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Article

Keywords: Neurocysticercosis, transcriptomics, drug repositioning, neuroinflammation, neurodegeneration

Posted Date: October 21st, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11408185/v1>

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Additional Declarations: No competing interests reported.

Transcriptomics-based drug repositioning in a neurocysticercosis rat model identifies putative therapeutic candidates reported to mitigate neuroinflammation and neurodegeneration

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Abstract

Neurocysticercosis (NCC) is a major cause of epilepsy and neurological symptoms in low- and middle-income countries. Although antiparasitic treatment targets the parasite, it often fails to fully resolve symptoms and can exacerbate brain tissue damage. Using a rat model of NCC and transcriptomic profiling, we assessed the effects of infection and treatment on brain gene expression to uncover disease molecular pathways and identify putative therapeutic candidates through in silico drug repurposing. We analyzed transcriptomic profiles at two stages of infection (4- and 6-month post-infection (MPI)), and after treatment at 6 MPI (6 MPI +T). At 6 MPI, fewer immune-related genes and pathways were enriched compared to 4 MPI, likely due to MAPK pathway repression, but immune activation increased significantly after treatment, possibly due to cyst degeneration. Drug repositioning identified 30 candidate drugs. Among these, vorinostat, ciclosporin, papaverine, valproic acid, and chlorpromazine have been reported to mitigate neuroinflammation and neurodegeneration. Taken together, these results provide a molecular rationale for drug repositioning in neurocysticercosis; however, further experimental validation in larger cohorts is required to confirm the therapeutic potential of the identified candidates.

Keywords: Neurocysticercosis, transcriptomics, drug repositioning, neuroinflammation, neurodegeneration.

Introduction

Neurocysticercosis (NCC) is a central nervous system infection caused by the cyst of *Taenia solium*. It is responsible for approximately 30% of the cases of late-onset

epilepsy/seizure in developing countries worldwide [1,2]. Pathological studies of cysts localized at brain parenchyma showed the presence of neuroinflammation, gliosis, axonal swelling, neuronal death, and blood-brain barrier (BBB) disruption, all of them exacerbated as the parasite gets degenerated over time or by antiparasitic treatment [2]. Given that antiparasitic treatment can intensify the inflammatory response and worsen symptoms, it is typically co-administered with corticosteroids such as Dexamethasone as a standard therapeutic approach in most NCC cases. However, this approach doesn't warrant the permanent remission of the symptoms, and long-term use of corticosteroids is limited by serious side effects [2,3]. This underscores the need for complementary therapies that are both effective and associated with minimal adverse effects. Additionally, limited access to human brain tissue has hindered our understanding of the molecular mechanisms underlying disease- and treatment-driven pathogenesis, which is crucial for developing more effective treatments.

A rat model of NCC developed in our laboratory shares similarities with the human NCC pathology described above; moreover, it allowed us to describe axonal swelling in NCC for the first time, in both rats and humans. Likewise, this model contributed to the identification of some markers associated with BBB disruption and angiogenesis associated with NCC [4–7]. Additionally, a study using RT-qPCR and this animal model showed overexpression of inflammatory cytokine genes such as IFN- γ , TNF- α , and IL-1 in brain tissue close to the parasite compared to non-infected animals [8]. While valuable information was obtained from these studies focusing on individual markers, a more comprehensive analysis is essential to understand the interconnected nature of these changes.

RNA-seq transcriptomic profiling has proven to be a powerful tool to characterize thousands of differentially expressed genes (DEGs) and altered biological pathways in

host-parasite interaction studies, including helminth infections [9–11]. Furthermore, these altered expression profiles can be used for drug repositioning, an emerging approach that identifies drugs already approved for human use to be repurposed for new therapeutic indications based on biological signatures, such as transcriptomic or proteomic profiles, thereby shortening the time a drug is available for patients compared to de novo drug discovery [12,13]. A drug repositioning tool called COGENA (co-expressed gene-set enrichment analysis) based on co-expression analysis of gene expression signatures and gene set enrichment analysis of co-expressed genes, enabling simultaneous, pathway-driven disease and drug repositioning analysis, has shown to be a powerful tool for infectious and non-infectious diseases drug repositioning studies [13–15].

In the present study, we used mRNA-seq, differential gene expression analysis, and drug repositioning analysis *in-silico* with COGENA to identify some deregulated pathways and possible drugs that could revert the changes at the molecular level caused by the NCC infection on a rat model treated and not treated with antiparasitic drugs at two times point, 4 and 6 months post-infection (MPI).

Results

Sequencing, quality control, and reads assignment.

RNA integrity number (RIN) of purified RNA from brain cortex tissues ranged from 6.5 to 8.5 (mean = 7.36 ± 0.60 SD) (Supplementary Table S1). RNA sequencing yielded a total of 725.71million reads. Of these, 667.04 million reads (91.92%) passed the quality control using Timmmomatic. Among the high-quality reads, 638.33 million (95.70%) aligned to the *Rattus norvegicus reference* genome/transcriptome, and 557.93 million reads (83.64%) were assigned to a gene with FeatureCount (Supplementary Table S2), generating gene-level count matrices per sample.

Rat model of NCC shows a time-dependent decline in the number of DEGs and a marked increase upon anthelmintic treatment at 6 MPI

Differential gene expression analysis was performed comparing infected and uninfected rats at 4 MPI, 6 MPI, and 6 MPI + T to characterize transcriptional changes across the course of infection and in response to treatment. The infection induced dysregulation of several genes in a time-dependent manner, with the number of DEGs declining over time: 503 DEGs were identified at 4 MPI (440 upregulated, 63 downregulated), declining to 191 at 6 MPI (157 upregulated, 34 downregulated). However, anthelmintic treatment at 6 MPI (6 MPI + T) led to a marked increase in DEGs, yielding 2,866 DEGs (2,180 upregulated, 686 downregulated) — a nearly 15-fold increase relative to untreated 6 MPI animals (Fig. 1A–D). Venn diagram analysis identified 82 genes consistently upregulated across all three conditions (Fig. 1E), while no genes were found to be consistently downregulated (Fig. 1F).

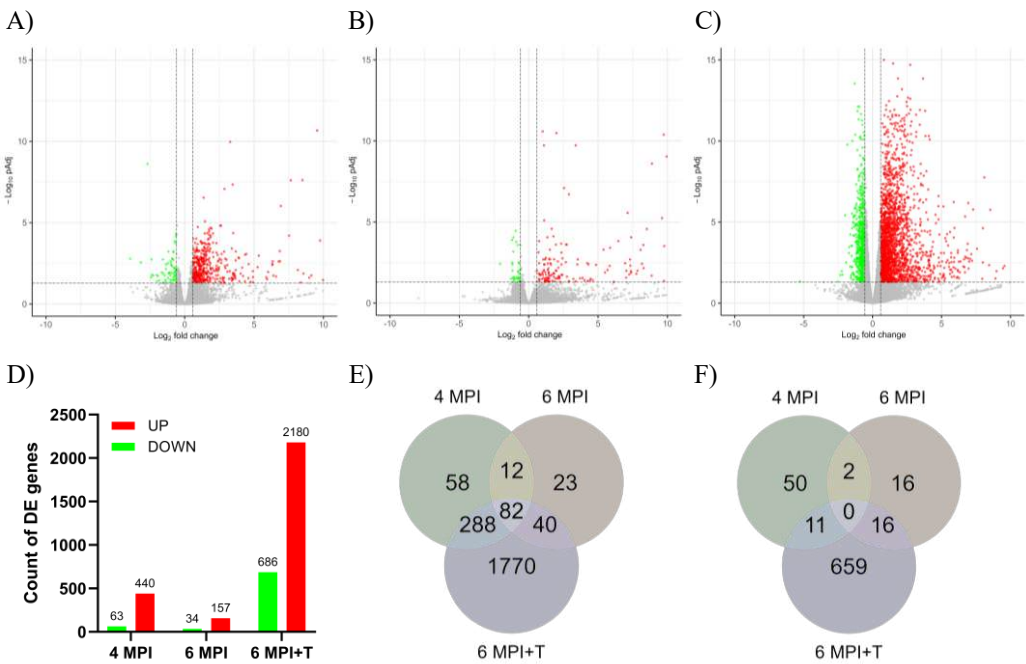


Figure 1. DEGs comparing infected and uninfected rats at 4 MPI, 6 MPI, and 6 MPI +T. (A, B, C) Volcano plots for 4 MPI, 6 MPI, and 6 MPI +T, respectively. Horizontal line represents a pAdj of 0.05 and vertical lines represent -1.5 and 1.5 foldchange. (D) Bar plot of upregulated and downregulated DEGs. (E) Shared DEGs upregulated between groups. (F) Shared DEGs downregulated between groups.

Enriched pathways for 4 MPI reveal robust upregulation of innate and adaptive immune

COGENA identified significant enriched pathways collectively reflecting a robust upregulation of both innate and adaptive immune responses, alongside significant inflammatory and cellular migration pathways. Clusters 1 and 3 — comprising 237 and 105 upregulated genes, respectively — shared pathways in inflammatory and cell migration pathways (Chemokine signaling, Cytokine-Cytokine receptor interaction, Cell adhesion molecules, Leukocyte transendothelial migration), specific to pathogens and diseases (Leishmania infection, Systemic lupus erythematosus), and hematopoietic cell development. Cluster 1 additionally showed strong innate (Complement and coagulation cascades, Fc gamma R-mediated phagocytosis, NK cell-mediated cytotoxicity, Toll-like receptor and Cytosolic DNA sensing pathways) and adaptive immune response (B cell receptor signaling, antigen processing and presentation, Fc epsilon RI signaling). Cluster 3, by contrast, showed a more restricted innate and adaptive immune response signature (Toll-like receptor signaling pathway and antigen processing and presentation, respectively) alongside cellular migration pathways, specifically Focal adhesion and ECM receptor interaction. The sole downregulated cluster (Cluster 2; 53 genes) was only associated with cellular migration (ECM receptor interaction and Focal adhesion) (Fig. 2A).

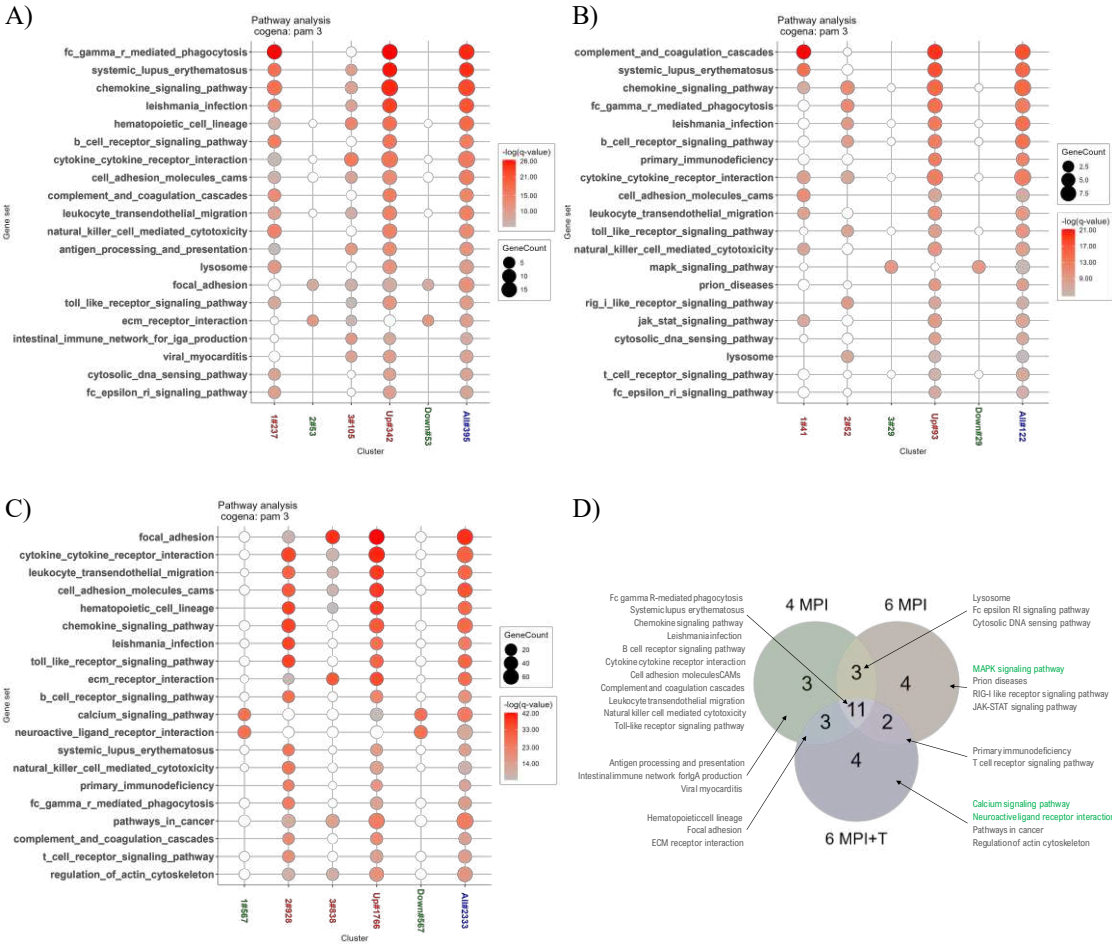


Figure 2. KEGG Pathway Enrichment for all the DEGs and clusters of coexpressed genes for 4 MPI (A), 6 MPI (B), and 6 MPI +T (C); clusters in red and green are composed of upregulated and downregulated genes, respectively. Pathways enriched with COGENA and shared between 4 MPI, 6 MPI, and 6 MPI+T; pathways in green are enriched by downregulated genes (D).

Enriched pathways for 6 MPI reveal an attenuation of immune response and cellular migration alongside downregulation of the MAPK pathway.

KEGG Pathway Enrichment for 6 MPI revealed a shift in host response, characterized by a reduction in the number of DEGs that enrich pathways associated with immune response

and cellular migration, coupled with downregulation of the MAPK signaling pathway. Clusters 1 (41 genes) and 2 (52 genes) retained upregulation of pathways mainly associated with inflammation and cellular migration (Chemokine signaling pathway, cytokine-cytokine receptor interaction, Cell adhesion molecules CAMs, Leukocyte transendothelial migration), innate immune response (Fc gamma R mediated phagocytosis, Toll-like receptor signaling pathway, Lysosome, Complement and coagulation cascades and Natural killer cell-mediated cytotoxicity), adaptive immune response (B cell receptor signaling pathway) and specific to pathogens and diseases (Systemic Lupus Erythematosus and Leishmania Infection) (Fig. 2B). However, the number of genes underlying these enrichments was substantially lower than that observed at 4 MPI. Cluster 1 additionally encompassed JAK-STAT signaling pathway, while Cluster 2 featured RIG-I-like receptor signaling. Notably, Cluster 3, composed of 29 downregulated genes, was only associated with the MAPK signaling pathway (Fig. 2B).

Anthelmintic Treatment at 6 MPI intensifies immune and inflammatory responses while downregulate cellular communication and signaling.

Following anthelmintic treatment at 6 months post-infection (6 MPI +T), KEGG Pathway Enrichment revealed an exacerbation in immune and inflammatory response, alongside a downregulation of cellular communication and signaling pathways. Cluster 1, composed of 567 downregulated genes, was related mainly to cellular communication and signaling (Calcium signaling pathway and Neuroactive ligand-receptor interaction). In contrast, Clusters 2 and 3 — comprising 928 and 838 upregulated genes, respectively — converged on inflammatory and migratory pathways (Focal adhesion, Cytokine-Cytokine receptor interaction, Leukocyte transendothelial migration, Cell adhesion molecules, ECM-receptor interaction, Regulation of actin cytoskeleton) and hematopoietic development.

Cluster 2 further encompassed a comprehensive innate immune response (Toll-like receptor signaling, NK cell-mediated cytotoxicity, Fc Gamma R-mediated phagocytosis, Complement and coagulation cascades), adaptive immunity (B and T cell receptor signaling), disease-specific pathways (Leishmania infection, Systemic Lupus Erythematosus, Primary immunodeficiency) and chemokine signaling pathway (Fig. 2C).

Drug repositioning with COGENA identifies putative candidate therapeutic drugs with reported neuroprotective and anti-neuroinflammatory properties for NCC.

The drugs enriched by COGENA were ordered by cluster 1 for 4 MPI and cluster 2 for 6 MPI and 6 MPI + T, since these clusters exhibited the highest number of protein-protein interactions according to STRING-DB (Supplementary Table S3) and might be more biologically relevant to the disease phenotype and, therefore, more suitable for drug intervention [13]. The Cmap Down database was used for drug enrichment as the clusters were composed of upregulated genes. 30 drugs were found in total for the three groups (Fig. 3), from them, 16 were approved for treating different human diseases according to PubChem or DrugBank (Table 1).

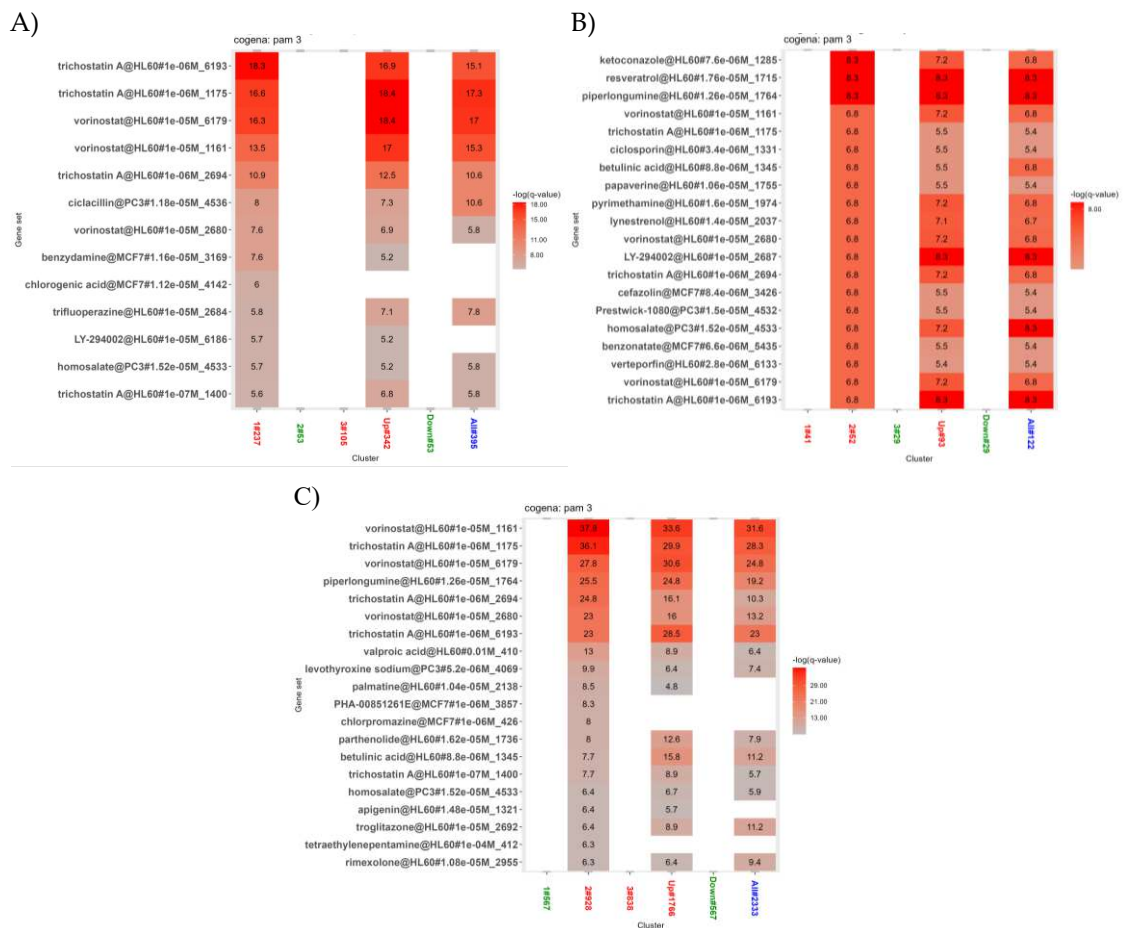


Figure 3. Drug repositioning analysis with COGENA using CmapDn database ordered by cluster 1, for 4 MPI (A), and cluster 2 for 6 MPI (B) and 6 MPI + T (C); clusters in red and green are composed of upregulated and downregulated genes, respectively.

These 16 drugs could be organized based on their mechanism of action (MoA) or indication such as antineoplastic (Vorinostat), β -lactam antibiotic (Ciclacillin and Cefazolin), Non-steroidal anti-inflammatory drugs (NSAIDs) (Benzylamine), antipsychotics (Trifluoperazine and Chlorpromazine), antifungal (Ketoconazole), anti-inflammatory drugs (Ciclosporin and Rimexolone), vasodilator (Papaverine), antiparasitic (Pyrimethamine), hormones and endocrine regulators (Lynestrenol, and Levothyroxine sodium), anesthetic (Benzonatate), photosensitizer (Verteporfin), anticonvulsant (valproic acid) (Table 1).

214 **Table 1.** Drugs approved for human use enriched across the study groups.

Drugs	DrugBank ID PubChem ID	Mechanism of Action (MoA)	Indication	BBB Penetration (Percentile %)	Impact on Neurodegene- ration	Impact on Neuroinflam- mation
Vorinostat ^{a,b,c}	DB02546 5311	HDAC inhibitor; increases acetylation of histones, inducing cell cycle arrest and/or apoptosis	Cutaneous T-cell lymphoma	0.96 (79.57)	↓[16,17]	↓[17,18]
Ciclacillin ^a	DB01000 19003	β-lactam antibiotic; binds to penicillin-binding proteins (PBPs), inhibiting bacterial cell wall synthesis	Bacterial infections	0.10 (6.17)	-	-
Benzydamine ^a	DB09084 12555	Locally-acting NSAID; inhibits the synthesis of pro inflammatory cytokines like TNF-α and IL-1β	Inflammation and pain in oral and throat cavity	0.98 (87.98)	-	↓[19]
Trifluoperazine ^a	DB00831 5566	Antipsychotic; blocks dopaminergic D1 and D2 receptors	Anxiety, Psychosis, Schizophrenia	1.00 (98.22)	↓[20,21] ↑[22]	↓[23]
Ketoconazole ^b	DB01026 456201	Antifungal; inhibits 14-α-sterol demethylase (cytochrome P-450 enzyme), impairing ergosterol synthesis in fungi and increasing fungal cellular permeability	Systemic and topical fungal infections, Cushing's syndrome	0.45 (27.37)	↓[24]	-
Ciclosporin ^b	DB00091 5284373	Calcineurin inhibitor; inhibits T-cell activation by blocking IL-2, IL-4, IFN-γ and TNF-α transcription and reducing inflammation	Inflammatory conditions (rheumatoid arthritis, psoriasis and Transplant rejection prevention)	0.05 (2.29)	↓[25,26]	↓[27]
Papaverine ^b	DB01113 4680	Vasodilator; inhibits phosphodiesterase, increasing cAMP and cGMP, and inducing smooth muscle relaxation	Smooth muscle spasms, erectile dysfunction	0.83 (58.32)	↓[28–30]	↓[28–30]
Pyrimethamine ^b	DB00205 4993	Antiparasitic; inhibits dihydrofolate reductase (DHFR), blocking the biosynthesis of purines and pyrimidines in parasites	Toxoplasmosis, malaria	0.87 (63.98)	-	-
Lynestrenol ^b	DB12474 5857	Synthetic progestogen used for contraception; modulates estrogen and progesterone receptors, affecting hormonal pathways	Contraception, menstrual disorders	0.08 (4.81)	-	-
Cefazolin ^b	DB01327 33255	β-lactam antibiotic; binds to penicillin-binding proteins (PBPs), inhibiting bacterial cell wall synthesis	Bacterial infections	0.12 (7.64)	-	-
Benzonate ^b	DB00868 7699	Local anesthetic; desensitizes vagal stretch receptors in the respiratory tract, inhibiting the cough reflex	Cough suppression	0.71 (47.11)	-	-
Verteporfin ^b	DB00460 5362420	Photosensitizer; activated by light generates reactive oxygen species that result in local damage to neovascular endothelium, leading to vessel occlusion.	Subfoveal choroidal neovascularization	0.45 (27.49)	-	-
Valproic acid ^c	DB00313 3121	HDAC inhibitor and anticonvulsant; inhibits gamma-aminobutyric acid (GABA) transaminase and voltage-gated sodium channels, stabilizing neural activity	Epilepsy, Seizures, bipolar disorder, migraine	0.87 (63.94)	↓[31,32]	↓[31,33]
Levothyroxine sodium ^c	DB00451 23666112	Synthetic T4 thyroxine hormone; is converted to triiodothyronine (T3) which exerts stimulatory effects on cellular respiration; thermogenesis; cellular growth and differentiation; and cellular metabolism.	Hypothyroidism	0.31 (19.12)	-	-
Chlorpromazine ^c	DB00477 2726	Antipsychotic, anxiolytic, and antiemetic; antagonist on multiple postsynaptic receptors (dopaminergic, serotonergic, histaminergic, alpha-adrenergic, and cholinergic receptors)	Schizophrenia, Bipolar disorder, Severe nausea/vomiting	1.00 (99.15)	↓[34,35]	↓[36,37]
Rimexolone ^c	DB00896 5311412	Glucocorticoid receptor agonist; reduces inflammation by inducing lipocortins that inhibit phospholipase A2 and arachidonic acid, ultimately controlling the biosynthesis of prostaglandins and leukotrienes.	Ocular inflammation	0.95 (76.04)	-	-

^a Enriched in 4 MPI cluster 1; ^b Enriched in 6 MPI cluster 2; ^c Enriched in 6 MPI+T cluster 2.

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216 Subsequently, BBB penetration probabilities were predicted using ADMET-AI, and the

217 potential effects of these drugs on neurodegeneration and neuroinflammation were

identified exclusively through a comprehensive bibliographic search. BBB penetration probability was scored on a scale from 0 to 1, where 0 indicates the lowest probability of penetration and 1 indicates the highest. Drugs with a high probability of penetrating the BBB (>0.9) included Vorinostat, Benzydamine, Trifluoperazine, Chlorpromazine, and Rimexolone. Regarding the impact on neurodegeneration, it was found that six drugs (Vorinostat, Ketoconazole, Ciclosporin, Papaverine, Valproic Acid, and Chlorpromazine) have documented evidence of mitigating neurodegeneration (neuroprotective activity), while only Trifluoperazine has been reported to exacerbate it. Furthermore, seven drugs have been reported to mitigate neuroinflammation (anti-inflammatory effect); these included Vorinostat, Benzydamine, Trifluoperazine, Ciclosporin, Papaverine, Valproic Acid, and Chlorpromazine.

Discussion

Although anthelmintic treatment effectively targets the parasite in NCC, it can exacerbate neuroinflammation and neurodegeneration, often leading to irreversible neurological symptoms despite the use of anti-inflammatory drugs. This underscores the need for complementary treatments to modulate the host response. In this study, we first analyzed the transcriptomic profiles in the cerebral cortex among three experimental groups (4 MPI, 6 MPI and 6 MPI+T), revealing a dynamic gene dysregulation mainly associated with immune response, inflammatory and neurodegenerative pathways. We subsequently utilized a transcriptomics-based drug repositioning approach to identify putative therapeutic candidates capable of reversing these infection- and treatment-induced gene expression changes in the cerebral cortex.

Transcriptomic profiling revealed a robust presence of 11 pathways across all groups predominantly associated with innate and adaptive immune response, inflammation and

cellular migration (Fig. 2D). Our findings support previous studies showing that NCC induces a strong innate and adaptive immune response involving inflammatory infiltrate cells and proinflammatory cytokines at different stages of the infection in humans, swine, and rat models [4,8,38–40].

At 4 MPI, innate immune responses were predominantly activated, with enrichment of pathways related to leukocyte migration, adhesion, and inflammation, likely reflecting the host's attempt to control the infection through the recruitment of immune cells to the site of infection, which may contribute to localized neuroinflammation. This is consistent with previous studies showing a robust activation of innate immune mechanisms at early stage of NCC involving microglia and cellular infiltrates (macrophages and eosinophils); as well as the role of eosinophils in promoting leukocyte recruitment and contributing to tissue damage despite increasing host susceptibility when absent in eosinophil-deficient mice (Δ dblGATA) [38,40,41]. Additionally, some adaptive immune-related pathways (B cell receptor signaling, antigen processing and presentation and Fc epsilon RI signaling) were enriched even at this relatively early stage, suggesting that the humoral and cellular response of the immune system had begun mounting a targeted response, an event also supported by other studies at early stages of the infection [38,40].

By 6 MPI, a reduction in the number of DEGs was observed, which may indicate a more regulated or stabilized immune response, potentially due to host adaptation or parasite-driven immunomodulation. This is supported by a histopathological study that used the same rat model of NCC at the same times postinfection where it was found less proportion of cysts with moderate to severe infiltration (>25 inflammatory cells/ $40\times$ field) with scar formation at 6 MPI (65.2%) compared to 4 MPI (84.6%) [42]. Interestingly, downregulation of genes associated with the MAPK signaling pathway—a central regulator of both innate and adaptive immune responses—was observed (Fig. 2B), which

could explain the attenuation of the host response. MAPK signaling is known to regulate microglial activation, pro-inflammatory cytokine production (TNF- α , IL-1 β , IL-6), CD4⁺ T cell differentiation (Th1/Th2 responses, promoting the production of IFN- γ and IL-4, respectively), and CD8⁺ T lymphocytes IFN- γ production [43,44]. Its repression may be linked to parasite-derived immunomodulatory mechanisms, evidence suggests that secreted extracellular vesicles from *T. solium* viable cysts may exert immune suppression as they induce anti-inflammatory gene expression (IL-10, IL-4) and promote macrophage apoptosis via AKT–mTOR pathway modulation in vitro [45]. Furthermore, similar strategies were described in other parasites, as soluble factors derived from the related helminth *Mesocostoides corti* can prevent MAPK (JNK and ERK1/2) and NF- κ B activation by inhibiting calcium entry, thereby blocking the production of inflammatory cytokines (IL-6 and TNF- α) in primary microglia culture [46].

In contrast, the 6 MPI + T group showed a remarkable increase in DEGs, with a notable upregulation of pathways involved in innate and adaptive immune response, inflammatory processes, and cellular recruitment and migration (Fig. 2C), consistent with previous findings suggesting that anthelmintic treatment exacerbates the host's immune response as it reacts to the parasite in a degenerative process [47]. In NCC swine and rat models, anthelmintic treatment with praziquantel alone or in combination with other drugs (albendazole or oxfendazole) has been shown to promote cyst degeneration, increase blood–brain barrier permeability, exacerbate inflammatory responses, as evidenced by upregulation of proinflammatory genes, downregulation of anti-inflammatory genes, and marked immune cell infiltration around the parasite, compared with untreated animals [42,48]. Furthermore, the downregulation of pathways related to neuroactive ligand–receptor interaction and calcium signaling (Fig. 2C) suggests impaired neuronal communication and potential neurotoxic effects, which may contribute

to the neurodegenerative changes associated with treatment-induced inflammation in NCC, characterized by severe spongiosis, axonal swelling and spheroids formation [5,42].

Drug repositioning analysis identified 30 drugs, 16 of which are currently approved for human use. Among these, vorinostat, ciclosporin, papaverine, valproic acid, and chlorpromazine have been reported to reduce neuroinflammation or neurodegeneration—two key pathological processes in NCC—suggesting their potential as therapeutic candidates for this disease. Notably, although adverse effects have been documented for each of these compounds, their established regulatory approval for human use and well-characterized safety profiles support the feasibility of their controlled repositioning in NCC, provided that appropriate dosing strategies and patient selection criteria are applied [12].

Vorinostat, a histone deacetylase (HDAC) inhibitor approved for cutaneous T-cell lymphoma, stands out as a possible candidate due to its high predicted BBB penetration (0.98), consistent enrichment across all groups, and high enrichment scores across multiple instances (indicating consistent action in different cell lines and drug doses; Supplementary Fig. S1). It has demonstrated anti-neuroinflammatory and neuroprotective effects across multiple pathological models—including traumatic brain injury, stroke, and age-related cognitive impairment—by suppressing pro-inflammatory cytokines like $\text{TNF}\alpha$, reducing necroptosis, inhibiting the NLRP3 inflammasome, and promoting autophagy, as well as attenuating oxidative stress via the iNOS/Nrf2/ARE pathway and enhancing neurite outgrowth through MEK1/2 and PI3K signaling [16–18,49–51]. Similarly, valproic acid, papaverine and chlorpromazine appear to modulate anti-inflammatory and neuroprotective processes, reinforcing the biological relevance of our findings. Valproic acid, beyond its established role as broad-spectrum anticonvulsant,

demonstrates neuroprotective and immunomodulatory effects, including downregulation of apoptosis- and neurodegeneration-related genes (cleaved Casp-3, Iba1, GFAP, amyloid- β , p-Tau), enhancement of neural plasticity by increasing brain-derived neurotrophic factor (BDNF), modulation of NF- κ B/I κ B α signaling, restoration of autophagic flux, promotion of anti-inflammatory microglial polarization, and suppression of NLRP1 and NLRP3 inflammasomes [31–33], all of which are relevant to the inflammatory and degenerative processes observed in NCC. Likewise, papaverine, a phosphodiesterase inhibitor with vasodilatory activity, have been reported to exert anti-neuroinflammatory effects through activation of cAMP/PKA/CREB signaling, leading to reduced expression of pro-inflammatory cytokines (TNF- α , IL-1 β) and increased IL-10; and inhibition of NF- κ B and MAPK pathways, NLRP3 inflammasome, microglial activation, and ROS production; while also mitigating edema, apoptosis, and microglia activation in TBI mouse models [28–30]. Similarly, chlorpromazine, a multi-receptor antagonist with antipsychotic, anxiolytic, and antiemetic properties, has demonstrated anti-inflammatory and neuroprotective properties by decreasing IL-1 β and TNF- α and increasing IL-10 expression; inhibiting microglial Kv1.3 channels reducing proinflammatory cytokines (IL-1 β and IL-6) and NF- κ B (p65) phosphorylation level; reducing infarct size in ischemia models; and protecting against apoptosis through repress the expression of cleaved caspase-3, cytochrome c, Bax, and increases the expression of Bcl-2 [34–37]. In contrast, although ciclosporin has demonstrated neuroprotective effects in preclinical TBI models, including a reduction in parenchymal injury volume by 35% [25], its very low BBB penetration probability (0.05) and associated neurotoxicity at higher doses limit its translational potential in NCC; although modified formulations such as NIM811 have improved CNS delivery and demonstrated effectively suppress NLRP3

inflammasome, pyroptosis, and cell death, as well as reduce the production of reactive oxygen species (ROS) [27].

While our drug repositioning analysis identified putative therapeutic candidates for NCC, these findings must be interpreted within the context of our study design. A primary consideration is the limited number of biological replicates per group (Table 2) which is a direct consequence of the stringent inclusion criteria applied to infected animals. Specifically, only male rats harboring at least one cortical cyst and no more than two cysts in total throughout the rest of the brain were included, to ensure tissue transcriptional profiles reflected focal cortical NCC pathology rather than a diffuse or multifocal parasitic burden. Given the inherently variable cyst localization (parenchymal, ventricular, or submeningeal), infection efficiency of this rat model (83% approximately), and the requirement for confirmed cortical localization at necropsy, a substantial proportion of inoculated rats could not be included [4]. Additionally, we used a 1.5-foldchange with adjusted p-value < 0.05 threshold for DEGs, unless it could increase the false positive rate, to retain biologically interpretable changes that may be missed by stricter cutoffs, consistent with prior work showing that small fold changes can still produce meaningful pathway-level signals [52–54]. Consequently, our results should be interpreted as a hypothesis-generating pilot study, providing a foundation that necessitates further validation in large cohorts.

In conclusion, this study provides a comprehensive overview of the host response during NCC infection and anthelmintic treatment, revealing a complex interplay between immune activation, neuroinflammation, and neuronal function, suggesting that therapeutic strategies for NCC should aim to control inflammation while preserving neuronal function to prevent neurological sequelae. Finally, future research should prioritize the in vitro and in vivo validation of these repositioned drugs to confirm their efficacy in mitigating the neuroinflammation and neurodegeneration associated with neurocysticercosis.

Methods

Ethical statement

The Institutional Ethics Committee for Animal Use (CIEA) of the Universidad Peruana Cayetano Heredia reviewed the study protocol and approved the experimental procedures described in this research (Approval number: 204581). All experimental procedures were performed in accordance with institutional guidelines and regulations of the UPCH and the Guide for the Care and Use of Laboratory Animals (National Research Council, 8th edition, 2011).

Rat infection and biological samples

Rats (*Rattus norvegicus*, Albinus, Holtzman) were inoculated with *T. solium* oncospheres as described before [4]. Briefly, three groups of ten 13- to 15-day-old rats were injected intracranially with 400-500 activated *T. solium* oncospheres suspended in 50 μ L of 0.9% sterile saline solution (infected groups). As a control group, 10 rats per group were intracranially injected with 50 μ L of saline solution (uninfected groups). At four months post-infection (MPI), a group of infected and uninfected rats was administered with anthelmintic treatment (oxfendazole 37 mg/kg and praziquantel 50 mg/kg/day for 9 days), and the others received saline solution (untreated), as described in Table 2. Rats were euthanized 4 and 6 MPI by an overdose of ketamine (150 mg/kg) and xylazine (20 mg/kg). Following confirmation of deep anesthesia, rats were transcardially perfused with phosphate-buffered saline (PBS, pH 7.2) and the brains were immediately collected.

Brain cortex tissues surrounding the cyst were collected from infected male rats harboring at least one cortical cyst and no more than two cysts in total throughout the rest of the brain. Posterior brain cortex tissues were collected from uninfected male rats. Approximately 50 mg of brain tissues were collected and soaked in 600 μ L of 1X

DNA/RNA shield (Zymo Research), incubated for 2 hours at room temperature to promote DNA/RNA shield permeabilization, before being stored at -70 °C until RNA isolation.

Table 2. Sample description.

Group	Infection	Anthelmint treatment	Euthanization (MPI)	Number of rats ^a (brain tissues)	Brain tissue localization
4 MPI	Uninfected	Untreated	4	3	Posterior cortex
	Infected	Untreated	4	3	Posterior cortex surrounding the cyst
6 MPI	Uninfected	Untreated	6	3	Posterior cortex
	Infected	Untreated	6	2	Posterior cortex surrounding the cyst
6 MPI + T	Uninfected	Treated at 4 MPI	6	3	Posterior cortex
	Infected	Treated at 4 MPI	6	2	Posterior cortex surrounding the cyst

MPI: months post-infection

MPI + T: months post-infection and treated

^a Number of brain tissue samples considered for RNA-seq.

RNA extraction and sequencing.

RNA was purified from tissue samples using RNeasy Plus Mini Kit (QIAGEN, Hilden, Germany). Isolated total RNA sample quality was assessed by RNA TapeStation (Agilent Technologies Inc., California, USA) and quantified by Qubit 2.0 RNA BR assay (ThermoFisher, Massachusetts, USA). mRNA was isolated for library construction according to the NEBNext® Ultra™ II Directional RNA Library Prep Kit for Illumina® (New England BioLabs Inc., Massachusetts, USA). The sequencing was done with Illumina® NovaSeq 6000 (Illumina, California, USA) with a read length configuration of 150 PE for 60 M PE reads per sample (30 M in each direction). All sequencing analysis were performed at Admera Health (South Plainfield, NJ, United States).

Transcriptomic and drug repositioning analysis

Reads were quality filtered and trimmed with Trimmomatic (v0.39) [55], aligned with STAR (v2.7.10b) [56]. using rat reference genome from ENSEMBL (www.ensembl.org, release 109), and uniquely mapped reads were counted with featureCounts function from

Subread (v2.0.3) [57]. Differential gene expressions and drug repositioning analysis were made in R (v4.3.3). DE analysis was made with DESeq2 (v1.42.1) and genes with $|\log_2 \text{foldchange}| \geq 0.58$ ($-1.5 \geq \text{foldchange} \geq 1.5$) and adjusted p-value < 0.05 were considered DEGs. Orthogene (v1.8.0) was used to convert the identified DEGs from rat to their human orthologs, as an approximation for further analyses relevant to humans. Pathway enrichment and drug repositioning analysis were performed with COGENA (v1.36.0). It grouped the DEGs into 3 clusters of co-expressed genes using Partitioning Around Medoids (PAM) clustering algorithm, each of these clusters represents a group of genes with highly correlated expression patterns, suggesting a shared biological function, and was used as the basis for downstream enrichment analyses [13]. KEGG database (www.genome.jp/kegg/) was used for pathway enrichment analysis, and CMAP database (<https://www.broadinstitute.org/connectivity-map-cmap>) was used for drug repositioning analysis. Protein-protein interaction analysis among co-expressed genes within each cluster was made with STRINGdb (v2.14.3, <https://string-db.org/>). Mechanism of action (MoA), approval status, and indication of enriched drugs found with COGENA were obtained from drug repositories such as DrugBank (<https://go.drugbank.com/>) and PubChem (<https://pubchem.ncbi.nlm.nih.gov/>). Their ability to cross the BBB was predicted with ADMET-AI (v1.3.1), which estimates the absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties of molecules using machine learning models [58]. Additionally, drugs were described based on their impact on neurodegeneration and neuroinflammation through a bibliographic search.

References

1. Tellez-Zenteno, J. F. & Hernandez-Ronquillo, L. Epidemiology of neurocysticercosis and epilepsy, is everything described? *Epilepsy & Behavior* **76**, 146–150 (2017).
2. Bustos, J., Gonzales, I., Saavedra, H., Handali, S. & Garcia, H. H. Neurocysticercosis. A frequent cause of seizures, epilepsy, and other neurological morbidity in most of the world. *J. Neurol. Sci.* **427**, 117527 (2021).
3. Nash, T. E., Mahanty, S., Garcia, H. H. & Cysticercosis Group in Peru. Corticosteroid use in neurocysticercosis. *Expert Rev. Neurother.* **11**, 1175–83 (2011).
4. Verastegui, M. R. *et al.* Novel Rat Model for Neurocysticercosis Using *Taenia solium*. *Am. J. Pathol.* **185**, 2259 (2015).
5. Mejia Maza, A. *et al.* Axonal swellings and spheroids: a new insight into the pathology of neurocysticercosis. *Brain Pathol.* **29**, 425–436 (2019).
6. Carmen-Orozco, R. P. *et al.* Blood-brain barrier disruption and angiogenesis in a rat model for neurocysticercosis. *J. Neurosci. Res.* **97**, 137–148 (2019).
7. Garcia, H. H., Verastegui, M. R., Arroyo, G., Bustos, J. A. & Gilman, R. H. New animal models of neurocysticercosis can help understand epileptogenesis in neuroinfection. *Front. Mol. Neurosci.* **15**, (2022).
8. Carmen-Orozco, R. P. *et al.* Changes in inflammatory gene expression in brain tissue adjacent and distant to a viable cyst in a rat model for neurocysticercosis. *PLoS Negl. Trop. Dis.* **15**, (2021).
9. Greenwood, J. M., Ezquerra, A. L., Behrens, S., Branca, A. & Mallet, L. Current analysis of host–parasite interactions with a focus on next generation sequencing data. *Zoology* **119**, 298–306 (2016).
10. Zhou, G., Stevenson, M. M., Geary, T. G. & Xia, J. Comprehensive Transcriptome Meta-analysis to Characterize Host Immune Responses in Helminth Infections. *PLoS Negl. Trop. Dis.* **10**, e0004624 (2016).
11. Wu, T. *et al.* clusterProfiler 4.0: A universal enrichment tool for interpreting omics data. *The Innovation* **2**, 100141 (2021).
12. Hua, Y. *et al.* Drug repositioning: Progress and challenges in drug discovery for various diseases. *Eur. J. Med. Chem.* **234**, 114239 (2022).
13. Jia, Z. *et al.* Cogena, a novel tool for co-expressed gene-set enrichment analysis, applied to drug repositioning and drug mode of action discovery. *BMC Genomics* **17**, 1–11 (2016).
14. Jia, Z., Song, X., Shi, J., Wang, W. & He, K. Transcriptome-based drug repositioning for coronavirus disease 2019 (COVID-19). *Pathog. Dis.* **78**, 36 (2020).
15. Liu, T. *et al.* Novel integrated Omics based computational approach for drug repurposing for non-muscle invasive bladder cancer (NMIBC). *J. Biomol. Struct. Dyn.* <https://doi.org/10.1080/07391102.2024.2302343> (2024). doi:10.1080/07391102.2024.2302343.
16. Shukla, S., Shariat-Madar, Z., Walker, L. A. & Tekwani, B. L. Mechanism for neurotropic action of vorinostat, a pan histone deacetylase inhibitor. *Molecular and Cellular Neuroscience* **77**, 11–20 (2016).
17. Wang, D. *et al.* The histone deacetylase inhibitor vorinostat prevents TNF α -induced necroptosis by regulating multiple signaling pathways. *Apoptosis* **18**, 1348–1362 (2013).
18. Fang, P. *et al.* NLRP3 inflammasome inhibition by histone acetylation ameliorates sevoflurane-induced cognitive impairment in aged mice by activating the autophagy pathway. *Brain Res. Bull.* **172**, 79–88 (2021).

19. Zhang, Y. *et al.* Benzydamine attenuates microglia-mediated neuroinflammation and ischemic brain injury by targeting cathepsin s. *Int. Immunopharmacol.* **146**, 113824 (2025).
20. Khaledi, E. *et al.* Trifluoperazine reduces cuprizone-induced demyelination via targeting Nrf2 and IKB in mice. *Eur. J. Pharmacol.* **909**, 174432 (2021).
21. Höllerhage, M. *et al.* Trifluoperazine rescues human dopaminergic cells from wild-type α -synuclein-induced toxicity. *Neurobiol. Aging* **35**, 1700–1711 (2014).
22. Hong, S., Lee, M. yeong, Shin, K. S. & Kang, S. J. Perphenazine and trifluoperazine induce mitochondria-mediated cell death in SH-SY5Y cells. *Anim. Cells Syst. (Seoul)*. **16**, 20–26 (2012).
23. Huang, H. T. *et al.* Inhibitory Effects of Trifluoperazine on Peripheral Proinflammatory Cytokine Expression and Hypothalamic Microglia Activation in Obese Mice Induced by Chronic Feeding With High-Fat-Diet. *Front. Cell. Neurosci.* **15**, 752771 (2021).
24. Styczyńska-Soczka, K., Zechini, L. & Zografos, L. Validating the Predicted Effect of Astemizole and Ketoconazole Using a Drosophila Model of Parkinson's Disease. <https://home.liebertpub.com/adt> **15**, 106–112 (2017).
25. Karlsson, M. *et al.* Neuroprotective Effects of Cyclosporine in a Porcine Pre-Clinical Trial of Focal Traumatic Brain Injury. *J. Neurotrauma* **36**, 14–24 (2019).
26. Kawakami, M. Molecular Dissection of Cyclosporin A's Neuroprotective Effect Reveals Potential Therapeutics for Ischemic Brain Injury. *Brain Sciences* **2013**, Vol. 3, Pages 1325-1356 **3**, 1325–1356 (2013).
27. Zhang, M., He, Q., Chen, G. & Andy Li, P. Suppression of NLRP3 Inflammasome, Pyroptosis, and Cell Death by NIM811 in Rotenone-Exposed Cells as an in vitro Model of Parkinson's Disease. *Neurodegener. Dis.* **20**, 73–83 (2020).
28. Saglam, E., Zırh, S., Aktas, C. C., Muftuoglu, S. F. & Bilginer, B. Papaverine provides neuroprotection by suppressing neuroinflammation and apoptosis in the traumatic brain injury via RAGE- NF- κ B pathway. *J. Neuroimmunol.* **352**, 577476 (2021).
29. Leem, Y. H., Park, J. S., Park, J. E., Kim, D. Y. & Kim, H. S. Papaverine Exerts Neuroprotective Effect by Inhibiting NLRP3 Inflammasome Activation in an MPTP-Induced Microglial Priming Mouse Model Challenged with LPS. *Biomol. Ther. (Seoul)*. **29**, 295–302 (2021).
30. Lee, Y. Y. *et al.* The phosphodiesterase 10 inhibitor papaverine exerts anti-inflammatory and neuroprotective effects via the PKA signaling pathway in neuroinflammation and Parkinson's disease mouse models. *J. Neuroinflammation* **16**, 1–17 (2019).
31. Chang, P. *et al.* Valproic Acid and Neural Apoptosis, Inflammation, and Degeneration 30 Days after Traumatic Brain Injury, Hemorrhagic Shock, and Polytrauma in a Swine Model. *J. Am. Coll. Surg.* **228**, 265–275 (2019).
32. Zheng, Z. *et al.* Valproic acid affects neuronal fate and microglial function via enhancing autophagic flux in mice after traumatic brain injury. *J. Neurochem.* **154**, 284–300 (2020).
33. Samadianzakaria, A., Abdolmaleki, Z. & Faedmaleki, F. The effect of valproic acid and furosemide on the regulation of the inflammasome complex (NLRP1 and NLRP3 mRNA) in the brain of epileptic animal model. *Brain Res. Bull.* **191**, 20–29 (2022).
34. Li, H. J. *et al.* Chlorpromazine confers neuroprotection against brain ischemia by activating BKCa channel. *Eur. J. Pharmacol.* **735**, 38–43 (2014).

35. Wu, J. *et al.* Chlorpromazine Protects Against Apoptosis Induced by Exogenous Stimuli in the Developing Rat Brain. *PLoS One* **6**, e21966 (2011).
36. Lee, H. Y. *et al.* The antipsychotic chlorpromazine reduces neuroinflammation by inhibiting microglial voltage-gated potassium channels. *Glia* **73**, 210–227 (2025).
37. Obuchowicz, E., Bielecka-Wajdman, A. M., Paul-Samojedny, M. & Nowacka, M. Different influence of antipsychotics on the balance between pro- and anti-inflammatory cytokines depends on glia activation: An in vitro study. *Cytokine* **94**, 37–44 (2017).
38. Londoño, D. P., Alvarez, J. I., Trujillo, J., Jaramillo, M. M. & Restrepo, B. I. The inflammatory cell infiltrates in porcine cysticercosis: immunohistochemical analysis during various stages of infection. *Vet. Parasitol.* **109**, 249–259 (2002).
39. Restrepo, B. I. *et al.* Brain granulomas in neurocysticercosis patients are associated with a Th1 and Th2 profile. *Infect. Immun.* **69**, 4554–4560 (2001).
40. Alvarez, J. I. *et al.* Granuloma Formation and Parasite Disintegration in Porcine Cysticercosis: Comparison with Human Neurocysticercosis. *J. Comp. Pathol.* **127**, 186–193 (2002).
41. Mishra, P. K. *et al.* Reduced Leukocyte Infiltration in Absence of Eosinophils Correlates with Decreased Tissue Damage and Disease Susceptibility in Δ dblGATA Mice during Murine Neurocysticercosis. *PLoS Negl. Trop. Dis.* **10**, e0004787 (2016).
42. Castillo, G. *et al.* Understanding the pathogenic mechanisms and therapeutic effects in neurocysticercosis. *Brain Pathology* **34**, e13237 (2024).
43. Kaminska, B., Gozdz, A., Zawadzka, M., Ellert-Miklaszewska, A. & Lipko, M. MAPK Signal Transduction Underlying Brain Inflammation and Gliosis as Therapeutic Target. *The Anatomical Record: Advances in Integrative Anatomy and Evolutionary Biology* **292**, 1902–1913 (2009).
44. Dong, C., Davis, R. J. & Flavell, R. A. MAP kinases in the immune response. *Annu. Rev. Immunol.* **20**, 55–72 (2002).
45. Rawat, S. S. *et al.* *Taenia solium* cysticerci's extracellular vesicles Attenuate the AKT/mTORC1 pathway for Alleviating DSS-induced colitis in a murine model. *J. Extracell. Vesicles* **13**, e12448 (2024).
46. Sun, Y. *et al.* Inhibition of store-operated calcium entry in microglia by helminth factors: Implications for immune suppression in neurocysticercosis. *J. Neuroinflammation* **11**, 1–12 (2014).
47. Prodjinotho, U. F. *et al.* Host immune responses during *Taenia solium* Neurocysticercosis infection and treatment. *PLoS Negl. Trop. Dis.* **14**, e0008005 (2020).
48. Mahanty, S. *et al.* Post-treatment Vascular Leakage and Inflammatory Responses around Brain Cysts in Porcine Neurocysticercosis. *PLoS Negl. Trop. Dis.* **9**, e0003577 (2015).
49. Lu, Y. *et al.* HDAC inhibitor attenuates rat traumatic brain injury induced neurological impairments. *Heliyon* **9**, e18485 (2023).
50. Sukumari-Ramesh, S., Alleyne, C. H. & Dhandapani, K. M. The Histone Deacetylase Inhibitor Suberoylanilide Hydroxamic Acid (SAHA) Confers Acute Neuroprotection After Intracerebral Hemorrhage in Mice. *Transl. Stroke Res.* **7**, 141–148 (2016).
51. Xu, J., Shi, J., Zhang, J. & Zhang, Y. Vorinostat: a histone deacetylases (HDAC) inhibitor ameliorates traumatic brain injury by inducing iNOS/Nrf2/ARE pathway. *Folia Neuropathol.* **56**, 179–186 (2018).

52. St. Laurent, G. *et al.* On the importance of small changes in RNA expression. *Methods* **63**, 18–24 (2013).
53. Golovan, S. & Husain, M. Identification of biologically significant genes using Gene Ontology (GO) and pathways analysis (144.16). *The Journal of Immunology* **184**, 144.16-144.16 (2010).
54. Halasz, G. *et al.* Optimized murine sample sizes for RNA sequencing studies revealed from large scale comparative analysis. *Nature Communications* **16**, 10173- (2025).
55. Bolger, A. M., Lohse, M. & Usadel, B. Trimmomatic: a flexible trimmer for Illumina sequence data. *Bioinformatics* **30**, 2114–2120 (2014).
56. Dobin, A. *et al.* STAR: ultrafast universal RNA-seq aligner. *Bioinformatics* **29**, 15 (2013).
57. Liao, Y., Smyth, G. K. & Shi, W. featureCounts: an efficient general purpose program for assigning sequence reads to genomic features. *Bioinformatics* **30**, 923–930 (2014).
58. Swanson, K. *et al.* ADMET-AI: a machine learning ADMET platform for evaluation of large-scale chemical libraries. *Bioinformatics* **40**, (2024).

Acknowledgments

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Members of the CWGP include: Hector H. Garcia, Robert H. Gilman, Armando E. Gonzalez, Manuela Verastegui, Mirko Zimic, Javier Bustos, Seth E. O’Neal, Silvia Rodriguez, Isidro Gonzalez, Herbert Saavedra, Sofia Sanchez, Manuel Martinez, Saul Santivañez, Holger Mayta, Yesenia Castillo, Monica Pajuelo, Gianfranco Arroyo, Nancy Chile, Luz Toribio, Miguel A. Orrego, Maria T. Lopez, Luis Gomez, Cesar M. Gavidia, Ana Vargas-Calla, Eloy Gonzales, Luz M. Moyano, Ricardo Gamboa, Claudio Muro, Percy Vichez, Sukwan Handali, John Noh, Theodore E. Nash, and Jon Friedland.

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prepared the original draft of the manuscript. M.V. and N.C. supervised the study. N.C. administered the project. N.C., O.M., M.V., and R.G. acquired funding. All authors reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

Data availability statement

The RNA-seq data that support the findings of this study are publicly available from GEO repository with the accession number GSE306561.

Funding

This work was supported by PROCENCIA-CONCYTEC (<https://prociencia.gob.pe/>) under grant number 169-2020-FONDECYT awarded to NC; the National Institutes of Health (NIH) (<https://www.nih.gov/>) under grant number 1R01AI150544-01 awarded to M.V; the FIC-NIH (<https://www.fic.nih.gov/>) under the training grant D43 TW001140 awarded to HHG, and by the unrelated research funding from Moderna awarded to RG and SGG. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Additional Information

Competing Interests

The authors declare no competing interests.

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