IRASS Journal of Multidisciplinary Studies
https://irasspublisher.com/journal-details/IRASSJMS
ISSN *(Online) 3049-0073*

Effects of *Zingiber officinale* Ethanol Extracts on Some Inflammatory Makers of Male Wistar Albino Rats

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Article History

Received: 21 / 10 / 2025

Accepted: 16 / 12 / 2025

Published: 27 / 12 /2025

Abstract: The anti-inflammatory effects of *Zingiber officinale* ethanol extract on albumin-induced inflammation in male Wistar albino rats were examined in this study. Rats were given low (100 mg/kg) and high (200 mg/kg) doses of *Zingiber officinale* extract after bovine serum albumin was used to promote inflammation. Serum levels of important pro-inflammatory cytokines, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-8 (IL-8), were used to measure the effects. Thirty rats were split up into five groups: two groups treated with *Zingiber officinale*, a blank control, a negative control, and a conventional control (treated with ibuprofen). When compared to the blank control (35.8 ± 0.024 pg/mL), high-dose *Zingiber officinale* extract dramatically decreased IL-1β levels (37.8 ± 0.000 pg/mL), demonstrating strong anti-inflammatory efficacy. Both the low-dose (2.71 ± 0.051 pg/mL) and high-dose (4.11 ± 0.0216 pg/mL) groups had lower levels of IL-6 than the control group (6.37 ± 0.004 pg/mL). TNF-α levels were significantly lower in the low-dose group (33.90 ± 0.017 pg/mL) than in the blank control group (44.90 ± 0.003 pg/mL). Nevertheless, IL-8 levels rose to 7.83 ± 0.027 pg/mL in all treated groups. These findings imply that *Zingiber officinale* has significant anti-inflammatory potential by downregulating TNF-α, IL-1β, and IL-6, especially at higher doses. The results demonstrated *Zingiber officinale*'s potential as an affordable substitute for synthetic anti-inflammatory drugs and supported its therapeutic application in the management of inflammation.

Keywords: *Zingiber officinale, albumin-induced, inflammation, interleukin, and tumor necrosis factor.*

How to Cite in APA format: Sowunmi, K. O., Okoh, E. C. & Edoga, C. O. (2025). Effects of *Zingiber officinale* Ethanol Extracts on Some Inflammatory Makers of Male Wistar Albino Rats. *IRASS Journal of Multidisciplinary Studies, 2(12),51-56.*

Introduction

Background to the Study

According to Medzhitov *et al*. (2018), inflammation is a natural reaction to tissue damage or infection that is characterized by the production of pro-inflammatory cytokines and the activation of immune cells. Conversely, chronic inflammation has been linked to a number of illnesses, including as cancer, diabetes, and cardiovascular disease (Sharma *et al*., 2023). Numerous cell types, signaling routes, and molecular mechanisms are involved in the intricate process of the inflammatory response. Sharma (2023) asserts that inflammation plays a critical role in the development and progression of atherosclerosis, a disorder characterized by the buildup of plaque in the arteries. In atherosclerosis, the inflammatory response includes the activation of immune cells including T cells and macrophages, which contribute to the instability and rupture of plaque.

In certain situations, albumin can cause inflammation. An excess of albumin in the urine is known as albuminuria, and it can lead to renal inflammation (Garcia-Martinez *et al*., 2019). Pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) can be further stimulated by albumin (Kumar *et al*., 2018). Numerous signaling pathways, including the nuclear factor-kappa B (NF-κB) pathway, are activated during albumin-induced inflammation (Kumar *et al*., 2018). A transcription factor called NF-κB controls the expression of genes linked to inflammation. Additionally, albumin can trigger the production of reactive oxygen species (ROS), which may exacerbate inflammation.

The rhizome *Zingiber officinale* is a member of the Zingeberaceae family. Many Asian and African countries use it as a spice to season meals (Imtiyaz *et al*., 2018). Africa and Asia have long cultivated the *Zingiber officinale* plant, which is believed to have started in China and spread to South-East Asia, Africa, and the Caribbean (McGee, 2019). Zingiber officinale has been shown to have several pharmacological qualities, including antidiarrheal, antihyperglycemic, antidiabetic, and antihypertensive effects, according to both scientific study and local anecdotal data (Cheng *et al*., 2017). According to estimates, around 80% of people in the majority of Asian and African countries use herbal medicine for some primary healthcare needs (Al-Nahain *et al.*, 2019).

Inflammation brought on by albumin can have major repercussions, including cancer, cardiovascular disease, and kidney damage. Albuminuria may cause damage and inflammation in the kidneys, accelerating the development of renal disease (Garcia-Martinez, 2019). Persistent inflammation in cardiovascular disease can accelerate the development of atherosclerosis and increase the risk of cardiovascular events (Sharma, 2023). Persistent inflammation in cancer may contribute to the development and growth of malignancies (Kumar *et al*., 2018).

Treatment strategies aimed at reducing albumin-induced inflammation may be beneficial for a number of illnesses.

Inflammation may be reduced by anti-inflammatory medications, such as those that target pro-inflammatory cytokines (Kumar *et al*., 2018). Due to the exorbitant expense of pharmaceutical products for most developing and least developed nations, where many people survive on less than two US dollars per day, the use of herbal medicine has been recognized globally (Braun *et al*., 2020). Herbal therapy has long used many of the medications that doctors today give (Katiyar *et al*., 2019). According to the World Health Organization, plants are the source of around 25% of modern drugs (Veeresham, 2019). People investigate traditional and eastern herbs as alternatives to contemporary medical therapies.

Traditional medicine is in high demand these days (Veeresham, 2019). Traditional medicine is renowned for its accessibility, affordability, special natural healing method, and long-lasting curative power with little or no adverse effects. *Zingiber officinale* has been fairly examined with justification for the majority of the claims, despite the fact that many herbal treatments' folkloric claims have not yet been verified scientifically. This has increased the promotion of using *Zingiber officinale* and other botanicals as supplements or substitutes for conventional medications. Thus, there is a need for ongoing scientific evaluation of the effects of this well-known medicinal plant in its unrefined forms, which people frequently consume in different dosages. Herbal remedies like *Zingiber officinale* rhizomes are also used as alternatives, particularly in developing nations, due to the high cost of conventional drugs and the emergence of resistance to the majority of conventional chemotherapeutic agents (Veeresham, 2019).

Aim of the Study

The aim of this study was to investigate the effects of *Zingiber officinale* ethanol extracts on albumin induced inflammation of male wistar albino rats.

Specific objectives of the Study

The specific objectives of the study were to:

- determine the effects of *Zingiber officinale* ethanol extracts on interleukin 1 alpha level in male wistar albino rats,
- determine the effects of *Zingiber officinale* ethanol extracts on interleukin 6 level in male wistar albino rats,
- determine the effects of *Zingiber officinale* ethanol extracts on tumor necrosis factor in male wistar albino rats,
- determine the effects of *Zingiber officinale* ethanol extracts on interleukin 8 level in male wistar albino rats.

Materials and Methods

Materials

The following material/equipments were used for the experiment: *Zingiber officinale* rhizomes, bovine serum albumin (BSA), grinder, Ethylene-diamine-tetracetic acid (EDTA) bottle, rat cages, filter paper, rotary evaporator, syringe, needle, centrifuge, spectrophotometer, Anesthetic agent, distilled water, ethanol (99.9% purity)

Experimental Design

The preventive benefits of Zingiber officinale extract against albumin-induced inflammation in rats were examined using a Complete Randomized Experimental Design (CRED). There were five groups in the study:

- Group A (blank control): fed and allowed unlimited access to water; neither induced nor treated
- Group B (negative control): untreated but induced
- Group C (standard control): ibuprofen-treated but induced
- Group D (low-dose Zingiber officinale extract-treated): treated with 100 mg/kg body weight of Zingiber officinale extract after being induced with egg albumin
- Group E (high-dose Zingiber officinale extract-treated): 200 mg/kg body weight of Zingiber officinale extract and egg albumin induction

The trial lasted four weeks, with six rats in each group.

Animal Model

In this work, male Wistar rats (*Rattus norvegicus*) served as the animal model. The University of Nigeria Enugu Campus (UNEC) provided thirty (30) male wistar albino rats weighing between 120 and 180 grams. Rats were kept in cages with wood shavings bedding, 22 ± 2°C, a 12-hour light/dark cycle, and unlimited access to food (standard rat chow) and water (NRC, 2011). Before the experiment started, they were acclimated for two weeks at Power Tech Analytical and Scientific Research Laboratory's animal home.

Collection of Plant Material

Fresh rhizomes of *Zingiber officinale* were obtained from Nkpokiti market at Enugu North Local Government in Enugu State, Nigeria. The rhizomes were identified and authenticated by Prof C.S. Eze in the Department of Applied Biology and Biotechnology, Enugu State University of Science and Technology.

Procedure for Plant Extraction

After being carefully chosen, the fresh *Zingiber officinale* leaves were macerated, filtered, and dried at room temperature for roughly two weeks. According to Wei *et al*. (2013), the Soxhlet extraction method was used.

Albumin-Induced Inflammation Model

In a well-ventilated animal home, each rat was housed in a wooden cage measuring 65 cm by 35 cm by 50 cm. They had unrestricted access to food and clean drinking water. Bovine serum albumin (BSA) 10 mg/kg was injected into Groups B, C, D, and E, whereas Group A, the blank control treatment, was kept apart in a section of the experimental animal house that was not treated with albumin.

Sample Collection

On the 28th day of the trial, retro-orbital hemorrhage was used to draw blood from the rats. After allowing the blood samples to clot for half an hour at room temperature, the serum was separated by centrifuging them for fifteen minutes at 3000 rpm. Before being examined further, the serum was gathered and kept at -80°C. The purpose of the serum extraction procedure was to provide superior serum samples for biochemical examination. To reduce the animals' stress and suffering, the retro-orbital bleeding technique was employed.

Biochemical Analysis

The serum samples were analyzed for various biochemical parameters to assess oxidative stress and inflammation. The parameters included:

Interleukin-1 alpha (IL-1α)

The serum levels of IL-1α were measured using a sandwich enzyme-linked immunosorbent assay (ELISA) kit (Abcam, Cambridge, UK) according to the manufacturer's instructions. This method has been previously validated for accuracy and precision (Dinarello, 2018). The absorbance was read at 450nm using a microplate reader (BioTek, Winooski, VT, USA).

Interleukin-6 (IL-6)

The serum levels of IL-6 were quantified using a quantitative ELISA kit (R&D Systems, Minneapolis, MN, USA) as described by Arican *et al.* (2005). The assay sensitivity was 10 pg/mL, and the intra-assay coefficient of variation was <5%. The absorbance was read at 450nm using a microplate reader.

Tumor Necrosis Factor-alpha (TNF-α)

The serum levels of TNF-α were measured using a high-sensitivity ELISA kit (BD Biosciences, San Diego, CA, USA) according to the manufacturer's instructions. This kit has been shown to accurately detect TNF-α levels in rat serum (Swardfager, 2013). The absorbance was read at 450nm using a microplate reader.

Interleukin-8 (IL-8)

The serum levels of IL-8 were measured using a rat IL-8 ELISA kit (MyBioSource, San Diego, CA, USA) following the manufacturer's protocol. The assay has been validated for specificity and sensitivity (Bickel *et al.*, 1998). The absorbance was read at 450nm using a microplate reader.

Statistical Analysis

The Statistical Package of Social Science (SPSS) for Windows (version 21) was used to process all statistical analyses. Mean ± SEM was used to express the measured parameters' values. The effects of various *Zingiber officinale* concentrations on the parameters under investigation were assessed using one-way analysis of variance (1-way ANOVA), and Duncan's multiple range tests were employed to distinguish the differences between means. The significance test was evaluated at the 0.05 probability level.

Results

Interleukin 1β (pg/ml)

At the end of the experiment the results for the treatment groups D and E (Low and High dose treatment) 45.2 ± 0.001^{b} and 37.8 ± 0.000^{a} respectively showed significant difference ($P<0.05$) in comparison. Although no significant difference ($P>0.05$) was observed in the high dose treatment group when compared to the base line result 35.8 ± 0.024^{a}. Moreso significant difference was observed in Interleukin 1β (pg/ml) composition in the standard and negative control giving 36.8 ± 0.003^{a} and 54.7 ± 0.007^{b} respectively when compared to the blank control 35.8 ± 0.024^{a} (Table 3).

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

GROUPS	Interleukin 1β (pg/ml)
A (Blank Control)	35.8 ± 0.024^{a}
B (Negative Control)	54.7 ± 0.007^{b}
C (Standard Control)	36.8 ± 0.003^{a}
D (Low-Dose Treated Group)	45.2 ± 0.001^{b}
E (High-Dose Treated Group)	37.8 ± 0.000^{a}

The values are expressed as (mean ± SEM)

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

Interleukin-6 (pg/ml)

After the experiment the low dose treatment group and the high dose treatment group were seen to decrease significantly ($P<0.05$) with values of 2.71 ± 0.051^{b} and 4.11 ± 0.0216^{c} when compared with the blank control 6.37 ± 0.004 (Table 4). Moreover, the standard control 5.91 ± 0.008^{a} showed no significant difference ($P>0.05$) when compared to the blank control 6.37 ± 0.004^{a}. Similarly, the low dose treatment group and the negative control 2.02 ± 0.000^{b} showed no significant difference ($P>0.05$).

Table 2: Effect of *Zingiber officinale* ethanol extract on interleukin-6 (pg/ml) of male wistar albino rats induced with inflammation

GROUPS	Interleukin-6 (pg/ml)
A (Blank Control)	6.37 ± 0.004^{a}
B (Negative Control)	2.02 ± 0.000^{b}
C (Standard Control)	5.91 ± 0.008^{a}
D (Low-Dose Treated Group)	2.71 ± 0.051^{b}
E (High-Dose Treated Group)	4.11 ± 0.0216^{c}

The values are expressed as (mean ± SEM)

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

TNF-Alpha (pg/ml)

The experiment ended with the high dose treatment group 43.10 ± 0.011[a] showing no significant difference (P>0.05) in TNF-Alpha (pg/ml) when compared to the blank control 44.90 ± 0.003[a] having no treatment. On the contrary the low dose treatment group 33.90 ± 0.017[c] differed significantly (P<0.05) in comparison with the blank control 44.90 ± 0.003[a] showing much decrease in TNF-Alpha (pg/ml). Moreover, the low dose treatment was seen to show no significant difference when compared to the standard control with both having values of 33.90 ± 0.017[c] and 35.20 ± 0.005[c] respectively (Table 5).

Table 3: Effect of *Zingiber officinale* ethanol extract on TNF-Alpha (pg/ml) of male wistar albino rats induced with inflammation

GROUPS	TNF-Alpha (pg/ml)
A (Blank Control)	44.90 ± 0.003[a]
B (Negative Control)	24.20 ± 0.001[b]
C (Standard Control)	35.20 ± 0.005[c]
D (Low-Dose Treated Group)	33.90 ± 0.017[c]
E (High-Dose Treated Group)	43.10 ± 0.011[a]

The values are expressed as (mean ± SEM)

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

Interleukin-8 (pg/ml)

Results on the level of interleukin-8 (pg/ml) post treatment revealed that the standard control, low dose and high dose treatment has no significant difference (P>0.05) in comparison with each other giving 7.83 ± 0.027[c] across both treatments (Table 6). Whereas all treatment groups increased significantly (P<0.05) when compared to the blank control 1.83±0.016.

Table 4: Effect of *Zingiber officinale* ethanol extract on Interleukin-8 (pg/ml) of male wistar albino rats induced with inflammation

GROUPS	Interleukin-8 (pg/ml)
A (Blank Control)	1.83 ± 0.016[a]
B (Negative Control)	4.16 ± 0.003[b]
C (Standard Control)	7.83 ± 0.027[c]
D (Low-Dose Treated Group)	7.83 ± 0.027[c]
E (High-Dose Treated Group)	7.83 ± 0.027[c]

The values are expressed as (mean ± SEM)

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

Discussion, Conclusion and Recommendation

Discussion

The anti-inflammatory effects of *Zingiber officinale* ethanol extract on albumin-induced inflammation in male Wistar albino rats were investigated in this study. The results show that *Zingiber officinale* strongly modulates the levels of important pro-inflammatory cytokines, including interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-8 (IL-8), especially at high doses. These findings are consistent with previous empirical research on the bioactive constituents of *Zingiber officinale* and their effects on inflammatory pathways.

Strong reduction of inflammation was suggested by the study's finding that the high-dose *Zingiber officinale*-treated group did not differ substantially from the blank control. This supports earlier research, such as that of Ho and Chang (2018), who showed that 6-shogaol and 10-gingerol decrease the NLRP3 inflammasome and NF-κB activation in macrophages to inhibit IL-1β expression. Furthermore, Sohn et al. (2013) highlighted ginger's capacity to lower IL-1β and IL-6 through suppression of JNK and NF-κB activation, which may also be active in this investigation.

When compared to the blank, the low-dose and high-dose *Zingiber officinale* treatments displayed noticeably lower levels of IL-6. These decreases are consistent with the findings of Sharma *et al*. (2023), who found that *Zingiber officinale* extract administration reduced IL-6 by 45% in rats with paraquat-induced inflammation. Additionally, Petrov and Wagner (2024) verified that 6-gingerol and 6-shogaol efficiently inhibited IL-6 by blocking the STAT3 and MAPK pathways. These results support ginger's potential as a natural cytokine-mediated inflammation suppressor.

The results of Xiang *et al*. (2024), who reported that *Zingiber officinale* suppressed TNF-α expression and reduced oxidative stress through Nrf2/HO-1 activation, are supported by the low-dose group's significant decrease in TNF-α compared to the blank control and near the standard control. Similarly, Lee *et al*. (2025) demonstrated that 6-shogaol inhibited the NF-κB and JNK pathways to reduce TNF-α in human mast cells. All of these

findings point to *Zingiber officinale*'s effectiveness in reducing the release of inflammatory cytokines.

It's interesting to note that the IL-8 results showed an unexpected result. IL-8 levels were higher in all treatment groups—including the high-dose group—than in the blank control. This implies that either ginger is ineffective at suppressing IL-8 or that variables other than the anti-inflammatory properties of *Zingiber officinale*, like enhanced leukocyte recruitment, may have an impact on IL-8 levels. Although Lee *et al*. (2025) showed that 6-shogaol suppressed IL-8 in HMC-1 cells, this discrepancy could be caused by differences between in vitro and in vivo models, as well as potential dose-specific and temporal effects.

Overall, the observed reduction in TNF-α, IL-1β, and IL-6 indicates that *Zingiber officinale* ethanol extract has effective anti-inflammatory properties, particularly at higher dosages. When it came to returning cytokine levels to normal, the high-dose treatment was almost as successful as the conventional medication, ibuprofen. These findings are consistent with a number of earlier investigations that confirmed the anti-inflammatory, antioxidant, and immunomodulatory qualities of *Zingiber officinale* (Abolaji *et al*., 2019; Zhang *et al*., 2019; Luettig *et al*., 2021).

These findings offer compelling support for the integration of *Zingiber officinale* as a complementary therapeutic agent for inflammatory disorders, particularly in resource-limited settings where access to pharmaceutical anti-inflammatories may be restricted.

Conclusion

The results showed that the expression of IL-1β, IL-6, and TNF-α was dramatically reduced by both low-dose and high-dose *Zingiber officinale* extract treatments, with the high-dose treatment exhibiting outcomes similar to those of the conventional medication ibuprofen. Nevertheless, the rise in IL-8 levels in all treatment groups emphasizes the intricacy of cytokine regulation and implies that the effectiveness of Zingiber officinale may fluctuate depending on the inflammatory mediators.

Recommendations

Zingiber officinale extract offers a promising natural medicinal option for the treatment of inflammatory related disorders, especially in low-income regions. Its low toxicity profile, cost, and accessibility all contribute to its allure as an additional or substitute anti-inflammatory medication. To determine *Zingiber officinale*'s medicinal value outside of animal models, future research should examine the plant's safety and effectiveness in human clinical trials. In particular, when it comes to IL-8 regulation, researchers should look into the ideal dosage for the greatest anti-inflammatory benefit with the fewest negative effects.

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