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Dose-Dependent Effects of Snakehead Fish (Channa Striata) Oil Extract on Lipid Profile and Inflammatory Markers in Diet-Induced Dyslipidemic Rats

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Abstract

Dyslipidemia is a major cardiovascular risk factor closely associated with chronic inflammation. Snakehead fish (*Channa striata*) contains omega-3 fatty acids and bioactive peptides with lipid-modulating and anti-inflammatory potential. However, its dose-dependent effects on lipid and inflammatory parameters remain unclear. This study investigated the dose-dependent effects of *C. striata* oil extract on lipid profile and inflammatory markers in diet-induced dyslipidemic rats. Twenty-four male Wistar rats were randomized into four groups (n=6): normal control, dyslipidemia model, low-dose extract (150 mg/kgBW), and high-dose extract (250 mg/kgBW). Dyslipidemia was induced using quail egg yolk (4 mL/kgBW/day) for 14 days, while treatments were administered orally. Serum LDL, HDL, TNF-α, and IL-10 levels were analyzed using spectrophotometry and ELISA. Dyslipidemia induction significantly increased LDL and TNF-α and reduced HDL and IL-10 (p<0.001). Both extract doses improved all parameters, with the 250 mg/kgBW dose producing the strongest effects: LDL reduction of 55%, HDL restoration to 76% of control, TNF-α reduction of 64%, and IL-10 elevation to 74% of control. These findings demonstrate clear dose-response effects. *C. striata* oil extract exhibits significant anti-dyslipidemic and anti-inflammatory properties, supporting its potential as a natural adjunct therapy for dyslipidemia management.

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Introduction

Dyslipidemia, defined as elevated total cholesterol, triglycerides, and low-density lipoprotein (LDL) levels accompanied by decreased high-density lipoprotein (HDL) levels, is recognized as a major cardiovascular risk factor worldwide (Hidayatullah et al., 2022). In Indonesia, the prevalence of dyslipidemia has reached 18.2%, with 14.8% of adults experiencing elevated LDL-cholesterol

levels. This indicates that approximately one in seven Indonesian adults is at increased cardiovascular risk (Kemenkes, 2018). The growing burden of dyslipidemia is strongly associated with the increasing consumption of high-fat, low-fiber diets combined with sedentary lifestyles (Pappan & A, 2023).

The pathophysiology of dyslipidemia involves complex inflammatory processes. Elevated LDL-cholesterol promotes the development of atherosclerotic plaques, which are composed of inflammatory cells such as macrophages (Henein et al., 2022; Vekic et al., 2023). These macrophages release pro-inflammatory cytokines, notably tumor necrosis factor-alpha (TNF-α), which enhance inflammatory responses (Markin et al., 2023; Meidayanti, 2021; Yan et al., 2023). This cascade simultaneously suppresses the production of anti-inflammatory cytokines such as interleukin-10 (IL-10), creating a persistent pro-inflammatory state that accelerates atherosclerosis progression and increases the risk of cardiovascular disease (Berenice Martínez-Shio et al., 2022; Masfufatun et al., 2018)

Current management strategies for dyslipidemia focus primarily on lifestyle modifications, particularly dietary interventions involving unsaturated fatty acids (Kirkpatrick et al., 2023). Omega-3 fatty acids have been widely studied and are known to improve lipid profiles through multiple mechanisms, including inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, suppression of hepatic triglyceride synthesis, and modulation of inflammatory pathways (Djuricic & Calder, 2021; Virginia et al., 2016). In addition, omega-3 fatty acids influence inflammatory markers by incorporating into cell membranes, reducing arachidonic acid content, and promoting the synthesis of anti-inflammatory eicosanoids that enhance IL-10 levels (Silva et al., 2017).

Snakehead fish (Channa striata), a freshwater species abundant in Indonesia, has attracted attention as a promising natural source of bioactive compounds, including omega-3 and omega-6 fatty acids, peptides, and amino acids (Ikhsan et al., 2021; Pandiangan, 2022; Sasongko, 2022). Previous studies have demonstrated that omega-3 supplementation at 36 mg/kgBW effectively reduced cholesterol levels in hypercholesterolemic rats (Kedokteran et al., 2022), while a single therapeutic dose of Channa striata extract at 500 mg/kgBW significantly lowered inflammatory markers, including TNF-α, in hyperglycemic rats (Haryanto et al., 2025; Sasongko et al., 2023). However, no study has simultaneously evaluated the dose-dependent effects of C. striata oil extract on both lipid profiles and inflammatory markers within a single dyslipidemia animal model, and the optimal therapeutic dose range for achieving synergistic lipid-inflammatory benefits remains unestablished.

Therefore, this study was designed to comprehensively investigate the therapeutic potential of C. striata oil extract in dyslipidemia management through three specific objectives: (1) to evaluate dose-dependent effects on serum lipid profiles (HDL and LDL cholesterol), (2) to assess dose-dependent modulation of inflammatory markers (TNF-α and IL-10), and (3) to determine optimal dosing for synergistic therapeutic benefits.

Based on previous research on omega-3 fatty acids and fish-derived bioactive compounds, we hypothesized that: (H1) C. striata oil extract would significantly improve lipid profiles (increase HDL, decrease LDL) in a dose-dependent manner compared to untreated dyslipidemic controls; (H2) extract treatment would modulate inflammatory balance by significantly reducing pro-inflammatory TNF-α levels and enhancing anti-inflammatory IL-10 production in a dose-dependent fashion; and (H3) the higher dose (250 mg/kgBW) would demonstrate superior therapeutic efficacy across all measured parameters compared to the lower dose (150 mg/kgBW), suggesting an optimal therapeutic window. The findings are expected to provide evidence-based dosing recommendations and mechanistic insights for the potential clinical translation of C. striata oil extract as a natural therapeutic intervention for dyslipidemia management.

Despite the promising bioactive profile of C. striata, several critical knowledge gaps remain unaddressed in the literature. First, while previous studies have examined either the lipid-lowering effects or the anti-inflammatory properties of fish-derived compounds separately, no research has comprehensively evaluated the simultaneous, dose-dependent modulation of lipid profiles and inflammatory markers by C. striata extract (Hakim et al., 2024). Second, existing studies have primarily used chemical extraction methods or high-temperature processing, which may compromise the integrity of bioactive compounds. In contrast, the therapeutic potential of cold-pressed C. striata oil remains unexplored. Third, the optimal dosing regimen for achieving synergistic lipid-inflammatory benefits has not been established. These gaps limit our understanding of C. striata's full therapeutic potential and hinder translation toward clinical applications (Haryanto et al., 2025).

Materials and Methods

Experimental Design and Animals

This study employed a randomized controlled design using 24 male Wistar rats (Rattus norvegicus, 8 weeks old, ~200g) obtained from the Nutrition Laboratory, Inter-University Research Center, Faculty of Medicine, Universitas Gadjah Mada. Animals were randomly assigned to four groups (n=6 per group): (1) K_1 (Control): Standard feed throughout the study period, without dyslipidemia induction or any extract treatment (2) K_2 (Dyslipidemia model): Standard feed + oral administration of quail egg yolk (4 mL/kgBW/day for 14 days) without extract treatment (3) K_3 (Low dose treatment): Standard feed + oral administration of quail egg yolk (4 mL/kgBW/day for 14 days) + 150 mg/kgBW C. striata oil extract (4) K_4 (High dose treatment): Standard feed + oral administration of quail egg yolk (4 mL/kgBW/day for 14 days) + 250 mg/kgBW C. striata oil extract. All animals were housed in standard laboratory conditions with 12-hour light/dark cycles and provided ad libitum access to water. The study protocol was conducted over 35 days, including a 7-day acclimatization period (see Figure 1).

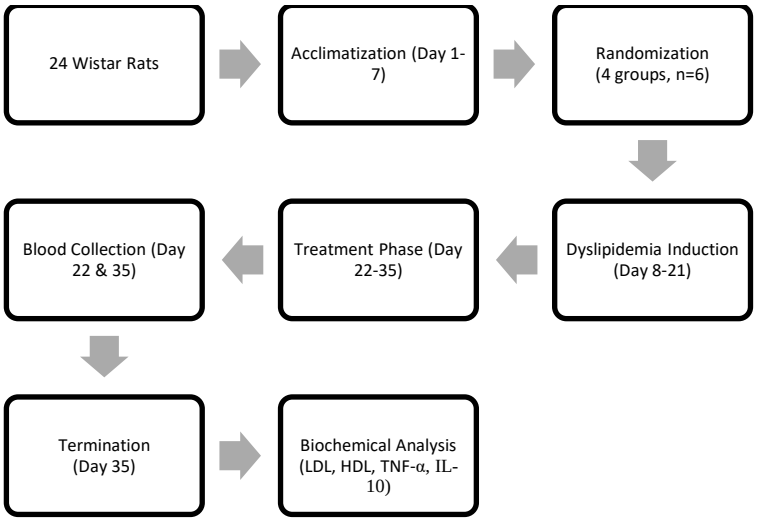

Figure 1. Experimental design and treatment protocol of the study

Extract Preparation

Snakehead fish (Channa striata) oil was extracted using the cold hydraulic press technique at 100-600 bar pressure. This solvent-free extraction method was chosen to preserve heat-sensitive

bioactive compounds, particularly omega-3 fatty acids, while preventing oxidation that could occur with chemical extraction or high-temperature processing.

Dyslipidemia Induction Protocol

Following the acclimatization period, dyslipidemia was induced using fresh quail egg yolk administered orally at 4 mL/kgBW daily for 14 consecutive days. Quail egg yolk was selected due to its exceptionally high cholesterol content (2,100.17 mg/100g), which effectively elevates blood cholesterol levels by overwhelming the body's homeostatic regulation mechanisms. During the 14-day induction period, K_1 continued receiving standard feed only, while K_2, K_3, and K_4 received standard feed + daily quail egg yolk administration. On the other side, K_3 and K_4 additionally received their respective snakehead fish extract doses simultaneously with egg yolk administration. All oral administrations were performed using feeding tubes to ensure accurate dosing and minimize stress-related variables.

Treatment Administration

Snakehead fish extract was administered daily via oral gavage for 14 days, concurrent with dyslipidemia induction in treatment groups. Extract doses (150 mg/kgBW for K_3 and 250 mg/kgBW for K_4) were calculated based on individual body weights measured weekly. The dose selection was based on previous studies demonstrating the therapeutic effects of Channa striata extract in metabolic disorders.

Blood Collection and Sample Processing

Blood samples were collected at two time points: Day 22 (immediately after the 14-day dyslipidemia induction period, to confirm model establishment) and Day 35 (upon treatment completion, for outcome assessment). Blood collection was performed via retro-orbital puncture under light ether anesthesia. Samples were collected into serum separator tubes, allowed to clot for 30 minutes at room temperature, then centrifuged at 805 × g for 15 minutes. Serum was separated and stored at −20 °C until analysis. Samples were collected into serum separator tubes, allowed to clot for 30 minutes at room temperature, then centrifuged at 805 × g for 15 minutes. Serum was separated and stored at −20 °C until analysis.

Biochemical Analyses

Lipid Profile Measurement: Serum HDL and LDL cholesterol levels were measured using spectrophotometric methods with commercial kits. Reference ranges for rats were: HDL ≥35 mg/dL and LDL 7-27.2 mg/dL (Diajeng, 2013). Inflammatory Marker Analysis: TNF-α and IL-10 concentrations were quantified using enzyme-linked immunosorbent assay (ELISA) with Fine test commercial kits. Analyses were performed according to the manufacturer's protocol, and results were expressed in pg/mL. Quality Control: All biochemical analyses were performed in duplicate, with a coefficient of variation <10% for acceptance. Standard curves were prepared for each assay batch, and positive and negative controls were included in each run.

Statistical Analysis

Data normality was assessed using the Shapiro-Wilk test, and variance homogeneity was evaluated using Levene's test. Normally distributed data with homogeneous variance were analyzed using one-way analysis of variance (ANOVA), followed by post hoc LSD tests for multiple comparisons. Non-parametric data were analyzed using the Kruskal-Wallis test followed by Mann-Whitney U tests for pairwise comparisons (Jiménez et al., 2021). LDL and HDL cholesterol data met the assumptions of normality and homogeneity. They were therefore analyzed using one-way ANOVA with the LSD post hoc test.

In contrast, TNF-α and IL-10 data showed non-normal distributions and were analyzed using the Kruskal-Wallis test followed by Mann-Whitney U pairwise comparisons. Changes within groups over time were evaluated using paired t-tests for normally distributed data. All statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA), which has been validated for the statistical procedures applied in this study.

Sample Size Justification

Sample size was calculated using G*Power 3.1 with α = 0.05, power = 0.80, and effect size f = 0.40, yielding a minimum sample size of n = 5 per group. We used n = 6 to increase statistical power.

Randomization

Simple randomization was performed using a computer-generated random number sequence via Research Randomizer (https://www.randomizer.org), with each rat independently assigned to one of four groups prior to the acclimatization period.

Blinding

This study employed a single-anonymized design: biochemical analyses (HDL, LDL, TNF-α, IL-10) were performed by laboratory technicians who were blinded to group assignments. However, the investigators administering treatments were aware of group allocation.

Inclusion/Exclusion Criteria

Only healthy male Wistar rats (8 weeks, 190–210g) were included. Animals showing signs of illness during acclimatization were excluded.

Animal Housing Details

Temperature 22 ± 2°C, humidity 50–60%, light–dark cycle 12/12 hours, maximum three animals per cage.

Results and Discussions

Dyslipidemia Model Validation

Quail egg yolk administration successfully induced dyslipidemia in all treatment groups. After 14 days of induction, groups K_2, K_3, and K_4 showed significantly elevated lipid levels compared to the control group (K_1):

Total cholesterol: K_1: 85.2 ± 1.79 mg/dL vs. K_2-K_4: 204.4-206.8 mg/dL ($p < 0.001$)
Triglycerides: K_1: 71.8 ± 2.1 mg/dL vs. K_2-K_4: 132.9-138.3 mg/dL ($p < 0.001$)
LDL cholesterol: K_1: 24.5 ± 1.37 mg/dL vs. K_2-K_4: 77.1-78.3 mg/dL ($p < 0.001$)
HDL cholesterol: K_1: 83.2 ± 2.1 mg/dL vs. K_2-K_4: 24.1-25.9 mg/dL ($p < 0.001$)
No significant differences were observed among the three dyslipidemia groups (K_2, K_3, K_4) at baseline, confirming consistent model establishment across treatment groups.

Effects of Snakehead Fish Extract on Lipid Profile

LDL Cholesterol

After 14 days of treatment, snakehead fish extract significantly reduced LDL levels in a dose-dependent manner.

Table 1. Effects of Channa striata oil extract on lipid profile (mean ± SD)

Group	LDL (mg/dL)	HDL (mg/dL)
K_1 (Control)	25.7 ± 1.53	84.6 ± 2.37
K_2 (Dyslipidemia)	83.7 ± 2.40	23.9 ± 2.07
K_3 (150 mg/kgBW)	50.3 ± 2.00*	47.7 ± 2.37*
K_4 (250 mg/kgBW)	41.1 ± 2.25*†	64.2 ± 2.33*†

*$p < 0.001$ vs. K_2; †$p < 0.001$ vs. K_3

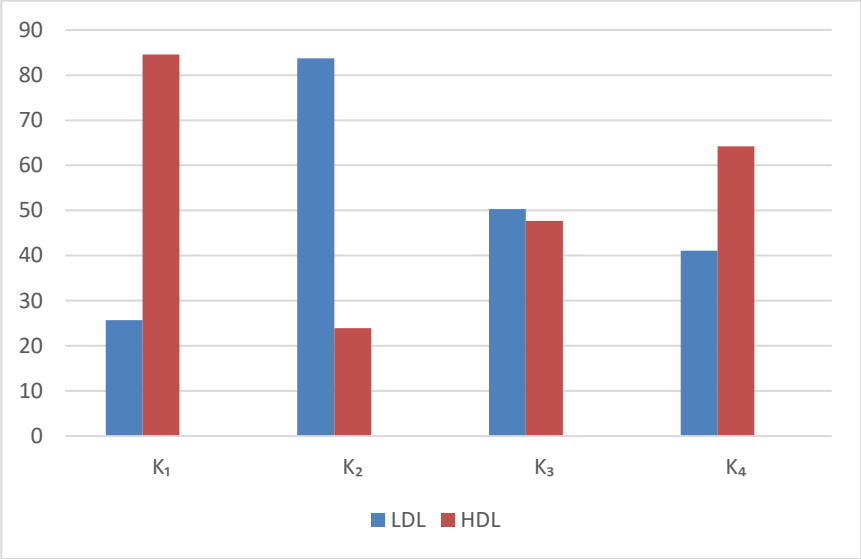

Figure 2. Effects of Channa striata oil extract on LDL and HDL levels

Data are presented as mean ± SD. *$p < 0.001$ vs. K_2; †$p < 0.001$ vs. K_3.

K_1 (Control): 25.7 ± 1.53 mg/dL
K_2 (Dyslipidemia): 83.7 ± 2.40 mg/dL
K_3 (150 mg/kgBW): 50.3 ± 2.00 mg/dL*
K_4 (250 mg/kgBW): 41.1 ± 2.25 mg/dL*†
*$p < 0.001$ vs. K_2; †$p < 0.001$ vs. K_3

Both treatment doses significantly reduced LDL compared to the untreated dyslipidemia group, with the higher dose (K_4) showing superior efficacy (55% reduction vs. 40% reduction in K_3).

HDL Cholesterol

Snakehead fish extract significantly increased HDL levels dose-dependently:
K_1 (Control): 84.6 ± 2.37 mg/dL
K_2 (Dyslipidemia): 23.9 ± 2.07 mg/dL
K_3 (150 mg/kgBW): 47.7 ± 2.37 mg/dL*
K_4 (250 mg/kgBW): 64.2 ± 2.33 mg/dL*†
*$p < 0.001$ vs. K_2; †$p < 0.001$ vs. K_3

The higher dose restored HDL to approximately 76% of control levels, while the lower dose achieved 56% restoration.

Effects on Inflammatory Markers

TNF-α Levels

Snakehead fish extract significantly reduced pro-inflammatory TNF-α levels (Figure 3):

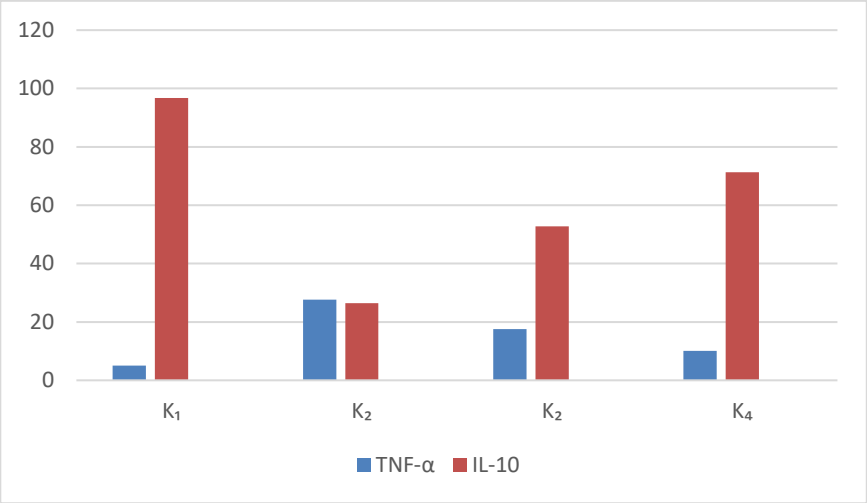

Figure 3. Effects of Channa striata oil extract on TNF-α and IL-10 levels in dyslipidemic rats

Data are presented as mean ± SD. *p < 0.001 vs. K_2; †p < 0.001 vs. K_3.

- K_1 (Control): 5.1 ± 0.47 pg/mL
- K_2 (Dyslipidemia): 27.7 ± 0.79 pg/mL
- K_3 (150 mg/kgBW): 17.6 ± 0.68 pg/mL*
- K_4 (250 mg/kgBW): 10.1 ± 0.77 pg/mL*†

*p < 0.001 vs. K_2; †p < 0.001 vs. K_3

The higher dose achieved a 64% reduction in TNF-α levels compared to the dyslipidemia group, while the lower dose produced a 36% reduction.

IL-10 Levels

Anti-inflammatory IL-10 levels were significantly increased by snakehead fish extract treatment:

- K_1 (Control): 96.8 ± 1.45 pg/mL
- K_2 (Dyslipidemia): 26.4 ± 1.12 pg/mL
- K_3 (150 mg/kgBW): 52.8 ± 2.01 pg/mL*
- K_4 (250 mg/kgBW): 71.3 ± 2.16 pg/mL*†

*p < 0.001 vs. K_2; †p < 0.001 vs. K_3

Treatment resulted in dose-dependent increases in IL-10, with the higher dose achieving 74% of control levels, compared with 55% with the lower dose.

Body Weight Changes

All groups showed weight gain throughout the study period. The dyslipidemia groups (K_2, K_3, K_4) gained significantly more weight during the induction period compared to controls (K_1: 17.0 ± 6.32g vs. K_2-K_4: 31.2-47.8g, p < 0.001). Treatment with snakehead fish extract showed a modest effect on weight gain, with K_4 showing the least additional weight gain among dyslipidemia groups.

Summary of Treatment Effects

Snakehead fish extract demonstrated significant therapeutic effects across all measured parameters. The 250 mg/kgBW dose consistently outperformed the 150 mg/kgBW dose, showing:

- Greater LDL reduction (55% vs. 40%)
- Superior HDL restoration (76% vs. 56% of control levels)
- More pronounced TNF-α suppression (64% vs. 36% reduction)
- Better IL-10 enhancement (74% vs. 55% of control levels)

All treatment effects were statistically significant ($p < 0.001$) and demonstrated clear dose-response relationships.

Principal Findings

This study demonstrates that snakehead fish (Channa striata) oil extract effectively ameliorates dyslipidemia and modulates inflammatory markers in a dose-dependent manner. The key findings include: (1) significant improvements in lipid profiles with LDL reductions up to 55% and HDL increases up to 76% of control levels; (2) substantial anti-inflammatory effects with TNF-α reductions up to 64% and IL-10 increases up to 74% of control levels; and (3) clear dose-response relationships across all measured parameters, with 250 mg/kgBW demonstrating superior efficacy compared to 150 mg/kgBW.

Mechanisms Underlying Lipid Profile Improvements

The observed lipid-lowering effects are primarily due to the omega-3 fatty acid content of snakehead fish extract, particularly EPA and DHA. These polyunsaturated fatty acids improve lipid metabolism through multiple complementary pathways. Our findings align with established mechanisms whereby omega-3 fatty acids suppress hepatic triglyceride synthesis by inhibiting SREBP-1c expression and activating PPAR-γ to enhance fatty acid β-oxidation (Pandiangan, 2022). The significant LDL reduction observed in our study (40-55% across doses) is consistent with omega-3 fatty acids' ability to prevent LDL oxidation and upregulate hepatic LDL receptors, thereby facilitating enhanced LDL clearance. The concurrent HDL elevation (56-76% restoration toward control levels) reflects improved reverse cholesterol transport mediated by increased LCAT enzyme activity, a well-documented effect of EPA and DHA supplementation (Virginia et al., 2016).

Importantly, our results demonstrate superior efficacy compared to previous studies using isolated omega-3 supplements, suggesting synergistic effects from the complex bioactive profile in snakehead fish extract, including amino acids and other fatty acids beyond EPA and DHA.

Anti-Inflammatory Effects and Clinical Relevance

The pronounced anti-inflammatory effects observed represent a particularly significant finding, as the intersection of dyslipidemia and inflammation drives cardiovascular disease progression. The substantial TNF-α reduction (36-64%) and IL-10 enhancement (55-74% of control levels) indicate that snakehead fish extract addresses both sides of the inflammatory balance. These effects likely result from omega-3 fatty acids' ability to replace arachidonic acid in cell membranes, shifting eicosanoid production from pro-inflammatory mediators (prostaglandin E2, leukotriene B4) toward anti-inflammatory compounds (resolvins, protectins) (P. D. Panjaitan & Damanik, 2022; T. F. C. Panjaitan et al., 2025). Additionally, the extract's amino acid content, particularly glycine and glutamic acid, contributes to NF-κB pathway inhibition and enhanced antioxidant capacity through glutathione synthesis (Cruzat et al., 2018). The magnitude of improvement in inflammatory markers observed in our study suggests potential clinical relevance, as elevated TNF-α levels are strongly associated with cardiovascular events in dyslipidemic patients. At the same time, IL-10 enhancement provides cardiovascular protection through multiple pathways.

Dose-Response Relationship and Therapeutic Implications

The clear dose-response relationship observed across all parameters supports the therapeutic potential of snakehead fish extract and provides important guidance for potential clinical translation. The superior efficacy of the 250 mg/kgBW dose suggests this may represent an optimal therapeutic range, though dose-escalation studies would be needed to establish maximum effective and safe doses. Notably, even the lower dose (150 mg/kg BW) produced significant improvements across all measured parameters, suggesting a relatively wide therapeutic window. This finding is practically important as it suggests that effective treatment may be achievable with moderate doses, potentially minimizing adverse effects while maintaining therapeutic benefit.

Comparison with Existing Therapies

Our results compare favorably with established dyslipidemia treatments. The LDL reductions observed (40-55%) approach those achieved with moderate-intensity statin therapy, while the concurrent anti-inflammatory effects provide additional cardiovascular benefits not typically seen with statins alone. The natural origin and apparent safety profile of snakehead fish extract may offer advantages for patients seeking alternative or complementary therapies. Furthermore, the simultaneous improvement in both lipid and inflammatory parameters addresses the complex pathophysiology of cardiovascular disease more comprehensively than single-target interventions. This dual mechanism of action may translate to superior clinical outcomes compared to isolated lipid-lowering approaches.

Study Strengths and Limitations

This study's strengths include the well-validated dyslipidemia model, comprehensive outcome assessment including both lipid and inflammatory markers, clear dose-response evaluation, and rigorous statistical methodology. The use of quail egg yolk to induce dyslipidemia effectively mimicked human dietary hyperlipidemia and created a clinically relevant disease model. However, several limitations must be acknowledged. First, the animal model limits direct extrapolation to humans, particularly regarding optimal dosing and long-term safety. Second, the relatively short treatment duration (14 days) prevents assessment of long-term therapeutic effects and potential adverse outcomes. Third, the specific bioactive compound concentrations in the extract were not characterized, limiting mechanistic understanding and reproducibility. Fourth, inflammatory markers were assessed only at the study endpoint, preventing evaluation of temporal response patterns. Finally, the study did not include positive control treatments (e.g., statins) for comparative efficacy assessment.

Clinical Translation Considerations

While these preclinical findings are promising, several considerations are important for potential clinical translation. The optimal human-equivalent dose should be established through pharmacokinetic studies, as direct scaling from animal doses may not be appropriate. Additionally, long-term safety studies would be essential, particularly regarding potential interactions with existing cardiovascular medications. Standardizing snakehead fish extract composition would be crucial for clinical applications, requiring the establishment of quality control measures for bioactive compound content. Furthermore, large-scale sustainable sourcing of snakehead fish would require careful consideration, given environmental and economic factors.

Future Research Directions

Future studies should prioritize several key areas. First, dose-escalation studies are needed to establish optimal therapeutic doses and safety margins. Second, longer-term studies should evaluate sustained efficacy and potential adverse effects. Third, mechanistic studies should

characterize specific bioactive compounds responsible for therapeutic effects and their individual contributions. Additionally, comparative studies with established therapies would provide important context for clinical positioning. Investigation of the effects of extracts across different dyslipidemia subtypes and patient populations would inform therapeutic applications. Finally, clinical trials in human subjects would be essential for establishing safety, efficacy, and optimal dosing in target populations.

Conclusion

Snakehead fish (Channa striata) oil extract demonstrates significant dose-dependent therapeutic effects in diet-induced dyslipidemic rats. Treatment at 250 mg/kgBW produced the most pronounced outcomes: LDL cholesterol reduction of 55%, HDL restoration to 76% of control levels, TNF-α suppression of 64%, and IL-10 elevation to 74% of control levels. The 150 mg/kgBW dose also yielded significant improvements across all parameters, indicating a wide therapeutic window. These findings support the potential of C. striata oil extract as a natural adjunct for the management of dyslipidemia and warrant further long-term and clinical investigation. Future research should examine TNF-α and IL-10 levels pre- and post-treatment in each group, analyze the bioactive content of snakehead fish oil extract, and conduct longer-term studies to better understand the long-term effects of this intervention.

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