

# INTERLEUKIN 5 AND TUMOR NECROSIS FACTOR ALPHA- LOWERING EFFECT OF BALINESE TRADITIONAL LACTATING RECIPE CONTAINING SAUROPODS ANDROGYNOUS (L) MERR ON PRIMIPAROUS COLOSTRUM PROFILE: RANDOMIZED CONTROL TRIAL

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## Abstract

This study investigates the effects of *Sauropus androgynus* (L.) Merr, a traditional Balinese lactating recipe, on lowering Interleukin-5 (IL-5) and Tumor Necrosis Factor Alpha (TNF- $\alpha$ ) levels in colostrum of primiparous mothers. The research employed a randomized control trial involving 90 participants, divided into a treatment group that consumed the recipe for seven days and a control group. Colostrum samples were collected on the first and seventh days postpartum, and immune mediators were measured using ELISA. The results indicated that the administration of *Sauropus androgynus* (L.) Merr significantly reduced TNF- $\alpha$  levels and increased IL-5 levels in the treatment group, compared to the control group. These findings suggest that *Sauropus androgynus* (L.) Merr has potential anti-inflammatory effects in postpartum mothers, improving colostrum quality, which may contribute to better neonatal immunity. The study highlights the potential of traditional medicinal plants in maternal health and their role in immune modulation during lactation. Further research is recommended to explore the long-term benefits and mechanisms underlying these effects.

**Keywords:** *Sauropus Androgynus*, TNF- $\alpha$ , IL-5, Colostrum, Primiparous Mothers, Traditional Medicine, Anti-Inflammatory, Lactation.

## INTRODUCTION

The mammary gland undergoes extensive remodeling and differentiates as an immunologically active organ during lactation.<sup>1</sup> The mammary gland's immune capacity, as mentioned in Bu et al. (2017), is significant, with a larger innate immune system capacity compared to the liver.<sup>2</sup> Cansever et al. (2023) identifies a unique macrophage population, liMacs, which emerges during lactation and contributes to mammary gland remodeling. These macrophages are distinct from pregestational

subsets and are involved in immune defense and tissue homeostasis.<sup>3</sup> Additionally, Yong et al. (2023) highlights the presence of T-bet+ lymphoid cells in breast milk, which accumulate in the mammary gland during pregnancy and lactation, suggesting a role in mammary epithelium remodeling and the transfer of immunity to neonate, with breast milk composition adapting to the infant's immunological needs.<sup>4,5</sup>

Sauropods androgynous Merr, commonly known as *katuk* or star gooseberry, is a tropical plant with a long history of traditional medicinal uses. However, it is known that Sauropods androgynous (L.) Merr, are traditionally consumed in Indonesia and are used in various dishes according their nutritional benefits to improve weight loss and elevate breastmilk production.<sup>6</sup> One of its notable properties is its potential anti-inflammatory effect, which has garnered significant interest in the scientific community. Numerous studies have highlighted the phytochemical richness of Sauropods androgynous, which includes a diverse array of bioactive compounds such as flavonoids, polyphenols, and saponins.<sup>7</sup> These compounds have been associated with a range of pharmacological activities, including antioxidant, anti-inflammatory, and anti-obesity properties. Additionally, the prior study highlight the anti-inflammatory effects of Sauropods androgynous (L.) Merr and its potential use in modern medical applications, such as anti-inflammatory patches and as a potential complementary medicine for COVID-19.<sup>8,9</sup> Anastasia et al. (2018) demonstrates that a patch containing katuk leaf extract at a dose of 400 mg/kg body weight (BW) exhibits significant anti-inflammatory activity in rats, with an inhibition range of 66.67-100%.<sup>8</sup> Additionally, Istiqomah et al. (2022) reports that katuk leaf ethanol extract at a dose of 150 mg/kgBW possesses anti-inflammatory properties, as evidenced by its activity in white male Wistar rats induced with a high-fat and carbohydrate diet.<sup>10</sup> Interestingly, while these studies confirm the anti-inflammatory potential of katuk, they also highlight the importance of the method of administration and dosage.

Tumor necrosis factor-alpha (TNF- $\alpha$ ) is a cytokine involved in systemic inflammation, synthesized by various cell types upon stimulation by endotoxins, inflammatory mediators, or other cytokines.<sup>11,12</sup> Its synthesis and molecular mechanisms are complex, involving the binding to specific cell surface receptors, activation of signal transduction pathways, and the induction of gene expression in response to the cytokine.<sup>13,14</sup> Meanwhile, IL-5 expression in the mammary gland is typically associated with immune responses during lactation or inflammation.<sup>15</sup> The synthesis of IL-5 in mammary tissue can be induced by various stimuli such as infections, allergens, or tissue damage. Immune cells within the mammary gland, including T lymphocytes, macrophages, and eosinophils, are potential sources of IL-5.<sup>16,17</sup> The anti-inflammatory properties of Sauropods androgynous have been attributed to its ability to modulate the immune system. Numerous phytochemicals derived from plant sources, including polyphenols, flavonoids, and polysaccharides, have demonstrated immunomodulatory and anti-inflammatory activities.<sup>18</sup> If Sauropods androgynous exhibits anti-inflammatory effects systemically, it could potentially reduce inflammation in mammary tissue and alter the cytokine profile of colostrum. This might involve decreasing pro-inflammatory cytokines (such as TNF-alpha, IL-6) and increasing anti-inflammatory cytokines (such as IL-10). This project aims to investigate the current understanding of the anti-inflammatory properties of Sauropods androgynous and its impact on the colostrum profile, a critical component of early-life best nutrition and neonatal immune inducer.

## RESEARCH METHODS

### Design

This experimental study was conducted by enrolled 60 eligible primiparous mother pairs recruited from the postnatal ward. The inclusion criteria: at term infant, vaginal delivery without complication. Mothers with severe disease and postpartum complication, also unable to provide colostrum or decline to consumed traditional recipes containing Sauropods androgynous (L) Mer regularly were excluded from this study. Eligible participant was subsequently randomized to divide group as (i) treated Sauropods androgynous (L) Merr group for seven days and (ii) non-treated group as control. Informed consent was obtained from each participant, before colostrum collection and questionnaire. This investigation and sample collections has been approved by the ethics committee of Warmadewa University, Bali Indonesia (approval number 11/UNWAR/FKIK/EC-KEPK/I/2023).

### Colostrum and Data Collection

The clinical data were acquired from participant's medical record. Sample collection was conducted in the Premagana hospital by a highly professional midwifery research team. Each participant received breast massage procedure during colostrum sample collection at first day and seven<sup>th</sup> day after delivery. All collected samples were centrifuged for 20 min at 1000xg in 2-8<sup>o</sup>C and supernatant was taken and put into an Eppendorf tube and stored at -80<sup>o</sup>C until analysis in the physiological laboratory of Warmadewa University.

### Intervention

Traditional recipes containing Sauropus androgynus (L) Merr by senior professional midwifery with good knowledge regarding postpartum culture in Gianyar Regency, Bali as a research area. The traditional recipe is made from 300 grams of Sauropus Androgynus (L) Merr leaves and shallot liver which are washed clean and then boiled with 300 ml of boiled water until the water becomes 150-200 ml and is ready to be given to each participant. Traditional recipes are made with the same composition by one person to maintain the quality of ingredients and minimize recipe variations. The midwife delivered the Sauropus Androgynus (L) Merr decoction and ensured that it was consumed by the participants for 7 days.

### Immune Mediator Measurement

We used enzyme-linked immunosorbent assay (ELISA) to measure immune mediators in colostrum samples, for IL-5 and TNF- $\alpha$  measurement. Human IL-5 (Assay Ginie, Dublin, Ireland) and TNF- $\alpha$  (Assay Ginie, Dublin, Ireland) ELISA kit was used to quantitatively the colostrum IL-5 and IgA levels. Samples were run according to the manufacturer's protocol, using a 6-point standard curve. Samples were diluted to 1:2 for the IL-5 quantifications and no dilution was used for the IgA analysis. Briefly, this kit had highly specific antibodies pre-coated onto a 96-well microtiter plate. Samples were incubated with the specific biotin-conjugated primary antibody and Avidin conjugated Horseradish Peroxidase (HRP). After the plate was washed, the TMB (3,3',5,5'-Tetramethylbenzidine) solution was added, and terminated and the signal intensity was measured on a plate reader at 450nm.

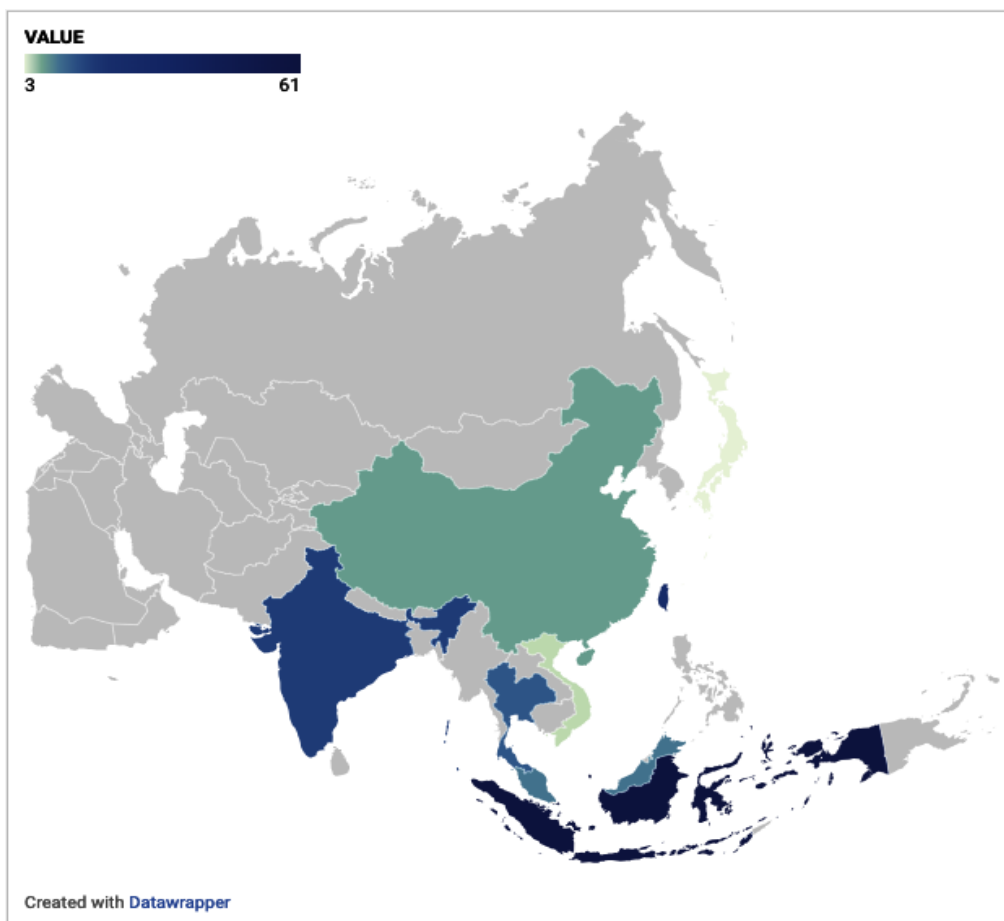
Meanwhile for TNF- $\alpha$ , standards or samples were added to the ELISA plate wells and combined with the pre-coated antibodies. The biotinylated detection antibody is specific for Secretory Immunoglobulin A and Avidin- Horseradish Peroxidase (HRP) conjugate was added to each plate well and incubated. The enzyme-substrate reaction is terminated by the addition of a stop solution. The optical density (OD) is measured spectrophotometrically at a wavelength of 450 nm  $\pm$  2 nm.

### Statistical Analysis

The differences between the concentrations of IL-5 and IgA in the treatment and control group were calculated by Wilcoxon and Mann-whitney test using STATA version 14. Normality and homogeneity tests were performed. The results were considered significant when the p-values were reported at a level less than 0.05.

## RESULT AND DISCUSSION

### Result



**Figure 1: Asian Map *Sauropus Androgynus (L) Merr***

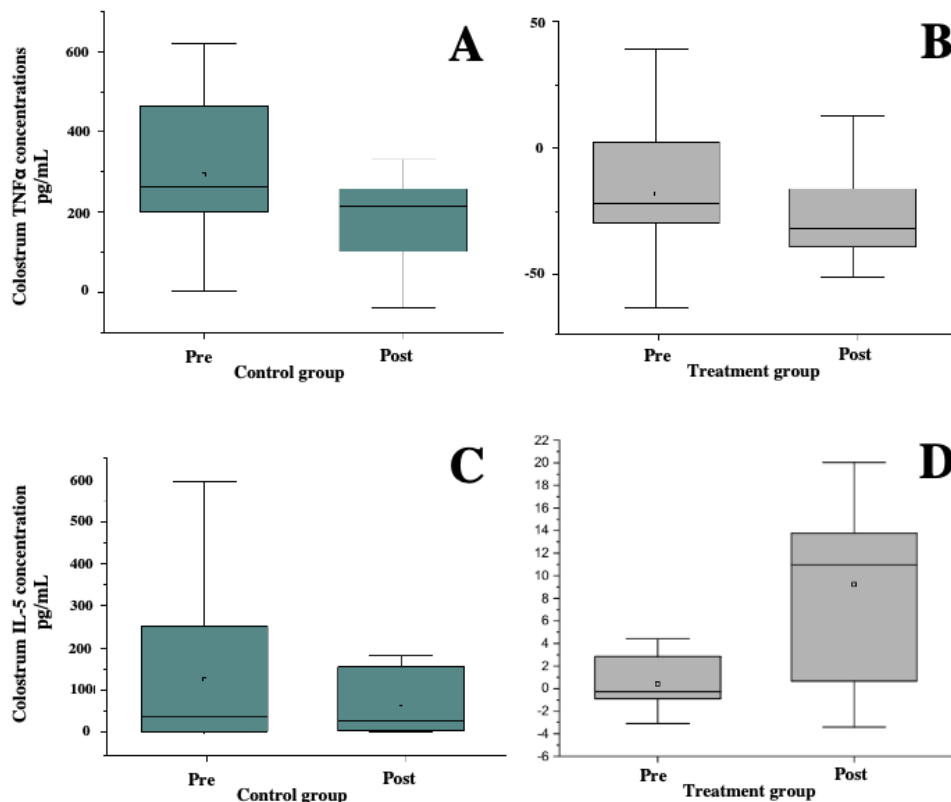
The results of the publication search via <https://www.scopus.com/sources.uri> show that Indonesia is a country with the most studies of *Sauropods androgynous (L) Merr*. In the Asian region with 61 papers. And Bali Indonesia is one of the populations with consumption of *Sauropods androgynous (L) Merr* leaves as a postpartum culture to increase breast milk production. The results of this study were conducted on 90 primiparous mothers with the profiles presented in table 1.

**Table 1: Basic Characteristics of Participants**

Indicator	Group		p-value
	Control Group (n=45)	Treatment group (n=45)	
Age (year), mean±SD	24,9±0,6	24,1±0,4	0,059
Education, n(%)			
Senior high School	16(53,3)	23(76,7)	0,574
Diploma	9(30)	3(10)	
Bachelor	5(16,7)	4(13,3)	
Occupation, n(%)			
Housewife	8(26,7)	9(30)	0,936
Teacher	1(3,3)	-	
Private	16(53,3)	16(53,3)	
Self-employed	5(16,7)	5(16,7)	
Weight (kg), mean±SD	65,4±0,9	66,3±1,2	0,547
Height (cm), mean±SD	160,2±0,8	163,1±1,3	0,1
Weight gain during pregnancy, mean±SD	12,7±2,6	14±2,1	0,003*
infant birth weight, mean±SD	3240±243,7	3290,7±244,7	0,382

**Description:** p= homogeneity of variance test; \*p<0.05

Based on Figure 2, it is known that administration of Sauropod androgynous (L) Merr for 7 days in primiparous mothers has the effect of reducing the inflammatory cytokine TNF $\alpha$  in colostrum, but the decrease in TNF $\alpha$  levels was also confirmed in the control group without treatment. In contrast, the levels of IL-5 in colostrum showed a significant increase in the group of mothers treated with Sauropod androgynous (L) Merr for 7 days, while the control group showed an insignificant decrease.



**Figure 2: Representation of Colostrum Inflammatory Cytokines in Primiparous Mothers**

## DISCUSSION

Low-grade inflammation in the mammary gland can influence physiological changes during lactation, may have been beneficial in the development of lactation.<sup>19,20</sup> Tumor necrosis factor-alpha (TNF alpha) has identified as a significant factor in the development of the mammary gland. TNF alpha and its receptors are expressed in mammary epithelial cells (MECs), with TNF alpha mRNA and the transmembrane form of TNF protein levels increasing during pregnancy, suggesting a role in mammary gland growth and development.<sup>21,22</sup> TNF-alpha and IL-5 produced locally in the mammary gland or systemically can potentially affect the levels and types of immunoglobulins transferred to the newborn through colostrum and milk. TNF-alpha is primarily known for its pro-inflammatory actions but also has regulatory effects on B cells, which are responsible for producing immunoglobulins (antibodies).<sup>23</sup>

TNF-alpha can enhance B cell proliferation and differentiation, thereby promoting immunoglobulin production. However, chronic elevation of TNF-alpha levels may lead to dysregulation of B cell function and contribute to autoimmune diseases where autoantibodies are produced.

Meanwhile, IL-5 is crucial for the growth, activation, and differentiation of eosinophils, but it also plays a role in B cell activation and antibody production. IL-5 promotes class switching to IgA, the predominant immunoglobulin in mucosal secretions including colostrum and milk. It can enhance the production of IgA antibodies, which are important for mucosal immunity, including in the mammary gland during lactation<sup>24,25</sup>. Research findings demonstrate that Sauropods androgynous (L) Merr treatment significantly lowering TNF-alpha but not for IL-5 colostrum concentration. Understanding how Sauropus androgynus affects cytokine profiles in colostrum is essential for exploring its potential benefits in maternal and infant health.

The exact mechanisms through which Sauropus androgynus influences cytokine profiles in colostrum are not fully elucidated. Sauropus androgynus (L.) Merr contains a variety of natural compounds with diverse biological activities. Studies have identified the presence of carotenoids, vitamin E, vitamin C, protein, sterol compounds (Subekti et al., 2008), papaverine alkaloids, fats, vitamins, minerals, saponins flavonoids, tannins (Lidyawati et al., 2021), and phenolic compounds (Lidyawati et al., 2021).<sup>26,27</sup> Additionally, GC-MS analysis of katuk leaves extract revealed fatty acids, tocopherol, alkaloids, parabens, and glycerol as major components.<sup>28</sup>

Interestingly, flavonoids also exhibit antioxidant activities, which contribute to their anti-inflammatory effects by attenuating oxidative stress and tissue damage.<sup>29</sup> Moreover, specific flavonoids like hesperidin have been shown to modulate signaling pathways, particularly the nuclear factor-kappa B (NF-kappa B) pathway, which is central to the inflammatory process.<sup>30</sup> Berry-derived polyphenols, a subgroup of flavonoids, have been reported to modulate gut microbiota, further influencing inflammation and related diseases.<sup>31</sup>

In summary, flavonoids inhibit inflammation through multiple pathways, including the inhibition of enzyme activity, modulation of proinflammatory gene expression, antioxidant effects, and interaction with gut microbiota. These diverse mechanisms highlight the therapeutic potential of flavonoids in managing inflammatory conditions. However, further research is needed to fully elucidate the specific molecular targets and to confirm these effects in clinical settings.<sup>28,29,31</sup>

Papaverine exhibits anti-inflammatory properties through various mechanisms. According to the studies, papaverine suppresses the HMGB1-RAGE inflammatory signaling pathway and inhibits cancer cell proliferation.<sup>32</sup> Additionally, it has been shown to significantly reduce infarct volume in mice with cerebral ischemia, with pathway enrichment analysis indicating that papaverine targets multiple immunomodulatory processes related to neuro-vascular inflammation.<sup>33</sup>

Interestingly, while papaverine's relaxant effect on smooth muscle is not related to its inhibitory action on mitochondrial respiration, its anti-inflammatory action seems to be associated with the suppression of specific signaling pathways and the modulation of immune responses. This suggests that the therapeutic effects of papaverine extend beyond its vasodilatory properties. In summary, papaverine's anti-inflammatory action is multifaceted, involving the suppression of the HMGB1-RAGE axis and the targeting of immunomodulatory pathways in cerebral ischemia.<sup>32,33</sup> These findings support the potential of papaverine as an anti-inflammatory agent, although the exact mechanisms by which it exerts these effects warrant further investigation.

However, its anti-inflammatory effects could involve inhibition of NF- $\kappa$ B signaling, which regulates the expression of pro-inflammatory cytokines including TNF- $\alpha$ , or modulation of JAK-STAT pathways that are crucial for cytokine signaling. JAK-STAT signaling plays a crucial role in mediating both pro-inflammatory and anti-inflammatory responses in various tissues and cell types throughout the body, including crucial for IL-5 receptor activation and downstream effects, potentially affecting immune cell recruitment and activation within the mammary tissue. Therefore, further research is needed to elucidate the specific mechanisms through which TNF- $\alpha$  and IL-5 influence immunoglobulin synthesis in different physiological contexts.

## CONCLUSION

Administration of Sauropod androgynous (L) Merr for 7 days in primiparous mothers has the effect of reducing the inflammatory cytokine TNF $\alpha$  in colostrum and elevate the IL-5 colostrum concentration.

### Author Contributions

Conceptualization: KAK, WN, SW, NN and SA. Methodology: SW, NN and SA Software: WN and KAK. Formal analysis: WN. Investigation: KAK. Resources: KAK. Data curation: WN. Writing—original draft preparation: WN. Writing—review and editing: WN. Visualization: WN. Supervision: KAK, SW, NN and SA. Project administration: KAK. All authors have read and agreed to the published version of the manuscript." Authorship must be limited to those who have contributed substantially to the work reported.

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**Institutional Review Board Statement:** The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of The Health Research Ethics Commission (HREC) of the Faculty of Medicine and Health Science of Universitas Warmadewa with Ethical Clearance Certificate Number: 293/Unwar/FKIK/ECKEPK/I/2023, ob 28 January 2023.

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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