Trop J Nat Prod Res, November 2025; 9(11): 5406 - 5413 **ISSN 2616-0684 (Print)**
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

Immunomodulatory Effects of *Launaea sarmentosa* Extract on Cyclophosphamide-Induced Immunosuppressed Mice

Hung T. Bui[1,2], Ngoc H. Phan[3], Ly NC. Pham[4], Su Q. Pham[5], Hang TT. Nguyen[4], Van Anh T. Bui[4], Quang V. Trinh[4], Hang TT. Dinh[4], Van Anh T. Pham[4]*

[1]*Vinmec Smart City International Hospital, Hanoi 10000, Vietnam*
[2]*Vinmec Healthcare System, Hanoi 10000, Vietnam*
[3]*Central Acupuncture Hospital, Hanoi 10000, Vietnam*
[4]*Hanoi Medical University, Hanoi 10000, Vietnam*
[5]*Vietnam University of Traditional Medicine, Hanoi 10000, Vietnam*

ARTICLE INFO

Article history:
Received 18 September 2025
Revised 05 November 2025
Accepted 13 November 2025
Published online 01 December 2025

ABSTRACT

Traditional medicine and herbal extracts offer potential for enhancing immune responses. This study investigated the immunomodulatory effects of *Launaea sarmentosa* extract in a cyclophosphamide-induced immunosuppression mouse model, aiming to validate its traditional use and explore its potential as a novel immunotherapeutic adjunct. *Swiss* mice were divided into six groups, including controls and three *L. sarmentosa* treatment groups (36, 72, 108 mg/kg). Immunosuppression was induced by cyclophosphamide (200 mg/kg) on day 4 of a 7-day treatment. Key immune parameters evaluated included relative organ weights, leukocyte counts, delayed-type hypersensitivity (DTH) response, serum cytokine levels (IL-4, IL-6, IFN-γ, TNF-α, IgG), and lymphoid organ histopathology. *L. sarmentosa* extract significantly ameliorated cyclophosphamide-induced immunosuppression. Treatment, especially at 108 mg/kg/day, restored relative spleen weight and tended to enhance DTH reactions. The extract significantly elevated IL-4, IL-6, and IgG concentrations, modulating humoral and innate immune responses. Histopathological examination showed marked improvement in lymphoid organ damage, with increased lymphocyte density and restored tissue architecture in both spleen and thymus. While TNF-α and IFN-γ levels showed upward trends, these were not statistically significant. These findings suggest *L. sarmentosa* possesses potent immunomodulatory effects by protecting lymphoid organs, enhancing cytokine production, and supporting immune responses. Further studies are needed to elucidate its exact mechanisms and identify active compounds.

Keywords: Cyclophosphamide, Cytokine, Herbal Medicine, Immunodeficiency, *Launaea Sarmentosa*, Mice.

Introduction

The immune system constitutes a complex and sophisticated defense network, essential for protecting the host against pathogenic invaders and maintaining bodily homeostasis. It is broadly categorized into two interconnected arms: the innate immune system, which provides immediate, non-specific defense, and the adaptive immune system, which confers antigen-specific, long-lasting immunity.[1,2] This intricate system relies on the coordinated function of various cells—including lymphocytes, phagocytes, and dendritic cells—and organs such as the bone marrow, thymus, and spleen.[3] Immunodeficiency arises from a failure, absence, or deficiency of these critical components, leading to an increased susceptibility to infections, autoimmune disorders, and cancer. This state can be primary (genetic) or, more commonly, secondary, induced by factors like viral infections (e.g., HIV/AIDS), malnutrition, or iatrogenic causes such as chemotherapy.[4,5] A significant iatrogenic cause of immunosuppression is cancer chemotherapy.[6]

*Corresponding author. Email: phamvananh@hmu.edu.vn
Tel.: +84 91 559 56 90

Citation: Bui HT, Phan NH, Pham LNC, Pham SQ, Nguyen HTT, Bui VAT, Trinh QV, Dinh HTT, Pham VAT. Immunomodulatory Effects of *Launaea sarmentosa* Extract on Cyclophosphamide-Induced Immunosuppressed Mice. Trop J Nat Prod Res. 2025; 9(11): 5406 – 5413 https://doi.org/10.26538/tjnpr/v9i11.21

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria

While cytotoxic drugs are indispensable for treating malignancies and autoimmune diseases, they often cause severe collateral damage to the immune system.[6,7]Cyclophosphamide (CY), a prominent alkylating agent of the oxazaphosphorin group, is a classic example. It is widely used for its immunosuppressive properties but is notorious for inducing myelosuppression, pancytopenia, and atrophy of lymphoid organs, thereby suppressing both humoral and cellular immune responses.[8,9] Consequently, patients undergoing such treatments often experience a debilitating compromise in their immune competence, highlighting a critical need for effective strategies to mitigate these adverse effects and support immune recovery. Current management of chemotherapy-induced immunosuppression often involves supportive care, growth factors like granulocyte colony-stimulating factor (G-CSF) to boost neutrophil counts, and, in severe cases, treatment delays.[5] However, these approaches can be costly, may have their own side effects, and do not always fully restore broad-spectrum immune function. This limitation has spurred significant interest in complementary and alternative medicine, particularly the use of medicinal herbs, for their potential immunomodulatory properties. Numerous plant-derived compounds have been shown to act as immunostimulants or immunomodulators by enhancing the proliferation and activity of immune cells, promoting cytokine production, and protecting lymphoid organs from damage.[2,10] The exploration of natural products offers a promising avenue for developing adjunctive therapies that can help bolster the immune system with potentially fewer side effects.[11–15]
Among the vast repertoire of medicinal plants, *Launaea sarmentosa* (Willd.) Schultz-Bip. ex Kuntze stands out as a promising candidate. This perennial creeping herb is indigenous to coastal regions of East Africa, India, and Southeast Asia, including Vietnam.[16] It is not

only consumed as a nutritious vegetable but also holds a venerable place in traditional medicine systems. Various parts of the plant have been used to treat a range of ailments; for instance, the roots are employed to stop bleeding and prevent infection in postpartum women, while the leaves and stems are used to address inflammatory conditions like gout and rheumatoid arthritis.[17] Phytochemical investigations have identified a rich array of bioactive constituents in *L. sarmentosa*, including flavonoids (luteolin), sterols (α-amyrin acetate, β-amyrin acetate), phenolic compounds, and saponins.[18,19] These compounds are associated with diverse pharmacological activities, most notably anti-inflammatory, antifungal, and immunomodulatory effects as demonstrated in previous studies.[20–22] Despite its traditional uses and known anti-inflammatory properties, scientific evidence specifically validating the immunomodulatory potential of *L. sarmentosa* remains scarce. The existing literature has yet to systematically explore its capacity to counteract drug-induced immunosuppression, representing a significant scientific gap. Given the plant's chemical richness, particularly in compound classes like saponins, flavonoids, and phenolic compounds, which are known for immunomodulatory effects,[23–26] it is hypothesized that *L. sarmentosa* extract could serve as an effective natural agent to stimulate immune recovery. Therefore, the present study was designed to evaluate the immunomodulatory effects of *L. sarmentosa* extract in a cyclophosphamide-induced immunosuppression mouse model. The objective was to assess its impact on key immune parameters, including lymphoid organ weight and histology, leukocyte counts, delayed-type hypersensitivity response, and serum cytokine levels, to scientifically validate its traditional use and explore its potential as a novel immunotherapeutic adjunct.

Materials and Methods

Plant material

Launaea sarmentosa (Willd.) Schultz-Bip. ex Kuntze was harvested from Ben Tre Province, Vietnam. The whole plant, including leaves, stems, and roots, was thoroughly washed with tap water to remove soil and impurities, followed by a final rinse with distilled water. The cleaned plant material was shade-dried at room temperature (25-30°C) for two weeks until fully desiccated (moisture content <10%). The dried material was ground into a coarse powder using a mechanical grinder.

The aqueous extract was prepared using an automated reflux extraction system. Briefly, 500 g of plant powder was extracted with 5 L of distilled water (1:10 w/v) at 90°C for 2 hours. This extraction process was repeated twice to maximize yield. The combined aqueous extracts were filtered through a muslin cloth and then through Whatman No. 1 filter paper. The filtrate was concentrated under reduced pressure (- 0.5 atm) at 60°C using a rotary evaporator (Heidolph, Germany). The resulting concentrated extract was subsequently spray-dried (inlet temperature: 180°C, outlet temperature: 90°C) to obtain a fine, dry powder. This powder was stored in an airtight container at 4°C until use.

Drugs and Chemicals

Cyclophosphamide (Endoxan®, Baxter, Germany) was used as the immunosuppressant and prepared fresh in sterile normal saline (0.9% NaCl) for intraperitoneal (i.p.) injection. Levamisole (Tetramisole hydrochloride powder, Sigma-Aldrich Chemicals Pvt. Ltd., USA) served as the positive control and was dissolved in distilled water for oral administration. Pentobarbital (Sigma-Aldrich Chemicals Pvt. Ltd., USA) was used as the anesthetic agent, diluted in sterile saline for i.p. injection at a dose of 50 mg/kg body weight (b.w.) to ensure deep anesthesia prior to euthanasia and blood collection. For sensitization, ovalbumin (OVA; grade V, Sigma-Aldrich, USA) emulsion was prepared by dissolving OVA at 1 mg/mL in phosphate-buffered saline (pH 7.4) and mixing 1:1 (v/v) with aluminum hydroxide [$Al(OH)_3$] adjuvant (20 mg/mL in PBS; Pierce Alum Adjuvant, Thermo Fisher Scientific, USA). Sheep red blood cells (SRBC) were collected from sheep venous blood under sterile conditions and preserved in Alsever's solution (composition: 24.6 g glucose, 9.6 g sodium citrate, 5.05 g sodium chloride, distilled water to 1,200 mL, pH adjusted to 6.1 with citric acid). SRBC were stored at 4°C and used within 2 weeks. Before use, SRBC were washed three times by centrifugation (1,500 × g for 10 minutes at 4°C) in sterile PBS, resuspended to a 5% (v/v) concentration (approximately 5×10^8 cells/mL), and confirmed for viability and sterility.

Hematological analysis was performed using the Exigo-VET biochemical analyzer (Exigo, Sweden) with commercial Exigo diagnostic kits for complete blood count. Blood dilution was achieved with ABX Minidil LMG solution (ABX Diagnostics, Italy), and quantification was conducted on the Horiba ABX Scil ABC Vet analyzer (Horiba Medical, France).

Animals

A total of 60 healthy *Swiss* mice (both sexes, 8 weeks old) were procured from the National Institute of Hygiene and Epidemiology (NIHE), Hanoi, Vietnam. The animals were acclimatized to laboratory conditions for 7-10 days prior to the experiment. They were housed in polypropylene cages (n = 5 per cage) under standard environmental conditions (temperature: 27 ± 2°C, relative humidity: 80 ± 10%, and a 12:12 hour light-dark cycle). The mice had free access to a standard rodent diet and water *ad libitum*. All experimental procedures were reviewed and approved by the Institutional Animal Ethics Committee of Hanoi Medical University (Approval Reference No.: IRB00003121) and were conducted in accordance with the ARRIVE guidelines and the National Research Council's guide for the care and use of laboratory animals.

Animal study design

After acclimatization, the mice were randomly divided into six groups (n = 10 per group):

Group I (Normal control): Received distilled water (0.2 mL/10 g b.w., p.o.) for 7 days.

Group II (Model): Received distilled water (0.2 mL/10 g b.w., p.o.) for 7 days and a single intraperitoneal (i.p.) injection of cyclophosphamide (CY, 200 mg/kg b.w.) on day 4.[27,28]

Group III (Levamisole): Received levamisole (10 mg/kg b.w. in distilled water, p.o.) for 7 days and a single i.p. injection of CY (200 mg/kg b.w.) on day 4.

Group IV: Received *L. sarmentosa* extract (36 mg/kg b.w. in distilled water, p.o.) for 7 days and a single i.p. injection of CY (200 mg/kg b.w.) on day 4.

Group V: Received *L. sarmentosa* extract (72 mg/kg b.w. in distilled water, p.o.) for 7 days and a single i.p. injection of CY (200 mg/kg b.w.) on day 4.

Group VI: Received *L. sarmentosa* extract (108 mg/kg b.w. in distilled water, p.o.) for 7 days and a single i.p. injection of CY (200 mg/kg b.w.) on day 4.

Doses for *L. sarmentosa* were selected based on preliminary toxicity studies and traditional use equivalents.[20] To induce an immune response for subsequent challenge, all mice were immunized on day 2 via intraperitoneal injection of 5% SRBC suspension (0.5 mL/mouse) and subcutaneous injection of ovalbumin antigen emulsion (0.1 mL/mouse).

Sampling and Analytical Procedures

Relative organ weight

The spleen and thymus were carefully dissected out, trimmed of excess fat, and weighed immediately on a precision analytical balance (Precisa Swiss, Model 321LX). The relative organ weight was calculated as follows (Equation 1):

$$\text{The relative organ weight (‰)} = \frac{Weight\ of\ spleen\ or\ thymus\ (miligrams)}{Weight\ of\ mice\ (grams)}$$

Hematological analysis

Blood was collected via cardiac puncture. A complete blood count, including total leukocyte count (WBC), lymphocyte, neutrophil, and monocyte counts, was performed immediately using an automated hematology analyzer.

Serum cytokine and IgG analysis

Following blood collection, serum was separated by allowing the blood to clot at room temperature, followed by centrifugation at 3500 rpm for 10 minutes. Serum samples were then aliquoted and stored at -80°C for

subsequent analysis. The concentrations of interleukin-4 (IL-4), interleukin-6 (IL-6), interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and immunoglobulin G (IgG) were determined using commercial sandwich enzyme-linked immunosorbent assay (ELISA) kits (Cloud-Clone Corp., USA; Catalog numbers: SEA077Mu, SEA079Mu, SEA049Mu, SEA133Mu, and SEA544Mu, respectively). The assays were performed following the manufacturer's protocol. In brief, 100 µL of standards and serum samples were added in duplicate to the appropriate wells and incubated for 1 hour at 37°C. Wells were aspirated, and 100 µL of prepared detection reagent was added, followed by incubation for 1 h at 37°C. Wells were washed three times, 100 µL of another detection reagent was added, and incubated for 30 minutes at 37°C, followed by five washes. Next, 90 µL of substrate solution was added and incubated for 15 minutes at 37°C. The reaction was stopped by adding 50 µL of stop solution, and absorbance was read immediately at 450 nm using a microplate reader (BioTek, USA). Concentrations were determined from standard curves generated for each assay.

Histopathological examination

The spleen and thymus from each mouse were harvested and immediately fixed in 10% neutral buffered formalin for 48 hours to prevent autolysis. Following fixation, the tissues were processed for paraffin embedding using a standard protocol. Briefly, the tissues were dehydrated through a series of graded ethanol solutions, cleared with xylene, and then infiltrated with and embedded in paraffin wax. The resulting paraffin blocks were sectioned at a thickness of 5 µm using a rotary microtome. The sections were then mounted on glass slides and stained with Hematoxylin and Eosin (H&E) for morphological evaluation.[29] The stained sections were examined under a light microscope (Olympus BX10, Japan) by a pathologist blinded to the treatment groups. Photomicrographs were captured at 20x magnification using an attached digital camera (Olympus DP12, Japan). Histopathological changes such as lymphocyte density, presence of degenerated cells, inflammation, and necrosis were evaluated.

Delayed-type hypersensitivity (DTH) response

On day 7, the DTH response was elicited by injecting 50 µL of OVA antigen (100 µg) into the subcutaneous tissue of the right hind footpad. The left hind footpad received an equal volume of saline (0.9% NaCl) as an internal control. The footpad thickness was measured 24 hours post-injection (on day 8) using a digital micrometer caliper. The DTH response was expressed as the difference in thicknes between the antigen-injected and the saline-injected footpad.

Statistical analysis

All data are presented as mean ± standard deviation (SD). Statistical analysis was performed using SPSS software (Version 26.0, IBM Corp., USA). Differences between groups were analyzed by one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test for multiple comparisons. A p-value of less than 0.05 was considered statistically significant.

Results and Discussion

Launaea sarmentosa, a perennial creeping herb from the Asteraceae family, is naturally distributed across coastal sandy regions in East Africa, India, the Indian Ocean islands, and Southeast Asia, including Vietnam.[16] This plant serves not only as a nutritious vegetable in daily diets but also holds a longstanding role in traditional folk medicine for treating conditions such as diabetes and chronic inflammation.[22] The present study represents the first evaluation of *L. sarmentosa* extract in a cyclophosphamide (CY)-induced immunosuppression mouse model, aiming to assess its potential immunomodulatory and immunostimulatory effects.

Cyclophosphamide, a well-established chemotherapeutic and immunosuppressive agent, was used to induce immunosuppression in this study. It is known to cause atrophy of lymphoid organs, reduce white blood cell and lymphocyte counts, suppress bone marrow function, and inhibit both humoral and cellular immune responses.[30] These effects were evident in our model group, confirming the successful induction of immunosuppression and aligning with established literature on CY's mechanisms.

Levamisole, an imidazothiazole derivative, was selected as the positive control due to its ability to enhance cellular and humoral immunity. It promotes T-cell function, stimulates antibody production, particularly against thymus-dependent antigens, and regulates pro-inflammatory cytokines.[31,32] This makes it a suitable benchmark for evaluating novel immunomodulators.

Throughout the 8-day experimental period, all sixty mice remained alive and exhibited normal health. No adverse effects or behavioral changes, such as reduced activity, altered feeding patterns, or signs of distress, were observed in any treatment group. Body weight changes were monitored and are presented in Table 1. All groups maintained stable weights, confirming the tolerability of both the cyclophosphamide insult and the treatments administered.

Table 1: Effect of *L. sarmentosa* extract on body weight and relative organ weight.

Group	Treatment (n = 10)	Body weight – before treatment (g)	Body weight – after treatment (g)	Relative spleen weight (‰)	Relative thymus weight (‰)
I	Normal control	26.00 ± 4.14	28.70 ± 4.22	7.75 ± 2.24	2.93 ± 1.02
II	Model	27.70 ± 4.27	28.90 ± 4.95	2.43 ± 0.55***	0.73 ± 0.21***
III	Levamisole	26.20 ± 4.34	26.20 ± 4.76	2.57 ± 0.37***	1.02 ± 0.51***
IV	*L. sarmentosa* 36 mg/kg/day	26.70 ± 1.83	27.50 ± 2.42	2.37 ± 0.35***	0.78 ± 0.30***
V	*L. sarmentosa* 72 mg/kg/day	26.70 ± 3.47	27.20 ± 3.05	2.42 ± 0.55***	0.87 ± 0.24***
VI	*L. sarmentosa* 108 mg/kg/day	27.50 ± 3.72	28.60 ± 3.10	3.13 ± 0.71***	1.06 ± 0.49***

Values are expressed as mean ± SD. Body weight was measured before and after treatment.
*** indicates a significant difference compared to the normal control group ($p < 0.001$).

Effect of L. sarmentosa extract on relative organ weight

Cyclophosphamide (CY) administration induced significant atrophy of the primary lymphoid organs. As shown in Table 1, the relative weights of both the spleen and thymus in the model group were drastically reduced compared to the normal control group ($p < 0.001$).

Treatment with levamisole resulted in a slight, non-significant increase in the relative weights of both organs compared to the model group ($p > 0.05$). Administration of *L. sarmentosa* extract showed a dose-dependent influence on organ recovery. While the 36 mg/kg and 72 mg/kg doses did not significantly alter spleen weight, the 108 mg/kg dose produced a notable increase in relative spleen weight compared to the model group ($p < 0.05$). A similar upward trend in thymus weight was observed across all *L. sarmentosa*-treated groups (IV-VI), though these changes did not reach statistical significance ($p > 0.05$).

The spleen and thymus are central lymphoid organs critical for immune function. The thymus is essential for T-cell maturation, while the spleen, rich in white pulp, houses B cells, T cells, macrophages, dendritic cells, natural killer cells, and erythrocytes.[33,34] Immune responses initiate here when antigen-presenting cells (e.g., macrophages or dendritic cells) activate B or T cells, leading to antibody production by B cells.[35] Lymphocytes and hematopoietic cells

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

from the bone marrow significantly contribute to the weight of these organs. In our study, the model group showed marked reductions in spleen and thymus weights compared to the normal control, reflecting CY-induced immunosuppression. Treatment with *L. sarmentosa* extract at all doses (36, 72, and 108 mg/kg b.w.) exhibited a trend toward increased relative thymus weights, though not statistically significant, suggesting potential immune recovery. Notably, the dose of 108 mg/kg b.w. led to an apparent increase in spleen weight, indicating restoration or proliferation of immune cells in this organ and underscoring its role in enhancing overall immune activity.

Effect of L. sarmentosa extract on leukocyte counts

The immunosuppressive effect of cyclophosphamide was clearly evidenced in the hematological analysis (Table 2). The model group exhibited severe leukopenia, with significant reductions in total WBC, lymphocyte, neutrophil, and monocyte counts compared to the normal controls ($p < 0.001$).

Table 2: Effect of *L. sarmentosa* extract on leukocyte counts

Group	Treatment (n = 10)	WBC (G/L)	LYM (G/L)	NEU (G/L)	MONO (G/L)
I	Normal control	5.84 ± 1.02	3.25 ± 0.78	1.39 ± 0.44	1.20 ± 0.50
II	Model	0.93 ± 0.39***	0.62 ± 0.27***	0.25 ± 0.11***	0.06 ± 0.05***
III	Levamisole	1.17 ± 0.48***	0.66 ± 0.24***	0.30 ± 0.22***	0.21 ± 0.10***
IV	*L. sarmentosa* 36 mg/kg/day	0.74 ± 0.17***	0.43 ± 0.16***	0.21 ± 0.06***	0.10 ± 0.07***
V	*L. sarmentosa* 72 mg/kg/day	0.87 ± 0.25***	0.49 ± 0.22***	0.23 ± 0.10***	0.15 ± 0.06***
VI	*L. sarmentosa* 108 mg/kg/day	0.99 ± 0.26***	0.51 ± 0.08***	0.30 ± 0.15***	0.18 ± 0.07***

Values are expressed as mean ± SD for total white blood cells (WBC), lymphocytes (LYM), neutrophils (NEU), and monocytes (MONO) in G/L.
*** indicates a significant difference compared to the normal control group ($p < 0.001$).

Neither levamisole nor any of the three doses of *L. sarmentosa* extract elicited a statistically significant recovery in peripheral leukocyte counts within the 7-day treatment period when compared to the model group ($p > 0.05$ for all comparisons). All cyclophosphamide-treated groups remained significantly leukopenic relative to the normal control. Leukocytes play diverse roles in immune defense, classified into myeloid cells for innate immunity and lymphoid cells for adaptive responses.[36,37] Peripheral blood leukocyte counts serve as key indicators of systemic immune health. Although *L. sarmentosa* extract significantly boosted lymphocyte numbers in the spleen and thymus, this was not mirrored in peripheral blood within the study's 7-day timeframe. This discrepancy may stem from lymphocyte recirculation kinetics: Mature lymphocytes recirculate between lymphoid organs and blood, spending approximately 2.5 hours in the spleen and 10 hours in lymph nodes before entering circulation.[38] Thus, early-stage recovery in tissues may precede detectable peripheral changes, especially in short-term studies.[39]

Effect of L. sarmentosa extract on delayed-type hypersensitivity (DTH) response

The cell-mediated immune response, assessed by the DTH reaction, was significantly suppressed by CY treatment. The percentage increase in footpad thickness was markedly lower in the model group compared to the normal control group ($p < 0.05$, Table 3).

Table 3: Effect of *L. sarmentosa* extract on delayed-type hypersensitivity (DTH) response

Group	Treatment (n = 10)	Right foot thickness (µm)	Left foot thickness (µm)	% increase in foot thickness
I	Normal control	2.92 ± 0.57	1.48 ± 0.16	97.59 ± 35.54
II	Model	2.5 ± 0.52	1.53 ± 0.17	62.68 ± 22.71
III	Levamisole	3.4 ± 0.52	1.7 ± 0.43	107.88 ± 45.62$^{\Delta}$
IV	*L. sarmentosa* 36 mg/kg/day	3.16 ± 0.51	1.78 ± 0.17	78.22 ± 26.41
V	*L. sarmentosa* 72 mg/kg/day	2.96 ± 0.37	1.68 ± 0.16	77.36 ± 27.05
VI	*L. sarmentosa* 108 mg/kg/day	3.22 ± 0.45	1.81 ± 0.25	80.32 ± 30.71

Values are expressed as mean ± SD. Footpad thickness was measured 24 hours post-injection of ovalbumin antigen (right foot) and saline (left foot). The percentage increase in foot thickness reflects the DTH response.
$^{\Delta}$ indicates a significant difference compared to the model group ($p < 0.05$).

As expected, levamisole treatment significantly enhanced the DTH response compared to the model group ($p < 0.05$). Mice treated with *L. sarmentosa* extract showed a consistent, dose-dependent tendency toward improved DTH responses. However, this improvement did not achieve statistical significance compared to the model group ($p > 0.05$). The delayed-type hypersensitivity (DTH) response, a T-cell-mediated measure of cell-mediated immunity, operates independently of antibodies,[40] was significantly enhanced by levamisole compared to the model group ($p < 0.05$), consistent with its T-cell stimulatory effects.[31,32] *L. sarmentosa* extract showed an upward trend in DTH at all doses but lacked statistical significance, suggesting a mild or time-dependent impact on cell-mediated immunity. A hallmark of DTH is interferon-gamma (IFN-γ) release, which promotes cytotoxic CD8+ T-cell responses, NK cell activity, antigen presentation, and macrophage activation.[41] In our study, IFN-γ levels remained unchanged across doses compared to the model, potentially explaining the non-significant DTH improvement and indicating limited Th1 pathway activation by the extract.[42,43]

Effect of L. sarmentosa extract on serum IL-4, IL-6, TNF-α, IFN- γ and IgG concentrations

Serum levels of IL-4, IL-6, and IgG were significantly lower in the cyclophosphamide-induced model group compared to the normal control group ($p < 0.01$ for all). Levels of IFN-γ and TNF-α also trended downward in the model group, but these changes were not statistically significant ($p > 0.05$). In the levamisole-treated group, all markers (IL-4, IL-6, TNF-α, IFN-γ, and IgG) showed non-significant upward trends compared to the model group ($p > 0.05$) (Figure 1).

L. sarmentosa extract treatment elicited dose-dependent effects: IL-4 concentrations increased significantly at all doses compared to the model group ($p < 0.01$ to $p < 0.001$) and were also significantly higher than in the levamisole group ($p < 0.01$). IL-6 levels displayed an upward trend across all doses, with the highest dose (108 mg/kg b.w.) achieving statistical significance compared to the model group ($p < 0.05$). TNF-α levels followed a dose-responsive increasing pattern but did not reach significance ($p > 0.05$). No significant changes were observed in IFN-γ levels compared to the model group ($p > 0.05$). For IgG, only the highest dose of *L. sarmentosa* extract produced a significant increase compared to both the model and levamisole groups ($p < 0.05$) (Figure 1).

Tumor necrosis factor-alpha (TNF-α), a pro-inflammatory cytokine primarily from macrophages, activates macrophages, triggers a series of various inflammatory molecules, including other cytokines and chemokines, and enhances antigen presentation.[44,45] Our results showed a dose-dependent increase in TNF-α with *L. sarmentosa extract*, though not statistically significant. This suggests the extract may restore inflammatory signaling pathways disrupted by CY, aiding re-

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

establishment of innate immune function under immunosuppressive conditions. Interleukin-4 (IL-4), a Th2-type cytokine, promotes humoral immunity by supporting B-cell growth, IgG class switching, memory B-cell formation, and IgG1 production.[46,47] IL-4 levels increased significantly at all doses compared to the model ($p < 0.01$ to $p < 0.001$), and were higher than in the levamisole group ($p < 0.01$), indicating activation of Th2 responses and initiation of antibody-mediated immunity. This elevation likely reflects enhanced B-cell activation in lymphoid tissues.

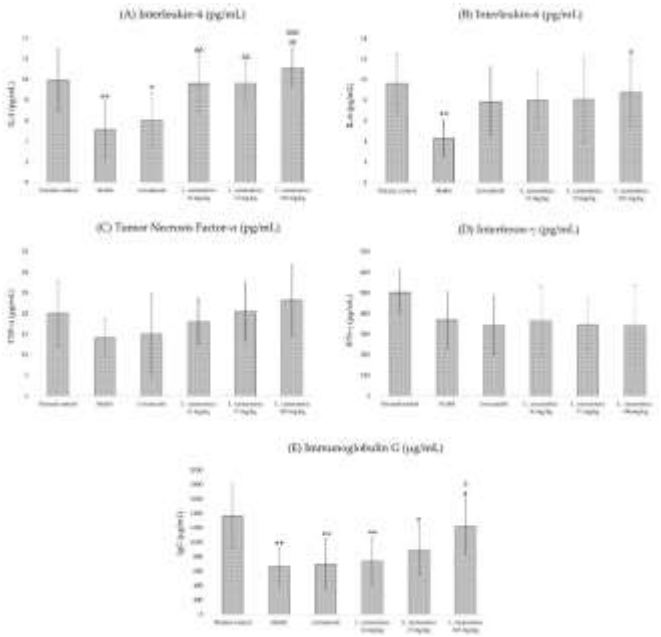

Figure 1: Effect of *L. sarmentosa* extract on serum IL-4, IL-6, TNF-α, IFN-γ, and IgG concentrations. Mice were treated as described. Data are presented as mean ± SD (n=10). (A) IL-4, (B) IL-6, (C) TNF-α, (D) IFN-γ, and (E) IgG concentrations in serum samples. *, ** *indicate significant differences compared to the normal control group ($p < 0.05$, $p < 0.01$);* $^{\Delta}$, $^{\Delta\Delta}$, $^{\Delta\Delta\Delta}$ *indicate significant differences compared to the model group ($p < 0.05$, $p < 0.01$, $p < 0.001$);* $^{\$}$, $^{\$\$}$ *indicate significant differences compared to the levamisole-treated group ($p < 0.05$, $p < 0.01$).*

Building on this, interleukin-6 (IL-6), a pleiotropic cytokine, bridges innate and adaptive immunity by stimulating acute-phase responses, hematopoiesis, and B-cell differentiation into antibody-producing plasma cells.[48] It also regulates inflammation and can promote Th2 polarization in certain contexts.[49,50] In CY-induced models, IL-6 suppression contributes to impaired immune recovery. Our study showed an upward trend in IL-6 levels across doses, with significance at the highest dose (108 mg/kg b.w.; $p < 0.05$) compared to the model. This suggests *L. sarmentosa* extract may support immune restoration by enhancing IL-6-mediated processes, such as progenitor cell proliferation in bone marrow, potentially aiding recovery from myelosuppression. Immunoglobulin G (IgG), a key humoral immunity marker, reflects B-cell activation and antibody production.[51] Model group IgG levels were significantly reduced ($p < 0.01$), but the highest dose of *L. sarmentosa* extract (108 mg/kg b.w.) significantly increased IgG compared to both model and levamisole groups ($p < 0.05$). This dose-dependent effect may be linked to elevated IL-4 and IL-6, as both cytokines facilitate IgG class switching and plasma cell differentiation.[52,53] However, the overall modest increase suggests humoral immunity activation was initiated but incomplete, possibly requiring longer treatment to achieve robust antibody responses.

Histopathological study of spleen and thymus

Histopathological analysis revealed marked structural damage in the model group, including reduced lymphocyte density in both the spleen and thymus compared to the normal control group, consistent with cyclophosphamide-induced lymphoid atrophy (Figure 2 and Figure 3). Treatment with levamisole and *L. sarmentosa* extract at all doses significantly ameliorated this damage, restoring lymphocyte counts in both organs compared to the model group. The highest dose of *L. sarmentosa* extract (108 mg/kg b.w.) demonstrated the most substantial recovery, with increased moderate and dense lymphocyte populations that outperformed levamisole. The 36 and 72 mg/kg b.w.doses also improved lymphocyte density, albeit to a lesser degree. No notable inflammation, necrosis, or degenerated cells were observed beyond the model-induced changes. These microscopic findings align with the macroscopic organ weight data, supporting the extract's role in repairing lymphoid tissue and promoting immune cell repopulation, particularly at a dose of 108 mg/kg.

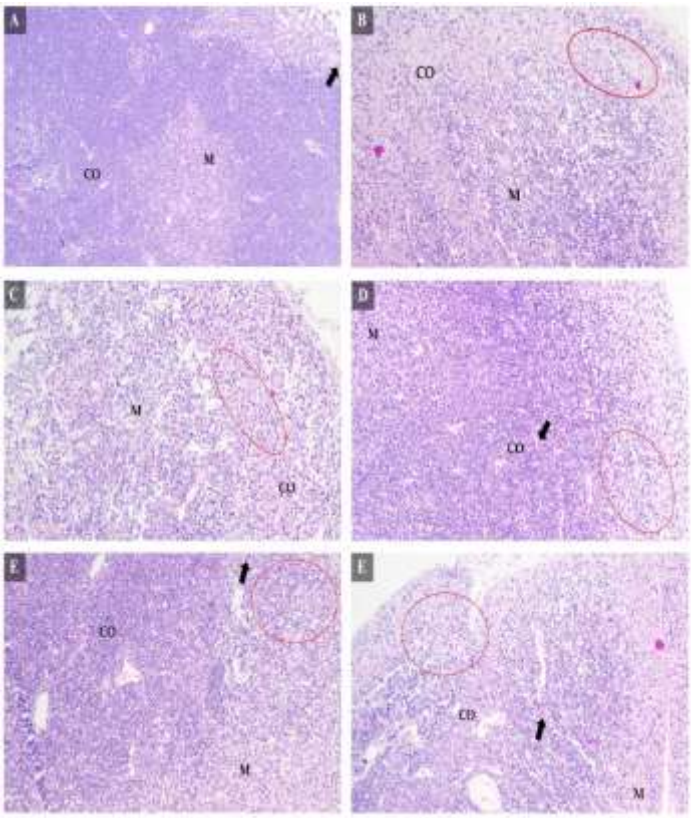

Figure 2: Histopathological examination of the thymus in immunosuppressed mice. Representative photomicrographs (H&E staining, 20x magnification) of thymus sections from each experimental group. (A) Normal control group, showing a clear distinction between the cortex and medulla with high lymphocyte density. (B) Model group, showing severe cortical atrophy, loss of corticomedullary demarcation, and significant lymphocyte depletion. (C) Levamisole group, showing partial recovery of cortical cellularity. (D-F) *L. sarmentosa* extract-treated groups (36, 72, and 108 mg/kg, respectively), showing an increase in cortical lymphocyte density and improved corticomedullary differentiation. *(M: Medulla; CO: Cortex; black arrows: Hassall's corpuscles; red circles: cortex with different levels of reduced lymphocyte density).*

While direct studies on *L. sarmentosa*'s immunomodulatory effects are lacking, its phytochemical profile includes saponins,[16] which are known to stimulate immune organ growth, activate signaling pathways, enhance cytokine production, and boost cellular and humoral responses.[23] This may explain our observed improvements in organ weights and histology. The limited humoral effects could stem from saponin concentration or study duration, warranting optimization.

Overall, *L. sarmentosa* extract shows promise as an immunomodulator in CY-induced immunosuppression, particularly in restoring lymphoid structure at 108 mg/kg b.w., outperforming levamisole histologically. However, this study has several limitations. Firstly, while the result exhibited significant changes in organ weights, cytokine profiles, and histopathology, the precise molecular mechanisms underlying these effects were not fully elucidated. Further investigations are needed to identify the active compounds responsible for the observed immunomodulatory activities and to delineate their cellular and molecular targets. Secondly, the study was conducted in an animal model, and the findings may not directly translate to human physiology. Clinical trials are necessary to confirm the efficacy and safety of *L. sarmentosa* in human subjects. Thirdly, the study duration was relatively short, and the long-term effects of *L. sarmentosa* on immune function and overall health warrant further investigation. Lastly, while the findings showed a tendency for improvement in DTH response and leukocyte counts, these did not reach statistical significance, suggesting that *L. sarmentosa* may have a more selective impact on certain immune parameters or that higher doses or longer treatment durations might be required to elicit more comprehensive effects. Future research should focus on isolating and characterizing the bioactive compounds, conducting detailed mechanistic studies, and exploring the clinical applicability of *L. sarmentosa* as an immunomodulatory agent.

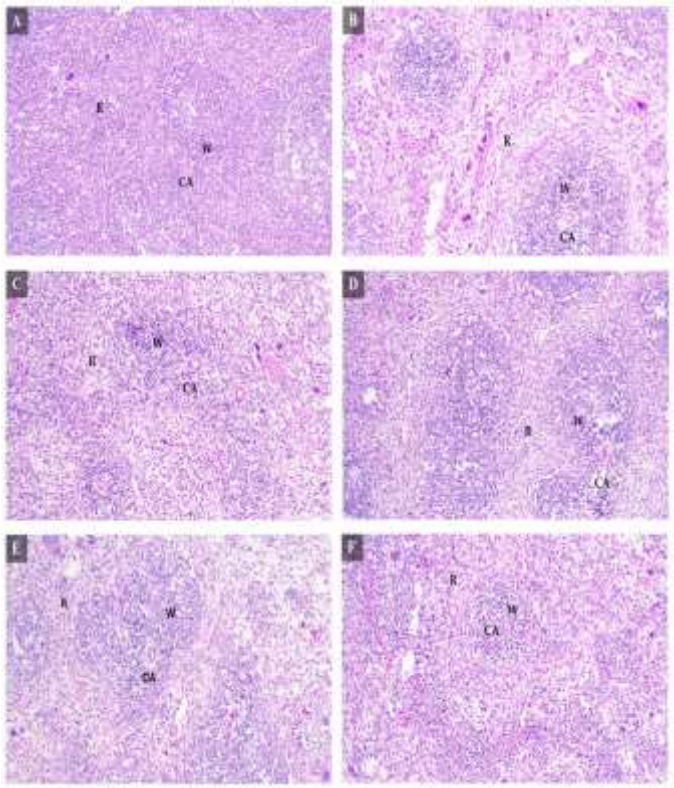

Figure 3: Histopathological examination of the spleen in immunosuppressed mice. Representative photomicrographs (H&E staining, 20x magnification) of spleen sections from each experimental group. (A) Normal control group, showing well-defined white pulp and red pulp with dense lymphocyte populations. (B) Model group, showing severe lymphocyte depletion, blurred boundaries between white pulp and red pulp, and necrotic cells. (C) Levamisole group, showing partial recovery of lymphocyte density. (D-F) *L. sarmentosa* extract-treated groups (36, 72, and 108 mg/kg, respectively), showing an improvement in lymphocyte density and restoration of splenic architecture. The high-dose group (F) shows a near-complete recovery of the standard spleen structure. *(W: White pulp; R: Red pulp; CA: Central artery).*

Conclusion

This study demonstrates that *Launaea sarmentosa* extract effectively counteracts cyclophosphamide-induced immunosuppression in mice. The highest dose (108 mg/kg/day) was particularly effective, significantly restoring spleen and thymus architecture—surpassing levamisole—and stimulating humoral immunity via upregulation of IL-4, IL-6, and IgG. These findings suggest that *L. sarmentosa* could be a promising natural immunomodulatory agent, offering a potential therapeutic strategy for conditions involving compromised immune function. Future research should focus on isolating its active compounds, elucidating their precise mechanisms of action, and evaluating the long-term safety and efficacy of the extract.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

Acknowledgements

This study was supported by other Departments and Faculties at Hanoi Medical University (HMU), Hanoi, Vietnam. The authors, therefore, acknowledge with thanks the HMU staff for useful advice and technical support.

References

1. Nicholson LB. The immune system. Essays Biochem. 2016;60(3):275-301. https://doi.org/10.1042/EBC20160017
2. Alanazi HH, Elasbali AM, Alanazi MK, El Azab EF. Medicinal Herbs: Promising Immunomodulators for the Treatment of Infectious Diseases. Mol Basel Switz. 2023;28(24):8045. https://doi.org/10.3390/molecules28248045
3. Chaplin DD. Overview of the immune response. J Allergy Clin Immunol. 2010;125(2 Suppl 2):S3-23. https://doi.org/10.1016/j.jaci.2009.12.980
4. Morimoto Y, Routes JM. Immunodeficiency Overview. Prim Care Clin Off Pract. 2008;35(1):159-173. https://doi.org/10.1016/j.pop.2007.09.004
5. Rébé C, Ghiringhelli F. Cytotoxic effects of chemotherapy on cancer and immune cells: how can it be modulated to generate novel therapeutic strategies? Future Oncol Lond Engl. 2015;11(19):2645-2654. https://doi.org/10.2217/fon.15.198
6. Öhrmalm L, Smedman C, Wong M, Broliden K, Tolfvenstam T, Norbeck O. Decreased functional T lymphocyte-mediated cytokine responses in patients with chemotherapy-induced neutropenia. J Intern Med. 2013;274(4):363-370. https://doi.org/10.1111/joim.12100
7. Lagou MK, Anastasiadou DP, Karagiannis GS. A Proposed Link Between Acute Thymic Involution and Late Adverse Effects of Chemotherapy. Front Immunol. 2022;13:933547. https://doi.org/10.3389/fimmu.2022.933547
8. Ahlmann M, Hempel G. The effect of cyclophosphamide on the immune system: implications for clinical cancer therapy. Cancer Chemother Pharmacol. 2016;78(4):661-671. https://doi.org/10.1007/s00280-016-3152-1
9. Loeffler M, Krüger JA, Reisfeld RA. Immunostimulatory effects of low-dose cyclophosphamide are controlled by inducible nitric oxide synthase. Cancer Res. 2005;65(12):5027-5030. https://doi.org/10.1158/0008-5472.CAN-05-0646
10. Zhong Z, Vong CT, Chen F, Tan H, Zhang C, Wang N, Cui L, Wang Y, Feng Y. Immunomodulatory potential of natural products from herbal medicines as immune checkpoints inhibitors: Helping to fight against cancer via multiple targets. Med Res Rev. 2022;42(3):1246-1279. https://doi.org/10.1002/med.21876
11. Nikiema WA, Ouédraogo M, Ouédraogo WP, Fofana S, Ouédraogo BHA, Delma TE, Amadé B, Abdoulaye GM,

Sawadogo AS, Ouédraogo R, Semde R. Systematic Review of Chemical Compounds with Immunomodulatory Action Isolated from African Medicinal Plants. Molecules. 2024;29(9):2010. https://doi.org/10.3390/molecules29092010
12. Shorinwa OA, Otu VS. Immunomodulatory Activity of the Aqueous Extract of the pith of *Citrus limon L.* (Rutaceae) Using Cyclophosphamide Induced Myelosuppression. Trop J Nat Prod Res. 2023;7(3):2660-2664. http://www.doi.org/10.26538/tjnpr/v7i3.29.
13. Ezeagha CC, Ajaghaku DL, Ajaegbu EE, Ngwoke KG, Osadebe PO, Okoye FBC. Molucidine and Desmethylmolucidine as Immunostimulatory Lead Compounds of *Morinda lucida* (Rubiaceae). Trop J Nat Prod Res. 2021;5(5):977-982. http://www.doi.org/10.26538/tjnpr/v5i5.29
14. Marbun RAT, Rosidah, Yuandani, Sitorus P. Immunomodulatory effect of *Artemisia vulgaris L.* ethanol extract and its marker compound on antibody and cytokine release in non-immunosuppressed and immunosuppressed rats. Trop J Nat Prod Res. 2025;9(3):1228-1231. https://doi.org/10.26538/tjnpr/v9i3.44
15. Kan LLY, Chan BCL, Leung PC, Wong CK. Natural-Product-Derived Adjunctive Treatments to Conventional Therapy and Their Immunoregulatory Activities in Triple-Negative Breast Cancer. Molecules. 2023;28(15):5804. https://doi.org/10.3390/molecules28155804
16. Tran DQ, Pham AC, Nguyen TTT, Vo TC, Vu HD, Ho GT, Mohsin SM. Growth, Physiological, and Biochemical Responses of a Medicinal Plant *Launaea sarmentosa* to Salinity. Horticulturae. 2024;10(4):388. https://doi.org/10.3390/horticulturae10040388
17. Salih Y, Harisha CR, Shukla VJ, Acharya R. Pharmacognostical evaluation of *Launaea sarmentosa* (Willd.) schultz-bip.ex Kuntze root. Ayu. 2013;34(1):90-94. https://doi.org/10.4103/0974-8520.115439
18. Nguyen TT, Nguyen TTA, Nguyen TM, Nguyen THL, Nguyen TH, Vu TD, Tran HT, Nguyen TH, Nguyen MK, Do TH. Chemical constituents from the aerial parts of *Launaea sarmentosa* (Asteraceae). Biochem Syst Ecol. 2023;110:104706. https://doi.org/10.1016/j.bse.2023.104706
19. Pham TV, Hoang TX, Nguyen HN, Do BH, Vo HHN, Tran GB. Chemical Composition, Anti-bacterial Activity and Molecular Docking Studies of Essential Oil Isolated from Sa Sam Nam (*Launaea sarmentosa*). J Oleo Sci. 2024;73(5):787-799. https://doi.org/10.5650/jos.ess23254
20. Raju GS, RahmanMoghal MM, Hossain MS, Hassan MM, Billah MM, Ahamed SK, Rana SM. Assessment of pharmacological activities of two medicinal plant of Bangladesh: *Launaea sarmentosa* and *Aegialitis rotundifolia* Roxb in the management of pain, pyrexia and inflammation. Biol Res. 2014;47(1):55. https://doi.org/10.1186/0717-6287-47-55
21. Das S, Priyanka KR, Prabhu K, Vinayagam R, Rajaram R, Kang SG. Anticandidal Properties of *Launaea sarmentosa* among the Salt Marsh Plants Collected from Palk Bay and the Gulf of Mannar Coast, Southeastern India. Antibiotics. 2024;13(8):748. https://doi.org/10.3390/antibiotics13080748
22. Nguyen T, Hong T, Vo Thanh K, Y H, Pham DT, Giao D, Tran T, Kamei K. Anti-inflammatory Constituents Isolated From *Launaea sarmentosa* Against Infection by LPS-stimulated Macrophages. Rec Nat Prod. 2024;6:663-73 https://doi.org/10.25135/rnp.487.2410.3343
23. Shen L, Luo H, Fan L, Tian X, Tang A, Wu X, Dong K, Su Z. Potential Immunoregulatory Mechanism of Plant Saponins: A Review. Mol Basel Switz. 2023;29(1):113. https://doi.org/10.3390/molecules29010113
24. Oo AM, Nor MNM, Lwin OM, Simbak N, Mohd Adnan LH, Rao USM. Immunomodulatory effects of apigenin, luteolin, and quercetin through natural killer cell cytokine secretion. J Appl PharmSci.2022;12(09):121-26. https://doi.org/10.7324/JAPS.2022.120914
25. Tungmunnithum D, Thongboonyou A, Pholboon A, Yangsabai A. Flavonoids and Other Phenolic Compounds from Medicinal Plants for Pharmaceutical and Medical Aspects: An Overview. Medicines. 2018;5(3):93. https://doi.org/10.3390/medicines5030093
26. Martínez G, Mijares MR, De Sanctis JB. Effects of Flavonoids and Its Derivatives on Immune Cell Responses. Recent Pat Inflamm Allergy Drug Discov. 2019;13(2):84-104. https://doi.org/10.2174/1872213X13666190426164124
27. Pham BQ, Nguyen NKT, Pham SQ, Nguyen CD, Trinh LV, Dinh HTT, Trinh QV, Pham VAT. Potential effects of Linh Loc Son hard capsule – a Vietnamese herbal combination in immunodeficiency induced by cyclophosphamide on mice. J Pharm Pharmacogn Res. 2024;12(5):892-899. https://doi.org/10.56499/jppres23.1751_12.5.892
28. Van Pham AT, Luong MH, Dinh HTT, Mai TP, Trinh QV, Luong LH. Immunostimulatory Effect of *Moringa oleifera* Extracts on Cyclophosphamide-induced Immunosuppressed Mice. J Herbs Spices Med Plants. 2021;27(4):377-385. https://doi.org/10.1080/10496475.2021.1934620
29. Fischer AH, Jacobson KA, Rose J, Zeller R. Hematoxylin and eosin staining of tissue and cell sections. CSH Protoc. 2008;2008:pdb.prot4986. https://doi.org/10.1101/pdb.prot4986
30. Zhong W, Huang H, Yang Z, Chang P. rhCNB Improves Cyclophosphamide-Induced Immunodeficiency in BALB/c Mice. Evid-Based Complement Altern Med ECAM. 2022;2022:4891399. https://doi.org/10.1155/2022/4891399
31. Khan S, Uddin M, Hridoy A, Islam K, Miah M. The Effect of Levamisole on Growth Performance, Humoral Immunity and Blood Biochemical Profile in Broiler Chickens. J Bangladesh Agric Univ. 2020;18. https://doi.org/10.5455/JBAU.13301
32. Pourahmad M, Soltani R, Noroozi MH, Khorvash F, Ataei B, Shams M, Nikokar F. Effectiveness of levamisole in the treatment of patients with severe COVID-19: a randomized controlled clinical trial. J Infect Dev Ctries. 2024;18(12.1):S275-S281. https://doi.org/10.3855/jidc.18659
33. Thapa P, Farber DL. The Role of the Thymus in the Immune Response. Thorac Surg Clin. 2019;29(2):123-131. https://doi.org/10.1016/j.thorsurg.2018.12.001
34. Xu J, Xu Z, Zhu S, Tovanich S, Wu B. Abstract C43: Cancer effects on the function of the host immune organs: Thymus and spleen. Cancer Prev Res (Phila Pa). 2013;6(11_Supplement):C43-C43. https://doi.org/10.1158/1940-6215.PREV-13-C43
35. Kolathingal-Thodika N, Usha PTA, Sujarani S, Suresh NN, Priya PM, Naseef PP, Kuruniyan MS, Ollakkode S, Elayadeth-Meethal M. A cyclophosphamide-induced immunosuppression *Swiss* Albino mouse model unveils a potential role for cow urine distillate as a feed additive. J Ayurveda Integr Med. 2023;14(5):100784. https://doi.org/10.1016/j.jaim.2023.100784
36. Dubyak GR. Chapter 21 - GPCRs in innate and adaptive immune responses. In: Jastrzebska B, Park PSH, editors. GPCRs: Academic Press; 2020. 429-461 p. https://doi.org/10.1016/B978-0-12-816228-6.00021-0
37. McDaniel MM, Meibers HE, Pasare C. Innate control of adaptive immunity and adaptive instruction of innate immunity: bi-directional flow of information. Curr Opin Immunol. 2021;73:25-33. https://doi.org/10.1016/j.coi.2021.07.013
38. Ganusov VV, Auerbach J. Mathematical modeling reveals kinetics of lymphocyte recirculation in the whole organism. PLoS Comput Biol. 2014;10(5):e1003586. https://doi.org/10.1371/journal.pcbi.1003586
39. Goldberg GL, Dudakov JA, Reiseger JJ, Seach N, Ueno T, Vlahos K, Hammett MV, Young LF, Heng TSP, Boyd RL, Chidgey AP. Sex Steroid Ablation Enhances Immune Reconstitution Following Cytotoxic Antineoplastic Therapy in Young Mice. J Immunol. 2010;184(11):6014-6024. https://doi.org/10.4049/jimmunol.0802445
40. Kalish RS, Askenase PW. Molecular mechanisms of CD8+ T cell–mediated delayed hypersensitivity: Implications for allergies, asthma, and autoimmunity. J Allergy Clin Immunol. 1999;103(2):192-199.https://doi.org/10.1016/S0091-6749(99)70489-6
41. Thorn M, Hudson AW, Kreeger J, Kawabe TT, Bowman CJ, Collinge M. Evaluation of a novel delayed-type hypersensitivity

assay to *Candida albicans* in adult and neonatal rats. J Immunotoxicol.2015;12(4):350-360. https://doi.org/10.3109/1547691X.2014.980925
42. Ou JY, Liu FL, Chen CL, Fang MC, Huang CH. Immunomodulatory effects of *Ulva*-derived polysaccharides, oligosaccharides, and residues in a murine model of delayed-type hypersensitivity. Biosci Microbiota Food Health. 2024;43(2):128-134. https://doi.org/10.12938/bmfh.2023-065
43. Chongpison Y, Sriswasdi S, Buranapraditkun S, Thantiworasit P, Rerknimitr P, Mongkolpathumrat P, Chularojanamontri L, Srinoulprasert Y, Rerkpattanapipat T, Chanprapaph K, Disphanurat W, Chakkavittumrong P, Tovanabutra N, Srisuttiyakorn C, Sukasem C, Tuchinda P, Pongcharoen P, Klaewsongkram J. IFN-γ ELISpot-enabled machine learning for culprit drug identification in nonimmediate drug hypersensitivity. J Allergy Clin Immunol. 2024;153(1):193-202. https://doi.org/10.1016/j.jaci.2023.08.026
44. Jang D in, Lee AH, Shin HY, Song HR, Park JH, Kang TB, Lee SR, Yang SH. The Role of Tumor Necrosis Factor Alpha (TNF-α) in Autoimmune Disease and Current TNF-α Inhibitors in Therapeutics. Int J Mol Sci. 2021;22(5):2719. https://doi.org/10.3390/ijms22052719
45. Psarras A, Antanaviciute A, Alase A, Carr I, Wittmann M, Emery P, Tsokos G, Vital E. TNF-α Regulates Human Plasmacytoid Dendritic Cells by Suppressing IFN-α Production and Enhancing T Cell Activation. J Immunol. 2021;206(4):785-796. https://doi.org/10.4049/jimmunol.1901358
46. Silva-Filho JL, Caruso-Neves C, Pinheiro AAS. IL-4: an important cytokine in determining the fate of T cells. Biophys Rev. 2014;6(1):111-118. https://doi.org/10.1007/s12551-013-0133-z
47. Chakma CR, Good-Jacobson KL. Requirements of IL-4 during the Generation of B Cell Memory. J Immunol. 2023;210(12):1853-1860. https://doi.org/10.4049/jimmunol.2200922
48. Rath T, Billmeier U, Waldner MJ, Atreya R, Neurath MF. From physiology to disease and targeted therapy: interleukin-6 in inflammation and inflammation-associated carcinogenesis. Arch Toxicol. 2015;89(4):541-554. https://doi.org/10.1007/s00204-015-1461-5
49. Gabay C. Interleukin-6 and chronic inflammation. Arthritis Res Ther. 2006;8(2):S3. https://doi.org/10.1186/ar1917
50. Lin YL, Chen SH, Wang JY. Critical role of IL-6 in dendritic cell-induced allergic inflammation of asthma. J Mol Med. 2016;94(1):51-59. https://doi.org/10.1007/s00109-015-1325-8
51. Nauta J. Humoral and Cellular Immunity. In: Statistics in Clinical Vaccine Trials. Berlin Heidelberg: Springer; 2011. 13-17 p. https://doi.org/10.1007/978-3-642-14691-6_2
52. Manetti M, Pratesi S, Romano E, Rosa I, Martiradonna A, Bellando-Randone S, Guiducci S, Ibba-Manneschi L, Maggi E, Matucci-Cerinic M. FRI0362 Angiogenic t cell expansion correlates with severity of peripheral vascular damage in systemic sclerosis. Ann Rheum Dis. 2017;76:623. https://doi.org/10.1136/annrheumdis-2017-eular.3017
53. Xu YD, Cheng M, Shang PP, Yang YQ. Role of IL-6 in dendritic cell functions. J Leukoc Biol. 2022;111(3):695-709. https://doi.org/10.1002/JLB.3MR0621-616RR