Jurnal Jamu Indonesia (2026) 11(6): 525–531
https://jamu-journal.ipb.ac.id/index.php/JJI/index

ISSN 2407-7178
eISSN 2407-7763

Research Article
DOI: https://doi.org/10.29244/jji.v11i6.594

Effectiveness of Ethanol Extract of Kluwih (*Artocarpus camansi*) Leaves on Total Cholesterol in Rats Given a High-Fat Diet and Streptozotocin

Efektivitas Ekstrak Etanol Daun Kluwih (*Artocarpus camansi*) terhadap Kolesterol Total Tikus yang Diberi Pakan Tinggi Lemak dan Streptozotocin

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ARTICLE INFO

Article history:
Received on: 2026-09-26
Revised on: 2026-09-30
Accepted on: 2026-09-30
Published on: 2026-11-02

Keywords:
Breadnut
Hypercholesterolemia
Lipid-lowering
Phytochemical screening
Simvastatin

Kata kunci:
Hiperkolesterolemia
Kluwih
Penapisan fitokimia
Penurun lipid
Simvastatin

ABSTRACT

Leaves of *Artocarpus camansi* (kluwih) are used in Indonesian folk medicine, but their effect on blood lipids, which are often disturbed in type 2 diabetes, is untested in vivo. This study evaluated an ethanol extract of *A. camansi* leaves in rats given a high-fat diet followed by low-dose streptozotocin. Thirty male rats formed six groups (n = 5): normal, vehicle, simvastatin, and extract at 300, 350 or 400 mg/kg daily for 14 days. Total cholesterol, measured on days 0, 14, 21, 28 and 35, rose from 43–48 to 127–141 mg/dL after induction. The extract then lowered it by a mean of 57.2%, 48.0% and 43.5% at the three doses, against 64.9% for simvastatin, while vehicle rats kept rising (group × time interaction, $p < 0.001$). At 300 mg/kg, final total cholesterol (53.4 ± 5.1 mg/dL) did not differ from the normal or simvastatin groups. Its active constituents remain unquantified.

ABSTRAK

Daun *Artocarpus camansi* (kluwih) digunakan dalam pengobatan tradisional Indonesia, tetapi pengaruhnya terhadap lipid darah, yang sering terganggu pada diabetes tipe 2, belum diuji secara in vivo. Penelitian ini mengevaluasi ekstrak etanol daun *A. camansi* pada tikus yang diberi pakan tinggi lemak lalu streptozotocin dosis rendah. Tiga puluh tikus jantan dibagi menjadi enam kelompok (n = 5): normal, pembawa, simvastatin, serta ekstrak 300, 350, atau 400 mg/kg per hari selama 14 hari. Kolesterol total, yang diukur pada hari ke-0, 14, 21, 28, dan 35, naik dari 43–48 menjadi 127–141 mg/dL setelah induksi. Ekstrak kemudian menurunkannya rata-rata sebesar 57.2%, 48.0%, dan 43.5% pada ketiga dosis, dibandingkan 64.9% pada simvastatin, sedangkan kelompok pembawa terus naik (interaksi kelompok × waktu, $p < 0.001$). Pada 300 mg/kg, kolesterol total akhir (53.4 ± 5.1 mg/dL) tidak berbeda dari kelompok normal maupun simvastatin. Senyawa aktifnya masih perlu dikuantifikasi.

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Citation: Alaydrus, S., Dewi, N. P., Rianto, L., Charles, C., Susanti, Y., Utami, I. K., Liya, F. M., Utami, F. D., & Palipadang, M. N. (2026). Effectiveness of ethanol extract of kluwih (*Artocarpus camansi*) leaves on total cholesterol in rats given a high-fat diet and streptozotocin. *Jurnal Jamu Indonesia, 11*(6), 525–531. https://doi.org/10.29244/jji.v11i6.594

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1. INTRODUCTION

Cardiovascular disease remains the leading cause of death worldwide, and the number of deaths attributed to it rose from 12.1 million in 1990 to 18.6 million in 2019 (Roth et al., 2020). Over the same period, elevated low-density lipoprotein cholesterol moved from the 15th to the 8th leading risk factor for death, and hypercholesterolemia remains the most common form of dyslipidemia (Pirillo et al., 2021). The problem is compounded in type 2 diabetes, in which insulin resistance increases hepatic output of very-low-density lipoprotein and produces an atherogenic lipid profile (Hirano, 2018). Statins are the first-line treatment, yet about 9% of treated patients are intolerant of them, with diabetes among the predictors of intolerance (Bytyçi et al., 2022), and discontinuation because of muscle symptoms or concern about new-onset diabetes is common in practice (Newman et al., 2019). These limitations keep interest alive in plant-derived agents that could complement lipid-lowering therapy.

The genus *Artocarpus* (Moraceae) is rich in prenylated flavonoids, and several of its species lower blood lipids in rodents (Gupta et al., 2023; Sitorus et al., 2022). A methanol leaf extract of *A. lakoocha* at 250 mg/kg reduced total cholesterol, triglycerides and low-density lipoprotein in rats fed a high-fat diet while suppressing hepatic expression of HMG-CoA reductase and squalene synthase (Shafaq et al., 2022), and an ethyl acetate extract of *A. altilis* leaves reduced total cholesterol from 172 to 101 mg/dL in dyslipidemic rats over 28 days (Dewi et al., 2024). *Artocarpus camansi* Blanco, known in Indonesia as kluwih and elsewhere as breadnut, has received far less attention (Silalahi, 2022). Its 96% ethanol leaf extract contains 23–31 mg quercetin equivalents/g of flavonoids depending on the extraction method (Gita et al., 2024), and an ethanol leaf extract gave the highest phenolic content and radical-scavenging activity among the solvents compared by Vianney et al. (2018), while aqueous leaf extracts combined strong antioxidant activity with low toxicity in a bacterial bioassay (Vianney et al., 2020). In vivo, the ethanol leaf extract at 175–700 mg/kg showed anti-inflammatory activity in rats, approaching that of diclofenac at the highest dose (Nofiyanti et al., 2024), and in mice 50 and 100 mg/kg improved glucose tolerance more than 200 and 400 mg/kg (Marianne et al., 2011).

Despite this chemical profile, a recent comparative review concluded that *A. camansi* leaves remain insufficiently investigated relative to those of *A. altilis* (Masiala et al., 2026), and no published study has examined their effect on blood cholesterol. Lipid-lowering evidence within the genus comes from other species and cannot simply be transferred, because leaf composition differs between species. The question matters most where hypercholesterolemia coexists with impaired glucose metabolism. Rats fed a high-fat diet and then given low-dose streptozotocin develop hyperlipidemia together with partial β-cell loss, and this combined model is widely used to screen agents for that state (Brito et al., 2025; Srinivasan et al., 2005); it has recently been applied to other Indonesian medicinal plants (Wirawan et al., 2026). The doses tested here, 300–400 mg/kg, lie within the range used for *Artocarpus* leaf extracts in earlier rodent studies (Nofiyanti et al., 2024; Shafaq et al., 2022), and a 28-day study of *A. altilis* leaf extract found no biochemical toxicity at 400 mg/kg (Fitrya et al., 2025).

This study aimed to determine whether an ethanol extract of *A. camansi* leaves lowers total cholesterol in rats given a high-fat diet followed by low-dose streptozotocin, and how the effects of 300, 350 and 400 mg/kg compare with that of simvastatin. The extract was first screened for major phytochemical classes, and total cholesterol was then followed in every animal before induction, after induction, and twice during 14 days of treatment.

2. METHODS

2.1. Materials

Leaves of *A. camansi* were collected from Jatiluwih Village, Balinggi District, Parigi Moutong Regency, Central Sulawesi Province, Indonesia. The plant was identified by UPT Sumber Daya Hayati Sulawesi Tengah (Herbarium Celebense) under determination letter No. 138/UN.28.UPT-SDHS/LK/2020. The leaves were washed, dried at room temperature in a well-ventilated area protected from direct sunlight until completely dry, ground in a blender and passed through a 40-mesh sieve.

Thirty healthy male rats (*Rattus norvegicus*), aged 3–4 months and weighing 200–250 g at the start of the study, were obtained from Mice Gold Farm, Makassar, Indonesia. Before the experiment the animals were acclimatised for 14 days in cages with standard feed and drinking water available *ad libitum*. Only males were used so that the oestrous cycle would not add variation to lipid measurements.

Ethanol 96%, chloroform, methanol, diethyl ether, hydrochloric acid (2 N and concentrated), iron(III) chloride, magnesium powder and Dragendorff's reagent were used for extraction and phytochemical screening. The animal experiment used sodium carboxymethylcellulose (Na-CMC), streptozotocin, citrate buffer (pH 4.5), simvastatin 10 mg tablets, pork lard, quail eggs and an enzymatic colorimetric total cholesterol reagent kit.

2.2. Instruments and Software

Extraction used maceration vessels, a rotary vacuum evaporator and a water bath. Blood samples were processed in a centrifuge, and total cholesterol was read on a UV-Vis spectrophotometer Evolution 201 (Thermo Fisher Scientific, Madison, USA). An analytical balance, micropipettes (10–1000 µL), 3 mL oral gavage needles and 3 mL syringes were also used. Statistical analyses were run in Python 3.11 (Python Software Foundation, Wilmington, USA) with statsmodels 0.15 and SciPy 1.17, and figures were drawn with Matplotlib 3.10.

2.3. Procedures

The leaf powder (1000 g) was divided among four maceration vessels (250 g each) and macerated in 96% ethanol (1.5 L per

vessel, 6 L in total) for 72 h (3 × 24 h), protected from light and stirred occasionally. The filtrate was collected through filter paper, concentrated in the rotary evaporator and dried to a thick extract on a water bath, and the extract was kept until use.

The extract was screened with standard qualitative tests (Shaikh & Patil, 2020). Alkaloids were detected with Dragendorff's reagent (red precipitate), flavonoids with magnesium powder and concentrated hydrochloric acid (orange colour), saponins by shaking the extract with water (foam persisting for 5 min) and tannins with iron(III) chloride (greenish-black colour).

The high-fat diet consisted of melted pork lard and quail egg yolk mixed 1:1 and was given orally once daily from day 0 to day 13 to all rats except the normal group, which received standard feed only. On day 14 these rats received a single intraperitoneal injection of streptozotocin (40 mg/kg) freshly dissolved in citrate buffer pH 4.5 (0.32 g in 100 mL). Total cholesterol was measured again on day 21, seven days after the injection, and treatment began that day.

The rats were allocated to six groups of five using a randomised block design; the person measuring cholesterol was aware of the group allocation. The groups were normal control (standard feed, no induction), vehicle control (0.5% Na-CMC), positive control (simvastatin) and extract at 300, 350 or 400 mg/kg body weight. The extract was suspended in 0.5% Na-CMC. Simvastatin tablets were ground, suspended in 0.5% Na-CMC and given at 1.8 mg/kg body weight, the rat equivalent of the human therapeutic dose. All preparations were given by oral gavage once daily for 14 days from day 21 at 1 mL per 100 g body weight.

Blood (2 mL) was collected from the tail vein on days 0, 14, 21, 28 and 35 after a 10-h fast, and serum was separated by centrifugation at 3,000 rpm for 10 min. Total cholesterol was determined with the enzymatic kit according to the manufacturer's instructions, reading absorbance on the Evolution 201 spectrophotometer at 500 nm.

2.4. Ethical Approval

The protocol was approved by the Medical and Health Research Ethics Committee (approval No. 2582/UN 28.1.30/KL/2021, dated 15 June 2021). The study is reported in line with the ARRIVE 2.0 guidelines for animal research (Percie du Sert et al., 2020).

2.5. Data Analysis

Each rat was the experimental unit (n = 5 per group, 30 in total). With six groups this gives 24 error degrees of freedom for a between-group analysis of variance (ANOVA), above the minimum of 10 set by the resource-equation approach (Arifin & Zahiruddin, 2017). Results are given as mean ± SD. At each time point the groups were compared by one-way ANOVA followed by Tukey's honestly significant difference (HSD) test; normality of residuals was checked with the Shapiro–Wilk test and homogeneity of variance with Levene's test, and Welch's ANOVA and the Kruskal–Wallis test were run as sensitivity analyses.

Because each rat was measured repeatedly, the treatment phase (days 21, 28 and 35) of the five induced groups was also analysed with a linear mixed-effects model with group, day and their interaction as fixed effects and rat as a random intercept, and the interaction was tested by a likelihood-ratio test. Day-35 values were compared by analysis of covariance (ANCOVA) with the day-21 value as covariate, an approach preferred to change scores when pre-treatment values vary (Clifton & Clifton, 2019). The percentage reduction for each rat was calculated as $(TC_{day\ 21} - TC_{day\ 35})/TC_{day\ 21} \times 100$, where TC is total cholesterol, and compared among groups by one-way ANOVA with Tukey's HSD. A linear dose term was tested among the three extract groups. Differences were considered significant at $p < 0.05$, and exact p values are reported except when $p < 0.001$.

3. RESULTS AND DISCUSSION

3.1. Phytochemical Profile of the Extract

The ethanol extract gave positive reactions for alkaloids, flavonoids, saponins and tannins (**Table 1**). The detection of flavonoids and tannins agrees with the flavonoid and phenolic contents reported for ethanol extracts of *A. camansi* leaves (Gita et al., 2024; Vianney et al., 2018). The screen shows only which compound classes are present. It gives no amounts, and the extract was not standardised to a marker compound, so any link drawn below between these classes and the cholesterol response is a hypothesis rather than a finding.

Table 1. Qualitative phytochemical screening of the ethanol extract of *Artocarpus camansi* leaves

Compound class	Reagent	Observation	Result
Alkaloids	Dragendorff's reagent	Red precipitate	+
Flavonoids	Magnesium powder and concentrated HCl	Orange colour	+
Saponins	Water (shaking)	Foam persisting for 5 min	+
Tannins	$FeCl_3$	Greenish-black colour	+

Note. + indicates a positive reaction for the compound class. The tests are qualitative and do not indicate the amount present. $FeCl_3$, iron(III) chloride; HCl, hydrochloric acid.

3.2. Induction of Hypercholesterolemia

Baseline total cholesterol ranged from 42.7 to 47.5 mg/dL and did not differ among groups ($F(5, 24) = 0.54$, $p = 0.743$; **Table 2**), values within the reference interval of 26–68 mg/dL reported for healthy male Sprague-Dawley rats (He et al., 2017). After 14 days of the high-fat diet, mean total cholesterol in the five induced groups was 112–127 mg/dL, 2.6–2.9 times that of the normal group (43.5 mg/dL; $p < 0.001$ for each comparison), and it rose further to 127–141 mg/dL on day 21, seven days after

Table 2. Total cholesterol (mg/dL) of rats before induction (day 0), after the high-fat diet (day 14), after streptozotocin (day 21) and during treatment with *Artocarpus camansi* leaf ethanol extract (days 28 and 35)

Group	Day 0	Day 14	Day 21	Day 28	Day 35	Reduction (%)
Normal	42.8 ± 6.9	43.5 ± 7.2^{a}	44.3 ± 6.7^{a}	46.6 ± 5.3^{a}	45.8 ± 6.1^{a}	−3.5 ± 3.4^{a}
Vehicle	46.4 ± 5.7	120.0 ± 16.7^{b}	135.6 ± 9.7^{b}	145.0 ± 21.6^{c}	151.9 ± 16.9^{d}	−12.1 ± 10.3^{a}
Simvastatin	42.7 ± 6.8	126.9 ± 29.7^{b}	140.6 ± 18.9^{b}	79.3 ± 10.4^{b}	48.9 ± 2.7^{ab}	64.9 ± 4.0^{c}
E300	43.4 ± 8.1	122.5 ± 27.5^{b}	131.1 ± 28.2^{b}	89.9 ± 2.9^{b}	53.4 ± 5.1^{ab}	57.2 ± 12.6^{bc}
E350	47.5 ± 5.9	121.9 ± 11.3^{b}	127.0 ± 11.1^{b}	90.6 ± 14.5^{b}	65.6 ± 11.4^{bc}	48.0 ± 9.5^{b}
E400	46.5 ± 5.8	112.5 ± 28.0^{b}	131.9 ± 22.3^{b}	107.0 ± 20.2^{b}	73.7 ± 9.3^{c}	43.5 ± 7.7^{b}
p value	0.743	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Note. Values are mean ± SD of five rats per group (n = 5). Different superscript letters within a column indicate significant differences between groups (one-way ANOVA followed by Tukey's HSD, $p < 0.05$); groups did not differ on day 0. Reduction is the percentage fall in total cholesterol from day 21 to day 35 in each rat; negative values denote an increase. The p values are from one-way ANOVA at each time point. All groups except the normal group received the high-fat diet on days 0–13 and streptozotocin (40 mg/kg, intraperitoneal) on day 14; treatments were given orally once daily from day 21 for 14 days. ANOVA, analysis of variance; E300, E350 and E400, extract at 300, 350 and 400 mg/kg body weight; HSD, honestly significant difference; SD, standard deviation.

streptozotocin (**Table 2**). On days 14 and 21 the five induced groups did not differ from one another (Tukey's HSD, all $p > 0.8$), so all began treatment from the same level.

The rise produced by lard and quail egg yolk is consistent with the report that an egg-yolk diet raises serum cholesterol in rats more than beef-fat or vegetable-fat diets (Nasution et al., 2022). The further increase after streptozotocin matches the original description of the model, in which the injection raised cholesterol only in rats already fed a high-fat diet (Srinivasan et al., 2005). Protocols for inducing hypercholesterolemia in rats are not standardised (Cunha et al., 2021), so the roughly threefold rise seen here is best compared with studies that used a similar diet.

3.3. Cholesterol-Lowering Effect of the Extract and Simvastatin

The treatment phase separated the groups clearly (group × time interaction, $\chi^2(8) = 69.9$, $p < 0.001$; **Table 2**). Cholesterol in the vehicle group kept rising, from 135.6 ± 9.7 mg/dL on day 21 to 151.9 ± 16.9 mg/dL on day 35. After seven days of treatment (day 28), all three extract doses and simvastatin had lowered total cholesterol below the vehicle group ($p \leq 0.004$), although none had yet returned to the normal level ($p \leq 0.016$ against the normal group).

By day 35, simvastatin had reduced total cholesterol by 64.9 ± 4.0%, and the extract by 57.2 ± 12.6%, 48.0 ± 9.5% and 43.5 ± 7.7% at 300, 350 and 400 mg/kg (**Figure 1**). The reduction at 300 mg/kg did not differ from that produced by simvastatin ($p = 0.720$), whereas the reductions at 350 and 400 mg/kg were smaller ($p = 0.048$ and $p = 0.007$). In absolute terms, total cholesterol in the 300 mg/kg group fell by 77.7 ± 31.7 mg/dL to 53.4 ± 5.1 mg/dL, a value that differed from neither the normal group (45.8 ± 6.1 mg/dL; $p = 0.817$) nor the simvastatin group (48.9 ± 2.7 mg/dL; $p = 0.976$). ANCOVA adjusted for day-21 values gave the same pattern (group effect $F(4, 19) = 81.1$, $p < 0.001$), with adjusted day-35 means of 53.6, 66.2 and 73.8 mg/dL for the three doses against 48.1 mg/dL for simvastatin and 151.7 mg/dL for the vehicle.

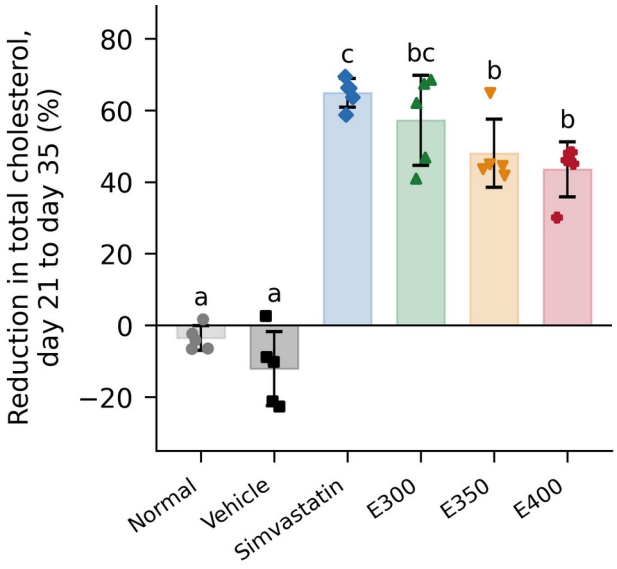

Figure 1. Percentage reduction in total cholesterol between day 21 and day 35 in rats given a high-fat diet and streptozotocin and treated with *Artocarpus camansi* leaf ethanol extract. Points are individual rats and bars are group means. Error bars are SD (n = 5 per group). Different letters indicate significant differences (one-way ANOVA followed by Tukey's HSD, $p < 0.05$); negative values denote an increase. E300, E350 and E400, extract at 300, 350 and 400 mg/kg; HSD, honestly significant difference; Na-CMC, sodium carboxymethylcellulose; SD, standard deviation.

The size of the effect is similar to that of other *Artocarpus* leaf extracts. An ethyl acetate extract of *A. altilis* leaves lowered total cholesterol by about 41% over 28 days in dyslipidemic rats (Dewi et al., 2024), and *A. lakoocha* leaf extract at 250 mg/kg significantly reduced total cholesterol in high-fat-fed rats in a study that used simvastatin at 10 mg/kg as the comparator (Shafaq et al., 2022). The 57% fall at 300 mg/kg in this study was reached within 14 days and in animals also given streptozotocin, in which

reduced insulin action tends to sustain hepatic lipoprotein output (Hirano, 2018). Differences in species, extract, diet and duration nevertheless limit direct comparison, and the present result establishes activity for *A. camansi* rather than superiority over related species.

3.4. Dose–Response Relationship

Within the range tested, a higher dose did not produce a larger effect. Final total cholesterol increased with dose among the extract groups (slope 0.20 mg/dL per mg/kg, $p = 0.003$), and the 400 mg/kg group ended higher than the 300 mg/kg group (73.7 ± 9.3 versus 53.4 ± 5.1 mg/dL; $p = 0.033$), although the percentage reductions of the three doses did not differ significantly from one another ($p \geq 0.16$). A similar pattern has been reported for *A. camansi* before, when 50 and 100 mg/kg of the ethanol leaf extract improved glucose tolerance in mice more than 200 and 400 mg/kg (Marianne et al., 2011).

Biphasic dose–responses are well documented for phytochemicals, including saponins and polyphenols, where constituents with opposing actions or saturable uptake can flatten or reverse the effect at higher doses (Jodynis-Liebert & Kujawska, 2020). Physical explanations, such as poorer absorption from more concentrated suspensions, cannot be judged without viscosity or pharmacokinetic data, which were not collected. Because only three closely spaced doses were tested, the data identify 300 mg/kg as the most effective dose within this range rather than as an optimal dose; by body-surface-area conversion it corresponds to about 49 mg/kg in humans (Nair & Jacob, 2016). Doses below 300 mg/kg should be included in future work to define the shape of the curve.

3.5. Possible Contributions of the Detected Compound Classes

Each compound class detected has plausible lipid-lowering actions described in other systems. Flavonoids can inhibit hepatic cholesterol synthesis through HMG-CoA reductase and SREBP signalling, reduce intestinal absorption and promote reverse cholesterol transport (Chen et al., 2025; Millar et al., 2017). Saponins bind cholesterol and bile acids in the gut and can inhibit pancreatic lipase (Marrelli et al., 2016), while polyphenols, tannins among them, can raise bile-acid synthesis through CYP7A1 and increase faecal bile-acid loss (Chambers et al., 2019).

None of these mechanisms was examined here. Only total cholesterol was measured, the constituents were detected as classes, and no enzyme activity or gene expression was assessed, so the data cannot attribute the effect to a particular class or pathway. The time course, which resembled that of simvastatin, is compatible with an action on hepatic synthesis, but a fall in total cholesterol could equally arise from reduced absorption or greater bile-acid excretion.

3.6. Limitations and Implications

Several limitations qualify these findings. First, the extract was characterised only qualitatively; no total phenolic or flavonoid content, chromatographic fingerprint or marker compound was determined, so the dose cannot be expressed in terms of any constituent and batch-to-batch reproducibility is unknown. Second, total cholesterol was the only endpoint. Low- and high-density lipoprotein cholesterol, triglycerides and hepatic lipids were not measured, and blood glucose is not reported, so the diabetic status of individual rats after streptozotocin was not verified; for this reason the model is described here as high-fat diet and streptozotocin-treated rather than diabetic. Third, each group contained five animals and treatment lasted 14 days, which limits precision and says nothing about longer-term efficacy or safety. Fourth, the three doses spanned a narrow range.

Within these limits, the results provide the first in vivo evidence that *A. camansi* leaves lower blood cholesterol, and at 300 mg/kg the effect approached that of simvastatin. They justify standardising the extract against a quantified marker, measuring the full lipid profile together with glycaemia, and testing a wider range of doses before the plant is considered further as a lipid-lowering candidate.

4. CONCLUSION

The ethanol extract of *A. camansi* leaves lowered total cholesterol in rats given a high-fat diet and low-dose streptozotocin. Over 14 days, 300 mg/kg reduced total cholesterol by 57.2 ± 12.6% to 53.4 ± 5.1 mg/dL, a level that did not differ from the normal or simvastatin groups, whereas 350 and 400 mg/kg produced smaller reductions of 48.0% and 43.5%. The extract contains alkaloids, flavonoids, saponins and tannins, but the constituents responsible for the effect are not yet known. Chemical standardisation of the extract, measurement of the full lipid profile and blood glucose, and a wider dose range are the next steps.

AUTHOR CONTRIBUTIONS

Conceptualization, S.A. and N.P.D.; methodology, S.A., N.P.D. and M.N.P.; validation, L.R., C.C. and Y.S.; formal analysis, N.P.D. and F.D.U.; investigation, S.A., I.K.U., F.M.L. and F.D.U.; resources, L.R., C.C. and Y.S.; data curation, I.K.U. and F.M.L.; writing—original draft preparation, S.A.; writing—review and editing, N.P.D., L.R., C.C., Y.S. and M.N.P.; visualization, F.D.U.; supervision, M.N.P.; project administration, S.A. All authors have read and agreed to the published version of the manuscript.

INSTITUTIONAL REVIEW BOARD STATEMENT

The animal study protocol was approved by the Medical and Health Research Ethics Committee (protocol code 2582/UN 28.1.30/KL/2021; approved on 15 June 2021).

INFORMED CONSENT STATEMENT

Not applicable.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available upon reasonable request from the corresponding author.

FUNDING

This research received no external funding.

ACKNOWLEDGMENT

The authors thank Sekolah Tinggi Ilmu Farmasi Pelita Mas Palu for supporting this study.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

ROLE OF FUNDERS

The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

DECLARATION OF GENERATIVE ARTIFICIAL INTELLIGENCE (AI) USE

During the preparation of this manuscript, the authors used Claude (Anthropic) for the purposes of translating the original Indonesian text into English, restructuring the manuscript, and re-running the statistical analysis of the raw data in Python. The authors have reviewed and edited the output and take full responsibility for the content of this publication.

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