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# Development of Herbal Booster Product "A5I (Katuk (S. androgynus (L.) Merr.), Moringa (*M. oleifera*), Fenugreek (*T. foenum-graecum* L.), Torch Ginger (*Etlingera elatior*), Cinnamon (*Cinnamomum burmannii*))" as a Lactagogue Based on Clinical Observational Study

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**Abstrak:** Pemberian A51 eksklusif yang tidak adekuat merupakan faktor risiko stunting yang masih menjadi masalah kesehatan utama di Indonesia. Produk teh poliherbal A5I yang mengandung katuk (*Sauropus androgynus*), kelor (Moringa oleifera), klabet (*Trigonella foenum-graecum*), kecombrang (*Etlingera elatior*), dan kayu manis (*Cinnamomum burmannii*) dikembangkan sebagai laktagogum alami. Penelitian ini bertujuan mengevaluasi keamanan produk tersebut melalui analisis histopatologi organ vital dan jaringan mamae pada mencit betina setelah pemberian berulang. Uji toksisitas subkronis selama 28 hari dilakukan pada mencit betina yang dibagi menjadi kelompok kontrol dan kelompok perlakuan. Organ jantung, paru-paru, ginjal, dan mamae dipanen untuk pemeriksaan histopatologi menggunakan pewarnaan hematoksilin-eosin dengan sistem skoring terstandar. Histopatologi miokardium menunjukkan perdarahan minimal tanpa nekrosis. Paru-paru mengalami destruksi septum alveolar dan infiltrasi sel radang ringan tanpa edema paru, mengindikasikan barier alveolokapiler masih berfungsi baik. Ginjal hanya menunjukkan degenerasi tubular ringan tanpa nekrosis maupun infiltrasi radang. Jaringan mamae memperlihatkan dilatasi duktus luas dan distribusi sekret intraluminal yang melimpah, konsisten dengan aktivitas laktasi yang aktif. Pemberian teh poliherbal A5I secara subkronis tidak menimbulkan kerusakan histopatologi bermakna pada organ vital, serta gambaran mamae mendukung potensi efek laktagogumnya. Temuan ini memberikan bukti keamanan awal produk poliherbal sebagai ASI booster, meskipun diperlukan penelitian lanjutan dengan jumlah sampel yang lebih besar untuk mengonfirmasi keamanan dan efektivitasnya secara klinis.

**Kata kunci**: ASI Booster; Hispatologi; Kelenjar mamae; Laktagogum; Mencit; Poliherbal



**Abstract:** Inadequate exclusive A5I provision is a risk factor for stunting, which remains a major health problem in Indonesia. A polyherbal tea product A5I containing katuk (*Sauropus androgynus*), moringa (*Moringa oleifera*), klabet (*Trigonella foenum-graecum*), torch

ginger (*Etlingera elatior*), and cinnamon (*Cinnamomum burmannii*) was developed as a natural lactagogum. This study aimed to evaluate the safety of the product through histopathological analysis of vital organs and mammary tissue in female mice after repeated administration. A 28-day subchronic toxicity test was conducted on female mice divided into control and treatment groups. The heart, lungs, kidneys, and mammary organs were harvested for histopathological examination using hematoxylin-eosin staining with a standardized scoring system. Myocardial histopathology showed minimal bleeding without necrosis. The lungs exhibited alveolar septal destruction and mild inflammatory cell infiltration without pulmonary edema, indicating a functional alveocapillary barrier. The kidneys exhibited only mild tubular degeneration without necrosis or inflammatory infiltration. Mammary tissue exhibited extensive ductal dilation and abundant intraluminal secretion distribution, consistent with active lactation. Subchronic administration of A5I polyherbal tea did not cause significant histopathological damage to vital organs, and the mammary findings support its potential lactagogic effect. These findings provide preliminary evidence of the safety of this polyherbal product as a breast milk booster, although further studies with larger sample sizes are needed to confirm its safety and clinical effectiveness.

**Keyword:** Breastfeeding Booster; Histopathology; Lactagogue; Mammary Gland; Mice; Polyherbal

## 1. Introduction

Breast milk (ASI) is the optimal source of nutrition for infants, providing essential nutrients and bioactive compounds that support growth and immune development [1]. Despite its importance, insufficient milk production remains a common challenge among breastfeeding mothers, influenced by physiological, psychological, and environmental factors. To address this issue, lactagogues—substances that promote milk secretion—have been widely used [2]. In Indonesia, the use of plant-based lactagogues is deeply rooted in traditional practices, with katuk (*Sauropus androgynus*) and moringa (*Moringa oleifera*) being the most frequently consumed by breastfeeding mothers [3]. However, most of these practices remain empirical and lack comprehensive scientific validation, particularly regarding safety and efficacy in combined formulations.

Natural lactagogues are known to contain various bioactive compounds, including phytoestrogens such as flavonoids, alkaloids, tannins, saponins, and other polyphenols, which may stimulate milk

production through hormonal and metabolic pathways [4]. Several plants have been individually studied for their lactagogue potential, including katuk leaves [5], moringa leaves [6], fenugreek (*Trigonella foenum-graecum*) seeds [7], torch ginger (*Etlingera elatior*) flowers [8], and cinnamon (*Cinnamomum* spp.) [9]. These plants share similar classes of secondary metabolites that may act synergistically when combined. Polyherbal formulations are increasingly recognized for their potential to enhance therapeutic efficacy through multi-target mechanisms [10][11]. Nevertheless, scientific evidence regarding the safety profile of such combinations, particularly under repeated exposure conditions, remains limited.

Although previous studies have demonstrated the lactagogue potential of individual plants, research on polyherbal combinations and their subchronic toxicity profiles is still scarce, especially with respect to histopathological changes in vital organs. Most existing studies focus on short-term efficacy or single-herb interventions, without adequately addressing the potential cumulative or synergistic toxic effects of combined phytochemicals. Furthermore, limited studies have systematically evaluated organ-specific histopathological alterations following repeated administration of polyherbal lactagogues, leaving a critical gap in safety assessment.

This represents a critical gap, as the combination of multiple bioactive compounds may also increase the risk of organ toxicity. Therefore, systematic safety evaluation is essential, including the determination of the No Observed Adverse Effect Level (NOAEL) in accordance with OECD guidelines (2008) and Indonesian FDA regulations (BPOM Regulation No. 10 of 2022). Histopathological analysis is a key approach to detect tissue-level alterations in target organs such as the heart, lungs, kidneys, and mammary glands. The novelty of this study lies in evaluating the subchronic toxicity and histopathological effects of a five-component polyherbal formulation (A5I tea) as a lactagogue candidate, which has not been previously reported. Accordingly, this study aims to assess the histopathological characteristics of

the heart, lungs, kidneys, and mammary glands in female mice following subchronic administration of A5I polyherbal tea, thereby providing a scientific basis for its safety and potential application as a breastfeeding booster.

## 2. Research Method

### Determination of Polyherbal Tea Plants

The determination of plant species was conducted at the Herbarium Jatinangor, Taxonomy Laboratory, Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Padjadjaran (Determination Number 97–101/HB/07/2025), which verified the authenticity of five plant samples.

### Preparation of Raw Materials

The material used in this study was A5I polyherbal tea, consisting of a combination of five simplicia: katuk leaves (*Sauropus androgynus*), moringa leaves (*Moringa oleifera*), fenugreek seeds (*Trigonella foenum-graecum*), torch ginger flowers (*Etlingera elatior*), and cinnamon (*Cinnamomum burmannii*), which were obtained from the Lembang area, Bandung.

The simplicia were dried in an oven at 40–50°C, ground using a blender, and sieved through a 20-mesh sieve to obtain a uniform particle size. The final product was then packaged into 3-gram tea bags.

### Polyherbal Tea Formulation Design

The formulation of A5I polyherbal tea consisted of fenugreek seeds (1.65 g), moringa leaves (0.6 g), *Katuk* leaves (0.3 g), cinnamon (0.3 g), and torch ginger flowers (0.15 g), which were infused with boiling water at 90–95 °C in 100 mL of water.

### Experimental Animal Preparation

The experimental animals used were healthy female mice, nulliparous, non-pregnant, aged 6–8 weeks, with body weights ranging from

20–30 grams. Prior to treatment, the animals were acclimatized for 5–7 days and randomly grouped, with body weight variation not exceeding 20% of the average.

**Subchronic Toxicity Assessment and Histopathological Evaluation**

The subchronic toxicity test was conducted for 28 days in accordance with the OECD 2008 guidelines and the Indonesian National Agency of Drug and Food Control Regulation No. 10 of 2022. The mice were divided into two groups: a control group receiving distilled water and a treatment group administered A5I polyherbal tea preparation orally using an oral gavage at a dose volume of 1 mL daily.

Observations were carried out daily to monitor clinical signs such as skin condition, fur, eyes, mucous membranes, respiratory patterns, and motor activity. Body weight, as well as food and water intake, were measured weekly. At the end of the experimental period, the animals were sacrificed, and the mammary glands, lungs, heart, and kidneys were collected for histopathological examination.

**Preparation of Histopathological Specimens**

The collected organs were fixed in 10% formalin solution for 7 hours, then selected and cut into sections with a thickness of 2–3 mm. The tissues were placed into cassettes and processed using an Automatic Tissue-Tek Processor for 90 minutes. Subsequently, the tissues were embedded in paraffin and sectioned using a microtome at a thickness of 2–3 µm.

The tissue sections were then placed in an oven at 70–80 °C for 30 minutes, followed by deparaffinization in xylene in two stages, each for 20 minutes, and continued with rehydration through graded alcohols for 3 minutes each. Staining was performed using Harris hematoxylin for 10–15 minutes, followed by rinsing under running water for 15 minutes, differentiation in 1% acid alcohol, and counterstaining with eosin for 10–15 minutes. The prepared slides were then dehydrated through graded alcohols

(70%, 80%, 96%, and absolute alcohol), cleared in xylene, and observed under a microscope.

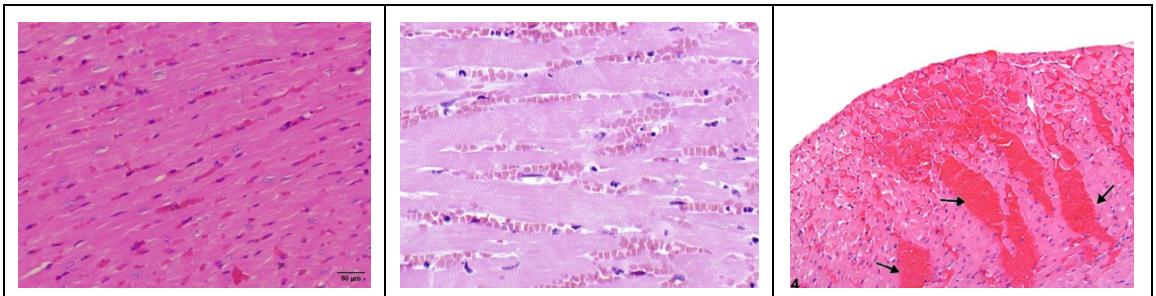
**Data Analysis Method**

Histopathological parameters were assessed using a standardized scoring system based on the extent of the affected area. The histopathological examination was conducted at the Anatomical Pathology Laboratory in Bandung. The data were statistically analyzed using ANOVA with a significance level of $p < 0.05$.

## 3. Results and Discussion

### Histopathological Analysis of the Heart

The results of histopathological observation of myocardial tissue showed a hemorrhage score of 0.5, which is interpreted as a condition that is not entirely normal but without evidence of significant tissue damage. No necrosis was observed in the myocardial tissue (score 0), as shown in Figure 1 below.



(a) Heart Histopathology | (b) Cellular Necrosis | (c) Bleeding

**Figure 1.** Cardiac Histopathology

The results of histopathological observation of myocardial tissue showed a hemorrhage score of 0.5, which is interpreted as a condition that is not entirely normal but without evidence of significant tissue damage. Normal myocardium is characterized by cardiac muscle fibers arranged in parallel with clear transverse striations, centrally located nuclei, and the absence of erythrocyte extravasation into the interstitial tissue [12].

Pathologically significant intramyocardial hemorrhage is defined as the extravasation of erythrocytes and blood components into the myocardial interstitial tissue due to microvascular damage. In HE-stained preparations, this appears as clusters of erythrocytes outside the vascular lumen, accompanied by surrounding morphological changes such as coagulative necrosis or inflammatory cell infiltration [13].

Clinically significant intramyocardial hemorrhage is generally accompanied by microvascular obstruction and cardiomyocyte damage. In this sample, the findings support the interpretation that the observed changes are minimal and subclinical. The absence of necrosis in the myocardial tissue (score 0) further confirms that A5I polyherbal tea does not cause significant damage to the heart [14].

The histopathological evaluation of myocardial tissue revealed a hemorrhage score of 0.5, indicating minimal and subclinical alterations without evidence of structural damage. Importantly, no necrosis was observed (score 0), suggesting preserved cardiomyocyte integrity.

Normal myocardial architecture is characterized by parallel-arranged muscle fibers, clear striations, and centrally located nuclei without erythrocyte extravasation. In contrast, pathological hemorrhage is typically associated with vascular injury, inflammatory response, and necrotic changes. However, in this study, the limited presence of erythrocytes outside vascular lumens was not accompanied by necrosis or inflammatory infiltration, indicating that the observed hemorrhage is likely incidental and not toxicologically significant.

These findings suggest that repeated administration of A5I polyherbal tea does not induce cardiotoxic effects. This result is consistent with previous studies reporting that plant-based polyphenols and flavonoids possess cardioprotective properties through antioxidant and anti-inflammatory mechanisms. However, unlike studies that demonstrated overt cardioprotection under pathological conditions, this study only confirms the

absence of toxicity under normal physiological conditions, highlighting the need for further functional and biochemical cardiac assessments.

**Histopathological Evaluation of the Lungs**

The results of histopathological observation of lung tissue showed alveolar septum destruction in 25–50% of the area (score 2), inflammatory cell infiltration in less than 25% of the area (score 1), and no pulmonary edema was observed (score 0) as shown in Figure 2 below.

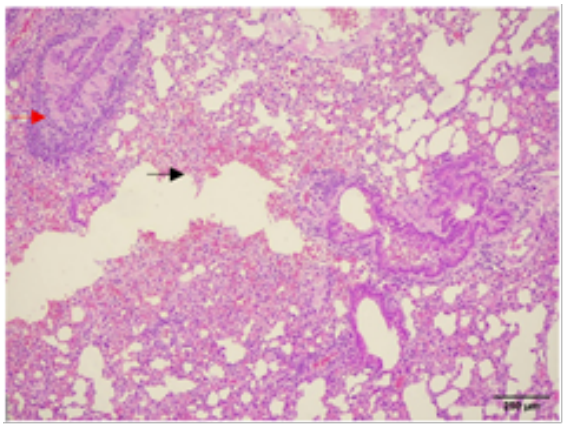


**Figure 2.** Pulmonary Histopathology

The obtained score of 2 indicates significant but not extensive damage, reflecting focal alveolar injury of mild to moderate degree. This damage is closely associated with the activity of inflammatory cells releasing proteolytic enzymes, which degrade the extracellular matrix of the alveolar walls [15].

The inflammatory cell infiltration observed in less than 25% of the area (score 1) indicates that the inflammatory response is still mild and localized. The infiltrating cells include lymphocytes and plasma cells, which play a role in the adaptive immune response to tissue injury [16].

The absence of pulmonary edema (score 0) is a significant finding. This condition indicates that the alveolar-capillary barrier is still functioning properly in maintaining pulmonary fluid homeostasis, despite the occurrence of septal destruction and inflammatory cell infiltration. Overall,

the histopathological findings of the lungs indicate mild to moderate changes without significant functional impairment.

Histopathological analysis of lung tissue demonstrated moderate alveolar septal destruction (score 2) and mild inflammatory cell infiltration (score 1), without evidence of pulmonary edema (score 0). These findings indicate the presence of localized structural alterations without significant impairment of alveolar-capillary barrier function.

Alveolar septal damage is commonly associated with inflammatory processes involving the release of proteolytic enzymes and reactive oxygen species. However, the limited distribution of inflammatory cells suggests that the observed response remains mild and controlled. The absence of edema is particularly important, as it reflects preserved vascular permeability and effective fluid regulation within the lung tissue.

Compared to previous toxicological studies, which often report severe inflammation and edema as hallmarks of pulmonary toxicity, the findings in this study indicate a substantially lower degree of tissue response. This suggests that the A5I formulation does not induce clinically relevant pulmonary toxicity. Nevertheless, the presence of moderate septal destruction warrants attention, as prolonged exposure or higher doses may potentially exacerbate tissue injury. Therefore, further studies involving dose variation and longer exposure periods are necessary to fully establish pulmonary safety.

**Histopathological Analysis of the Mammary Glands**

The histopathological analysis of the mammary glands showed that more than 75% of the observed mammary tissue area exhibited ductal dilation, as indicated by the highest score of 4. The intraluminal secretion distribution parameter also received a score of 4 (>75%), while alveolar epithelial vacuolization was observed in more than 25% of the area (score 1) as shown in Figure 3 below.

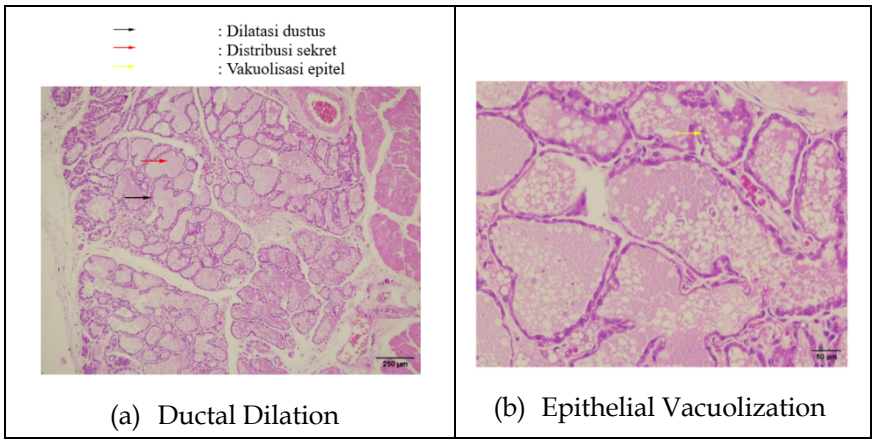



**Figure 3.** Histopathological Analysis of the Mammary Glands

Ductal dilation during the lactation phase is a physiological response that reflects the storage capacity of the ductal system in accommodating a high milk production volume. The accumulation of milk within the alveolar and ductal lumens generates hydrostatic pressure, causing structural distension proportional to the production volume. The score of 4 obtained in this sample indicates that the observed mammary tissue is in a highly active lactation phase, where nearly the entire ductal system has undergone structural adaptation to accommodate large volumes of milk production. The abundant secretion distribution appears as amorphous eosinophilic material in the alveolar and ductal lumens, providing direct evidence of intense milk biosynthesis activity [17].

The low vacuolization score does not indicate reduced secretion; rather, it reflects an efficient lipid secretion cycle that has occurred through the apocrine mechanism [18].

The mammary gland histopathology showed extensive ductal dilation and abundant intraluminal secretions, both with the highest score (4), indicating that more than 75% of the tissue area was actively involved in secretory activity. These findings strongly suggest enhanced lactational function.

Ductal dilation is a physiological adaptation to increased milk production, reflecting elevated secretory activity and storage capacity. The presence of abundant eosinophilic secretions within the lumen further confirms active milk biosynthesis. Interestingly, the relatively low epithelial vacuolization score does not indicate reduced function but rather suggests an efficient lipid secretion process via the apocrine mechanism.

These results support the proposed lactagogue effect of the A5I polyherbal formulation. Previous studies have reported that phytoestrogen-rich plants such as katuk, moringa, and fenugreek can stimulate prolactin and oxytocin pathways. However, most existing studies focus on single-plant extracts, whereas this study provides evidence from a polyherbal combination, suggesting potential synergistic effects. This highlights the novelty of the present study in demonstrating morphological evidence of lactation enhancement at the tissue level.

**Histopathological Analysis of the Kidney**

The histopathological observation of the kidneys showed tubular degeneration in only 5–25% of the area (score 1), while necrosis and inflammatory cell infiltration were not observed (score 0) as shown in Figure 4 below.

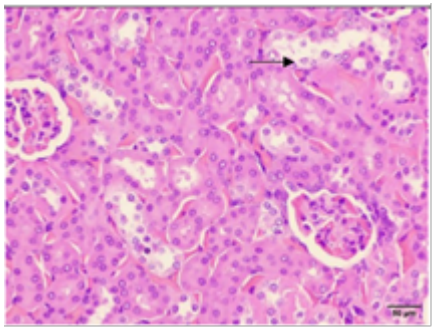


**Figure 4.** Histopathological Analysis of the Kidney

The obtained score of 1 indicates that degeneration was observed in only a small portion of the tissue area, reflecting mild and localized tubular injury. At this stage, the tubular cells still have the potential to recover if the

underlying cause is addressed, as the cell membranes and nuclei remain intact without signs of necrosis [19].

The absence of necrosis in this sample indicates that the administration of A5I polyherbal tea for 28 days did not cause irreversible tubular injury in the kidneys. The lack of inflammatory cell infiltration suggests that the observed damage did not trigger a significant immune response, which is consistent with the mild degenerative changes that were not severe enough to stimulate the recruitment of inflammatory cells from the circulation [20]. Overall, the renal histopathological findings indicate no significant nephrotoxicity associated with A5I polyherbal tea administration.

Renal histopathological evaluation revealed mild tubular degeneration affecting 5–25% of the observed area (score 1), with no evidence of necrosis or inflammatory cell infiltration (score 0). These findings indicate minimal and reversible cellular injury.

Tubular degeneration at this level is generally considered adaptive and does not necessarily reflect toxic injury, particularly in the absence of necrosis. The preservation of cellular structure suggests that renal function is unlikely to be significantly compromised. Additionally, the absence of inflammatory infiltration indicates that the observed changes did not trigger a substantial immune response [21][22][23].

In comparison with previous studies on nephrotoxicity, which typically report necrosis, interstitial inflammation, and glomerular damage, the findings in this study suggest that A5I polyherbal tea does not exert nephrotoxic effects under subchronic exposure conditions. Nevertheless, complementary biochemical parameters such as serum creatinine and urea levels would be necessary to strengthen this conclusion [24][25].

## 4. Conclusion

Subchronic administration of A5I polyherbal tea, containing a combination of katuk (*Sauropus androgynus*), moringa (*Moringa oleifera*), fenugreek (*Trigonella foenum-graecum*), torch ginger (*Etlingera elatior*), and cinnamon (*Cinnamomum burmannii*) for 28 days did not induce significant

histopathological damage in the heart and kidneys of female mice. The myocardium exhibited only minimal, subclinical hemorrhage without necrosis, and the kidneys showed mild, reversible tubular degeneration without necrosis or inflammatory infiltration. The lungs presented mild to moderate alveolar septal destruction and inflammatory cell infiltration but without pulmonary edema, indicating that the alveolar-capillary barrier function remained intact. Histopathological evaluation of the mammary glands revealed highly active lactation, characterized by extensive ductal dilation and abundant intraluminal secretion distribution, supporting the potential lactagogic effect of this formulation.

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