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Effect of *Zingiber officinale* Ethanol Extract on Neurohormone Concentration of Male Wistar Albino Rats Induced with Inflammation

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Abstract: This study investigated the effect of ethanol extract of Zingiber officinale on neurohormone concentrations in male Wistar albino rats subjected to albumin-induced inflammation. Inflammation was induced to evaluate the alterations in key neurohormones, dopamine, oxytocin, corticotropin, and norepinephrine, and assess the modulatory role of Z. officinale. Rats were grouped into blank control, negative control (inflammation without treatment), standard control (treated with ibuprofen), and two experimental groups treated with low and high doses of Z. officinale extract. The results revealed a significant decrease ($p < 0.05$) in dopamine, oxytocin, corticotropin, and norepinephrine levels in the negative control group (339±0.001, 5.60±0.001, 5.16±0.031, and 11.12±0.004, respectively) compared to the blank control, indicating the suppressive effect of inflammation on neurohormonal activity. However, treatment with Z. officinale, particularly at high doses, significantly restored these neurohormones toward normal levels, showing values statistically comparable to the standard control group ($p > 0.05$). These findings demonstrate that Zingiber officinale ethanol extract possesses neuroprotective and anti-inflammatory properties capable of reversing inflammation-induced neurohormonal disruptions. The study highlights Zingiber officinale's potential as a natural therapeutic agent for managing neuroinflammatory conditions.

Keywords: *Zingiber officinale*, inflammation, dopamine, oxytocin, corticotropin, and norepinephrine.

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Introduction

Inflammation is a vital biological response of body tissues to harmful stimuli such as infections, damaged cells, or irritants. In order to eliminate necrotic cells, initiate tissue repair, and eliminate the initial cause of cell injury, this protective response involves immune cells, blood vessels, and molecular mediators (Chen *et al*., 2020). Conversely, chronic inflammation is a detrimental process that has been linked to several systemic diseases, including neurodegenerative diseases, behavioral disorders, and cardiovascular disease (Furman *et al*., 2020).

Recent research has shown the complex relationship between inflammation and neuro-hormonal alterations. Neuro-hormones such as oxytocin, vasopressin, dopamine, norepinephrine, and corticotropin-releasing factor (CRF) largely regulate the physiological and behavioral responses to stress and inflammation (Ganguly *et al*., 2021). Because these neuro-hormones change immune responses, emotional behavior, and stress adaption mechanisms, they are linked to the pathophysiology of several inflammatory and neuropsychiatric illnesses.

The neuropeptide oxytocin is mostly produced in the hypothalamus and is widely recognized for its roles in social bonding, sexual reproduction, delivery, and the postpartum period. Apart from these functions, oxytocin also contains anti-inflammatory and antioxidant qualities that can lessen systemic inflammatory responses. Vasopressin, another hypothalamic neuropeptide, regulates water balance and vascular resistance and contributes to neuro-immune modulation in inflammatory circumstances (Ganguly *et al*., 2021).

Dopamine and norepinephrine, two significant catecholamines made in the brain and adrenal medulla, control motivation, mood, focus, and the body's response to stress (Meyer *et al*., 2021). Cognitive impairments, anxiety, and symptoms like depression have been linked to alterations in dopamine and norepinephrine signaling under inflammatory conditions (Beurel *et al*., 2020). The hypothalamic-pituitary-adrenal (HPA) axis response to stress is coordinated by corticotropin-releasing factor (CRF), an essential modulator of neuroendocrine, autonomic, and immunological responses (Zhou *et al*., 2020).

Given these connections, addressing neuro-hormonal abnormalities during inflammatory disorders may have therapeutic benefits. There is an increased need for natural compounds that can safely and effectively change the concentrations of neuro-hormones. One of these natural chemicals that has attracted a lot of attention is ginger, or *Zingiber officinale*.

The perennial herbaceous plant Zingiber officinale, which belongs to the Zingiberaceae family, has been used as a spice and medicine for many centuries (Rahmani *et al*., 2021). Its bioactive components, including as gingerols, shogaols, paradols, and zingerone, exhibit potent anti-inflammatory, antioxidant, antibacterial, and neuroprotective properties (Shanmugam *et al*., 2022). Ethanol extracts of *Zingiber officinale* have demonstrated significant biological activity due to their high concentration of phytochemicals.

Previous studies have demonstrated that ginger extracts reduce pro-inflammatory cytokine levels, enhance cognitive

function, and lessen oxidative stress in animal models of neuro-inflammation (Khandouzi *et al*., 2022). Furthermore, because ginger affects neurotransmitter systems like serotonin and dopamine, it may be able to change the levels of neuro-hormones affected by inflammation.

Knowing the effect of *Zingiber officinale* ethanol extract on neuro-hormonal changes during inflammation could illuminate new pathways for therapeutic intervention against neuro-immune dysfunctions.

Justification of the Study

Alternative treatments that are both effective and free of negative side effects must be investigated due to the rising incidence of inflammatory and neurodegenerative disorders as well as the shortcomings of existing therapeutic modalities. Chronic inflammation damages the central nervous system (CNS), causing altered neurotransmission, decreased neuroplasticity, and disrupted neuro-hormonal homeostasis, in addition to impairing the function of peripheral organs (Ganguly *et al*., 2021).

Promising therapeutic candidates include natural compounds like *Zingiber officinale* that have multi-targeted bioactivities. Ginger is a desirable alternative for treating inflammation-associated neuro-hormonal dysregulation because of its rich phytochemical content, which gives it anti-inflammatory, antioxidant, and neuroprotective qualities (Shanmugam *et al*., 2022).

The current study is therefore justified in three ways: First, it aims to add to the increasing amount of data regarding *Zingiber officinale*'s anti-inflammatory and neuroprotective properties, with a particular emphasis on its influence on neuro-hormonal regulation. The study will shed light on the mechanisms by which *Zingiber officinale* produces its therapeutic effects by measuring variations in the amounts of oxytocin, vasopressin, dopamine, norepinephrine, and CRF.

Second, by presenting experimental data on the effects of *Zingiber officinale* ethanol extract in a well-established animal model of inflammation, the study seeks to close a significant gap in the body of existing material. The results may open up new avenues for translational research to create innovative treatments for neuroendocrine illnesses associated with inflammation.

Thirdly, practically speaking, *Zingiber officinale* is easy to find, reasonably priced, and widely recognized as a medical herb and dietary supplement in many cultures. Its potential as an affordable and easily available treatment drug for populations at risk of inflammatory and neuropsychiatric illnesses would be strengthened if it could be shown to be effective in modifying neuro-hormonal abnormalities.

Aim of the Study

The study aimed to determine the effect of *Zingiber officinale* ethanol extract on neuro-hormonal concentration of male Wistar albino rats induced with inflammation.

Specific Objectives of the Study

The specific objectives were to:

- Determine the effect of *Zingiber officinale* ethanol extract on dopamine concentration of male Wistar albino rats induced with inflammation.
- Determine the effect of *Zingiber officinale* ethanol extract on oxytocin concentration of male Wistar albino rats induced with inflammation.
- Determine the effect of *Zingiber officinale* ethanol extract on norepinephrine concentration of male Wistar albino rats induced with inflammation.
- Determine the effect of *Zingiber officinale* ethanol extract on corticotropin-releasing factor of male Wistar albino rats induced with inflammation.

Materials and Methods

Plant Collection and Identification

Fresh rhizomes of *Zingiber officinale* were purchased from Nkpokiti Market, Enugu State. The plant material was authenticated by Prof. C. S. Eze in the Department of Applied Biology and Biotechnology at Enugu state University of Science and Technology.

Preparation of Ethanol Extract of *Zingiber officinale*

The rhizomes which weighed 76.4 grams were washed thoroughly with distilled water to remove dirt and dried using analytical oven 105°C. The dried rhizomes were ground into a fine powder using a mechanical grinder. The powdered sample was placed in a soxhlet apparatus, and 300 mL of pure ethanol was used as the solvent for extraction, which followed the study by **Adepoju *et al*. (2020)**. The soxhlet extraction process was carried out for 5 hours. The mixtutre was filtered using Whatman No. 1 filter paper. The filtrate was concentrated under reduced pressure using a rotary evaporator at 40°C to yield the crude ethanol extract.

Experimental Animals

A total of thirty (30) healthy male Wistar albino rats weighing 10–220 g were obtained from University of Nigeria Enugu Campus (UNEC) Animal House. The animals were housed in plastic cages under standard conditions of 12-hour light/dark cycle, temperature (25°C). Rats were acclimatized for two weeks before the commencement of the experiment and had standard rat feed and clean water.

Induction of Inflammation

Inflammation was induced by intraperitoneal injection of 0.5 ml of egg albumin solution and in the hind paw region. The inflammation peaked within 3-6 hours. The paw thickness was monitored using a Vernier caliper to confirm the presence and resolution of inflammation.

Experimental Design

The experiment was laid on a Complete Randomized Design (CRD), and animals were sampled and grouped into five comprising six rats:

- Group A (Blank Control): were neither induced nor treated, but retained feed and, water *ad libitum*
- Group B (Negative Control): induced with concentrated egg albumin, but received no treatment.
- Group C (Standard Control): induced with egg albumin + treated with standard inflammatory drug (ibuprofen).

- Group D (Low Dose *Zingiber officinale* Extract): induced with egg albumin + treated with 50 mg/kg body weight of *Zingiber officinale* extract.
- Group E (High Dose *Zingiber officinale* Extract): induced with egg albumin + treated with 200 mg/kg body weight of *Zingiber officinale* extract.

Treatments were administered orally (via intubation) once daily for 3 consecutive weeks following egg albumin induction.

Blood Sample Collection

At the end of the treatment period, the rats were anesthetized using chloroform. Blood samples were collected via ocular puncture into plain bottles for biochemical analysis.

Biochemical Analyses

Oxytocin Concentration

Blood and brain tissues (hypothalamus) are harvested post-euthanasia. Oxytocin is quantified using ELISA kits specific to rat oxytocin (e.g., MyBioSource or Elabscience), following the manufacturer's instructions. Oxytocin levels are associated with stress modulation and inflammation. *Zingiber officinale* has been shown to modulate oxytocinergic signaling (Ahmed *et al*., 2020).

Vasopressin Concentration

Vasopressin is measured in plasma or hypothalamic extracts. Quantitative ELISA or RIA (radioimmunoassay) is used. Brain tissues are homogenized in PBS and centrifuged. The supernatant is used for analysis. Vasopressin plays a role in fluid balance and stress response. Inflammatory conditions upregulate vasopressin secretion, and *Zingiber officinale* may normalize its levels (Bahramsoltani *et al*., 2022).

Dopamine Concentration

Brain regions like the striatum and prefrontal cortex are dissected. Dopamine is extracted using perchloric acid (0.1 M) and measured via HPLC-ECD (High Performance Liquid Chromatography with Electrochemical Detection) or ELISA (Omodan *et al*., 2021). Dopaminergic dysfunction is common in inflammation-induced neurodegeneration. *Zingiber officinale* enhances dopamine levels and mitigates neuronal damage (Tiwari *et al*., 2020).

Norepinephrine Concentration

Brain homogenates from the hippocampus or brainstem are used. Norepinephrine is quantified using HPLC or ELISA. Standard solutions are used to draw calibration curves. Norepinephrine is involved in stress and immune regulation. Inflammatory stimuli decrease its levels, but ginger extract may reverse this decline (Dey *et al*., 2019).

Corticotropin-Releasing Factor (CRF) Concentration

The hypothalamic area is homogenized. CRF concentration is measured using rat-specific ELISA kits. Samples are assayed in duplicate, and values are interpolated from standard curves. CRF is central to HPA axis activation in stress and inflammation. *Zingiber officinale* may help modulate HPA axis hyperactivity by reducing CRF overexpression (Alkasir *et al*., 2021).

Statistical Analysis

All the statistical analysis was processed using the Statistical Package of Social Science (SPSS) for the window (version 21). The values of the measured parameters were expressed as mean ± SEM. One-way Analysis of Variance (1-way ANOVA) was used to determine the effect of inflammation and *Zingiber officinale* ethanol extract on the parameters studied and the difference between means were separated using Duncan's multiple range test. Test for significance was at 0.05 probability level.

Results

Dopamine Level

The result of dopamine level as presented in table (Table 1). The dopamine level in the blank control group (Group A), which was not exposed to inflammation or treatment, was 653 ± 0.001 pg/ml. This served as the normal baseline. In contrast, the negative control group (Group B), which was subjected to inflammation without treatment, showed a significant reduction $p<0.05$ in dopamine level (339 ± 0.001 pg/ml). the standard control group (Group C), after receiving an anti-inflammatory drug had a significant increase in dopamine level (558 ± 0.001 pg/ml) higher than the negative control $p<0.05$, but still lower than the blank control. Similarly, the group treated with a low dose of *Zingiber officinale* extract (Group D) showed a moderate improvement ($p<0.05$) in dopamine levels (411 ± 0.004 pg/ml) compared to the negative control. The group treated with a high dose of *Zingiber officinale* extract (Group E) recorded a dopamine level of 618 ± 0.000 pg/ml, which was not significantly different from the blank control ($p > 0.05$) but significantly higher than the negative control ($p < 0.05$).

Table 1: Effect of Zingiber officinale ethanol extract on dopamine (pg/ml) of male wistar albino rats induced with inflammation

GROUPS	Dopamine (pg/ml)
A (Blank Control)	653±0.001[a]
B (Negative Control)	339±0.001[b]
C (Standard Control)	558±0.001[c]
D (Low-Dose Treated Group)	411±0.004[d]
E (High-Dose Treated Group)	618±0.000[a]

The values are expressed as (mean ± SEM)

Mean values with different letters as superscript are significantly different (p<0.05)

Oxytocin Level

The result of oxytocin level as presented in table (Table 2). Group A (Blank Control), which was not exposed to inflammation or treatment, had the highest oxytocin level at 15.21 ± 0.001 µg/L which represents the normal level of oxytocin in healthy rats. Group B (Negative Control), which was exposed to inflammation but not treated, showed a sharp decrease ($p<0.05$) in oxytocin level to 5.60 ± 0.001 µg/L when compared to Group A, indicating that inflammation significantly reduced oxytocin levels. Group C (Standard Control), which after treated with anti-inflammatory drug after inflammation, significantly increased than the negative control ($p<0.05$) having oxytocin levels of 13.04 ± 0.001 µg/L and not significantly different from the blank control (**$p > 0.05$**). Group D (Low-Dose Treatment) showed a slight increase in oxytocin (6.45 ± 0.002 µg/L) compared to the negative control, with no significant difference ($p>0.05$). Group E (High-Dose Treatment) had an oxytocin level of 13.12 ± 0.003 µg/L, which was significantly higher than the negative control (**$p < 0.05$**) and significantly similar to the blank and standard control groups (**$p > 0.05$**). This shows that the high dose of *Zingiber officinale* was effective in restoring oxytocin levels close to normal

Table 2: Effect of *Zingiber officinale* ethanol extract on oxytocin (µg/L) of male wistar albino rats induced with inflammation

GROUPS	Oxytocin (µg/L)
A (Blank Control)	15.21 ± 0.001^{a}
B (Negative Control)	5.60 ± 0.001^{b}
C (Standard Control)	13.04 ± 0.001^{a}
D (Low-Dose Treated Group)	6.45 ± 0.002^{b}
E (High-Dose Treated Group)	13.12 ± 0.003^{a}

The values are expressed as (mean ± SEM)

Mean values with different letters as superscript are significantly different ($p<0.05$)

Corticotropin Level

Group A (Blank Control), which was not exposed to inflammation or any treatment, recorded the highest corticotropin level at 11.21 ± 0.012 ng/ml, representing the normal physiological level in healthy rats. Group B (Negative Control), which was subjected to inflammation without any treatment, showed a significant reduction ($p < 0.05$) in corticotropin to 5.16 ± 0.031 ng/mL compared to Group A. Group C (Standard Control), treated with an anti-inflammatory drug after inflammation, had corticotropin levels of 10.26 ± 0.031 ng/ml. which was significantly higher than that of the negative control ($p < 0.05$) and significantly similar to the blank control ($p > 0.05$). Group D (Low-Dose Treatment) had corticotropin levels of 8.69 ± 0.012 ng/ml. Although this was a significant improvement over the negative control ($p < 0.05$), it was still significantly lower than the blank and standard control groups ($p < 0.05$), indicating only a moderate effect at the low dose. Group E (High-Dose Treatment) recorded corticotropin levels of 10.68 ± 0.013 ng/ml, which was significantly higher than the negative control ($p < 0.05$) and not significantly different from the blank and standard controls ($p > 0.05$). This suggests that the high dose of *Zingiber officinale* effectively restored corticotropin levels to near-normal (Table 3).

Table 3: Effect of *Zingiber officinale* ethanol extract on corticotropin (ng/ml) of male wistar albino rats induced with inflammation

GROUPS	Corticotropin (ng/ml)
A (Blank Control)	11.21 ± 0.012^{a}
B (Negative Control)	5.16 ± 0.031^{b}
C (Standard Control)	10.26 ± 0.031^{a}
D (Low-Dose Treated Group)	8.69 ± 0.012^{c}
E (High-Dose Treated Group)	10.68 ± 0.013^{a}

The values are expressed as (mean ± SEM)

Mean values with different letters as superscript are significantly different ($p<0.05$)

Norepinephrine Level

The table (Table 4) shows the effect of *Zingiber officinale* extract on norepinephrine levels in male Wistar albino rats induced with inflammation. Group A (Blank Control), which was neither inflamed nor treated, had the highest norepinephrine level at 21.46 ± 0.003 pg/ml. Group B (Negative Control), exposed to inflammation without any treatment, showed a significant drop ($p < 0.05$) in norepinephrine level to 11.12 ± 0.004 pg/ml, indicating that inflammation greatly suppressed norepinephrine production. Group C (Standard Control), treated with an anti-inflammatory drug after inflammation, had norepinephrine levels of 19.72 ± 0.004 pg/ml. This was significantly higher than the negative control ($p < 0.05$) and significantly similar to the blank control ($p > 0.05$). Group D (Low-Dose Treatment) recorded norepinephrine levels of 11.03 ± 0.003 pg/ml, which was not significantly different from the negative control ($p > 0.05$) but significantly lower than the blank and standard control groups ($p < 0.05$). This indicates that the low dose of *Zingiber officinale* had minimal effect on restoring norepinephrine levels. Group E (High-Dose Treatment) showed norepinephrine levels of

19.91 ± 0.023 pg/ml, which was significantly higher than the negative control ($p < 0.05$) and statistically similar to the blank and standard control groups ($p > 0.05$). This demonstrates that the high dose of ginger extract was effective in restoring norepinephrine levels close to normal.

Table 4: Effect of *Zingiber officinale* ethanol extract on norepinephrine (pg/ml) of male wistar albino rats induced with inflammation

GROUPS	Norepinephrine (pg/ml)
A (Blank Control)	21.46±0.003[a]
B (Negative Control)	11.12±0.004[b]
C (Standard Control)	19.72±0.004[a]
D (Low-Dose Treated Group)	11.03±0.003[b]
E (High-Dose Treated Group)	19.91±0.023[a]

The values are expressed as (mean ± SEM)

Mean values with different letters as superscript are significantly different ($p<0.05$)

Discussion

This study examined how *Zingiber officinale* ethanol extract affected the levels of neurohormones in male Wistar albino rats that were induced with inflammation, including dopamine, oxytocin, corticotropin, and norepinephrine. The results demonstrated the neuroprotective and anti-inflammatory potential of *Zingiber officinale* by showing that inflammation significantly decreased the levels of all evaluated neurohormones, but that high-dose *Zingiber officinale* treatment restored their concentrations to levels statistically comparable to the non-inflamed (blank control) and standard drug-treated groups.

The high-dose ginger treatment dramatically restored dopamine, a crucial neurotransmitter involved in motivation and movement, which had been severely repressed in the negative control group. The results of Khan *et al*. (2021), who found that *Zingiber officinale* extract enhanced dopaminergic activity and decreased neuroinflammation in rats, were in line with this. Similarly, *Zingiber officinale*'s bioactive components, especially gingerols and shogaols, have been shown by Ijaz *et al*. (2020) to improve brain neurotransmission and modify inflammatory mediators. The low-dose ginger treatment, on the other hand, only moderately improved, suggesting a dose-dependent impact.

The decrease in oxytocin levels seen in the inflammatory rats is consistent with the findings of Zhou *et al*. (2020), who showed that systemic inflammation inhibits the generation of oxytocin by interfering with hypothalamic signaling. In line with Huang *et al*.'s (2022) findings that *Zingiber officinale* extract could reverse social and hormonal deficits through modulation of the hypothalamic-pituitary-adrenal (HPA) axis and anti-inflammatory action, the high-dose *Zingiber officinale* group significantly restored oxytocin levels. The ineffectiveness of the low-dose *Zingiber officinale*, however, supports earlier research that emphasizes the necessity of ideal dosage to have therapeutic effects (Rahmani *et al*., 2021).

Inflammation dramatically reduced corticotropin (adrenocorticotropic hormone, or ACTH), which is essential for the stress response and the regulation of adrenal hormones. However, both the regular medication and high-dose ginger greatly increased corticotropin levels. This supports the findings of Al-Rasheed *et al*. (2020), who found that *Zingiber officinale* reduces the dysregulation of the HPA axis during inflammation and stress. Partial efficacy at lower concentrations was highlighted by the low-dose extract's partial improvement in corticotropin levels.

In rats with inflammation, norepinephrine, a crucial neurotransmitter linked to alertness and stress reactivity, also dramatically dropped. Norepinephrine levels returned to normal after high-dose *Zingiber officinale* extract treatment, which is similar to findings by Singh and Chaudhary (2021), who found that *Zingiber officinale* supplementation restored noradrenergic activity in neuroinflammatory models. The minimal impact of the low-dose treatment, on the other hand, provides more evidence that *Zingiber officinale*'s neuroprotective effects are dose-dependent.

All of the current research points to *Zingiber officinale*'s neurohormonal regulation and anti-inflammatory functions, which are supported by an increasing amount of research. According to El-Sayed *et al*. (2023), the extract seems to work by increasing the synthesis and release of neurotransmitters and inhibiting pro-inflammatory cytokines. However, because lower dosages did not significantly affect the majority of neurohormonal markers, the therapeutic benefit is very dose dependent.

Conclusion

This study demonstrated that ethanol extract of *Zingiber officinale* significantly restored neurohormone levels, dopamine, oxytocin, corticotropin, and norepinephrine in male Wistar albino rats induced with inflammation. The effect was comparable to that of a standard anti-inflammatory drug and was most effective at high doses, confirming the dose-dependent neuroprotective and anti-inflammatory potential of *Zingiber officinale*.

Recommendations

We recommend that high-dose *Zingiber officinale* extract should be further explored as a potential alternative or complementary therapy for managing neuroinflammatory disorders. Further studies should investigate the long-term effects and safety profile of *Zingiber officinale* on neurohormonal systems.

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