized in veterinary medicine, known for its broad-spectrum effectiveness against intestinal and tissue-dwelling helminths (Gonzalez et al., 2019). However, like other compounds in this class, OXF is characterized by poor aqueous solubility (44.12 mg/ml), which limits its bioavailability and therapeutic performance (An et al., 2019). In this regard, microencapsulation strategies represent a promising approach to overcome these limitations by enhancing solubility, dissolution, and improving drug stability (Bin Karim et al., 2021; da Silva et al., 2023; Nataren-Rodríguez et al., 2025). Microencapsulation strategies have improved the biopharmaceutical performance of benzimidazole derivatives (Piccirilli et al., 2014; Seremeta et al., 2026; Vargas Michelena et al., 2024); however, their application for targeted delivery in neurocysticercosis using microparticles remains unexamined. Thus, this study aimed, for the first time, to evaluate the immunomodulatory and histopathological effects of the OXF microparticulate system in a murine model of *Taenia crassiceps*, which is a consolidated experimental model for NCC due to its antigenic similarity to *T. solium* (Prodjinotho et al., 2020; Sitali et al., 2022).

2. Materials and methods

2.1. Materials

Oxfendazole (99.9% purity, lot 3132,104,903) and Eudragit® RL PO (lot 420,536,075) were kindly donated by Jiangsu Baozong & Baoda Pharmachem Co., Ltd (Rugao, China) and Evonik Industries AG (Essen, Germany), respectively. Purified water (Milli-Q, Millipore Corporation, Billerica, MA) was used. All other reagents, such as ethanol, HCl, Sipernat®, phosphate buffer, and solvents were of analytical grade and were used as received without further purification.

2.2. Spray drying of microparticles

Microparticles were prepared as reported elsewhere with some modifications (Seremeta et al., 2026). Each lot of OXF-loaded microparticles were obtained using 1 g of Eudragit® RL PO and 1 g of OXF (polymer: drug ratio of 1:1). Both polymer and the drug were dissolved in 60 mL of absolute ethanol with 1.710 μ L of HCl under magnetic stirring at 250 rpm until complete dissolution. The resulting organic phase was added dropwise using a syringe fitted with a 21 G needle (0.80 $\times$ 25 mm) at a controlled flow rate of 0.5 mL min⁻¹ (DK Infusetek Com, China) to a dispersion of Sipernat® (7.5% w/w of the total solid weight) in 540 mL of water and stirred magnetically for 1 h. Finally, the suspension was fed into a Mini Spray Dryer Büchi B-290 (Büchi Labor-technik AG, Switzerland) under constant magnetic stirring to ensure homogeneity. The process was carried out in open-loop mode and co-current flow at an air inlet temperature of 140 °C, an atomizing air flow rate of 600 L h⁻¹, a liquid flow rate of 1 mL min⁻¹, a carrier gas flow rate (aspirator) of 35 m³ h⁻¹, and a pressure of 4 bar. After recovery and weighing to determine the yield, the dried powder was stored at room temperature in sealed glass vials, protected from light and moisture.

The yield (%) was determined using Eq. (1), by weighing the powder obtained after the spray-drying process, where W_{MP} is the total weight of microparticles obtained after the spray-drying process, and W_0 is the total weight of excipients and OXF combined and employed in their production.

$$Yield = \frac{W_{MP}}{W_0} (x) \quad (1)$$

2.3. Loading capacity and entrapment efficiency

To determine the loading capacity (%LC) and encapsulation efficiency (%EE) of the different microparticle formulations, an aliquot (0.01 g) was dissolved in 5 mL of a solvent mixture of an ethanolic solution of HCl 0.1 N and water (4:1), and spectrophotometric measurements were performed after proper dilution. OXF concentration was determined using a UV–Visible spectrophotometer (UV-1800, Shimadzu, Japan) at 291 nm, based on a calibration curve prepared with OXF in the same solvent (2–20 μ g mL⁻¹; $Y = 0.0566x + 0.001$; $r^2 = 0.9997$). Measurements were performed in quintuplicate, and results are expressed as mean $\pm$ S.D.

The %LC of the microparticles was calculated according to Eq. (2), where W_{OXF} is the weight of the drug in the microparticles, and W_{MP} is the total weight of the obtained microparticles

$$\%LC = \frac{W_{OXF}}{W_{MP}} \times 100 (x) \quad (2)$$

The %EE of the microparticles was determined using Eq. (3), where LC_E and LC_T are the experimental and theoretical loading capacity of the microparticles, respectively.

$$\%EE = \frac{LC_E}{LC_T} \times 100 (x) \quad (3)$$

2.4. Equilibrium solubility

An equilibrium solubility assay was carried out by adding an excess amount (200 mg) of raw OXF and OXF-MICRO samples to 10 mL of the corresponding dissolution media (hydrochloric acid buffer, pH 1.2, or phosphate buffer, pH 7.4). The resulting dispersions were placed in hermetically sealed vessels and agitated for 72 h at 25 °C using an elliptical shaker operating at 180 rpm (Boeco Universal Orbital Shaker PSU-10i, Hamburg, Germany). Following equilibration, aliquots were withdrawn and centrifuged at 6000 rpm for 15 min (MIKRO 220, Andreas Hettich GmbH & Co. KG, Tuttlingen, Germany). The supernatants were carefully collected and filtered through a 0.45 μ m nylon membrane filter. The concentration of OXF in solution was quantified by

UV spectroscopy at 291 nm using a UV-Vis spectrophotometer (UV-1800, Shimadzu, Kyoto, Japan). Before analysis, it was confirmed that the excipients did not interfere at the selected wavelength. All measurements were performed in triplicate, and the results are expressed as mean $\pm$ standard deviation.

2.5. Parasite maintenance and animal model

The experimental protocol was conducted under the approval of the Ethics Committee on Animal Use (CEUA/UFG, N°. 032/22). Female BALB/c mice (8–12 weeks old) were obtained from the Multi-User Center for Animal Production and Experimentation (CMPEA/UFG). The *Taenia crassiceps* (ORF strain) was maintained through intraperitoneal passages every 90 days, where multiplication occurs via asexual budding (Vaz et al., 1997).

For NCC induction, mice were anesthetized with ketamine hydrochloride (100 mg/mL) and xylazine (20 mg/mL) at a 0.1 mL/10 g ratio. Following cranial trichotomy and antisepsis, a longitudinal incision and trepanation were performed using a micromotor drill (1/8). Five viable cysticerci were inoculated into the brain, 2 mm from the sagittal junction and transverse suture, using a technical needle adapted to minimize mechanical trauma (Matos-Silva et al., 2012).

2.6. Formulations and treatment

The OXF-MICRO were developed in collaboration with the Universidad Nacional de Rosario (Argentina) as described in Section 2.2.

In this study the “resource equation” method was used to determine sample size, in which a value “E” should lie between 10 and 20 animals. Using the equation provided by Charan and Kantharia (2013):

$E = \text{Total number of animals} - \text{Total number of groups}$; we have three experimental groups with 5 animals each, resulting in $E = (3 \times 10) - 5$; $E = 25$. Therefore, the sample size is acceptable.

Thirty days post-infection, animals were randomly assigned to four groups ($n = 10/\text{group}$), treated with a single oral dose, as recommended by the producer: Negative Control: 50 μL 0.9% NaCl; Albendazole (ABZ): 30 mg/kg; Conventional Oxfendazole (OXF): 30 mg/kg; Micro-encapsulated Oxfendazole (OXF-MICRO): 30 mg/kg in the formulation (Gomez-Puertta et al., 2012). The euthanasia performed within a CO_2 chamber was conducted 24 h post-treatment in order to capture the acute inflammatory response and early shifts in cytokine profiles.

2.7. Cytokine quantification (CBA)

Following euthanasia, brain tissue was removed and processed in a lysis buffer enriched with protease inhibitors (Complete EDTA-free, Roche®). The homogenized supernatant was subjected to the Cytometric Bead Array (CBA-BD®) technique for the simultaneous quantification of IL-2, IL-4, IL-6, IFN- γ , TNF, IL-17A, IL-10, and TGF- β . Concentrations (pg/g) were normalized against total protein levels determined by the Micro Lowry method. Data analysis was performed using FCAP Array 2.0 software.

2.8. Histopathological and morphometric analysis

Brain hemispheres were fixed in 10% buffered formalin, embedded in paraffin, and sectioned at 5 μm for Hematoxylin and Eosin (H&E) staining. Histopathological analysis was performed blindly using a semi-quantitative scale: 0: Absent; 1: Discrete (up to 25% area affected); 2: Moderate (26% to 50%); 3: Marked (above 50%).

The evaluated parameters included: polymorphonuclear (PMN) and mononuclear (MN) infiltrates, meningitis, ependymitis, choroiditis, microgliosis, vasculitis, hemorrhage, and ventriculomegaly. The evolutionary stage of the parasite (Initial, Larval, or Final/Degenerated) and its localization (3rd ventricle, lateral ventricle, or meningocortical) were also recorded. The histopathological analysis was performed blindly by

a single researcher (Matos-Silva et al., 2012).

2.9. Statistical analysis

Statistical analysis was performed using GraphPad Prism. Descriptive statistics were used to calculate means and standard deviations. All variables were evaluated for normality and homogeneity of variances. Comparisons among experimental groups were carried out using one-way analysis of variance (ANOVA), followed by Tukey's post hoc test. Differences were considered statistically significant at $p < 0.05$.

3. Results

3.1. Formulation of OXF-micro

OXF-loaded microparticles (OXF-MICRO) were prepared using a spray-drying technique. The encapsulation efficiency (%EE) was high, reaching $93.47 \pm 5.26\%$, while the drug loading capacity (%LC) was $44.40 \pm 2.45\%$. The overall process yield was 68%.

3.2. Equilibrium solubility assay

Fig. 1 shows the equilibrium solubility of OXF compared with OXF-loaded microparticles (OXF/RLPO) at two physiological pH conditions (pH 1.2 and pH 7.4). At pH 1.2 (acidic medium), both formulations exhibit relatively high solubility. Thus, under acidic conditions, raw OXF reached a maximum concentration of $241 \mu\text{g mL}^{-1} (\pm 2.24)$, while the spray-dried microparticles increased this value to $938.98 \mu\text{g mL}^{-1} (\pm 122.38)$, almost a 4-fold increase. At neutral media, a more pronounced increment was obtained, going from $3.11 \mu\text{g mL}^{-1} (\pm 1.89)$ for OXF to $46.42 \mu\text{g mL}^{-1} (\pm 3.11)$ for OXF/RLPO.

3.3. In vivo cytokines quantification

Concentrations of IL-4, a hallmark cytokine of the Th2 profile, were significantly higher in the tissues of mice receiving OXF-MICRO (274.17 pg/g ; $p = 0.0167$) and ABZ (285.10 pg/g ; $p = 0.0313$) compared to the control group (145.38 pg/g). In contrast, IL-10 dynamics exhibited an opposing trend. The control group displayed higher levels of this regulatory cytokine than all treated cohorts, with confirmed statistical differences relative to OXF-MICRO ($p = 0.005$), conventional OXF ($p = 0.0041$), and ABZ ($p = 0.0035$) (Fig. 3).

In contrast, conventional OXF induced a distinct Th1 response, with IFN- γ levels (49.07 pg/g) significantly higher than those in the control ($p = 0.0092$), OXF-MICRO ($p = 0.0087$), and ABZ ($p = 0.0126$) groups. Furthermore, the conventional OXF and ABZ groups showed

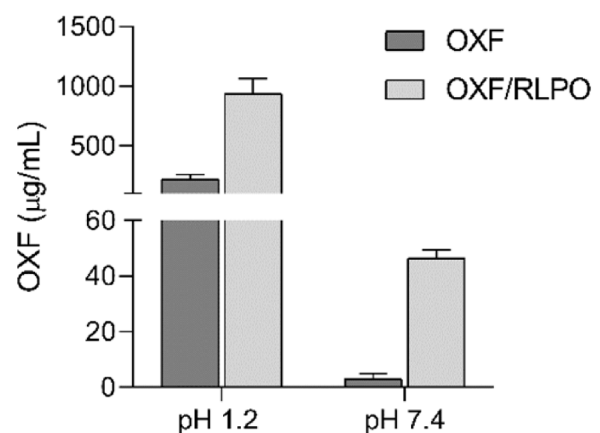


Fig. 1. Equilibrium solubility of oxfendazole (OXF) compared with OXF-loaded microparticles (OXF/RLPO) at two physiological pH conditions (pH 1.2 and pH 7.4).

higher IL-2 concentrations than the OXF-MICRO group ($p = 0.0008$ and $p = 0.0204$, respectively) (Fig. 2).

A consistent reduction in TNF-alpha and IL-17 was noted in all treated groups compared to the negative control, with TNF-alpha levels significantly lower in ABZ ($p = 0.0119$), OXF ($p = 0.0310$), and OXF-

MICRO ($p = 0.0091$) groups (Fig. 3).

Regarding IL-6 quantification, OXF microparticles exhibited a mean concentration of 138.90 pg/g, which was significantly higher than that of the control group (68.75 pg/g; $p = 0.0294$). Similarly, mice receiving ABZ (141.73 pg/g) also displayed a significant increase relative to the

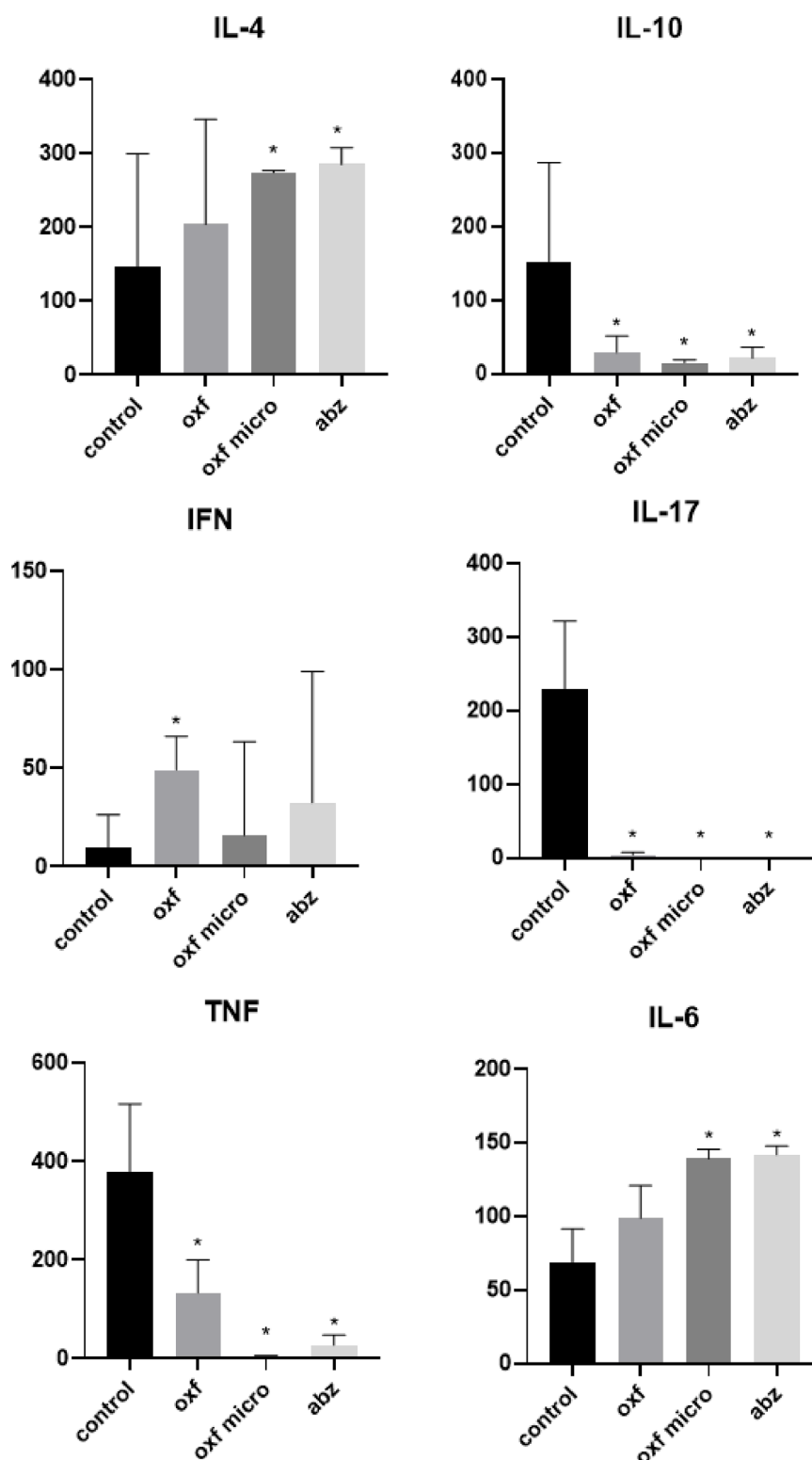


Fig. 2. In situ quantification (pg/g) of Th2 profile (IL-4 and IL-10), Th1 profile (IFN-gamma), inflammatory cytokines (IL-17 and TNF-alpha) and IL-6 24 h post-treatment by experimental group. Control group: mice treated with NaCl 0.9%; ABZ: mice treated with 30mg/kg of albendazole; OXF: mice treated with 30mg/kg of conventional oxfendazole; OXF MICRO: mice treated with 30mg/kg of oxfendazole-loaded microparticles. * $p < 0.05$, statistical significant difference in comparison to control group.

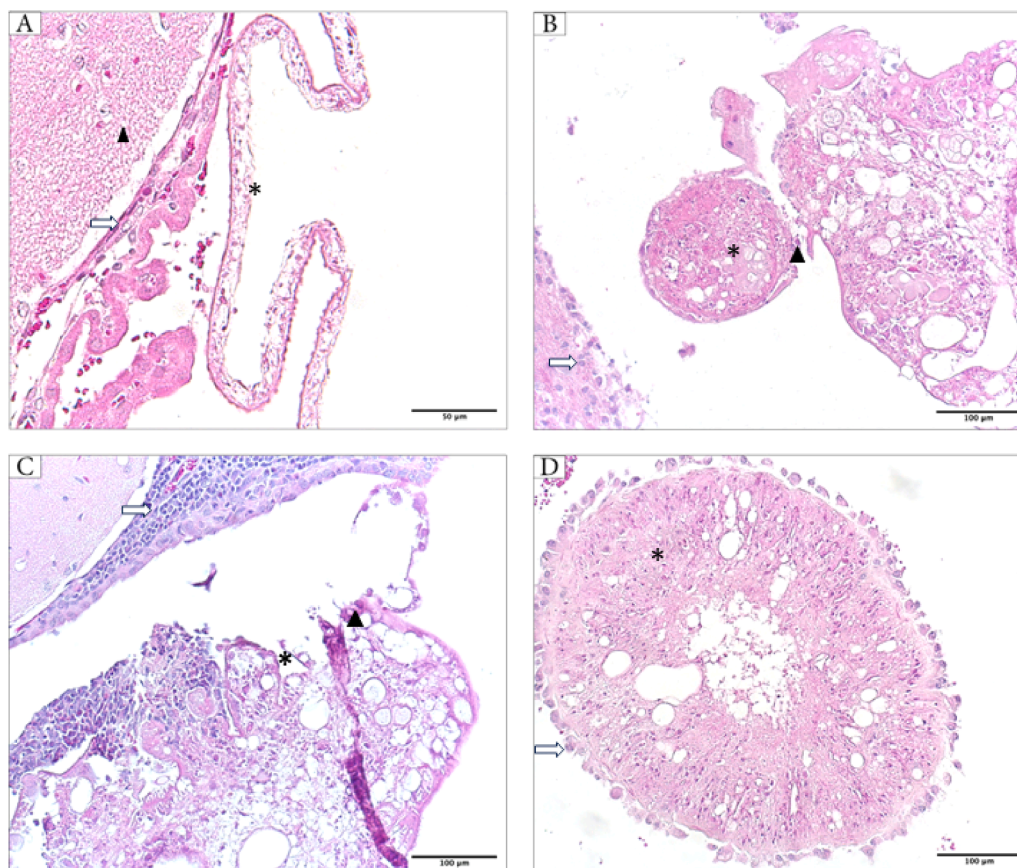


Fig. 3. Photomicrograph images of slides from brains from mice neuroinoculated with *Taenia crassiceps* cysticerci. A. Mouse treated with NaCl 0.9%. * tegument from initial stage cysticerci. Black arrow head: brain tissue. White arrow: inflammatory infiltration in the host-parasite interface. 40x magnification. B. Mouse treated with 30mg/kg of Albendazole. * final stage cysticerci with inflammatory infiltration with tegumentary alteration (black arrow head). White arrow: inflammatory infiltration in the host-parasite interface. 20x magnification. C. Mouse treated with 30 mg/kg of Oxfendazole. * final stage cysticerci with inflammatory infiltration with tegumentary alteration (black arrow head). White arrow: inflammatory infiltration in the host-parasite interface and ependymitis. 20x magnification. D. Mouse treated with 30mg/kg of oxfendazole-loaded microparticles. * final stage cysticerci. White arrow: mononuclear inflammatory infiltration adhered to its surface. 20x magnification. Hematoxylin-eosin.

untreated controls ($p = 0.0187$).

The general pathologic processes found in mice with experimental NCC are described in Table 1. Additionally, microscopic observation confirmed a transition of cysticerci into the final/degenerated stage in the treated groups, whereas the control group maintained initial or larval stages.

Control group: mice treated with NaCl 0.9%; ABZ: mice treated with 30mg/kg of albendazole; OXF: mice treated with 30mg/kg of conventional oxfendazole; OXF MICRO: mice treated with 30mg/kg of oxfendazole-loaded microparticles. PNM, Polymorphonuclear infiltrate; MN, Mononuclear infiltrate; Results expressed by median (minimum-

maximum). Statistical analysis was performed in a semi-quantitative form where: score 0 - absent (no tissue involvement), score 1 - discrete (up to 25% of the tissue affected), score 2 - moderate (26% to 50% involvement), and score 3 - severe (>50% tissue involvement). Statistical test used was ANOVA followed by Kruskal-Wallis post-test.

The histopathological evaluation revealed that all anthelmintic treatments induced distinct alterations in the inflammatory processes compared to the control group. In the brain tissue, a significant reduction in polymorphonuclear (PMN) leukocyte infiltration was observed in the group treated with the oxfendazole microparticles (OXF-MICRO; median 0, min-max 0–1) when compared to the control group ($p =$

Table 1

Histopathological evaluation of brains from mice neuroinfected with *Taenia crassiceps* cysticerci after treatment with oxfendazole-loaded microparticles.

		Control group	ABZ	OXF	OXF MICRO	Comparison between groups
Cysticerci	Evolutionary stage	Initial / Larval / Final	Initial / Larval / Final	Initial / Larval / Final	Larval / Final	
	PMN	0.5 (0–1)	0 (0–3)	0 (0–2)	0 (0–1)	$p > 0.05$
	MN	0.5 (0–1)	1 (0–3)	0 (0–2)	0 (0–3)	$p > 0.05$
Tissue	PMN	1 (0–3)	1 (0–3)	1 (0–2)	0 (0–1)	$p < 0.05$: CTRL > OXF-MICRO; ABZ > OXF-MICRO; OXF > OXF-MICRO
	MN	1 (0–3)	1 (0–3)	1 (0–2)	1 (0–2)	$p > 0.05$
	Ependymitis	0 (0–3)	1 (0–2)	1 (0–2)	1 (0–2)	$p > 0.05$
	Hemorrhage	1 (0–3)	1 (0–3)	1 (0–1)	1 (0–2)	$p > 0.05$
	Meningitis	0 (0–1)	0 (0–2)	0 (0–1)	0 (0–2)	$p < 0.05$: ABZ > CTRL
	Ventriculomegaly	1 (0–3)	1 (0–3)	2 (0–3)	2 (1–3)	$p < 0.05$: ABZ, OXF and OXF-MICRO > CTRL

0.029), as well as in comparison to both the albendazole (ABZ; $p = 0.006$) and the commercial oxfendazole (OXF; $p = 0.0445$) treatment groups. Regarding meningitis, the group treated with albendazole exhibited a statistically significant increase in the severity of this inflammatory process compared to the control group ($p = 0.0125$), while no significant differences were found between the treated groups and the control for mononuclear (MN) cells, ependymitis, choroiditis, vasculitis, or hemorrhage within the brain parenchyma ($p > 0.05$). The presence of ventriculomegaly was a consistent finding across all pharmacological intervention groups, with ABZ ($p = 0.0228$), OXF ($p = 0.0013$), and OXF-MICRO ($p = 0.0018$) all showing significantly higher degrees of ventricular enlargement relative to the control. While within the cysticerci, the inflammatory response composed of PMN and MN cells did not show statistically significant variations between the treated groups and the control ($p > 0.05$) (Fig. 3).

4. Discussion

For the first time, OXF has been successfully encapsulated within Eudragit® RS microparticles, enhancing its biopharmaceutical performance by reducing particle size and increasing surface area, which may lead to faster dissolution and improved oral absorption (Barrera et al., 2010; Rizi et al., 2011). The microparticles were created via spray drying, where a hydroalcoholic solution of drug and polymer was atomized into droplets. Rapid solvent evaporation upon contact with hot drying gas formed solid microparticles, enhancing crystallinity reduction and uniform drug distribution within the polymer matrix, both vital for dissolution behavior (Milanesi et al., 2025). Consistent with previous reports (García et al., 2018; Seremeta et al., 2019), rapid solvent evaporation in spray drying enhances the formation of amorphous systems, increasing the dissolution rate of OXF. Additionally, Eudragit® RS, a polymer with quaternary ammonium groups, improves wettability and promotes matrix swelling, facilitating drug release (Rongthong et al., 2015).

The equilibrium solubility of the raw drug and OXF-MICRO is higher in 0.1 M HCl (pH 1.2) than in phosphate buffer (pH 6.8). At pH 1.2, both formulations show high solubility, with OXF-MICRO reaching about 900–1000 µg/mL compared to raw OXF's 200–250 µg/mL. At pH 7.4, raw OXF exhibits very low solubility (3–5 µg/mL), while OXF/RLPO significantly increases to approximately 45–50 µg/mL, indicating a 10-fold improvement despite lower absolute solubility than at acidic pH. This pH-dependent behavior reflects OXF's requirement for an acidic environment to enhance ionization and solubility (El-Nahas et al., 2017; dos Santos et al., 2021; Real et al., 2018). As shown in Fig. 1, the enhanced solubility of OXF-MICRO can be attributed, in part, to the reduction in particle size achieved through the microencapsulation process. This effect may also be associated with the formation of a glass solution, in which OXF is molecularly dispersed within the amorphous polymeric matrix (Higashi et al., 2015). These findings are consistent with previous studies reporting improved dissolution of microencapsulated benzimidazole, another benzimidazole derivative (Leonardi et al., 2009).

Our data suggest that all pharmacological therapies examined had high pesticidal action, causing considerable morphological alterations in cysts. Untreated control mice had mostly live, early-stage cysts, whereas those treated with ABZ, OXF, or microencapsulated OXF showed cysticerci in later stages of degeneration. The treatments not only destroyed the cysts but also changed the anticipated cytokine response in the brain microenvironment. Both OXF-MICRO and ABZ elicit a Th2-skewed immunological profile, highlighted by elevated local IL-4 levels, which drives Th2 polarization, encouraging an anti-inflammatory and pro-fibrotic milieu via M2 macrophage activation (Anthony et al., 2007; Gause et al., 2013). OXF-MICRO treatment reveals a Th2 regulatory mechanism that activates host tolerogenic pathways and eradicates parasites. A noteworthy discovery is that treated cohorts had much lower levels of IL-10 than controls, underscoring its function as an

immunosuppressive cytokine associated with parasite survival. Cysticerci activate regulatory T cell (Treg) activity through cyst antigens, converting naïve CD4⁺ cells to IL-10-producing CD25⁺Foxp3⁺ Tregs (Adalid-Peralta et al., 2021).

The Treg population reduces neuroinflammation and promotes parasite colonization by secreting IL-10 on a continuous basis. A decrease in this mediator implies a breakdown in parasite-driven immunological tolerance, resulting in an unfavorable environment for parasite persistence. However, this may potentially exacerbate local neuroinflammation in the absence of alternate regulatory pathways to reduce its effects (Prodjinotho et al., 2020; Redpath et al., 2014). Additionally, Chavarría et al. (2005) found a clear association between severe types of neurocysticercosis, which are characterized by prominent pleocytosis and eosinophilia, and high IL-10 concentrations in the cerebrospinal fluid. Consequently, this post-treatment decline probably reflects both a general dampening of the global inflammatory stimulation and the destruction of the parasite's evasion capabilities.

On the other hand, administration of the traditional OXF solution guided the immune response toward a distinctive Th1 phenotype, characterized by notable elevations in IFN- γ and IL-2. These results show that a strong effector response is elicited by the traditional OXF formulation, which is consistent with active cyst degeneration. In this stage, CD4⁺ Th1 cells are significantly activated by the enormous release of parasitic antigens, creating a polarized inflammatory milieu that is traditionally necessary for parasite destruction and calcification in neurocysticercosis (Prodjinotho et al., 2020). The much greater IL-2 levels found in the standard OXF group, relative to both the microparticles and ABZ treatments, reflect a robust activation and expansion of T cells, notably the Th1 and CD8⁺ cytotoxic effector subsets (Boyman and Sprent, 2012). An increased cellular adaptive response that is specifically triggered to support parasite clearance in these animals is highlighted by the notable up-regulation of IL-2, a key T cell growth factor (Prodjinotho et al., 2020). All investigated interventions significantly lowered pro-inflammatory cytokines TNF- α and IL-17 levels relative to untreated infection. In neurocysticercosis, anthelmintic therapy can cause an initial inflammatory response mediated by TNF- α , leading to increased blood-brain barrier permeability and pericystic edema (Mahanty et al., 2017). Simultaneously, IL-17 acts on glial and endothelial cells to produce chemokines that powerfully attract neutrophils to the site of inflammation, causing tissue damage (Korn et al., 2009). This mechanism is consistent with observations in experimental *T. crassiceps* neurocysticercosis, where a strong influx of polymorphonuclear cells into the brain parenchyma is directly correlated with elevated local IL-17 levels (Moura et al., 2016). Furthermore, the pathophysiology of symptomatic NCC has been linked to both cytokines. Research indicates that increased TNF- α and IL-17 levels are linked to the emergence of severe clinical symptoms, including seizures (Verma et al., 2011). Consequently, the reduction in these pro-inflammatory mediators may suggest that the studied formulations had a protective impact, lowering the risk of host immunopathology. Morphological examination showed that only the OXF-MICRO cohort translated this immunological shift into genuine tissue protection, despite the fact that all tested medications were successful in lowering pro-inflammatory cytokine levels. In particular, microscopic analysis showed a marked decrease in polymorphonuclear (PMN) infiltration only in the OXF-MICRO-treated group's brain tissue. By uniquely mitigating this acute cellular influx, the microparticles demonstrate a superior dual therapeutic advantage: they retain oxfendazole's inherent parasitocidal efficacy while actively preventing the severe neuroinflammation that conventional treatments fail to block at the tissue level.

The observed ventriculomegaly is the result of parasite-induced morphological alterations and an acute inflammatory milieu. In the intraventricular neurocysticercosis model (*Taenia crassiceps*), cysticerci block CSF fluid dynamics and produce pro-inflammatory mediators including TNF- α , resulting in blood-brain barrier disruption, increased pericystic inflammation, and edema development. This process

exacerbates the obstruction of cerebrospinal fluid flow, leading to mechanical dilation of the ventricles (Mahanty et al., 2017; Moura et al., 2016; Sotelo and Marin, 1987). Furthermore, cytokines such as IL-6 play a pleiotropic role in immune modulation, as they are expressed across the different stages of cyst development (Prodjinotho et al., 2020).

The experimental model of neurocysticercosis (NCC) employing *Taenia crassiceps* in BALB/c mice is an important tool for studying the histopathological and immunological aspects of host-parasite interactions, as well as the efficacy of new pharmacological therapies (Vinaud and Ambrosio, 2020). However, it is important to note that the murine model differs significantly from the human disease, particularly in terms of brain size, morphology, and drug pharmacokinetics, as well as the fact that naturally acquired human NCC does not involve inoculation injury. In this procedure, the infection was produced by injecting five initial-stage cysticerci into the brain of female BALB/c mice to simulate the disease. The impact of treatment was analyzed at a single evaluation point, 24 h post-treatment, a duration chosen based on the drugs' pharmacokinetics and half-lives to determine their immediate efficacy. Assessing the host-parasite interface at this 24-hour mark demonstrated that even this short period was sufficient for the drugs to induce parasite degeneration and significant changes in inflammatory infiltration.

A histopathological study of experimental neurocysticercosis with a sample size of ten mice per experimental group has limitations, especially in terms of statistical power and generalizability of the findings. This cohort size may not accurately reflect the pleomorphic nature and clinical heterogeneity present in human neurocysticercosis, even though it is frequently adequate to detect statistically significant differences in acute pathological processes and cytokines quantification.

5. Conclusions

This study demonstrates that although conventional anthelmintic therapies, including oxfendazole and its microparticle formulation, effectively induce degeneration of *Taenia crassiceps* cysticerci, their impact on the host cerebral microenvironment differs substantially. The physicochemical characterization revealed that microencapsulation significantly enhanced the aqueous solubility of oxfendazole under both gastric (pH 1.2) and intestinal (pH 7.4) conditions, with a particularly marked improvement in acidic medium. This increase in solubility likely contributes to improved drug availability at the site of action and may underlie the distinct biological responses observed. From an immunological perspective, all treatments reversed parasite-induced immune tolerance, as evidenced by a marked reduction in IL-10, and suppressed key pro-inflammatory mediators associated with tissue damage, such as TNF- α and IL-17. However, immune polarization was strongly formulation-dependent. Conventional oxfendazole elicited a Th1-type response, characterized by increased IFN- γ and IL-2, whereas the microparticle formulation (OXF-MICRO) and albendazole promoted a predominantly Th2-oriented profile, with elevated IL-4 and IL-6 levels, suggesting activation of pathways involved in immune modulation and tissue repair. Histopathological analysis further revealed that ventriculomegaly remains a common structural consequence associated with parasite degeneration within the ventricular system. Notably, only the OXF-MICRO formulation translated systemic cytokine modulation into localized neuroprotective effects. Specifically, this formulation significantly reduced the acute infiltration of polymorphonuclear (PMN) cells into the surrounding brain parenchyma, a feature not observed with the other treatments. Overall, microencapsulation of oxfendazole provides a promising therapeutic strategy that enables effective parasite clearance while mitigating the neuroinflammatory damage that often limits the safety of neurocysticercosis treatment.

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CRediT authorship contribution statement

Anna Clara Lopes de Moura: Methodology, Data curation. **Giselle Rocío Bedogni:** Methodology, Formal analysis. **Geovana Batista de Campos:** Methodology, Formal analysis. **Jessica Yonara de Souza:** Methodology, Investigation, Data curation. **Rodrigo Saar Gomes:** Supervision, Methodology, Data curation. **Ruy de Souza Lino Júnior:** Supervision, Methodology, Investigation. **Claudio Javier Salomon:** Writing – original draft, Supervision, Methodology, Conceptualization. **Marina Clare Vinaud:** Writing – review & editing, Writing – original draft, Supervision, Resources, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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