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Hematological Parameters and Growth Performance of Nile Tilapia (*Oreochromis niloticus*) Fed Fermented Papaya (*Carica papaya* L.) Leaf Extract

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ABSTRACT

Nile tilapia (*Oreochromis niloticus*) is one of the most important aquaculture species worldwide, but intensive farming has increased susceptibility to bacterial infections, particularly Aeromonas hydrophila, which threatens productivity and survival. This study evaluated fermented papaya (*Carica papaya* L.) leaf extract (FPLE) as a natural immunostimulant and sustainable alternative to antibiotics in Nile tilapia culture. A 45-day feeding trial was conducted using a completely randomized design with five treatments (0, 16, 18, and 20 mL FPLE/kg feed) and three replicates. Hematological, immunological, growth, and bacterial resistance parameters were analyzed. Results showed that supplementation with 20 mL/kg FPLE significantly increased post-infection leukocyte counts (2.82×10^4 vs. 2.40×10^4 cells/mm^3), phagocytic activity (46.26% vs. 39.51%), and erythrocyte levels (5.85×10^6 vs. 5.25×10^6 cells/mm^3). Differential leukocyte analysis revealed lymphocyte dominance (90.33%) and elevated monocytes (13.33%), indicating enhanced adaptive and nonspecific immunity. In addition, total bacterial load decreased by 22.4%, and specific growth rate improved (4.34% vs. 4.22%/day), while water quality remained within optimal ranges. The synergistic effects of papaya-derived bioactive compounds and *Lactobacillus casei* probiotics from Yakult likely contributed to immune enhancement and nutrient absorption. FPLE supplementation at 20 mL/kg optimized immunostimulation without compromising survival (77–84%), demonstrating its dual role in disease prevention and growth promotion. These findings highlight FPLE as a safe, eco-friendly feed additive with strong potential for reducing antibiotic dependence and supporting sustainable tilapia aquaculture.

INTRODUCTION

Nile tilapia (*Oreochromis niloticus*) has become one of the most important freshwater aquaculture species globally due to its fast growth rate, adaptability to various environmental conditions, and high nutritional value (Ramlah *et al*., 2016). As consumer demand continues to rise, tilapia farming has expanded significantly, making it a crucial protein source for many communities. However, the intensification of aquaculture practices has led to increased disease outbreaks, particularly those caused by *Aeromonas hydrophila*, a Gram-negative bacterium that can cause mortality rates of 80-100% within two weeks of infection *(Nahar et al*., 2016). This pathogen attacks multiple organs, causing symptoms such as skin lesions, scale detachment, and internal hemorrhaging (Muslikha *et al*., 2016), posing a serious threat to aquaculture productivity.

The aquaculture industry has traditionally relied on antibiotics to control bacterial infections, but this approach has led to concerning issues such as antibiotic resistance, environmental contamination, and potential human health risks (Zhao *et al*., 2018). Dong *et al*., (2021) emphasize that *A. hydrophila* can rapidly develop resistance to common antibiotics, while Manik (2013) note its zoonotic potential, making it a public health concern. These challenges have driven the search for sustainable alternatives, particularly plant-based immunostimulants that can enhance fish immunity without the negative consequences associated with chemical treatments.

Papaya *(Carica papaya*) leaves have emerged as a promising natural solution due to their rich content of bioactive compounds, including carpain alkaloids, flavonoids, saponins, and papain enzymes (Setiawan & Oka, 2015). These components exhibit antimicrobial properties and immunomodulatory effects, as demonstrated by Sumarni (2011), who reported 91.67% survival rates in tilapia challenged with *A. hydrophila* when fed papaya leaf extract. However, the bitter taste of raw papaya leaves, caused by carpain alkaloids (Muahiddah & Diamahesa, 2023; Somdare *et al*., 2023) limits their palatability and effectiveness in fish feed, necessitating processing methods like fermentation to improve acceptability and bioavailability (Koh *et al*., 2017; Zusfahair *et al*., 2014).

Moreover, the immunomodulatory properties of papaya leaves are noteworthy, as they have been shown to enhance the non-specific immune response in aquatic species. Research indicates that feeding fish papaya leaf extracts can elevate white blood cell counts and promote overall health, including improved growth rates and feed utilization efficiencies (Abdul Hamid *et al*., 2022; Razak *et al*., 2021; Sathyapalan *et al*., 2020). This multifaceted utility reinforces the potential of Carica papaya as a functional feed additive in aquaculture, particularly in combating bacterial infections and augmenting fish immune responses.

Fermentation transforms the nutritional and functional properties of papaya leaves through microbial action, enhancing flavor and digestibility while preserving bioactive compounds (Koh *et al*., 2017; Leitão *et al*., 2023; Syawal *et al*., 2019). The addition of probiotics like *Lactobacillus casei* from Yakult further improves the ferment's effectiveness by promoting gut health and competitive exclusion of pathogens (Chen *et al*., 2018). This combination addresses multiple challenges: it enhances palatability, boosts immune function through bioactive compounds, and improves intestinal health via probiotics, creating a comprehensive approach to disease prevention (Fujita *et al*., 2017; Koul *et al*., 2022; Leitão *et al*., 2023; Veersain *et al*., 2023).

This study investigates the effects of fermented papaya leaf supplementation on Nile tilapia's immune response, growth performance, and resistance to *A. hydrophila* infection. By evaluating hematological parameters, phagocytic activity, and bacterial load reduction, the research aims to establish an evidence-based, sustainable alternative to antibiotics in aquaculture. The findings could significantly contribute to developing eco-friendly disease management strategies that support the growing tilapia industry while addressing food safety and environmental concerns.

METHODS

Research Time and Location

This research was conducted from December 2024 to January 2025. The maintenance activities were carried out at the Aquaculture Production and Reproduction Laboratory, Faculty of Agriculture, University of Mataram.

Research Method

The research method used in this study was an experimental method employing a Completely Randomized Design (CRD) consisting of 5 treatments with 3 replications, resulting in 15 experimental units. The treatments included the positive control group (P0), which consisted of a standard feed without any supplementation of fermented papaya leaf solution and was challenged *with Aeromonas hydrophila* to assess baseline effects. The experimental groups (P1, P2, and P3) received different concentrations of fermented papaya leaf solution (16 ml/kg, 18 ml/kg, and 20 ml/kg respectively), allowing a comparative analysis of the influence of various dosages on the experimental subjects against *A. hydrophila* challenge (Baušys *et al*., 2020; Dupont *et al*., 2012).

Tools and Materials

The tools used in this study included an aerator, DO meter, effendof, container, microscope, tray, pH meter, Sahli pipette, test tube rack, stopwatch, syringe, and measuring cylinder. The materials used were water, anticoagulant, aquadest, Giemsa stain, Nile tilapia (*Oreochromis niloticus*), HCl solution, methanol, and papaya leaf powder.

Research Procedure

Preparation of Containers

The maintenance containers used were 15 units of 40×30×30 cm containers. The containers were first washed thoroughly and filled with water, then treated with 25 ppm $KMnO_4$ (Potassium Permanganate) solution and left for 24 hours to ensure they were free from pathogenic microorganisms (El-Sayed, 2002; Sabwa *et al*., 2022) Afterward, the containers were rinsed with clean water and dried for 24 hours. Once cleaned, each container was filled with water to a height of 25 cm (30 L), sourced from a bore well that had been previously settled in a tank and aerated. Nile tilapia measuring 8–10 cm was then introduced into each aquarium at a stocking density of 15 fish per 30 L.

Preparation of Fermented Papaya Leaf Solution and Test Feed

The preparation of the fermented papaya leaf solution involved several steps and specific ingredients: 50 g of fresh papaya leaves, 1000 mL of boiled water, 1.4 g of tape yeast, 1 bottle of Yakult, 50 g of rice bran, and 10 g of palm sugar. The papaya leaves were finely sliced and combined with boiled water, then blended until a smooth, homogeneous mixture was achieved. This mixture was poured into a clean mineral water bottle. Next, the rice bran, palm sugar, Yakult, and crushed tape yeast were sequentially added into the bottle. The container was then tightly sealed and shaken thoroughly to ensure an even mix of all components before being stored in a dark room, away from direct sunlight. After four days of fermentation, the solution was shaken again, and the cap loosened to release accumulated gas. On the seventh day, the fermented papaya leaf solution was considered ready for use, as indicated by a distinctive tape fermentation aroma (Hasanah *et al*., 2019; Koni *et al*., 2019; Kusuma & Novianto, 2018).

Maintenance of Test Fish

The fish were maintained for 45 days and fed with feed supplemented with the fermented papaya leaf solution. Feeding was conducted at 5% of the total biomass, administered three times daily (08:00, 12:00, and 16:00 Central Indonesia Time).

Sterilization of Equipment

Sterilization was performed to eliminate contamination by pathogenic or unwanted microorganisms. All tools were washed thoroughly, dried, and wrapped in paper. Test tubes, Erlenmeyer flasks, and measuring cylinders were covered with cotton and gauze to prevent condensation. The wrapped tools were then autoclaved at 121°C and 1 atm pressure for 15 minutes.

Preparation of Bacterial Growth Media

The media used for bacterial inoculant growth included Tryptic Soy Agar (TSA), Tryptic Soy Broth (TSB), and Glutamate Starch Phenol (GSP) agar. The ratios to distilled water were as follows: TSA (40 g/L), TSB (30 g/L), and GSP (45 g/L).

Challenge Test

On day 32 of maintenance, fish were intramuscularly challenged with *Aeromonas hydrophila* at a density of 10^8 CFU/mL (0.1 mL/fish) using a 1 mL syringe. Post-challenge, fish were returned to aquaria and observed for 14 days.

Fish Blood Sampling

Blood was collected via the caudal vein using a 1 mL syringe pre-rinsed with 10% EDTA. Samples were transferred to EDTA-coated microtubes to prevent coagulation. Blood analysis was performed twice: at 14 days post-challenge. Parameters included total leukocyte count, leukocyte differentiation, phagocytic activity, hemoglobin, hematocrit, and total bacterial count.

Data Analysis

Data were analyzed descriptively and statistically using SPSS (version 16.0). One-way ANOVA (95% confidence level) was applied, followed by Duncan's test for significant differences.

RESULTS

Total Leukocyte Count

In this study, the total leukocyte count in Nile tilapia (*Oreochromis niloticus*) during the 45-day trial with fermented papaya leaf solution supplementation ranged from 1.92–1.95 × 10^4 cells/mm³ at the initial stage to 2.4–2.82 × 10^4 cells/mm³ post-infection (Figure 1).

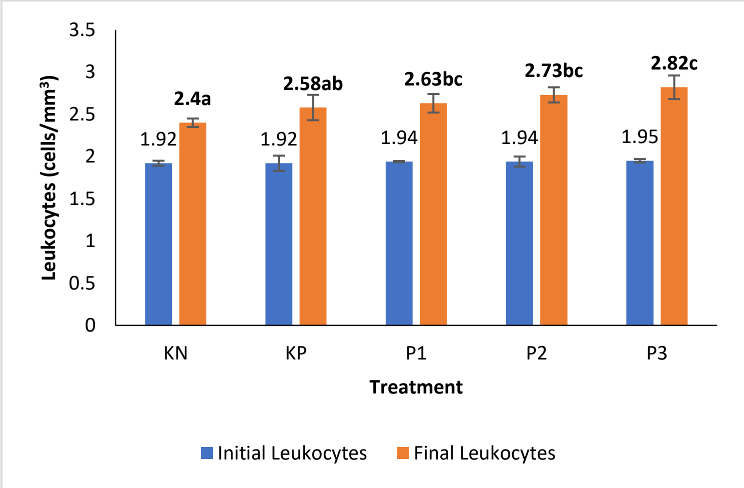

Figure 1. Total Leukocyte Count in Nile Tilapia

ANOVA results indicated that dietary supplementation with fermented papaya leaf solution had no significant effect ($P > 0.05$) on leukocyte counts during the initial rearing phase. However, post-infection analysis revealed a significant increase ($P < 0.05$) in leukocyte levels, prompting further Duncan's multiple range test. Post-infection leukocyte counts showed that the negative control (NC: 2.4×10^4 cells/mm³) did not differ significantly from the positive control (PC: 2.58×10^4 cells/mm³) but was significantly lower than treatments P1 (2.63×10^4 cells/mm³), P2 (2.73×10^4 cells/mm³), and P3 (2.82×10^4 cells/mm³).

Leukocyte Differential Count

The differential leukocyte count in Nile tilapia fed fermented papaya leaf extract for 45 days ranged from 47.33–49.66% initially to 58.33–90.33% post-infection (Figure 2).

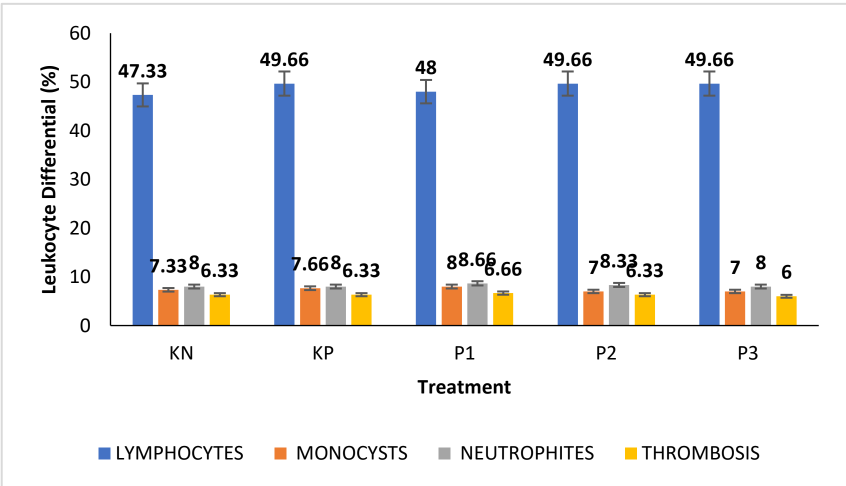

Figure 2. Differential Leukocyte Count in Nile Tilapia (Initial Phase)

ANOVA showed no significant effect ($P > 0.05$) of dietary supplementation on differential leukocyte counts during the initial phase. Lymphocytes (47.33–49.66%), monocytes (7–8%), thrombocytes (8–8.66%), and neutrophils (6.33–6.66%) remained stable across treatments.

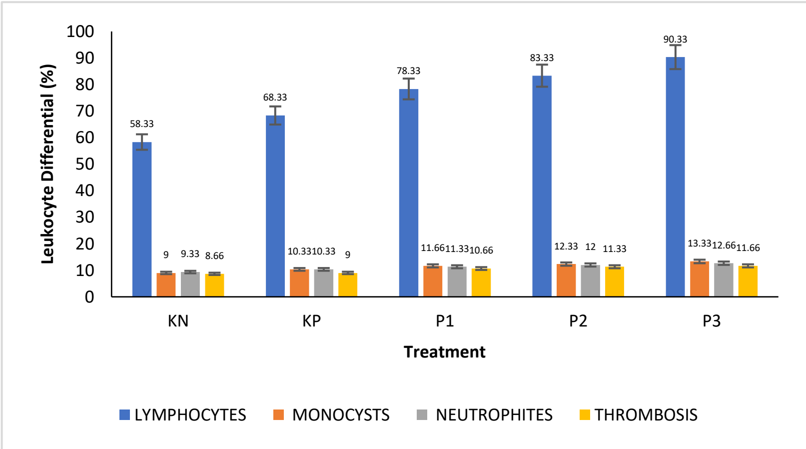

Figure 3. Differential Leukocyte Count in Nile Tilapia (Post-Infection)

Post-infection, ANOVA revealed a significant effect (P < 0.05) on differential leukocyte counts, leading to Duncan's test. Key findings: Lymphocytes: NC (58.33%) differed significantly from all treatments, while P3 (90.33%) showed no significant difference from P2 (83.33%). Monocytes: NC (9%) did not differ from PC (10.33%), P1 (11.66%), or P2 (12.33%) but differed from P3 (13.33%). Thrombocytes: NC (8.66%) showed no difference from PC (9%) or P1 (10.66%) but differed from P3 (11.66%). Neutrophils: NC (9.33%) did not differ from PC (8.33%), P1 (11.33%), or P2 (12%) but differed from P3 (12.66%).

Phagocytic Activity

The phagocytic activity of Nile tilapia (*Oreochromis niloticus*) fed with fermented papaya leaf extract for 45 days ranged from 39.51% to 46.26% during the initial rearing period (Figure 4).

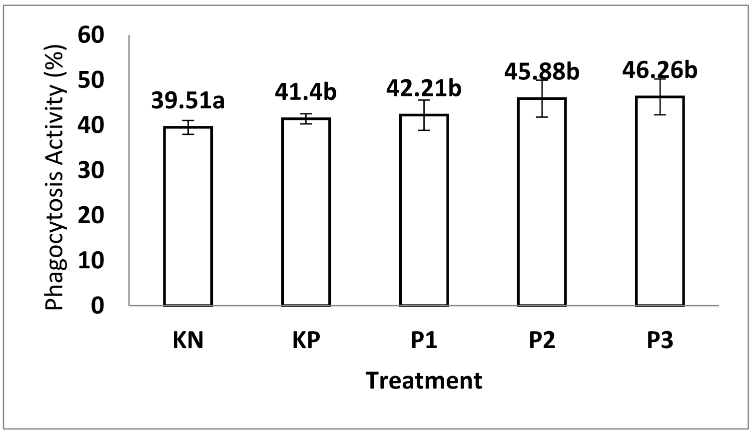

Figure 4. Phagocytic Activity of Nile Tilapia

ANOVA results indicated that dietary supplementation with fermented papaya leaf extract significantly enhanced (P < 0.05) phagocytic activity by the end of the trial period, warranting Duncan's post-hoc test. The test revealed that: The negative control (NC: 39.51%) showed no significant difference from other treatments. The positive control (PC: 41.4%) differed significantly from P1 (42.21%), P2 (45.88%), and P3 (46.26%). These results demonstrate that fermented papaya leaf extract significantly improved phagocytic activity in Nile tilapia.

Erythrocyte Count

The erythrocyte count of Nile tilapia ranged from 4.26 × 10^6 to 4.48 × 10^6 cells/mm^3 during the initial phase and increased to 5.25 × 10^6 to 5.85 × 10^6 cells/mm^3 post-infection (Figure 5).

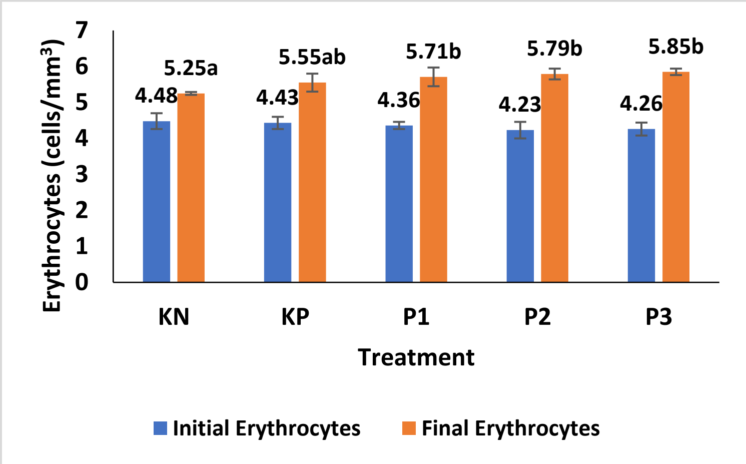

Figure 5. Erythrocyte Count of Nile Tilapia

ANOVA results showed: No significant effect ($P > 0.05$) during initial rearing. Significant enhancement ($P < 0.05$) post-infection. Duncan's test of post-infection results revealed: NC (5.25 × 10^6 cells/mm^3) showed no difference from PC (5.55 × 10^6 cells/mm^3). Both controls differed significantly from P1 (5.71 × 10^6 cells/mm^3), P2 (5.79 × 10^6 cells/mm^3), and P3 (5.85 × 10^6 cells/mm^3). This demonstrates that fermented papaya leaf extract significantly improved erythrocyte production following bacterial challenge.

Hematocrit Level

The hematocrit levels of Nile tilapia (*Oreochromis niloticus*) during the 45-day feeding trial with fermented papaya leaf extract supplementation ranged from 17.98% to 18.87% during the maintenance phase and increased to 23.48-29.55% post-infection (Figure 6).

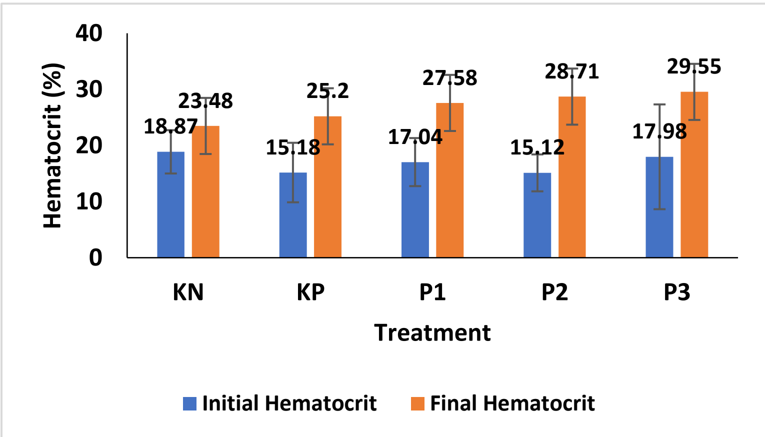

Figure 6. Hematocrit Levels of Nile Tilapia

ANOVA results indicated that dietary supplementation had no significant effect ($P > 0.05$) on hematocrit levels during either phase. The specific values were Maintenance phase: NC: 18.87%, PC: 15.18%, P1: 17.04%, P2: 15.12%, P3: 17.98%. Post-infection: NC: 23.48%, PC: 25.20%, P1: 27.58%, P2: 28.71%, dan P3: 29.55%.

Hemoglobin Level

Hemoglobin concentrations in Nile tilapia ranged from 6.20% to 6.83% during maintenance and 9.06% to 9.46% post-infection (Figure 7).

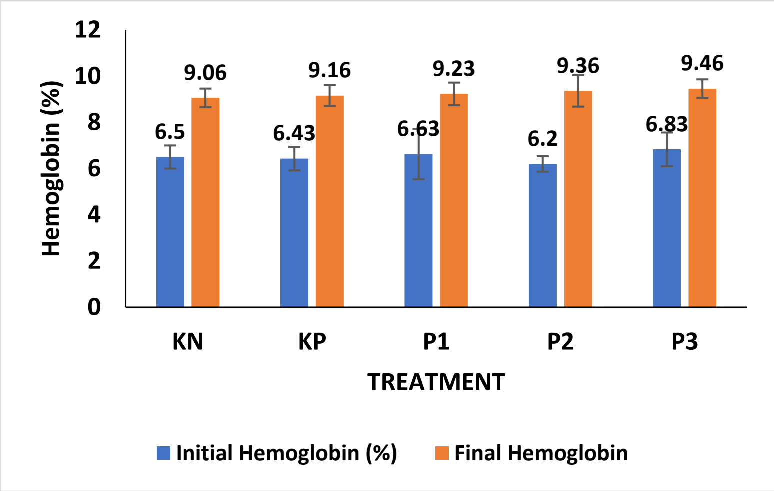

Figure 7. Hemoglobin Levels of Nile Tilapia

Statistical analysis revealed no significant differences (P > 0.05) among treatments in either phase: Maintenance phase: NC: 6.50%, PC: 6.43%, P1: 6.63%, P2: 6.20%, and P3: 6.83%. Post-infection: NC: 9.06%, PC: 9.16%, P1: 9.23%, P2: 9.36%, and P3: 9.46%

Total Bacterial Count (TBC)

The total bacterial count in Nile tilapia ranged from 923,333 to 1,190,000 CFU/mL during the maintenance phase (Figure 8).

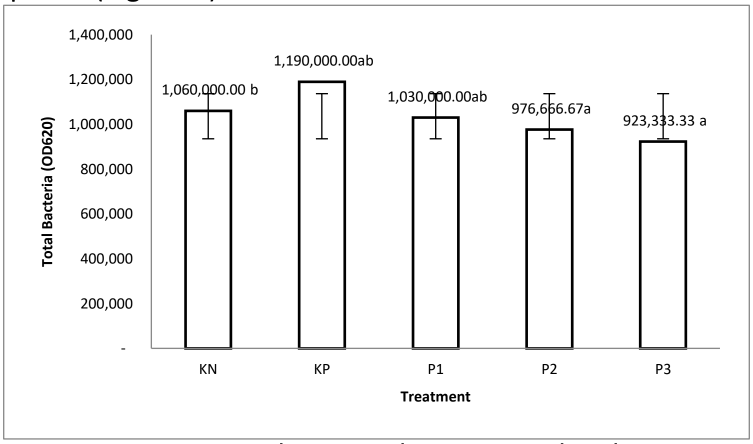

Figure 8. Total Bacterial Count in Nile Tilapia

ANOVA showed significant effects (P < 0.05) of fermented papaya leaf extract on bacterial load. Duncan's test revealed: NC showed no significant difference from PC and P1. Significant reduction in P2 and P3 compared to controls.

Absolute Weight

Absolute weight gain, calculated as the difference between final and initial fish weights, ranged from 8.25 to 8.86 g during the 45-day rearing period (Figure 9).

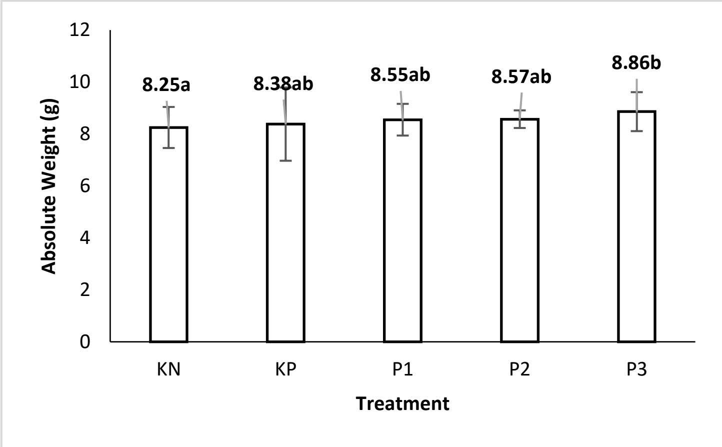

Figure 9. Absolute Weight Gain of Nile Tilapia

ANOVA revealed no significant differences (P > 0.05) in weight gain among treatments. However, Duncan's test showed: NC (8.25 g) showed the lowest weight gain but was not significantly different from PC (8.38 g), P1 (8.55 g), and P2 (8.57 g). P3 (8.86 g) demonstrated significantly higher weight gain compared to NC.

Absolute Length

Absolute length gain, measured as the difference between final and initial fish lengths, ranged from 4.53 to 5.44 cm (Figure 10).

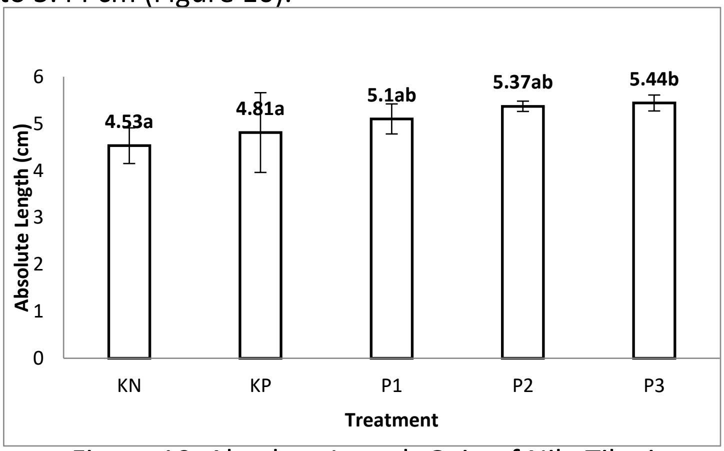

Figure 10. Absolute Length Gain of Nile Tilapia

Statistical analysis showed: No significant differences (P > 0.05) among treatments. NC showed the lowest length gain but was not significantly different from PC (4.53 cm), P1 (4.81 cm), and P2 (5.37 cm). P3 (5.44 cm) showed significantly greater length gain than NC.

Specific Growth Rate (SGR)

The specific growth rate of Nile tilapia ranged from 4.22% to 4.34%/day during the trial period (Figure 11).

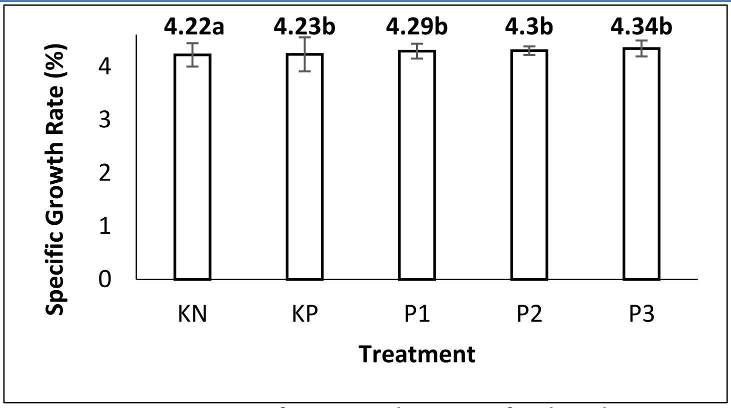

Figure 11. Specific Growth Rate of Nile Tilapia

ANOVA indicated significant effects ($P < 0.05$) of dietary treatments on SGR. Duncan's test revealed: NC (4.22%/day) differed significantly from all supplemented groups. PC (4.23%/day) showed no significant difference from P1 (4.29%/day), P2 (4.30%/day), and P3 (4.34%/day).

Water Quality Parameters

The monitored water quality parameters included temperature, dissolved oxygen (DO), and pH (acidity level). Table 1 presents the water quality measurements during the rearing period.

Table 1. Water Quality Parameters During the Maintenance Period

Parameter	Measured Range	Optimal Range (Arifin, 2016)
Temperature (°C)	27,6-29	28-32
pH	7.6-9	4-9
DO (mg/L)	7.3-9.3	>3

The measured water quality parameters throughout the study period remained within optimal ranges for Nile tilapia growth: Temperature: 27.6-29.0°C, pH: 7.6-9.0, and Dissolved oxygen: 7.3-9.3 mg/L. These values comply with both the Indonesian National Standard (SNI 7550:2009) and the reference values reported by Arifin (2016).

DISCUSSION

This study reveals the intelligent mode of action of fermented papaya leaf extract as an immunostimulant in Nile tilapia. Forty-five days of supplementation did not significantly increase the total leukocyte count during the initial maintenance phase, which is in fact a positive indicator that the extract does not induce immunological stress or excessive immune system activation under normal conditions. However, a markedly different response was observed post-bacterial infection, where a significant increase in total leukocyte count was recorded in the treatment groups. This pattern suggests that papaya leaf extract acts as a priming agent, preparing and enabling the immune system to be more strongly activated only when pathogen challenges are present—a highly efficient defense mechanism (Muahiddah & Diamahesa, 2023; Somdare *et al*., 2023; Tayal *et al*., 2019).

The post-infection increase in total leukocytes was driven by significant rises in specific leukocyte subsets, including lymphocytes, neutrophils, and monocytes. The increase in lymphocytes, particularly in the highest-dose group, indicates reinforcement of the adaptive immune system, which is responsible for more specific immune responses and immunological memory. Meanwhile, the elevations in neutrophils and monocytes—key cells of nonspecific immunity—reflect enhanced readiness to confront pathogens through mechanisms such as phagocytosis. These findings are consistent with the central role of lymphocytes in vertebrate inflammatory and immune responses, suggesting that papaya leaf extract strengthens cellular defense in a comprehensive manner (Razak *et al*., 2021).

Furthermore, the efficacy of fermented papaya leaf extract was demonstrated by a significant enhancement in phagocytic activity, which serves as a direct indicator of the destructive capacity of nonspecific immune cells. The increase in phagocytic activity from 39.51% to 46.26% in the highest-dose group highlights the improved ability of immune cells to engulf and destroy pathogens. In addition, the observed post-infection increase in erythrocyte count in the treatment groups indicates that supplementation also enhances the oxygen-carrying capacity of the blood. This directly supports the elevated metabolic processes required during recovery and immune response, in line with previous findings on physiological improvements mediated by herbal bioactive compounds (Ahmad *et al*., 2021; Dahl *et al*., 2020).

The safety aspect of this supplementation is evidenced by the stability of key hematological parameters. Hematocrit and hemoglobin levels showed no significant changes throughout the study, both before and after infection, confirming that fermented papaya leaf extract does not disrupt oxygen transport function or induce physiological stress in fish. This stability is a critical indicator of the supplement's safety for aquaculture species (Purba *et al*., 2023; Vuong *et al*., 2014). An additional advantage lies in its positive impact on the rearing environment, where the extract was shown to reduce the total bacterial load in ponds, thereby offering proactive and eco-friendly disease control potential (Akter *et al.*, 2023).

The combination of enhanced immune responses, stable hematological conditions, and naturally improved rearing environments directly contributes to improved fish growth performance. This study recorded significant increases in body weight and length in the highest-dose groups. Such superior growth performance can be attributed to better fish health and optimal metabolic efficiency, as energy typically allocated for combating disease or stress can instead be redirected toward growth. Thus, fermented papaya leaf extract functions as a functional feed additive that not only enhances disease resistance but also improves productivity (Hamid *et al*., 2022).

Overall, the findings of this study confirm the potential of fermented papaya leaf extract as a safe and effective natural immunomodulator. Its ability to trigger a robust and coordinated immune response only when required, combined with its favorable safety profile and additional benefits for growth and the culture environment, positions it as an ideal candidate for sustainable fish health management strategies. Its application in Nile tilapia aquaculture holds great promise in reducing reliance on antibiotics and synthetic chemicals, while simultaneously promoting more eco-friendly and sustainable aquaculture practices.

CONCLUSION

The 20 mL/kg fermented papaya leaf supplementation demonstrated optimal immunostimulation through: Leukocyte proliferation enhancement, Phagocytic activity potentiation, Hematological parameter improvement, Growth performance augmentation, and Pathogen load reduction. These effects are attributed to synergistic interactions between: Papaya's bioactive compounds (flavonoids, alkaloids), Probiotic activity (*L. casei*), and Nutrient bioavailability improvement. The results validate traditional use of papaya leaves in aquaculture while providing scientific evidence for its immunostimulatory mechanisms. Further research should investigate long-term effects and optimal administration protocols.

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