

# Effect of *Zingiber Officinale* Ethanol Extract on Reproductive Hormones of Male Albino Wistar Rats Induced with Inflammation

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**Abstract:** Reproductive function is known to be disrupted by inflammation, and *Zingiber officinale*, has long been used to treat inflammatory diseases. In this work, male albino Wistar rats with albumin-induced inflammation were used to assess the modulatory effects of *Zingiber officinale* ethanol extract on reproductive hormones, such as testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH). A control group, an inflammation-induced group, and groups treated with different dosages of *Zingiber officinale* ethanol extract comprised the five (5) groups of thirty (30) male albino Wistar rats. Albumin was used to cause inflammation, and the extract was taken orally for three weeks. Standard laboratory methods, such as enzyme-linked immunosorbent assay (ELISA) and radioimmunoassay (RIA), were used to evaluate hormone levels. The results showed that *Zingiber officinale* ethanol extract significantly modulated reproductive hormone levels in the treated groups compared to the control groups. Specifically, testosterone levels increased ( $14.39 \pm 0.0003$ ), while FSH and LH levels showed dose-dependent responses. The findings suggest that *Zingiber officinale* ethanol extract may have a regulatory effect on reproductive hormone production in male albino Wistar rats with albumin-induced inflammation, potentially due to its anti-inflammatory and antioxidant properties. These results have potential implications for the treatment of reproductive disorders associated with inflammation and warrant further investigation into the mechanisms underlying the modulatory effects of *Zingiber officinale* on reproductive hormones.

**Keywords:** *Zingiber officinale*, testosterone, FSH, and LH.

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## Introduction

### Background to the Study

A precise balance of endocrine signals regulates male reproductive health, ensuring that the testes operate properly and that fertility is maintained. The hypothalamic-pituitary-gonadal (HPG) axis, which controls the release of important reproductive hormones like testosterone, luteinizing hormone (LH), and follicle stimulating hormone (FSH), is at the center of this system (Simoni *et al.*, 1999). The primary male sex hormone, testosterone, which is responsible for spermatogenesis, desire, and secondary sexual traits, is produced by the Leydig cells in the testes in response to LH stimulation. In contrast, FSH supports sperm maturation and production via acting on the Sertoli cells.

Although inflammation is a natural physiological reaction to stress, injury, or illness, severe or persistent inflammation can have systemic effects, including disruption of the endocrine system. By inhibiting the release of GnRH, LH, and FSH, pro-inflammatory cytokines such interleukin-1B (IL-1B), tumor necrosis factor-alpha (TNF-a), and interleukin-6 (IL-6) are known to disrupt the HPG axis (Turner *et al.*, 2012). Furthermore, Leydig cell dysfunction and decreased testosterone synthesis have been linked to inflammation-induced oxidative stress, which impairs spermatogenesis and results in infertility (Aitken and Roman, 2008).

To mimic acute inflammatory reactions in animals, experimental models like albumin-induced inflammation are frequently employed. When administered subcutaneously, egg albumin elicits an immunological response that mimics the physiological manifestations of systemic inflammation, including edema, neutrophil infiltration, and increased cytokine levels (Okoli *et al.*, 2008). Investigating how anti-inflammatory and antioxidant treatments affect several physiological systems, including the reproductive axis, is made easier with the help of this model.

Plant-based substances that may have therapeutic utility in reducing oxidative stress and inflammation have drawn interest in recent years. The perennial herbaceous plant *Zingiber officinale*, commonly known as ginger, is used extensively in traditional medicine to treat conditions ranging from inflammation and infertility to gastrointestinal issues (Ali *et al.*, 2008). Bioactive substances such zingerone, parasols, shogaols, and gingerols are found in the rhizome of ginger and have been shown to have androgenic, anti-inflammatory, and antioxidant qualities (Mashhadi *et al.*, 2013).

By raising testosterone levels, enhancing sperm quality, and shielding testicular tissue from oxidative damage, ginger improves male reproductive function, according to several animal studies (Khaki *et al.*, 2009). Its potential to correct reproductive

hormone imbalances during inflammation-induced reproductive stress has not, however, been thoroughly studied.

This study intends to investigate the effects of *Zingiber officinale* ethanol extract on reproductive hormones – specifically LH, FSH, and testosterone – in male albino Wistar rats exposed to albumin-induced inflammation, given the increasing prevalence of male infertility and the need for safer, natural alternatives to conventional therapy.

### Justification of the Study

Alternative and complementary medicine is becoming more popular as a means of treating inflammatory diseases and infertility. With few adverse effects, ginger has promising medicinal promise as a natural antioxidant and anti-inflammatory. It has been demonstrated that the bioactive substances that give ginger its pharmacological properties, such as gingerol and shogaols, are more concentrated in the ethanol extract of ginger (Mashhadi *et al.*, 2013).

Ginger's benefits in diabetic and chemically-induced infertility models have been the subject of numerous studies; however, little is known about how well it works in inflammatory settings that closely resemble actual clinical situations. This study's use of albumin-induced inflammation offers a pertinent and viable model for examining the ways in which inflammation influences reproductive hormones and the ways in which ginger can mitigate these effects.

The findings of this study may lead to the creation of plant-based treatments for the treatment of inflammatory male reproductive dysfunction, particularly in low-resource environments with limited access to traditional medicine.

### Aim

The aim of the study was to determine the effect of ethanol extract of *Zingiber officinale* on reproductive hormone levels (LH, FSH, and testosterone) in male albino Wistar rats with albumin-induced inflammation.

### Specific Objective

The specific objectives of the study were to:

- Determine the effect of *Zingiber officinale* on Luteinizing hormone (LH) in male wistar albino rats induced with egg albumin.
- Determine the effect of *Zingiber officinale* on Follicle stimulating hormone (FSH) in male wistar albino wistar rats induced with egg albumin.
- Determine the effect of *Zingiber officinale* on Testosterone in male wistar albino rats induced with egg albumin.

## Materials and Methods

### Materials

The materials used during the study includes thirty (30) male albino Wistar rats, Animal feed, Ibuprofen (NSAIDs), Distilled water, Tween, Ethanolic extract of ginger, Hand gloves, Capillary tubes, Wire cage, Albumin, Syringes, Soxhlet apparatus, Water bowl, Dissecting kit, Mechanical grinder, Analytic oven, Specimen collection bottle, Cotton wool, Water bath, Normal saline.

### Procurement and Preparation of *Zingiber officinale* Extract

Fresh *Zingiber officinale* rhizome were procured from a local market Mkponkiti at Institute of Management and Technology road, Enugu State. The ginger rhizome were washed and oven dried using an analytic oven at 105 degree Celsius. The dried ginger was pulverized using a mechanical grinder into a coarse form, which after was soaked in 70% ethanol using Soxhlet apparatus for 6hour.

After 6hours, the mixture was sieved and filtered using whatmann no.1 filter paper into clean glass beaker. The filtrate was concentrated using a laboratory water bath to evaporate the ethanol, the water bath was set at 52 degree Celsius and which after the filtrate was transferred to a plastic container and labelled. The processed Ginger was dissolved in Tween to produce the suitable solution.

### Experimental Animals

The experiment was laid on complete randomized experimental design (CRED). Thirty (30) male albino Wistar rats weighing between 150–200g were procured from University of Nigeria Enugu Campus (UNEC) to be used for the experiment. They were fed with animal feed and water for a period of three (3) weeks to enable acclimatization with the new environment before oral administration began.

### Animal Housing

A four partitioned transparent cage was used to house the thirty male albino Wistar rats. The top of the cage was covered with wire gauze for proper ventilation.

### Animals Feeding and Acclimatization

The rats were acclimatized for three weeks after they were divided into groups. The animals were all fed with animal feed. The feed was provided in stainless plates. Favourable humidity, good ventilation and proper temperature conditions were ensured.

### Animal Grouping

The rats were divided into five groups (A, B, C, D, E,) of six rats each. They were measured with weighing scale and was recorded according to the group.

Group A (Blank control group)

Group B (standard control group)

Group C (negative control group)

Group D (low dose control group)

Group E (high dose control group)

The extract was given for three weeks through oral administration.

- Group A (Blank control): received no administration but received feed, water and libitum.
- Group B (standard control group): Induced with egg albumin and were administered standard control drug (ibuprofen).
- Group C (negative control group): Induced with concentrated egg albumin without treatment.
- Group D (low dose control group): Induced with egg albumin + treated with 50mg/kg body weight of *Zingiber officinale*.
- Group E (high dose control group): Induced with egg albumin and were administered high dose of *Zingiber officinale* extract 200mg/kg.

## Induction of Inflammation

On the last day of experiment, the rats in group three received 0.5ml of freshly prepared egg albumin solution injected in the hind paw region. The inflammation took peak within 3–6 hours. The paw thickness was monitored using a vernier caliper to confirm the presence and resolution of inflammation.

## Sacrifice and Sample Collection

Following induction of inflammation, the animal was anesthetized using chloroform. The blood was obtained from the eyes (Ocular Puncture) using capillary tubes and transferred to a plastic plain bottle for hormonal analysis.

## Hormonal Analysis

### Luteinizing hormone (LH)

Luteinizing hormone levels are determined using a sandwich enzyme linked immunosorbent assay (ELISA) technique (Elabscience, 2023) where the microplate wells are precoated with monoclonal antibodies specific to rat luteinizing hormone. Luteinizing hormone in the serum binds to these antibodies, a biotin-labeled secondary antibody and HRP-conjugate are added. Upon substrate addition (TMB), a color change occurs proportional to the luteinizing hormone (LH) concentration, absorbance is measured at 450 nm.

### Follicle Stimulating Hormone (FSH)

Same sandwich enzyme linked immunosorbent assay (ELISA) format as luteinizing hormone, but with antibodies specific to rat follicle stimulating hormone. Serum follicle stimulating hormone binds to coated anti-follicle stimulating hormone antibody. HRP-linked detection antibody binds the hormone, substrate reacts to produce a color signal proportional to follicle stimulating hormone concentration.

## Testosterone

Most testosterone assays use competitive enzyme linked immunosorbent assay (ELISA). Testosterone in serum competes with enzyme-labeled testosterone for antibody binding sites, higher testosterone in the sample results in less color development (inverse relationship). Absorbance at 450 nm is inversely proportional to testosterone concentration. (Stanczyk *et al.*, 2003).

## 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  $\pm$ SEM. One-way Analysis of Variance (1-way ANOVA) was used to determine the effects of *Zingiber officinale* extract on the parameters studied and the difference between were separated using Duncan's multiple range test. Test for significance was considered at 0.05 probability level.

## Result

### Luteinizing Hormone Concentration

Table 1 shows the effect of *Zingiber officinale* ethanol extract on luteinizing hormone (LH) in male albino wistar rats. The blank control group (A) recorded the highest LH level (22.17  $\pm$ 0.0049 Miu/ml), which was statistically similar to the high dose treated group (E) (20.93  $\pm$ 0.0011 Miu/ml;  $p>0.05$ ). The standard control group (C) (17.39  $\pm$ 0.0072 Miu/ml) was significantly lower than both A and E ( $p<0.05$ ). On the other hand, the negative control group (B) and the low dose treated group (D) exhibited the lowest luteinizing hormone (LH) levels (12.88  $\pm$ 0.0025 Miu/ml and 13.72 $\pm$ 0.0014 Miu/ml, respectively), both of which were significantly reduced compared to the blank control and high dose treated groups ( $p<0.05$ ).

**Table 1:** Effect of *Zingiber officinale* ethanol extract on luteinizing hormone (Miu/ml) of male albino wistar rats induced with inflammation

GROUP	LH (Miu/ml)
A (Blank Control)	22.17 $\pm$ 0.0049 <sup>a</sup>
B (Negative Control)	12.88 $\pm$ 0.0025 <sup>b</sup>
C (Standard Control)	17.39 $\pm$ 0.0072 <sup>c</sup>
D (Low-Dose Treated Group)	13.72 $\pm$ 0.0014 <sup>b</sup>
E (High- Dose Treated Group)	20.93 $\pm$ 0.0011 <sup>a</sup>

The values are expressed as (mean  $\pm$  SEM)

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

### Follicle Stimulating Hormone Concentration

Table 1 shows the effects of *Zingiber officinale* ethanol extract on the serum levels of follicle-stimulating hormone (FSH) in male Wistar rats induced with albumin-induced inflammation. The blank control group (Group A), which was neither inflamed nor treated, had the highest FSH concentration (9.21  $\pm$  0.0011 Miu/ml). The negative control group (Group B), which received albumin to induce inflammation without any treatment, showed a significant decrease in FSH levels (5.57  $\pm$  0.0036 Miu/ml;  $p<0.05$ ). Similarly, the low-dose treated group

(Group D) exhibited a comparable reduction in FSH levels (5.32  $\pm$  0.0004 Miu/ml), indicating minimal recovery at low extract concentration. However, treatment with a high dose of *Zingiber officinale* (Group E) resulted in a marked increase in FSH levels (7.20  $\pm$  0.0003 Miu/ml), which was significantly higher than both the negative control and low-dose groups ( $p<0.05$ ), though still lower than the blank control. The standard control group (Group C), treated with a reference drug, showed a moderate FSH level (7.88  $\pm$  0.0018 Miu/ml), close to that of the high-dose treated group.

**Table 2:** Effect of *Zingiber officinale* ethanol extract on Follicle Stimulating Hormone (Miu/ml) of male albino wistar rats induced with inflammation

GROUPS	FSH (Miu/ml)
A (Blank Control)	9.21 ± 0.0011 <sup>a</sup>
B (Negative Control)	5.57 ± 0.0036 <sup>c</sup>
C (Standard control)	7.88 ± 0.0018 <sup>c</sup>
D (Low-Dose Treated Group)	5.32 ± 0.0004 <sup>b</sup>
E (High-Dose Treated Group)	7.20 ± 0.0003 <sup>c</sup>

The values are expressed as (mean ± SEM)

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

**Testosterone**

Table 3 illustrate the effect of *Zingiber officinale* ethanol extract on serum testosterone levels in male albino Wistar rats using inflammation. The blank control group (A) exhibited the highest testosterone concentration (15.32±0.0075 ng/ml), which was statistically comparable to the high dose treated group (E) (14.39 ± 0.0003 ng/ml;  $p > 0.05$ ). The standard control group (C)

(13.51 ±0.0021 ng/ml) also showed no significant difference from groups A and E.

In contrast, the negative control group (B) displayed a significant reduction in testosterone levels (9.71 ±0.0004 ng/ ml), while the lowest level was observed in the low dose treated group (D) (7.11 ±0.0058 ng/ml). Both B and D were significantly different from the blank control and high dose treated groups ( $p < 0.05$ )

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

GROUPS	TESTO (ng/ml)
A (Blank Control)	15.32 ± 0.0075 <sup>a</sup>
B (Negative Control)	9.71 ± 0.0004 <sup>b</sup>
C (Standard Control)	13.51 ± 0.0021 <sup>a</sup>
D (Low-Dose Treated Group)	7.11 ± 0.0058 <sup>c</sup>
E (High-Dose Treated Group)	14.39 ± 0.0003 <sup>a</sup>

The values are expressed as (mean ± SEM)

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

**Discussion**

According to the current study, inflammation reduced the concentration of luteinizing hormone. This was consistent with Rivier and Rivest's work. (1990), who discovered that inflammation reduced the quantity of luteinizing hormone in a dose-dependent manner. Because of oxidative stress, which modifies the hypothalamus pituitary gonadal (HPG) axis and androgen production, inflammatory conditions are known to disturb endocrine balance and compromise testicular function.

On the other hand, the LH level increased after *Zingiber officinale* ethanol extract was administered. According to Ghasemzadeh *et al.* (2016), ginger phytochemicals, including gingerols, shogaols, and parasols, have anti-inflammatory and anti-androgenic properties that can restore steroidogenesis and the function of leydig cells.

By promoting Sertoli cells, controlling spermatogenesis, and preserving testicular function, follicle stimulating hormone (FSH) is essential for male reproduction. The suppression of gonadotropin release by systemic inflammation is confirmed by a significant decrease in FSH. This observation aligns with the findings of Rivest and Rivier. (1993), who pointed out that pro-inflammatory cytokines such interleukin-1B (IL-1B), which are

known to interfere with hypothalamic GnRH release and affect pituitary function, are to blame for this suppression. Despite the presence of inflammation, follicle stimulating hormone (FSH) secretion was restored in a dose-dependent manner upon administration of *Zingiber officinale* ethanol extract.

In males, testosterone is essential for spermatogenesis, desire, and the maintenance of secondary sexual traits. Systemic inflammation inhibits testicular steroidogenesis, which is reflected in a decrease in testosterone concentration (Rivier and Rivest, 1993). Moreover, oxidative stress brought on by inflammation can harm testicular tissues, further impairing the generation of androgens.

The administration of ethanol extract from *Zingiber officinale* resulted in a dose-dependent restoration of testosterone levels. This suggests that larger concentrations of ginger extract have strong stimulatory and protective effects on the production of testicular steroids. Ginger extract dramatically raised rats' blood testosterone and sperm quality, according to research by Khaki *et al.* (2009). Similarly, ginger may increase fertility via modifying gonadotropins and testicular function, according to Ogbuewu *et al.* (2013).

## Conclusion

The findings of this study inferred that ethanol extract of *Zingiber officinale* has protective and restorative effects on reproductive hormone levels in male albino Wistar rats subjected to albumin-induced inflammation. The extract significantly mitigated the inflammation-induced reduction in testosterone, luteinizing hormone (LH), and follicle stimulating hormone (FSH) levels, suggesting a regulatory influence on the hypothalamic pituitary gonadal (HPG) axis.

## Recommendation

Based on the findings of this study, we therefore recommend that there is a need for molecular studies to elucidate the precise mechanisms through which *Zingiber officinale* modulates reproductive hormones, particularly the interaction with GnRH, LH/FSH receptors, and testicular steroidogenesis pathways. Complementary histological analysis of testicular tissue and evaluation of sperm parameters (motility, morphology, and count) should be included in subsequent studies to corroborate the hormonal findings with functional reproductive outcomes.

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