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IN VIVO STUDY OF THE POTENTIAL OF BELUNTAS LEAF (*PLUCHEA INDICA*) *LOLOH* AS AN ANTIHYPERCHOLESTEROLEMIA

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ABSTRACT

Introduction: Non-Communicable Diseases (NCD) are the leading cause of death in Indonesia. One of the most prevalent NCDs is hypercholesterolemia. The most commonly used drug class is statins, which work by inhibiting HMG-CoA reductase; however, they carry side effects including myalgia, diabetes mellitus, and rhabdomyolysis. Traditional herbal medicine represents a potential alternative. According to the *lontar usadha duwe griya*, *loloh* of beluntas leaves is a traditional remedy used to treat conditions related to blood pressure disorders. This is supported by the phytochemical content of beluntas leaves, including flavonoids, alkaloids, and phenols, all of which have antihypercholesterolemic effects.
Methods: This study used a true experimental design with a post-test only controlled group design involving 30 male Wistar rats divided into three groups: Group K (aquadest 5 ml/day/rat), Group KS (simvastatin 0.36 mg/day/rat), and Group P1 (*loloh* of beluntas leaves 4.5 g/day/rat). Data were analyzed using One-Way ANOVA.
Results: One-Way ANOVA results for all variables showed $p > 0.05$, indicating no statistically significant difference. However, the findings may be clinically meaningful.
Conclusion: *Loloh* of beluntas leaves (*Pluchea indica*) was not statistically significant but demonstrated potential clinical significance, except for the triglyceride variable.
Kata kunci : *Pluchea indica, Loloh,* Antihypercholesterolemia.

INTRODUCTION

In developing countries such as Indonesia, Non-Communicable Diseases (NCDs) remain a serious public health problem. NCDs account for the highest number of deaths in Indonesia.[1] NCDs are defined as medical conditions that cannot be transmitted from one person to another.[2] One of the major risk factors for NCDs is hypercholesterolemia.[3]

Based on the "Profile of Non-Communicable Diseases 2016" published by the Indonesian Ministry of Health, hypercholesterolemia was the most prevalent NCD risk factor in Indonesia in 2015–2016, with an average prevalence of approximately 55.4%, with the incidence increasing with advancing age.[4]

Hypercholesterolemia is a condition in which total blood cholesterol exceeds the upper limit of normal.[5] It is characterized by at least one of three criteria: LDL cholesterol > 190 mg/dL; or > 160 mg/dL with one cardiovascular risk factor; or > 130 mg/dL with two or more cardiovascular risk factors.[6] If left untreated, hypercholesterolemia can lead to atherosclerosis and coronary heart disease, both of which can be fatal.[7]

Several drug classes are used to manage hypercholesterolemia, including statins and non-statins. Statins are the most commonly prescribed first-line therapy, acting by inhibiting HMG-CoA reductase.[8] However, statins are associated with notable side effects, including myalgia, diabetes mellitus, and rhabdomyolysis.[9]

In light of these side effects, research into new effective agents with fewer adverse effects is warranted. Traditional herbal medicine is one promising approach. Herbal medicines are formulations derived from plants, animals, and minerals passed down through generations.[10] Compared to modern drugs, traditional herbal medicines are generally associated with fewer serious side effects.[11]

According to the *lontar usadha duwe griya*, *loloh* of beluntas leaves is indicated for treating conditions related to blood pressure disorders.[12] Blood pressure disturbances can result from hypercholesterolemia, as cholesterol accumulation in vessel walls causes narrowing and stiffening.[13] Furthermore, Yuliani et al. demonstrated that beluntas leaf extract contains flavonoids, alkaloids, and phenols — all of which have antihypercholesterolemic properties.[14]

Based on the above background, hypercholesterolemia is a dangerous NCD risk factor that requires appropriate management. With scientific evidence supporting the phytochemical content of beluntas leaves, further investigation is needed to confirm the antihypercholesterolemic effect of beluntas leaf *loloh*. Therefore, this study aimed to evaluate the potential of beluntas leaf (*Pluchea indica*) *loloh* as an antihypercholesterolemia agent in a male Wistar rat model.

METHODS

This study was an exploratory true experimental study using a post-test-only controlled group design. The selection of experimental groups was conducted using random sampling, in which animals were randomly assigned to groups of equal size that met the experimental criteria. Rats were housed in six cages (5 rats/cage), and cages were randomly assigned to groups using a lottery method, resulting in two cages per group, minimizing stress-related confounders and preventing investigator-driven selection bias. To minimize selection bias, only rats meeting the inclusion criteria — male Wistar rats aged 2–3 months weighing 100–200 grams — were enrolled; rats in poor health were excluded, and rats that died during the study were recorded as dropouts.

This study was conducted from the preparation of *Pluchea indica* leaf *loloh* through the treatment phase on male Wistar rats to the collection of blood samples. Subsequently, lipid profile testing was performed, followed by data analysis and the preparation of the research report. This study was conducted from June to November 2021.

The study population consisted of 30 male Wistar rats divided into three groups: K, KS, and P1. Group K served as the negative control and received aquabidest 5 mL/day. Group KS served as the positive control and received simvastatin 0.36 mg/day/rat. Group P1 received fresh *Pluchea indica* leaf aqueous preparation (*loloh*) at a dose of 4.5 g/kg body weight/day in a volume of 5 mL. All treatments were administered orally once daily for 6 weeks. All three groups received an identical atherogenic diet throughout the study. The atherogenic diet was prepared daily by mixing 1000 g of standard feed with 100 g of lamb fat and 50 g of egg yolk. This amount was distributed for six cages per day. K served as the negative control as aquabidest is physiologically inert and does not interfere with lipid metabolism, while KS served as the positive control as simvastatin is a clinically established first-line anticholesterol agent providing a standard benchmark for comparison.

Fresh *Pluchea indica* leaves were obtained from a local plant supplier and prepared daily as a traditional aqueous herbal preparation locally known as *loloh*. The fresh leaves were mechanically crushed and mixed with aquabidest without boiling, preserving the thermolabile bioactive constituents of the fresh plant material. The preparation was administered orally to the P1 group at a dose of 4.5 g/kg body weight/day in a volume of 5 mL once daily for 6 weeks.

Sample size was determined using the Federer formula: $(t - 1)(n - 1) \geq 15$, where t represents the number of treatment groups and n represents the number of subjects per group. Each treatment group consisted of 8.5 rats, rounded up to a minimum of 9 samples per group; thus, when multiplied by 3 groups, the total was 27 rats. Considering the dropout criteria, the sample size was increased by at least 10% to the 27 rats, resulting in 3 additional rats. These were then distributed evenly among the 3 groups—1 rat per group—so that the total number of male Wistar rats per group was 10, and the total number of rats tested was 30.

Following preparation of the *loloh* and simvastatin solutions, male Wistar rats underwent the treatment protocol, after which blood samples were collected and plasma lipid profiles were analyzed. The results of the data analysis were used to prepare this research report. The data underwent descriptive statistical analysis, including tests for normality and homogeneity, as well as tests for differences in means. All of which were performed using IBM SPSS Statistics version 26.0. To minimize measurement bias, a single-blind design was implemented, in which the laboratory analyst responsible for lipid profile measurements was blinded to group assignments; blood samples were submitted under coded labels, with the coding key withheld until all analyses were completed.

RESULTS

Prior to group comparison, data normality was assessed using the Shapiro-Wilk test and homogeneity of variance was assessed using Levene's test. All six variables met the assumptions of normality (Shapiro-Wilk, all $P > 0.05$) and homogeneity of variance (Levene's test, all $P > 0.05$), confirming that one-way ANOVA was the appropriate statistical test.

The effects of fresh *Pluchea indica* leaf aqueous preparation (*loloh*), simvastatin, and aquabidest on total cholesterol, HDL, LDL, triglyceride, MDA, and body weight in atherogenic diet-fed male Wistar rats are presented in Tables 1 through 6.

Table 1. Mean results and one-way ANOVA test for total cholesterol in male wistar rats (*Rattus norvegicus*)

Group	Mean ± SD (mg/dL)	α	p
K	148.4044 ± 18.38550	0.05	0.555
P1	142.0189 ± 17.67809		
KS	140.2300 ± 13.21859		
Total	143.5511 ± 16.33139		

The data in Table 1 show the KS group demonstrated the lowest total cholesterol level, while the K group had the highest. The P1 group fell between the two. No statistically significant difference was found among the groups (P 0.555).

Table 2. Mean results and one-way ANOVA test of HDL levels in male wistar rats (*Rattus norvegicus*)

Group	Mean ± SD (mg/dL)	α	p
K	55.8100 ± 9.31379	0.05	0.783
P1	57.9322 ± 6.07591		
KS	56.3200 ± 3.21201		
Total	56.6874 ± 6.48647		

Table 2 shows that Group P1 had the highest HDL levels compared to Group K and Group KS. Group P1 also exceeded the overall average HDL level of all study groups. Group KS ranked second based on the average HDL level. Group K was the study group with the lowest average HDL level. No statistically significant difference was observed among the groups (P 0.783).

Table 3. Mean results and one-way ANOVA test of LDL levels in male wistar rats (*Rattus norvegicus*)

Group	Mean ± SD (mg/dL)	α	p
K	68.8089 ± 21.92615	0.05	0.525
P1	58.8756 ± 21.04399		
KS	60.7900 ± 14.44618		
Total	62.8248 ± 19.17360		

Table 3 presents data on the average LDL levels of male Wistar rats (*Rattus norvegicus*). The table shows that group K had the highest average LDL level. Meanwhile, group P1 had the lowest average LDL level.

Table 4. Mean and one-way ANOVA results for triglycerides in male wistar rats (*Rattus norvegicus*)

Group	Mean ± SD (n/mmol)	α	p
K	1.7356 ± 0.96549	0.05	0.601
P1	1.3322 ± 0.85152		
KS	1.6356 ± 0.79673		
Total	1.5678 ± 0.85778		

As shown in the data presented in Table 4, the highest average triglyceride level was found in Group P1, and the lowest average triglyceride level was found in Group KS. Group K had an average triglyceride level lower than the overall average but not lower than that of Group KS. No statistically significant difference was observed among the groups (P 0.490)

Table 5. Mean results and one-way ANOVA test of MDA levels in male wistar rats (*Rattus norvegicus*)

Group	Mean ± SD (gram)	α	p
K	149.4222 ± 20.75270	0.05	0.883
P1	144.4889 ± 18.78273		
KS	146.7111 ± 10.43796		
Total	146.8741 ± 16.69778		

Table 5 shows that Group K had the highest average MDA level. Group KS had the second-highest average MDA level, with a value that was still higher than the overall average. Group P1 had the lowest average MDA level and was the only group with a value below the overall average

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Table 6. Mean results and one-way ANOVA test of body weight in male wistar rats (*Rattus norvegicus*) over 6 weeks

Group	Mean ± SD (mg/dL)	α	p
K	118.9322 ± 7.88432	0.05	0.490
P1	126.0556 ± 27.78626		
KS	115.6022 ± 14.56194		
Total	120.1967 ± 18.48452		

Table 6 presents the average body weight data in grams, measured periodically over a 6-week period. Groups P1 and KS each had average values lower than the overall group average, with Group P1 having the lowest average body weight among the groups. Meanwhile, Group K had the highest average body weight of all the groups.

DISCUSSION

The mean total cholesterol levels were similar across the three groups. Group KS (simvastatin) had the lowest mean total cholesterol (140.2300 ± 13.21859 mg/dL), consistent with simvastatin's mechanism of inhibiting HMG-CoA reductase and enhancing LDL receptor affinity to accelerate LDL catabolism.[15]

Accordingly, Group KS also showed lower LDL levels than the negative control (Group K). Group P1 (*loloh* of beluntas leaves) had a mean total cholesterol lower than Group K and the overall mean, possibly due to the flavonoid, phenol, and alkaloid content of beluntas leaves.[16-19]

Specifically, quercetin — a flavonoid — may act similarly to statins by inhibiting early-stage cholesterol biosynthesis and upregulating LDL receptor affinity.[17,19,20] Ferulic acid, another flavonoid compound, is believed to reduce lipid levels by inhibiting lipid synthesis and promoting fat oxidation through gene-level regulation.[21] Catechins have also been reported to function in a manner similar to statins and quercetin, potentially inhibiting cholesterol absorption and increasing its excretion.[20,22]

Phenols may act as antioxidants to prevent LDL oxidation, while alkaloids may increase fat secretion through defecation.[16-19] Regarding HDL cholesterol (Table 2), results were similar across groups, which may be attributable to the physiological cholesterol metabolism of rats affecting HDL levels uniformly across groups.[23] Although the difference was not statistically significant, Group P1 showed a higher HDL level (57.9322 ± 6.07591 mg/dL) compared to Group K, which may be due to phenolic compounds in beluntas leaves that enhance reverse cholesterol transport (RCT) by macrophages.[24] Group KS also showed an HDL increase relative to Group K, consistent with the known ability of statins to raise HDL cholesterol, although the exact mechanism remains unclear.[25]

Malondialdehyde (MDA) is a product of lipid peroxidation and serves as a biochemical marker of free radical activity, oxidative capacity, and dyslipidemia.[25,26] Although no statistically significant difference was found, the flavonoid content of beluntas leaves is believed to reduce MDA levels by scavenging hydroxyl and superhydroxyl radicals, thereby inhibiting lipid peroxidation and blocking MDA formation.[27] Additionally, flavonoids can chelate Fe^{2+} ions involved in the initiation of lipid peroxidation.[27] MDA levels tend to rise in parallel with elevated LDL levels.[28]

Body weight was recorded every 10 days and the values presented represent the mean over 6 weeks. Rats were fed a high-fat diet throughout the study. No significant differences in body weight were found between groups, consistent with Nurmawati (2016), who reported that sustained high-fat feeding leads to energy storage as triglycerides in adipose tissue; when energy is required, these triglycerides are then mobilized, resulting in reduced appetite and no significant weight gain in the control group.[29] Individual variation in physical activity among rats also influenced energy expenditure and triglyceride storage, which may explain the elevated triglyceride levels in Group P1.[29]

The lack of statistical significance may also be related to the frequency of *loloh* administration. According to the lontar reference, *loloh* should be administered three times daily; however, in this study it was given once daily. This may have affected the outcome given the half-life pharmacokinetics of the active compounds involved.[30] Furthermore, the liquid formulation used in this study may be less stable compared to solid dosage forms such as capsules.[20]

Overall, the administration of beluntas leaf *loloh* in male Wistar rats showed no statistically significant difference in total cholesterol, HDL, LDL, triglycerides, MDA, or body weight compared to aquadest or simvastatin groups, as confirmed by One-Way ANOVA (all $p > 0.05$). However, the findings are clinically meaningful, as Group P1 demonstrated results comparable to, and in some variables better than, the simvastatin control group. It should also be noted that *loloh* or traditional herbal preparations inherently have a lower capacity to concentrate bioactive compounds compared to extraction-based methods.

CONCLUSION AND RECOMMENDATIONS

Fresh *Pluchea indica* leaf aqueous preparation (*loloh*) at a dose of 4.5 g/kg body weight produced directional reductions in total cholesterol, LDL, MDA, and body weight, as well as a directional increase in HDL, compared to the negative control group, consistent with the direction of effects observed in the simvastatin group. Triglyceride levels were not improved. However, none of these differences reached statistical significance (all $P > 0.05$). These findings suggest a possible exploratory biological signal in lipid modulation and oxidative stress reduction, but further studies using standardized plant material, multiple dose levels, phytochemical characterization, and adequately powered designs are required to confirm these effects.

The lack of statistical significance may be attributed to insufficient dose variation, a sample size at the minimum threshold, and the duration of treatment — as fresh herbal preparations generally require longer treatment periods to produce statistically measurable effects.

Future studies should investigate dose-response relationships and toxicity profiles, identify and quantify the active compounds in *Pluchea indica* leaf *loloh* responsible for lipid-modulating activity, and evaluate the efficacy of standardized capsule formulations compared to the fresh aqueous preparation.

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