# Original Article

# Assessment of the Analgesic, Anti-inflammatory and Antipyretic Activity of Amitriptyline in Chicks

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## ABSTRACT

**Background:** Amitriptyline is effective for pain relief in a variety of pain states, as evidence suggests that it influences various analgesic pathways.

**Objectives:** This study aimed to determine the analgesic dose, the analgesic effect over time, and the anti-inflammatory and antipyretic effects of amitriptyline in chicks.

**Methods:** Sixty-six broiler chicks were used in several successive experiments. Five and seven chicks were used to determine the median lethal dose ($LD_{50}$) and median effective analgesic dose ($ED_{50}$), respectively, using the Dixon method. Pain was induced and assessed using an electrical stimulator. Three sets of experiments were conducted to assess analgesic, anti-inflammatory, and antipyretic effects, using three groups of six chicks each (control, amitriptyline 50 and 100 mg/kg BW, administered orally). A formalin test was used to induce acute inflammatory pain, and a baker's yeast test was used to induce fever.

**Results:** The $LD_{50}$ and $ED_{50}$ of oral amitriptyline were 315 mg/kg and 23 mg/kg, respectively. Amitriptyline showed short-term analgesic effects lasting only two hours. Amitriptyline at 50 and 100 mg/kg showed dose-dependent, significant analgesic and anti-inflammatory effects by reducing the number of foot lifts and the foot thickness treated with formalin, respectively, compared to the control group. Amitriptyline exhibited a significant antipyretic effect, as the doses of 50 and 100 mg/kg were able to prevent the temperature rise for six and nine consecutive hours, respectively.

**Conclusion:** The study concluded that amitriptyline had a short-term analgesic effect with an acute anti-inflammatory effect, with a remarkable effect on reducing the induced fever.

**Keywords:** Amitriptyline, Analgesic, Anti-inflammatory, Antipyretic, Chicks

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## Introduction

Pain is a major clinical problem, and an effective analgesic would be a tremendous asset to modern medicine. Unfortunately, this is a challenging goal, and many studies are needed to properly evaluate a particular drug's efficacy and mechanisms of action when used as an analgesic (Brennan et al., 2007). Amitriptyline, a synthetic tricyclic molecule used to treat depression, was authorized by the Food and Drug Administration (FDA) in 1961 under the brand name Elavil (Braslow & Marder, 2019). Unconventional applications include therapy for anxiety, migraine, insomnia, autism, and fibromyalgia (Windsor et al., 2020). Amitriptyline was found to have analgesic qualities in clinical practice shortly after its discovery (Pereira et al., 2023). Amitriptyline is effective for pain alleviation in a variety of pain states because it affects various analgesic pathways (Bonilla-Jaime et al., 2022).

The body's response to harmful stimuli kick-starts the healing process. Inflammation is manifested by signs of redness, heat, swelling, pain, and loss of function (Chen et al., 2018). There are two types of inflammation: acute and chronic. Acute inflammation is a normal body response to microbial infection, physical or chemical stress, injury, and damage (Abdulkhaleq et al., 2018). Chronic inflammation, on the other hand, results in a progressive shift in the type of cells present at the site of inflammation and is often defined by the presence of activated lymphocytes and macrophages. It is accompanied by increased blood levels of immune markers, such as cytokines, chemokines, acute phase proteins, etc. Importantly, if unregulated, inflammation can damage the body (Nasef et al., 2017). Amitriptyline was reported to reduce the levels of C-reactive protein, inflammatory mediators, cytokines, monocytes, and neutrophils in people and mice in a laboratory setting (Vismari et al., 2012).

Fever is a key host-resistance characteristic and is generated by the preoptic area of the hypothalamus in response to pyrogens. Fever can also be a biological marker categorizing disease severity, and some infections are more likely to cause fever (Ogoina, 2011). The duration of the fever provides some data about the probable etiologic agent, since the viral infection has the shortest duration due to its life cycle. Chronic inflammatory conditions may blunt the fever reaction through decreased phagocytic cell synthesis and release of pyrogens and cytokines (El-Radhi, 2018).

Poultry and birds in general are very sensitive to currently available painkillers, especially non-steroidal anti-inflammatory drugs, which have serious side effects on both the liver and kidneys. Therefore, veterinary medicine needs to search for safer alternatives drugs. Due to the absence of previous studies addressing the analgesic effects of amitriptyline and determining the analgesic doses and the analgesic period in chicks, as well as the anti-inflammatory and antipyretic effects, this study was conducted.

## Materials and Methods

### Animals

Sixty-six Ross broiler chicks of both sexes were obtained from a local hatchery. The chicks were one day old at the start and placed in breeding cages under typical conditions of temperature (32–35 ˚C), ventilation, and constant lighting. Water and concentrated feed were ad libitum. They were reared, and experiments were conducted when they were 7–15 days old. During the experiments, they weighed 120–250 g.

### Experiments

#### Determination of the median lethal dose ($LD_{50}$)

Based on preliminary experiments on chicks, the first dose of amitriptyline (300 mg/kg) was administered orally to one bird, and after 24 hours, the result was recorded (survival indicated by the symbol O, death indicated by the symbol X). Doses ranged from 250– to 350 mg/kg for $LD_{50}$ determination, and the results were compared with the Dixon table, with the up-and-down method used to determine $LD_{50}$ (Dixon, 1980).

#### Determination of the median effective analgesic dose ($ED_{50}$)

Pain was induced in chicks using an electrical stimulator device (SRI Ltd, UK) (Mohammed & Albadrany, 2022). The device settings were adjusted to suit the current experimental conditions; the highest voltage was 25 volts, the electrical pulse width was 5 milliseconds, the frequency was 50 pulses/second, and continuous electrical pulses were used. Two electrodes linked to the device were attached to the skin under the wing. The skin was moistened with gel before placing the electrodes to smooth the passage of current through the skin. The voltage that causes pain was recorded as the baseline value before administration of the drug (pain was represented by wing flapping) and then again one hour

after drug administration. In the case of no analgesia, no increase in voltage was observed and symbolized by the symbol O. In the case of analgesia, an increase in voltage was observed and symbolized by the symbol X (Bashar & Albadrany, 2022). Briefly, the electrical stimulator was used to induce pain (via controlled voltage) and subsequently detect analgesia by measuring the voltage required to elicit a nociceptive response (wing flapping) post-treatment. Higher post-dose voltages indicated analgesia. Doses ranged from 20 to 50 mg/kg for $ED_{50}$ determination, and the results were compared with the Dixon table, with the up-and-down method used to find $ED_{50}$.

### Estimation the analgesic effect of amitriptyline against acute pain

Eighteen chicks were divided into three groups randomly. The first group served as the control and received distilled water at 5 mL/kg (BW) orally. The second group received amitriptyline at 50 mg/kg BW orally, and the third group received amitriptyline at 100 mg/kg BW orally. These doses were chosen based on previous experiments to achieve analgesia in all animals involved in the study, estimated as approximately doubling the $ED_{50}$ value of amitriptyline (i.e. 2 x $ED_{50}$ and 4 x $ED_{50}$, respectively). Notably, there were no fatalities observed among the treated chicks, and they remained in good health within 24 hours after administration.

An electrical stimulator device was used to induce pain. The voltage was measured at 0, 30, 60, 120, and 240 minutes for all groups, and the voltage was recorded for each chick within its group over time. By comparing the groups, the onset, latency, and duration of analgesic efficacy can be determined.

### Formalin test

Eighteen chicks were randomly divided into three groups:

First group (control): The chicks were orally administered distilled water at 5 mL/kg BW, and after one hour, 0.05 mL of formalin at a concentration of 0.1% was injected into the right foot (Sawynok & Liu, 2003).

Second group: The chicks were orally administered amitriptyline at a dose of 50 mg/kg BW, and one hour later, 0.05 mL of formalin at a concentration of 0.1% was injected into the right foot.

Third group: the chicks were orally administered amitriptyline at a dose of 100 mg/kg BW, and one hour later, 0.05 mL of formalin at a concentration of 0.1% was injected into the right foot. Immediately after injecting formalin into the right foot, each chick from the three groups was subjected to the following measurements for 3 minutes:

1. The onset of right foot lifting.

2. The number of right foot lifts.

The thickness of the right foot (mm) was measured using a digital caliber (Electronics Lab, China) before and 60 min after formalin injection into the right foot.

The Equation 1 was used to demonstrate the anti-inflammatory effects.

1. *Anti-inflammatory efficiency (%) = Change in foot thickness (control) – Change in foot thickness (treatment) / Change in foot thickness (control) ×100*

### Detection of the antipyretic effect.

Eighteen chicks were randomly divided into three groups:

First group (control): Chicks were administered distilled water at 5 mL/kg BW orally and baker's yeast at 135 mg/kg BW i.p (Tomazetti et al., 2005).

Second group: Chicks were administered amitriptyline at a dose of 50 mg/kg BW orally and baker's yeast at 135 mg/kg BW i.p.

Third group: Chicks were administered amitriptyline at a dose of 100 mg/kg BW orally and baker's yeast at 135 mg/kg BW i.p.

The body temperature of the chicks was measured before treatment by placing the thermometer at a depth of 2 cm in the cloacal orifice, which was considered the baseline. Then, the temperature was measured every hour for nine consecutive hours.

### Statistical analysis

One- or two-way analysis of variance (ANOVA) and the least significant difference (LSD) test were used for statistical analysis of the data using SPSS software (version 20.0; IBM Corp., Armonk, NY, USA). Dosedependency was assessed via linear regression analysis. The significance level was set at $P \leq 0.05$.

**Table 1.** $LD_{50}$ of amitriptyline in chicks

| Variables | Value |
|---|---|
| $LD_{50}$ (mg/kg) orally | 315 |
| Dose range (mg/kg) | 250-350 |
| 1st dose (mg/kg) | 300 |
| Last dose (mg/kg) | 300 |
| Increase or decrease in dose (mg/kg) | 50 |
| Total of chicks used, symbols, and their matching dose | 5 (xooxo)[a] (300-250-300-350-300) |
| Equation: $LD_{50}$=Xf + Kd | 300+(0.305)50=315.25 ≈ 315 |

[a]X: Death, O: Survival.

Note: Xf: Last dose, K: Table value, d: Increase or decrease in dose (mg/kg).

## Results

In the present study, the estimated $LD_{50}$ of amitriptyline in chicks was 315 mg/kg BW (Table 1) and the $ED_{50}$ was 23 mg/kg BW (Table 2).

In the experiment assessing analgesia for acute pain over time, a significant increase in voltage was observed. Between-group comparisons showed that voltage-induced pain was significantly higher in the groups treated with amitriptyline at doses of 50 and 100 mg/kg BW compared to the control group at 60 and 120 min, whereas there were no significant differences among the three groups at 0, 30, and 240 min. Within-group analyses revealed that voltage-induced pain in the groups treated with amitriptyline at doses of 50 and 100 mg/kg BW increased significantly at 60 and 120 min compared with 0, 30, and 240 min. The onset of analgesia appeared after one hour of treatment and persisted for only two hours, indicating a short duration of analgesia (Figure 1).

In the formalin test to induce acute pain and inflammation, a significant increase was observed in the onset of right foot lifting in the group treated with amitriptyline at a dose of 100 mg/kg BW compared with the group treated with amitriptyline at a dose of 50 mg/kg BW and the control group. A significant increase was also observed in the onset of right foot lifting in the group treated with amitriptyline at a dose of 50 mg/kg BW compared with the control group. There was a significant decrease in the number of right foot lifts in the group treated with amitriptyline at a dose of 100 mg/kg BW compared to the group treated with amitriptyline at a dose of 50 mg/kg BW and the control group. There was also a significant decrease in the number of right foot lifts between the group treated with amitriptyline at a dose of 50 mg/kg BW and the control group. Amitriptyline at doses of 50

**Table 2.** Median effective analgesic dose ($ED_{50}$) of amitriptyline after 60 minutes

| Variables | Value |
|---|---|
| $ED_{50}$ (mg/kg) orally | 23 |
| Dose range (mg/kg) | 20-50 |
| First dose (mg/kg) | 50 |
| Last dose (mg/kg) | 30 |
| Increase or decrease in dose (mg/kg) | 10 |
| Total of chicks used, symbols and their matching dose | 7 (xxxoxox)[a] (50-40-30-20-30-20-30) |
| Equation: $ED_{50}$=Xf + Kd | 30+(-0.741)10= 22.59 ≈ 23 |

[a]X: Analgesia; O: No analgesia.

**Table 3.** Analgesic and anti-inflammatory effects of amitriptyline in the formalin test

| Groups | Mean±SEM (6 Chicks/Group) | | | |
|---|---|---|---|---|
| | Onset of Right Foot Lifting (seconds) | Number of Right Foot Lifting (3 min) | Thickness of Paw (mm) | Anti-inflammatory Activity (%) |
| Control | 1.15±0.1[a] | 73±2.28[a] | 0.27±0.022[a] | 0 |
| Amitriptyline (50 mg/kg) | 3.63±0.47[b] | 58±1.71[b] | 0.17±0.009[b] | 37 |
| Amitriptyline (100 mg/kg) | 7.72±1.69[c] | 47±1.52[c] | 0.14±0.012[b] | 48 |

Note: The values with different letters in each column indicate significant differences (P≤0.05).

and 100 mg/kg BW showed a significant decrease in foot thickness compared to the control group. The formalin test showed that amitriptyline at doses of 50 and 100 mg/kg BW exerted a dose-dependent analgesic effect. It was also noted that both doses had anti-inflammatory effects by reducing the thickness of the foot treated with formalin; the percentage of inflammation inhibition was 37 and 48%, respectively (Table 3).

In the baker's yeast test to detect antipyretic effects, a time-dependent dose effect in the reduction of fever was noted. In a comparison between the groups, a significant decrease in body temperature was observed in the group treated with amitriptyline at a dose of 100 mg/kg BW compared to the control group at 3 to 9 h. A significant decrease in body temperature was observed in the group treated with amitriptyline at a dose of 50 mg/kg BW compared to the control group at 3 to 6 h. At the same time, there was no significant difference at 7 to 9 h. Within the control group, body temperature significantly increased at 3–9 h compared with 1–2 h. In the group treated with amitriptyline at 50 mg/kg BW, significantly lower body temperatures were observed from 1–6 h compared with 7–9 h. In the group treated with amitriptyline at 50 mg/kg BW, significantly lower body temperatures were observed from 1 to 6 h compared with 7 to 9 h. In the group treated with amitriptyline at a dose of 100 mg/kg BW, no significant difference in temperature was observed at any time point. This test demonstrated the antipyretic effects of amitriptyline in a time-dependent dose effect (Figure 2).

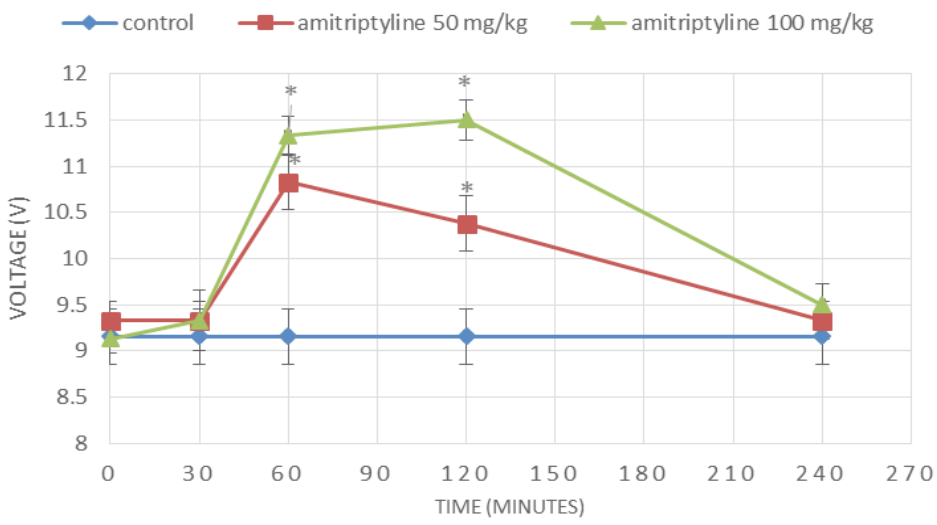


**Figure 1.** Analgesic effect of amitriptyline over time (time [min] vs voltage [V])

*Significantly (P≤0.05) different from the control group.

Note: Values are presented as Mean±SEM for 6 chicks/group.

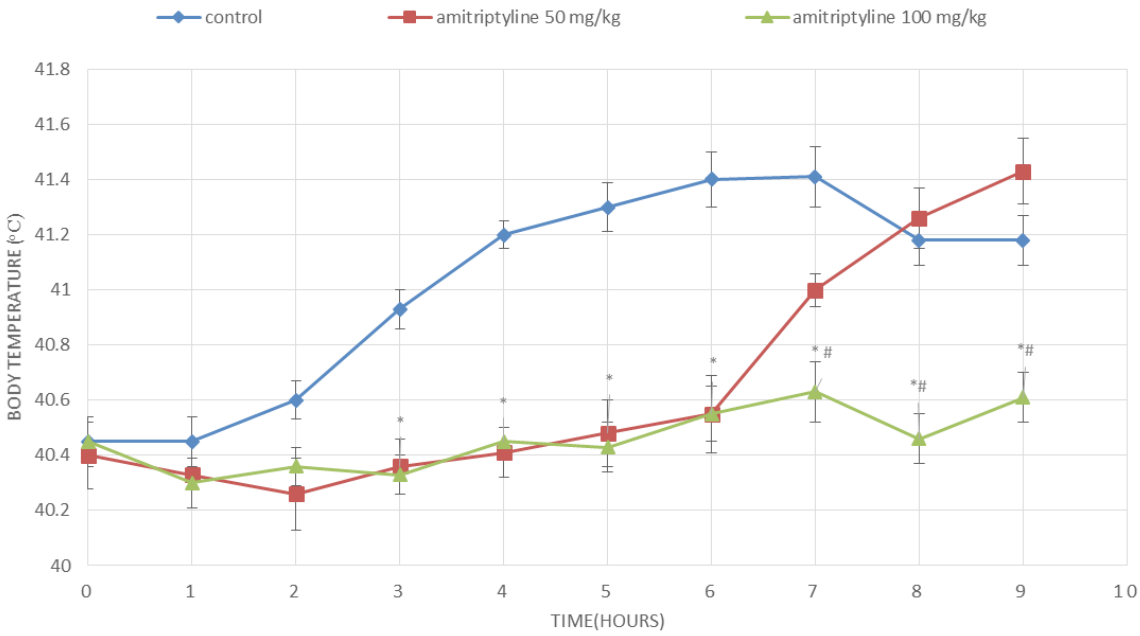


**Figure 2.** Antipyretic effect of amitriptyline over time (time [h] vs. temperature [˚C]).

*Significantly (P≤0.05) different from the control group, #Significantly (P≤0.05) different from the amitriptyline 50 mg/kg group.

Note: Values are presented as Mean±SEM for 6 chicks/group.

## Discussion

This study provides the first comprehensive evidence of amitriptyline's multimodal pharmacological activity in avian species. The $LD_{50}$ and $ED_{50}$ were determined as 315 mg/kg and 23 mg/kg, respectively. It also revealed that amitriptyline had short-term analgesic effects in chicks, with onset of action at one hour and duration of up to two hours post-administration. It also exhibited dose-dependent anti-inflammatory effects, reducing formalin-induced foot edema by 37% (50 mg/kg) and 48% (100 mg / kg), and inhibiting baker's yeast-induced fever for up to nine hours at the higher dose.

The results not only advance our understanding of amitriptyline's therapeutic potential beyond mammalian models but also address critical gaps in avian pharmacology, proposing an alternative to conventional non-steroidal anti-inflammatory drugs (NSAIDs) in poultry medicine.

### Dosage, safety, and practical implications

The $ED_{50}$ (23 mg/kg) and the $LD_{50}$ (315 mg/kg) reveal a promising safety margin ($LD_{50}$/ $ED_{50}$ ≈14), positioning amitriptyline as a possibly safer alternative to NSAIDs, which are associated with renal and hepatic toxicity in birds. However, the short analgesic duration (2 hours) requires frequent dosing, posing practical challenges in clinical settings. To address this, a sustained-release formulation or adjunct therapy could be suggested. Furthermore, while the acute models used here may be clinically relevant, more studies—especially those on chronic pain and inflammation models such as arthritis—are required to evaluate the long-term efficacy and safety of amitriptyline.

### Analgesic effects

Amitriptyline elicited dose-dependent analgesia, with peak effects at 1-2 hours post-administration. Previous research shows that amitriptyline can successfully reduce pain and thermal hyperalgesia in inflammatory and neuropathic pain in rats (Khan et al., 2002). Ahmad et al. (2019) revealed that amitriptyline shows significant analgesic effects in mice through both central and peripheral mechanisms, as demonstrated by radiant heat tail flick, Haffner's tail clip, and acetic acid-induced writhing tests. Paudel et al. (2007) explored the anti-nociceptive effects of amitriptyline in mouse models of acute pain. Using the hot-plate and tail-flick tests, investigators assessed the drug's efficacy alone and in combination with morphine. The study determined that amitriptyline augments acute pain relief, mainly when combined with morphine, potentially reducing morphine dose requirements and related risks. This analgesic effect can be explained by the fact that amitriptyline prevents

serotonin and norepinephrine from being reabsorbed in the presynaptic membrane (Frank et al., 2022). As a result, serotonin and norepinephrine concentrations in the synaptic cleft rise. The inhibitory descending route of pain is enhanced by both serotonin and norepinephrine (Sirucek et al., 2023). Furthermore, amitriptyline can modulate the opening of potassium channels, including KATP, $KCa^{2+}$, and voltage-gated potassium channels. It is also well known that activating potassium channels at the postsynaptic membrane level causes hyperpolarization, which in turn reduces the production of pain-related action potentials (Galeotti et al., 2001).

### Anti-inflammatory effects

Amitriptyline significantly reduced formalin-induced foot edema (37–48% inhibition), reflecting its anti-inflammatory effects. Several studies have revealed the anti-inflammatory effect of amitriptyline, such as its effects on carrageenan-induced foot edema in rats (Hajhashemi et al., 2010), rodent ulcerative colitis (Fattahian et al., 2016), and sepsis in rats (Xia et al., 2019). The formalin test's biphasic response (neurogenic and inflammatory phases) suggests that amitriptyline may act on both peripheral (e.g. cytokine suppression) and central (e.g. glial modulation) pathways (Zouikr et al., 2015). Remarkably, prior work in mammals links amitriptyline to reduced IL-6, TNF-α, and leukocyte infiltration (Więdłocha et al., 2018; Franco-Trepat et al., 2022), but this study is the first to demonstrate such effects in an avian acute inflammation model. The robust edema reduction highlights amitriptyline's potential for managing post-surgical or injury-related inflammation in poultry.

### Antipyretic effects

Baker's yeast, a fungal-derived pyrogenic substance, has been commonly employed in antipyretic studies on animals, like rats, mice, rabbits, and birds (Abdul-Ghani & Naser, 2022). Baker's yeast can cause pyrexia, lethargy, and lack of appetite by increasing the concentration of inflammatory cytokines, including interleukin-6 and tumor necrosis factor-α in the blood and triggering the transcription of inflammatory factors (Ferreira et al., 2012).

Our study evaluated the efficacy of amitriptyline in attenuating fever induced by baker's yeast following acute administration, with results demonstrating a dose-dependent reduction in pyrexia shortly after treatment. This contrasts with the study by Flanigan et al., which investigated LPS-induced fever and reported a delayed antipyretic effect emerging only after two weeks of daily amitriptyline administration. The authors noted in the conclusion, "The antipyretic effect of AMI was apparent only after two weeks of daily treatment". The disparity in outcomes likely stems from differences in experimental protocols, specifically, the duration of amitriptyline pretreatment (Flanigan et al., 1992).

Amitriptyline may target catecholamines, TRC, α7AChR, TNFR1, IL-1 receptors, MC4R, decapeptidases, $K^+$ channels, COX-1, and perhaps TLR4 (Obuchowicz et al., 2006; Franco-Trepat et al., 2022; Sohda et al., 2015; Li et al., 2018). Although the mechanism of action of amitriptyline in reducing pyrexia is unknown, we can assume that the effect of amitriptyline on one or more of the previously mentioned mechanisms may reduce body temperature in chicks treated with baker's yeast.

## Conclusion

This study demonstrated amitriptyline as a multimodal therapeutic drug in chicks, indicating its analgesic, anti-inflammatory, and antipyretic effects. Its novel antipyretic effect and satisfactory safety profile set it apart from other NSAIDs, making it a promising candidate in poultry medicine. Although transient analgesia highlights species-specific pharmacokinetic issues, our findings pave the way for refining dosage techniques and exploring molecular mechanisms specific to avian biology. Further studies to fill these gaps will improve its practical applications, perhaps managing pain and fever in veterinary medicine.

## Ethical Considerations

### Compliance with ethical guidelines

This study was approved by the Research Ethics Committee of the College of Veterinary Medicine, University of Mosul, Mosul, Iraq (Code: UM.VET.2024.008).

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### Authors' contributions

Conceptualization, methodology, and writing: Yasser M. Albadrany; Data collection and data analysis: Abdeslam M. Saleh.

### Conflict of interest

The authors declared no conflict of interest.

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