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Evaluation of Chemokine Levels on Albumin-Induced Inflammation treated with Ethanol Extract of Zingiber officinale

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Abstract-

This study evaluated the effect of ethanol extract of Zingiber officinale on chemokine levels, CCL2 – Monolyte Chemoattractant protein 1 (MCP-1), CCL5 - Rantes, and IL-8 (Inter leukin-8) in male Wistar albino rats with albumin-induced inflammation. Inflammation was experimentally induced by intraperitoneal injection of 0.5 ml of egg albumin solution in the hind paw region, and the animals were divided into five groups: blank control, negative control, standard control (treated with an anti-inflammatory drug), and two treatment groups administered low and high doses of Z. officinale extract. Chemokine levels were assessed to determine the extract's anti-inflammatory efficacy. The negative control group exhibited significantly elevated levels of CCL2 (227 ± 0.001 µg/L), CCL5 (143.60 ± 0.001 µg/L), and IL-8 (5.16 ± 0.003 pg/ml) compared to the blank control ($p < 0.05$), confirming inflammation. Treatment with Z. officinale extract resulted in a dose-dependent reduction in chemokine levels. The high-dose group notably decreased CCL2 to 128 ± 0.000 µg/L, CCL5 to 118.12 ± 0.003 µg/L, and IL-8 to 3.47 ± 0.041 pg/ml, with values statistically comparable to the blank and standard control groups ($p > 0.05$). In contrast, the low-dose group showed partial effectiveness, especially for IL-8 and CCL5. These findings indicated that Zingiber officinale possesses significant anti-inflammatory properties, effectively modulating chemokine expression and reducing inflammatory responses. The study supports its potential as a natural alternative for managing inflammation-related disorders.

Keywords: *Zingiber officinale, chemokine, Interleukins, Inflammation and Rantes*

Introduction-

Inflammation is a fundamental biological response to harmful stimuli, such as pathogens, damaged cells, or irritants. While acute inflammation is protective, chronic inflammation can lead to various pathological conditions, including cardiovascular diseases, diabetes, and renal disorders (Medzhitov, 2021). Chemokines is a subset of cytokines that play a pivotal role in the inflammatory process by directing the migration of immune cells to sites of inflammation. Among these, CCL2 (Monocyte Chemoattractant Protein-1 or MCP-1), CCL5 (Regulated upon Activation, Normal T Cell Expressed and Secreted or RANTES), and

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CXCL8 (Interleukin-8 or IL-8) are key mediators that recruit monocytes, T cells, and neutrophils, respectively, contributing to the amplification of inflammatory responses (Zlotnik and Yoshie, 2020). Zingiber officinale is a widely used spice and medicinal plant, has been recognized for its anti-inflammatory properties. The bioactive compounds in ginger, such as 6-gingerol and 6-shogaol, have demonstrated the ability to modulate inflammatory pathways. These compounds inhibit the activation of nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways, leading to reduced expression of pro-inflammatory cytokines and chemokines (Pazmandi et al., 2024). Recent studies have highlighted the potential of ginger extracts in attenuating inflammatory responses in various cell types, including dendritic cells and macrophages, by suppressing the production of chemokines like CCL2, CCL5, and CXCL8 (Zhou et al., 2022). Given the role of albumin in inducing chemokine-mediated inflammation and the anti-inflammatory potential of ginger, it is pertinent to explore the modulatory effects of ginger extract on chemokine expression in albumin-induced inflammation.

Justification

Chronic inflammation is a central feature in the progression of various diseases, including renal disorders characterized by albuminuria. The over expression of chemokines such as CCL2, CCL5, and CXCL8 in response to albumin exacerbates inflammatory cell infiltration, leading to tissue damage and fibrosis. While ginger's anti-inflammatory properties are documented, its specific effects on chemokine expression in the context of albumin-induced inflammation remain inadequately characterized. There is a need to investigate whether ginger extract can modulate the expression of these chemokines and thereby attenuate the inflammatory response induced by albumin. Chronic inflammation is a central feature in the progression of various diseases, including renal disorders characterized by albuminuria. Albuminuria, the presence of albumin in the urine, is not only a marker of kidney damage but also contributes to disease progression by inducing inflammatory responses in renal tubular cells. Excessive albumin in the renal tubules stimulates the production of pro-inflammatory chemokines such as CCL2 (MCP-1), CCL5 (RANTES), and CXCL8 (IL-8), leading to the recruitment of monocytes, T cells, and neutrophils, respectively. This chemokine-mediated infiltration exacerbates tubulointerstitial inflammation and fibrosis, ultimately impairing renal function (Tang et al., 2020). Understanding the interplay between albumin-induced chemokine expression and the modulatory effects of ginger extract holds therapeutic significance. If ginger extract can attenuate the expression of key chemokines, it may offer a complementary approach to managing inflammation in albuminuria-associated conditions. Recent studies have highlighted the potential of ginger extracts in attenuating inflammatory responses in various cell types, including dendritic cells and macrophages, by suppressing the production of

chemokines like CCL2, CCL5, and CXCL8 (Zhou et al., 2022). Moreover, ginger's bioactive compounds have been shown to inhibit the activation of NF-κB and MAPK pathways, which are critical in the transcription of pro-inflammatory genes. By targeting these pathways, ginger extract may reduce the expression of chemokines and cytokines involved in albumin-induced inflammation. This study aims to fill the knowledge gap by elucidating the effects of ginger extract on CCL2, CCL5, and CXCL8 levels in albumin-induced inflammatory settings. Current therapeutic approaches for managing albumin-induced inflammation are limited and often associated with adverse effects. Non-steroidal anti-inflammatory drugs (NSAIDs), commonly used to alleviate inflammation, can have nephrotoxic effects, further complicating renal conditions. Therefore, there is a pressing need to explore alternative therapies that can effectively modulate chemokine expression and mitigate inflammation without detrimental side effects.

Zingiber officinale, a widely used spice and medicinal plant, has been recognized for its anti-inflammatory properties. Bioactive compounds in ginger, including 6-gingerol and 6-shogaol, have demonstrated the ability to modulate inflammatory pathways. These compounds inhibit the activation of nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways, leading to reduced expression of pro-inflammatory cytokines and chemokines (Pazmandi et al., 2024). However, the specific effects of ginger extract on chemokine expression in the context of albumin-induced inflammation remain inadequately characterized.

Aim of the Study

The primary aim of this study was to evaluate chemokines level on albumin induced inflammation treated with ethanol extract of Zingiber officinale.

Objectives of the Study

The specific objectives of this study were to:

1. investigate CCL2 (Monocyte Chemoattractant Protein-1) level on albumin induced inflammation treated with ethanol extract of Zingiber officinale,

2. evaluate CCL5(Rantes) level on albumin induced inflammation treated with ethanol extract of Zingiber officinale, and

3. evaluate CXCL8 (Interleukin-8) level on albumin induced inflammation treated with ethanol extract of Zingiber officinale.

Materials and Method

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. 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 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 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 study adopted a Complete Randomized Experiential Design (CRED), and the animals were sampled and grouped into 5 comprising six rats:

1. Group A (Blank Control): The rats were neither induced nor treated, but received feed and, water ad libitum
2. Group B (Negative Control): The rats were induced with concentrated egg albumin, but received no treatment.
3. Group C (Standard Control): The rats were induced with egg albumin + treated with standard inflammatory drug (ibuprofen).
4. Group D (Low-Dose Zingiber officinale Extract): The rats were induced with egg albumin + treated with 50 mg/kg body weight of Zingiber officinale extract.
5. Group E (High Dose Zingiber officinale Extract): The rats were 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 Analyse

CCL2 (MCP-1)

The most commonly used method for detecting CCL2 is sandwich ELISA, which provides high specificity and sensitivity. For simultaneous measurement of multiple cytokines, Luminex-based assays are also utilized (Yuan et al., 2022). In research involving neuroinflammation, for example, brain homogenates or cerebrospinal fluid samples are used for MCP-1 quantification.

CCL5 (RANTES)

CCL5, also known as Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted (RANTES), is a chemokine that attracts T cells, eosinophils, and basophils. It

is involved in various autoimmune and inflammatory diseases and plays a dual role in tumorigenesis—either promoting or inhibiting tumor progression depending on the context (Zhao et al., 2020). Detection of CCL5 is commonly done using ELISA and multiplex immunoassays. In studies involving cardiovascular disease, CCL5 levels are often measured in plasma to evaluate inflammatory burden (Patel et al., 2022).

CXCL8 (IL-8)

CXCL8, or interleukin-8 (IL-8), is a pro-inflammatory chemokine primarily involved in neutrophil recruitment. It is secreted by several cell types, including macrophages, epithelial cells, and endothelial cells, in response to inflammatory stimuli. CXCL8 is critically involved in acute inflammation and is also implicated in cancer, particularly in angiogenesis and metastasis (Tang et al., 2022). Quantification of IL-8 is commonly performed using ELISA or cytometric bead array (CBA). Real-time PCR is also used for analyzing IL-8 mRNA expression in cell or tissue samples (Li 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

Chemokine Level

Groups A and C showed no significant difference ($p > 0.05$) in their CCL2 concentrations, with values of 153±0.001 µg/L and 148±0.001 µg/L, respectively. This suggests that the standard treatment was able to maintain CCL2 levels close to normal physiological conditions. The results of CCL5 and IL-8 followed a similar pattern. In contrast, Group B had a significantly elevated monokine concentration ($p < 0.05$), indicating a strong inflammatory response due to the induction of pathology and absence of treatment. Groups D and E, which were treated with low and high doses of the experimental agent, respectively, exhibited significantly reduced monokines levels compared to the negative control ($p < 0.05$). This reduction suggests that both doses of the treatment were effective in lowering inflammation, with the low dose appearing slightly more potent than the high dose. The data indicate that the treatment groups had a marked anti-inflammatory effect, as shown by the significant reduction in CCL2 levels compared to the untreated group even due the value did not return to the baseline. The high-dose treatment IN CCL5 and IL-8 demonstrated a significant anti-inflammatory effect comparable to the standard therapy and control conditions ($p < 0.05$). Table 1: Effect of Zingiber officinale ethanol extract on chemokines level (µg/L) of male wistar albino rats induced with inflammation

Groups	CCL2(µg/L)	CCL5 (µg/L)	IL-8 (pg/ml)
A	153 ± 0.001a	95.21 ± 0.001a	2.83 ± 0.016a
B	227 ± 0.001b	143.60 ± 0.001b	5.16 ± 0.003b
C	148 ± 0.001a	118.04 ± 0.001a	3.83 ± 0.027a
D	111 ± 0.004c	132.45 ± 0.002c	5.77 ± 0.063b
E	128 ± 0.000c	118.12 ± 0.003a	3.47 ± 0.041a

The values are expressed as (mean ± SEM). Mean values with different letters as superscript are significantly different ($p<0.05$).

Discussion

The present study investigated the modulatory effect of the ethanol extract of Zingiber officinale on chemokine levels, specifically CCL2, CCL5, and IL-8, in albumin-induced inflammation in male Wistar rats. The chemokines measured are key mediators in the inflammatory cascade and are often elevated in response to tissue injury or immune activation. The results revealed that administration of Z. officinale extract, particularly at high doses, significantly attenuated the elevated levels of these chemokines, indicating its anti-inflammatory potential. In the case of CCL2, a chemokine primarily responsible for monocyte recruitment (Yao et al., 2020), the negative control group exhibited a marked increase compared to the blank and standard controls ($p < 0.05$), signifying an acute inflammatory response due to albumin induction. However, treatment with Z. officinale extract led to a significant reduction in CCL2 levels, especially in the low-dose group ($p < 0.05$), aligning with findings by Ahmad et al. (2021) who reported that Z. officinale extracts suppressed MCP-1 (CCL2) in inflamed tissues. For CCL5, which plays a role in recruiting T cells and promoting chronic inflammation (Gorabi et al., 2021), the negative control group showed a significant rise in levels, while high-dose Z. officinale treatment brought CCL5 back to near-normal levels ($p > 0.05$) when compared to blank and standard controls. This outcome is consistent with previous studies highlighting Z. officinale ability to inhibit pro-inflammatory cytokines and chemokines in various models of inflammation (Li et al., 2022). Interestingly, the low-dose group still maintained significantly elevated CCL5 levels ($p < 0.05$), suggesting that dosage is a critical factor in Z. officinale therapeutic efficacy. Regarding IL-8, a chemokine central to neutrophil chemotaxis and acute inflammation (Zhao et al., 2019), both the negative and low-dose groups exhibited significantly elevated levels, whereas the high-dose group normalized IL-8 expression to levels statistically similar to those of the standard and blank controls ($p > 0.05$). This supports the observations of Abolaji et al. (2023), who demonstrated Z. officinale capacity to suppress IL-8 and other inflammatory markers in induced inflammation models.

Conclusion

The study demonstrated that the ethanol extract of Zingiber officinale effectively reduced elevated chemokine levels (CCL2, CCL5, and IL-8) associated with albumin-induced inflammation in Wistar rats. The high-dose treatment, in particular, showed results comparable to standard anti-inflammatory

treatment, highlighting Z. officinale potential as a natural anti-inflammatory agent.

Recommendations

We recommend that further studies should focus on identifying the optimal dose of Zingiber officinale extract for maximal anti-inflammatory effects without toxicity. Clinical evaluation of ginger extract in patients with inflammatory disorders is recommended to validate its therapeutic applicability.

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