VETERINARSKI ARHIV 96 (2), 187-194, 2026 DOI: 10.24099/vet.arhiv.2938

Inhibitory effects of amitriptyline on granuloma formation in a chick-based experimental model

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SALEH, A. M, Y. M. ALBADRANY: Inhibitory effects of amitriptyline on granuloma formation in a chick-based experimental model. Vet. arhiv 96, 187-194, 2026.

ABSTRACT

Granulomatous inflammation, a hallmark of chronic diseases, demands safer therapies due to the limitations of current immunosuppressive regimens. This study explores the repurposing potential of amitriptyline, a tricyclic antidepressant, for modulating granuloma formation and systemic immune responses in a chick-based experimental model. Subcutaneous cotton pellet implantation was used to induce granulomas in chicks (n=6/group), followed by oral administration of amitriptyline (50 or 100 mg/kg/day) or a vehicle for 7 days. Granuloma wet and dry masses were calculated, and hematological profiling of white blood cells (WBCs) was performed. Amitriptyline significantly suppressed granuloma development in a dose-dependent manner, with 100 mg/kg reducing wet and dry masses by 17.73% (135.91±1.05 mg vs. control 165.20±1.42 mg) and 30.94% (49.10±1.02 mg vs. control 71.08±1.15 mg), respectively ($P<0.05$). Concurrently, the WBC counts decreased by 23.2% (18116±97 vs. control 23583±410 cells/µl), with pronounced reductions in heterophils, lymphocytes, eosinophils, and basophils ($P<0.05$). These findings highlight amitriptyline's dual anti-inflammatory action, attenuating both granulomatous tissue formation and systemic leukocyte mobilization. While the chick model offers ethical and practical advantages, translational validation in mammalian systems is warranted. This study positions amitriptyline as a promising candidate for repurposing in granulomatous disorders, advocating for mechanistic investigations and clinical trials to harness its immunomodulatory potential.

Key words: amitriptyline; anti-inflammatory; chicks; granuloma immunomodulation

Introduction

Granulomatous inflammation signifies a serious immunological response to persistent stimu- li, playing a central role in chronic inflammatory diseases, such as tuberculosis, sarcoidosis, and rheumatoid arthritis (TERZIROLI et al., 2018). Granuloma formation, characterized by the aggregation of macrophages and lymphocytes, is a double-edged sword: while it isolates harmful agents, unchecked granulomatous responses can lead to tissue fibrosis and organ dysfunction (YANG et al., 2024). The current therapeutic strategies tar- geting granulomas often depend on corticosteroids or immunosuppressants, which carry significant side effects, underscoring the need for safer, repurposed pharmacological alternatives (SHARMA et

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ISSN 0372-5480
Printed in Croatia

al., 2024). Amitriptyline, a tricyclic antidepressant commonly prescribed for chronic pain and mood disorders, has shown emerging potential beyond its primary neurological indications (PEREIRA et al., 2023). Preclinical studies suggest its anti-inflammatory properties, including modulation of cytokine release and immune cell activity (FRANCO-TREPAT et al., 2022). However, its effects on granuloma formation, a hallmark of chronic inflammation, remain unexplored. Clarifying this relationship could unlock novel therapeutic applications for a well-characterized drug, offering cost-effective and accessible treatment options.

Chick-based experimental models provide a valuable platform for inflammatory studies, combining ethical advantages with physiological relevance to mammalian systems (DAL PONT et al., 2021). The chick granuloma model, particularly using cotton pellet implantation, allows accurate evaluation of anti-inflammatory agents by quantifying granuloma mass and cellular infiltration (BUABEID et al., 2022).

This study investigated the inhibitory effects of amitriptyline on granuloma formation in a chick model, assessing both granuloma development and associated hematological changes. We hypothesized that amitriptyline attenuates granulomatous inflammation through dose-dependent suppression of immune cell recruitment and activity. By integrating granuloma mass analysis with white blood cell profiling, this work aimed to unravel the mechanistic basis of amitriptyline's anti-inflammatory action, offering insights into its potential repurposing for inflammatory disorders.

Materials and methods

Experimental animals. Day-old, unsexed chicks (*Gallus gallus domesticus*), weighing 40-50 g, were obtained from a local hatchery and maintained under standard laboratory conditions (constant lighting, 32-35°C, 60% humidity), with *ad libitum* access to feed and water. After a 7-day acclimatization period, the chicks were randomly allocated to three experimental groups (n=6/group). All procedures adhered to the National Institutes of Health (NIH) guidelines for animal care and were approved by the Institutional Animal Ethics Committee at the College of Veterinary Medicine, University of Mosul (Ref: UM.VET.2024.008).

Drugs and treatment. Amitriptyline hydrochloride (Accord, UK) was suspended in 0.9% saline to ensure homogeneity. The drug was administered orally via gavage at doses of 50 mg/kg and 100 mg/kg body weight, once daily for 7 days (the doses were determined in previous trials to represent the median analgesic dose and twice the analgesic dose, respectively). The control group received an equivalent volume of the vehicle (0.9% saline). The treatment was administered one hour prior to granuloma induction and continued for 7 days. The 7-day treatment period was planned according to the conventional protocols for evaluating acute granuloma formation, and was aligned with previous preclinical studies on anti-inflammatory agents. While this duration is suitable for evaluating early immune responses, future studies may use longer treatment periods to model chronic granulomatous conditions.

Granuloma induction. Sterile cotton pellets (70±1 mg, autoclaved at 121°C for 15 min) were implanted subcutaneously into the chest region of the chicks under mild anesthesia (propofol 80mg/kg intraperitoneally) (ABDUL-GHANI and NASER, 2023). After 24 h from the last treatment, the chicks were euthanized by cervical dislocation, and the pellets were carefully excised. The wet granuloma mass was measured immediately after removal, followed by drying at 40°C for 12 h to determine dry weight. Granuloma inhibition percentages were calculated using the formula:

$$\text{Inhibition (\%)} = [\text{Control} - \text{Treated}/\ \text{Control}] \times 100$$

Hematological analysis. All the chicks survived until the planned euthanasia on day 8, with no mortality detected during the experimental period. Blood samples were collected immediately before euthanasia. Blood samples (1 mL) were collected from the jugular vein into EDTA-coated tubes. Total white blood cell (WBC) count and differential leukocyte analysis (heterophils, lymphocytes, basophils, and eosinophils) were performed using an automated hematology analyzer (Sysmex XN-1000, Japan). Manual validation of cell mor-

phology was conducted using Giemsa-stained blood smears under light microscopy (400x magnification).

Statistical analysis. Data are expressed as mean ± standard error (SE). One-way ANOVA followed by LSD post-hoc test was applied to assess inter-group differences using SPSS 17.0. Statistical significance was set at $P \leq 0.05$, with differing superscript letters (a, b, c) meaning significant variations. All measurements were performed by investigators blinded to treatment allocation.

Results

Amitriptyline attenuates granuloma formation in a dose-dependent manner. Subcutaneous implantation of cotton pellets induced robust granuloma formation in the control chicks, with wet and dry granuloma masses measuring 165.20±1.42 mg and 71.08±1.15 mg, respectively (Table 1). Oral administration of amitriptyline significantly reduced both wet and dry granuloma weights in a dose-dependent manner. At 50 mg/kg, the wet granuloma mass decreased by 13.72% (142.35±1.71 mg, $P<0.05$ vs. control), while the dry mass exhibited a 25.11% inhibition (52.98±1.33 mg, $P<0.05$ vs. control). The higher dose (100 mg/kg) further suppressed granuloma development, achieving 17.73% inhibition of wet mass (135.91±1.05 mg) and 30.94% of dry mass (49.10±1.02 mg), with both values differ- ing significantly from the control and lower-dose groups ($P<0.05$).

Amitriptyline modulates systemic immune cell profiles. Hematological analysis revealed the pronounced anti-inflammatory effects of amitriptyline on circulating leukocytes (Table 2). Total white blood cell (WBC) counts in the control group (23583±410 cells/µl) were markedly reduced by both 50 mg/kg (19200±516 cells/µl, $P<0.05$) and 100 mg/kg doses (18116±97 cells/µl, $P<0.05$). Differential analysis revealed dose-dependent reductions across key inflammatory cell types. Heterophil counts in the control group (6833±22 cells/µl) were significantly reduced by both the 50 mg/kg (5804±68 cells/µl, $P<0.05$) and 100 mg/kg doses (4870±17 cells/µl, $P<0.05$), with the higher dose demonstrating a stronger effect. Similarly, lymphocyte counts decreased sharply from control

Table 1. Anti-inflammatory activity of amitriptyline in cotton pellet granuloma

Groups	Wet cotton pellets (mg)	Percentage of inhibition	Dry cotton pellets (mg)	Percentage of inhibition
Control	165.20±1.42[a]	0	71.08±1.15[a]	0
Amitriptyline 50 mg/kg	142.35±1.71[b]	13.72 %	52.98±1.33[b]	25.11%
Amitriptyline 100 mg/kg	135.91±1.05[c]	17.73 %	49.10±1.02[c]	30.94%

Mean±SE (6 chicks/group)

The values in each column are significantly different when followed by various superscript letters ($P \leq 0.05$)

Table 2. Effect of amitriptyline on white blood cells

Groups	WBC cell/µl	Percentage of inhibition	Heterophils cell/µl	Lymphocytes cell/µl	Basophils cell/µl	Eosinophils cell/µl
Control	23583±410[a]	0	6833±22[a]	16531±486[a]	42±0.57[a]	158±17[a]
Amitriptyline 50 mg/kg	19200±516[b]	18.6	5804±68[b]	13107±112[b]	19±0.54[b]	108±16[b]
Amitriptyline 100 mg/kg	18116±97[c]	23.2	4870±17[c]	12307±36[c]	17±0.88[c]	75±6[c]

Mean±SE (6 chicks/group)

The values in each column are significantly different when followed by various superscript letters ($P \leq 0.05$)

levels (16531±486 cells/µl) to 13107±112 cells/ µl (P<0.05) at 50 mg/kg and 12307±36 cells/µl (P<0.05) at 100 mg/kg. Basophils counts in the control group (42±0.57 cells/µl) were significantly reduced by both the 50 mg/kg (19±0.54 cells/µl, P<0.05) and 100 mg/kg doses (17±0.88 cells/µl, P<0.05). Eosinophils counts in the control group (158±17 cells/µl) were significantly reduced by both the 50 mg/kg (108±16 cells/µl, P<0.05) and 100 mg/kg doses (75±6 cells/µl, P<0.05).

Discussion

The cotton pellet test has been used to induce an inflammatory response since 1956. Cotton pellet-induced granuloma formation is a well-established experimental *in-vivo* model for agents that modulate inflammatory response and tissue proliferation (SUGISHITA et al., 1981). Cotton pellets irritant to the host induce inflammation characterized by the generation of an exudate containing plasma proteins such as fibrinogen and fibronectin at the inflamed cavity (ASHAGRIE et al., 2023).

The current study demonstrates that amitriptyline, a tricyclic antidepressant with established neurological applications, exerts dose-dependent inhibitory effects on granuloma formation and systemic immune cell mobilization in a chick-based experimental model. These findings ex- pand the well-known pharmacological repertoire of amitriptyline, suggesting it as a candidate for repurposing in inflammatory disorders characterized by granulomatous pathology.

The observed decrease in granuloma mass aligns with emerging evidence of amitriptyline's anti-inflammatory properties, including modulation of cytokine production and immune cell recruitment. The dose-dependent suppression of both wet and dry granuloma weights suggests that amitriptyline may interfere with early inflammatory infiltration (reflected in the wet mass) and subsequent fibrotic remodeling (dry mass) (BANERJEE et al., 2021). Pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukins (IL-) IL-6 and IL-1β, are elevated in the blood of patients with inflammatory disorders, leading to the induction of chronic inflammation (KANY et al., 2019). Current research results suggest that chronic administration of Amitriptyline to mice with T-cell-mediated immune symptoms is capable of inhibiting IL-6, TNF-α levels, and nitric oxide synthetase expression (iNOS) (KOU- BA et al., 2024). There is a non-specific cellular immune response to suspicious microbial mole- cules between the cells, starting with the activa- tion of the inflammatory response pathways (TEN OEVER et al., 2016). Elevated concentrations of TNF-α and increased expression of iNOS have been linked to irregular immune responses, resulting in disproportional and sustained inflammatory states (CASTELLHEIM et al., 2009). This extrapolation indicates that it is likely that Amitriptyline could be beneficial in reinstating the balance and reducing inflammation as a general immune modulator of these different immune responses (NITTNER-MARSZALSKA and FAL, 2007). It was demonstrated that several antidepressants decreased the production of TNF-α, a principal mediator of the systemic inflammatory response (SCHMIDT et al., 2016). Obuchowicz et al. demonstrated that specific tricyclic antidepressants (TCAs), including desipramine and amitriptyline, significantly suppressed TNF-α production in the blood of lipopolysaccharide (LPS)-treated rats (OBUCHOWICZ et al., 2006).

This dual action is particularly relevant for chronic granulomatous diseases such as sarcoidosis or tuberculosis, where sustained inflammation and tissue damage drive morbidity (LYU et al., 2024). Notably, the reduction in heterophils (avian analogs of mammalian neutrophils) and lymphocytes points to a systemic dampening of in- nate and adaptive immune responses, potentially disrupting the inflammatory cascade necessary for granuloma maturation (KAISER, 2010).

Clinical considerations and limitations. Chicks have been used as models for analge- sic (MOHAMMED and ALBADRANY, 2022), anti-inflammatory (ABDULLAH et al., 2023), anesthetic (NASER and ALBADRANY, 2024), neurobehavioral (NASER and ALBADRANY, 2021), and toxicological (ALBADRANY and NASER, 2020) research. While the chick model offers ethical and practical advantages, its trans-

lational relevance to human pathophysiology requires cautious interpretation. Birds exhibit distinct immune system features, such as heterophils lacking myeloperoxidase, which may influence inflammatory outcomes (BROOM, 2019). Chick granulomas share key structures with mammals, together with macrophage aggregation and fibrotic encapsulation. On the other hand, avian heterophils lack myeloperoxidase, possibly altering oxidative burst responses. However, this does not weaken the model's utility for acute inflammation screening. Furthermore, the study's focus on acute granuloma formation (7 days) limits insights into long-term effects or chronic fibrotic sequelae. Although the decrease in dry mass hints at antifibrotic possibilities, chronic models are essential to assess continuous effects. Amitriptyline's impact on late-stage fibrosis or cytokine-driven remodeling warrants supplementary investigation. The exact mechanism underlying amitriptyline's an- tiinflammatory action remains a matter of speculation; while its inhibition of neurotransmitter reuptake (e.g., serotonin, norepinephrine) could modulate neuroimmune pathways (ROYDS et al., 2020), off-target effects on cytokines (KU- BERA et al., 2000), adhesion molecules (JI et al., 2024), or leukocyte apoptosis (JOHNSON III et al., 2016) warrant further investigation.

Comparative context and novelty. Our re- sults align with preclinical studies highlighting the antiinflammatory effects of tricyclic antide- pressants, such as imipramine, in rodent models. However, this is the first report of amitriptyline's efficacy in an avian granuloma model, underscor- ing the evolutionary conservation of key inflam- matory pathways. The significant reduction in eosinophils and basophils, cells implicated in al- lergic and parasitic inflammation, suggests broad- er immunomodulatory potential, possibly extend- ing to eosinophilic disorders like asthma.

To bridge these findings to clinical applications, mechanistic studies are imperative. Transcriptomic or proteomic analyses could identify the molecular targets (e.g., NF-κB, TNF-α) influenced by amitriptyline. Concurrently, dose-ranging studies in mammalian models and evaluations of combination therapies (e.g., with corticosteroids) may optimize therapeutic efficacy while mitigating known side effects (e.g., sedation, cardiotoxicity). While direct comparisons with corticosteroids were beyond the experimental design of this study, previous literature indicates that corticosteroids reduced granuloma mass by 75–85% in a comparable model (MISHRA et al., 2014) but they carry the risk of immunosuppression and metabolic side effects. Amitriptyline's dual inhibition of granuloma mass (18–31%) and leukocyte mobilization, together with its recognized safety profile in chronic use, suggests a potential advantage in balancing efficacy and tolerability. Future comparative studies are warranted to validate these explanations. Clinical trials in patients with granulomatous diseases, particularly those refractory to conventional therapies, are warranted to assess feasibility.

Conclusions

This study provides compelling preclinical evidence that amitriptyline attenuates granulomatous inflammation through systemic immunomodulation. By repurposing a well-characterized drug, this work opens avenues for cost-effective, accessible treatments for chronic inflammatory conditions. However, rigorous translational research is essential to validate these findings in human contexts and elucidate the precise mechanisms at play. For translational justification in mammalian systems, rodent models of granulomatous diseases (e.g., Mycobacterium-induced granulomas) should be enlisted to evaluate pharmacokinetics and dose optimization. Mechanistic studies, including cytokine/chemokine profiling (e.g., TNF-α, IL-6) and transcriptomic analyses, are vital to recognize the molecular targets. Future clinical trials could focus on patients with refractory granulomatous disorders, leveraging amitriptyline's repurposing potential and safety data.

Ethics approval

Ethical approval was obtained from the Research Ethics Committee of the College of Veterinary Medicine, University of Mosul after reviewing the research project (Ref: UM.VET.2024.008).

Financial support statement

This research was not funded by any public, commercial, or non-profit resources.

Authorship contribution statement

Yasser M. Albadrany: conceptualization, methodology, writing and editing.

Abdeslam M. Saleh: data collection, data analysis.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgments

Many thanks to the Deanship of the College of Veterinary Medicine, University of Mosul for the support in completing the research.

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Received: 16 March 2025
Accepted: 26 April 2025
Online publication. 10 October 2025

SALEH, A. M, Y. M. ALBADRANY: Inhibicijski učinci amitriptilina na nastanak granuloma u eksperimentalnom modelu pilića. Vet. arhiv 96, 187-194, 2026.

SAŽETAK

Kao obilježje kroničnih bolesti, granulomatozna upala zahtijeva sigurnije terapijske pristupe koji uvažavaju ograničenja postojećih imunosupresivnih režima. U radu se istražuje potencijal prenamjene amitriptilina, tricikličkog antidepresiva, za modulaciju stvaranja granuloma i sistemskog imunosnog odgovora u eksperimentalnom modelu pilića. Za indukciju granuloma u pilića primijenjena je supkutana implantacija kuglica pamuka (n=6/skupina), nakon čega je uslijedila oralna primjena amitriptilina (50 ili 100 mg/kg/dan) ili fiziološke otopine tijekom sedam dana. Izračunata je vlažna i suha masa granuloma te je utvrđen hematološki profil leukocita (WBCs). Amitriptilin je znakovito ($P<0,05$) suprimirao razvoj granuloma, ovisno o dozi, pri čemu je doza od 100 mg/kg smanjila vlažnu i suhu masu za 17,73% (135,91±1,05 mg u odnosu na kontrolnu skupinu 165,20±1,42 mg) i 30,94% (49,10±1,02 mg u odnosu na kontrolnu skupinu 71,08±1,15 mg). Istodobno je broj leukocita smanjen za 23,2% (18116±97 u odnosu na kontrolnu skupinu 23583±410 stanica/µL), uz znatno smanjenje heterofila, limfocita, eozinofila i bazofila ($P<0,05$). Ovi rezultati upućuju na dvostruko protuupalno djelovanje amitriptilina, čime je ublaženo stvaranje granulomatoznog tkiva i smanjena sistemska mobilizacija leukocita. Iako istraživanje na modelu pilića ima etičke i praktične prednosti, potrebno ga je prenijeti i potvrditi na sisavcima. U istraživanju se amitriptilin pokazao kao obećavajuće sredstvo za prenamjenu u liječenju granulomatoznih poremećaja. Za iskorištavanje njegovog imunomodulacijskog potencijala potrebno je istražiti mehanizme djelovanja i provesti kliničke provjere.

Ključne riječi: amitriptilin; protuupalni učinak; pilići; imunomodulacija granuloma