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# Effect of Kawa Gambir (*Uncaria gambir* Roxb.) Leaves on Serum LDL in Diabetic Model Rats

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**ABSTRACT**

***Background:*** *Kawa gambir leaves, dried in a furnace and brewed as tea, are rich in flavonoids, phenolics, steroids, and tannins and have antioxidant, antihyperglycemic, and antidyslipidemic properties. In diabetes, elevated low-density lipoprotein (LDL) is a dyslipidemic abnormality that increases atherogenic risk. However, the effect of Kawa gambir on LDL in diabetic conditions remains unclear.* ***Objective:*** *To evaluate the effect of Kawa gambir leaf administration on LDL in alloxan-induced diabetic rats.* ***Methods:*** *This experimental study used a post-test-only control group design in 36 Wistar rats randomized into six groups: K−, K+, MET, P1, P2, and P3. Diabetes was induced with alloxan in K+, MET, and P1–P3. MET received metformin, whereas P1, P2, and P3 received Kawa gambir infusions at 1, 2, and 4 g/100 mL once daily for 4 weeks. Serum LDL was estimated using the Friedewald formula. Data were analyzed by one-way ANOVA followed by Least Significant Difference post hoc testing.* ***Results:*** *Mean±SD LDL levels (mg/dL) were 37.16±3.03, 59.90±8.91, 41.30±6.74, 40.60±5.75, 38.95±10.15, and 40.33±7.01 in K−, K+, MET, P1, P2, and P3, respectively. Group differences were significant (p=0.001). The largest numerical reduction versus K+ was found in P2, with a difference of 20.95 mg/dL (95% CI 8.64–33.26).* ***Conclusion:*** *Kawa gambir infusion significantly reduced LDL compared with the untreated diabetic control. Although the 2 g/100 mL group showed the lowest LDL numerically, no significant differences were observed among active treatment groups. These findings support Kawa gambir as an antidyslipidemic agent in diabetic dyslipidemia.*

## 1. INTRODUCTION

Diabetes mellitus (DM) remains a major global health problem. In 2014, 8.5% of adults were living with DM, and in 2019 the disease accounted for 1.5 million deaths, with 48% of these deaths occurring before the age of 70.[1] The number of DM cases increased markedly from 108 million in 1980 to 422 million in 2014, and its prevalence continues to rise more rapidly in low- and middle-income countries.[2] Southeast Asia has the second-highest prevalence of DM, with approximately 90 million affected adults in 2021, and this number is projected to increase to 113 million by 2030 and 152 million by 2045.[3]

Dyslipidemia is one of the major metabolic disturbances associated with DM and plays an important role in the regulation of blood lipid levels. Studies on dyslipidemia in type 1 DM have shown differences in lipid profiles according to glycemic control status. In well-controlled

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patients, high-density lipoprotein (HDL) levels tend to be normal or increased, while low-density lipoprotein (LDL) and triglyceride (TG) levels are slightly decreased or remain within normal ranges. In contrast, poorly controlled patients tend to exhibit lower or normal HDL levels, along with increased LDL and TG levels, indicating altered lipid metabolism. Furthermore, experimental studies have shown that alloxan-induced diabetes increases reactive oxygen species (ROS) production and causes pancreatic β-cell destruction, which may subsequently influence lipid profile parameters in animal models. [4,5]

Gambir (*Uncaria gambir* Roxb.) is widely distributed in several countries, including Indonesia, India, and Japan, and Indonesia is one of the major gambir exporters. [6] Gambir leaves have been reported to possess antioxidant, antihyperlipidemic, and antibacterial properties.[7] Their catechin content is known to scavenge free radicals and exert other beneficial biological effects. [8] In West Sumatra, kawa gambir leaves are commonly consumed in several processed forms, including roasted, dried, and furnace-dried preparations.[9] One commonly used method is oven or furnace drying, which removes water content while leaving other soluble compounds as residues. This process increases tannin levels and promotes polymerization reactions, leading to the formation of condensed tannins.[10] Catechin-containing kawa preparations may also inhibit HMG-CoA reductase activity, thereby reducing cholesterol synthesis and absorption.[6,10] These properties suggest that kawa gambir leaves may have potential as a natural therapeutic agent for improving diabetic dyslipidemia, particularly elevated LDL levels.

However, to the best of our knowledge, no published study has specifically evaluated the effect of Kawa gambir leaf administration on serum LDL levels in alloxan-induced diabetic rats.[11] The closest available study investigated the effect of Kawa gambir leaves on hepatic malondialdehyde levels in alloxan-induced diabetic mice, with the main focus on oxidative stress rather than serum lipid parameters. This indicates a clear research gap, because the potential effect of Kawa gambir leaves on serum LDL as a marker of diabetic dyslipidemia remains unresolved in an alloxan-induced diabetic rat model.[12] Therefore, this study was conducted to determine the effect of Kawa gambir leaves on reducing serum LDL levels in alloxan-induced diabetic Wistar rats. The hypothesis of this study was that administration of Kawa gambir leaf infusion would significantly reduce serum LDL levels in alloxan-induced diabetic rats compared with untreated diabetic controls, with the 2 g/100 mL dose expected to provide the most optimal effect.

## 2. METHODS

This study was a true experimental study using a post-test-only control group design. The study was conducted at the Faculty of Medicine, Universitas Andalas, Indonesia, from 1 November 2022 to 1 November 2023. Ethical approval was obtained from the Research Ethics Committee, Faculty of Medicine, Universitas Andalas, under Description of Ethical Approval No. 528/UN.16.2/KEP-FK/2023.

This true experimental study used a *post-test-only control group* design and was conducted from January to November 2023 at Universitas Andalas, Indonesia. A total of 36 male Wistar rats aged 8–12 weeks and weighing 200–250 g were included. Sample size was based on the WHO recommendation of five animals per group for traditional medicine research, with a 10% correction applied to anticipate possible *drop out*, resulting in six rats per group.[13] Inclusion criteria were male Wistar rats aged 8–12 weeks, weighing 200–250 g, and free from anatomical abnormalities. Rats with reduced activity, poor food intake, or prior use in other studies were excluded.

After 7 days of acclimatization, the rats were randomly allocated into six groups: K−, K+, MET, P1, P2, and P3. Diabetes was induced in K+, MET, and P1–P3 by intraperitoneal alloxan at 125 mg/kg body weight. Rats with blood glucose levels >200 mg/dL at 72 hours after induction were considered diabetic. The K− group was not induced and received no treatment. The MET group received metformin. The P1, P2, and P3 groups received Kawa gambir leaf infusion at concentrations of 1, 2, and 4 g/100 mL, respectively, once daily for 4 weeks.

Fresh gambir leaves were collected from Pesisir Selatan, West Sumatra, Indonesia. The leaves

were dried using a furnace-assisted oven-drying method, then ground into powder and brewed with water at 90°C according to the assigned concentration. The selection of Kawa gambir doses was based on the previous study by Ansori et al., while dose conversion from humans to rats followed the Laurence conversion table. The administered concentrations were 1 g/100 mL, 2 g/100 mL, and 4 g/100 mL, corresponding to converted doses of 0.018 mg/L, 0.036 mg/L, and 0.072 mg/L, respectively.[12]

Blood glucose levels were measured using an Accu-Chek glucometer with blood obtained from the tail vein. Baseline blood glucose was measured after acclimatization, and blood glucose was remeasured 72 hours after alloxan induction to confirm the diabetic state. Rats in groups K+, MET, P1, P2, and P3 were induced intraperitoneally with alloxan at a dose of 125 mg/kg body weight. Rats with blood glucose levels >200 mg/dL at 72 hours after induction were considered diabetic.[14]

After 4 weeks of treatment, blood was collected intravenously and centrifuged at 1500 rpm for 10 minutes to obtain serum. Total cholesterol, HDL cholesterol, and triglyceride levels were measured using a Microlab 300, and LDL cholesterol was estimated indirectly using the Friedewald equation. In this calculation, LDL cholesterol is obtained from total cholesterol after subtracting HDL cholesterol and an estimate of very-low-density lipoprotein cholesterol, expressed as triglycerides divided by five. This method was selected because it was the available analytical method in this study, although it has recognized limitations and should not be used when triglyceride levels exceed 400 mg/dL. [15]]

Data were analyzed using parametric statistical methods when assumptions of normality and homogeneity were fulfilled. Normality was assessed using the Shapiro–Wilk test, and homogeneity of variance was assessed using Levene's test. Normally distributed and homogeneous data were analyzed using one-way ANOVA followed by Least Significant Difference (LSD) post hoc testing. If ANOVA assumptions were not met, the Kruskal–Wallis test was used as an alternative. Statistical significance was set at $p < 0.05$ with a 95% confidence level. Comparisons were made primarily between P1, P2, and P3 versus K+, and may also be presented against the MET group as a therapeutic comparator.

## 3. RESULTS

### Average Blood Glucose Level of Rats

Blood glucose was measured after alloxan induction to confirm the diabetic model. Rats in the induced groups showed blood glucose levels >200 mg/dL and were considered diabetic model rats before treatment. During the 4-week intervention period, blood glucose levels tended to decrease in the treatment groups and metformin group, while the untreated diabetic control group remained markedly hyperglycemic. The weekly glucose profile in the thesis showed end-of-week 4 values of 367.16±37.56 mg/dL for P1, 340.66±34.17 mg/dL for P2, 305.16±16.55 mg/dL for P3, and 322.00±61.58 mg/dL for MET, whereas K+ remained at 600.00±0.00 mg/dL.

**Table 1.**
*Average Blood Glucose Levels During the 4-Week Intervention*

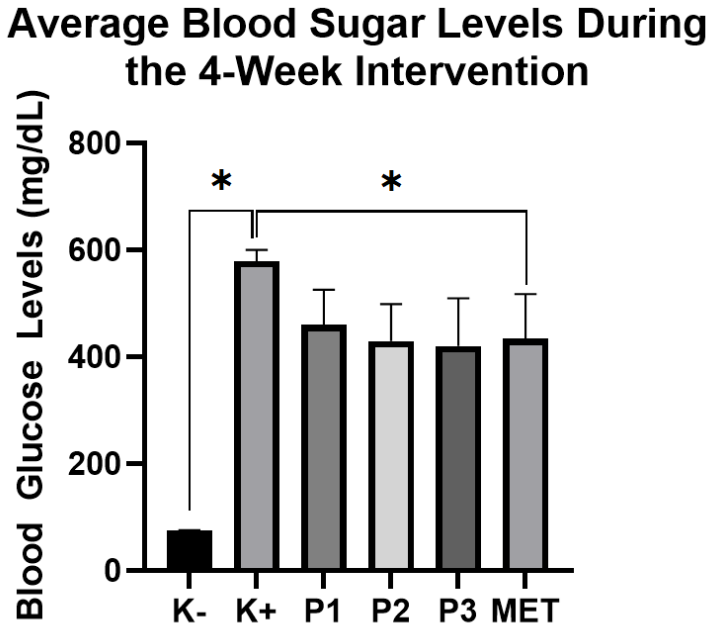
| Treatment | Group | Blood Glucose Level ± SD (mg/dL) | | | |
|---|---|---|---|---|---|
| | | Week 1 | Week 2 | Week 3 | Week 4 |
| Not induced with alloxan | K- | 74,5 ± 2,42 | 75,33 ± 3,93 | 75,5 ± 3,78 | 72,66 ± 4,63 |
| Alloxan-induced | K+ | 555,66 ± 51,22 | 568 ± 38,47 | 593 ± 16,32 | 600 ± 0 |
| | P1 | 522 ± 76,35 | 488,83 ± 71,14 | 459,66 ± 67,30 | 367,16 ± 37,56 |
| | P2 | 498,5 ± 64,25 | 466,16 ± 47,38 | 414,33 ± 61,28 | 340,66 ± 34,17 |
| | P3 | 514 ± 47,04 | 458,33 ± 33,35 | 404,16 ± 50,12 | 305,16 ± 16,55 |
| | MET | 517,66 ± 60,65 | 468,83 ± 57,61 | 428,66 ± 62,22 | 322 ± 61,58 |

**Table 2.**
*Significance of between-group differences in serum LDL levels based on the Least Significant Differences (LSD) analysis*

| Kelompok | K- | K+ | P1 | P2 | P3 | MET |
|---|---|---|---|---|---|---|
| K- | - | 0,000* | 0,442 | 0,675 | 0,458 | 0,335 |
| K+ | 0,000* | - | 0,000* | 0,000* | 0,000* | 0,000* |
| P1 | 0,442 | 0,000* | - | 0,698 | 0,950 | 0,869 |
| P2 | 0,675 | 0,000* | 0,698 | - | 0,745 | 0,581 |
| P3 | 0,458 | 0,000* | 0,950 | 0,745 | - | 0,820 |
| MET | 0,335 | 0,000* | 0,869 | 0,581 | 0,820 | - |

Notes: *Significant (p<0,05)

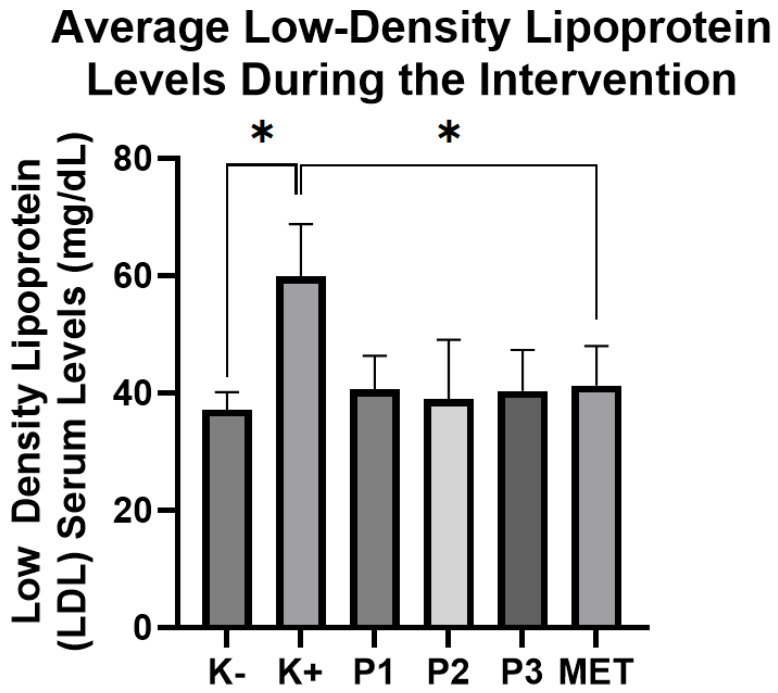
**Figure 1.**
*Average Blood Glucose Levels During the 4-Week Intervention*



Mean serum LDL levels differed significantly among groups. The negative control group had the lowest mean LDL level at 37.16±3.03 mg/dL, while the positive control group had the highest mean LDL level at 59.90±8.91 mg/dL. Mean LDL levels in the metformin and Kawa gambir groups were 41.30±6.74 mg/dL for MET, 40.60±5.75 mg/dL for P1, 38.95±10.15 mg/dL for P2, and 40.33±7.01 mg/dL for P3. One-way ANOVA showed a significant overall difference among groups ($p=0.001$). Post-hoc LSD analysis demonstrated that K+ differed significantly from K−, MET, P1, P2, and P3, with all relevant pairwise comparisons reported as $p<0.001$. In contrast, no significant differences were observed among MET, P1, P2, and P3. Among the treatment groups, the lowest mean LDL level was observed in P2, indicating the most favorable reduction at the dose of 2 g/100 mL.

To provide effect size estimates, the mean differences in LDL relative to the positive control group were 18.60 mg/dL for MET, 19.30 mg/dL for P1, 20.95 mg/dL for P2, and 19.57 mg/dL for P3. The corresponding 95% confidence intervals were 8.33 to 28.87 for MET, 9.43 to 29.17 for P1, 8.64 to 33.26 for P2, and 9.18 to 29.96 for P3. Based on these estimates, P2 showed the largest numerical reduction in LDL compared with K+.

**Figure 2.**
*Average Low-Density Lipoprotein Levels During the Intervention*




## 4. DISCUSSION

Alloxan induction successfully established a diabetic state in the induced groups, as shown by blood glucose levels exceeding the diabetic threshold and persistent hyperglycemia throughout the follow-up period. By week 4, the untreated diabetic control group remained the most hyperglycemic, whereas lower glucose levels were observed in the metformin and Kawa gambir groups. Among the Kawa gambir groups, blood glucose levels decreased numerically from P1 to P3, which may indicate a dose-related trend toward improved glycemic control. However, this observation should be interpreted cautiously because blood glucose was not subjected to formal between-dose statistical comparison, and the values remained above the normal range. The lower glucose level in the metformin group is biologically plausible because metformin reduces hepatic gluconeogenesis and improves peripheral glucose utilization. Kawa gambir may also contribute to glycemic improvement through its catechin-rich flavonoid and phenolic

constituents, which have antioxidant activity, scavenge reactive oxygen species, inhibit α-amylase and α-glucosidase, and may reduce oxidative injury to pancreatic β-cells. Taken together, these findings suggest that Kawa gambir was associated with partial improvement in hyperglycemia in this model, but the results should be regarded as supportive rather than conclusive because glucose was not the primary endpoint and previous gambir-related studies differed in animal species, formulations, treatment duration, and measured outcomes.[4,5,7,12,16].

The lipid findings followed the expected diabetic dyslipidemic pattern. The negative control group had the lowest mean LDL level, whereas the untreated diabetic control group had the highest mean LDL level. This pattern is biologically plausible because alloxan-induced β-cell injury leads to insulin deficiency, impaired glucose utilization, enhanced lipolysis, increased hepatic free fatty acid flux, oxidative stress, and disturbed lipid handling, all of which may contribute to increased LDL formation and a more atherogenic lipid profile. This interpretation is in line with previous literature showing that poor glycemic control in diabetes is associated with increased LDL and triglyceride levels. In the present study, LDL was lower in the MET, P1, P2, and P3 groups than in K+, indicating that both metformin and Kawa gambir attenuated diabetic dyslipidemia. Compared with K+, the mean LDL reductions were 18.60 mg/dL in MET, 19.30 mg/dL in P1, 20.95 mg/dL in P2, and 19.57 mg/dL in P3. Importantly, these values approached the negative control mean of 37.16 mg/dL. The absolute difference from the negative control was 4.14 mg/dL in MET, 3.44 mg/dL in P1, 1.79 mg/dL in P2, and 3.17 mg/dL in P3, indicating that the active treatment groups moved substantially toward the normal lipid profile rather than showing only a minor numerical shift.[4,5,17–19]

The metformin group showed a lower mean LDL level than the untreated diabetic group, supporting its role as a standard therapeutic comparator in experimental diabetic dyslipidemia. This effect is likely secondary to improved glycemic control and insulin action, which reduce hepatic glucose production, decrease lipolysis-driven fatty acid flux, and limit hepatic overproduction of atherogenic lipoproteins. However, metformin was not statistically different from P1, P2, or P3 in post hoc analysis. Therefore, the appropriate interpretation is not that Kawa gambir was superior to metformin, but that its LDL-lowering effect was comparable to metformin in this model. Several explanations may account for the absence of superiority. First, the active treatments may have reached a similar efficacy range in this model. Second, the relatively small sample size may have limited statistical power to detect smaller between-treatment differences. Third, LDL was estimated indirectly and measured only at the end of the intervention, which may reduce sensitivity for detecting subtle differences. Fourth, the use of a crude infusion rather than a standardized purified compound may have resulted in variability in the bioavailable active constituents.[7,15,20,21]

All three Kawa gambir treatment groups showed lower mean LDL levels than the positive diabetic control, namely 40.60±5.75 mg/dL in P1, 38.95±10.15 mg/dL in P2, and 40.33±7.01 mg/dL in P3. A plausible explanation for this effect is the phytochemical content of Kawa gambir, especially flavonoids, phenolics, catechins, and steroids, which have antioxidant, antihyperglycemic, and antihyperlipidemic properties. Catechin has been reported to inhibit HMG-CoA reductase, reduce cholesterol absorption, and modulate lipid metabolism, while gambir extracts have also shown antiatherosclerotic and metabolic benefits in previous studies.[12] Gambir-derived preparations have also been reported to show antiatherosclerotic effects, while catechin and proanthocyanidin fractions from Uncaria gambir have been shown to improve adipocyte differentiation and glucose uptake via SIRT1, PPARγ, and GLUT4-related pathways. These metabolic and redox effects provide a biologically plausible basis for the LDL-lowering tendency observed in the present study.[11,21]

The present findings are also coherent with the previous Kawa gambir study by Ansori et al., which demonstrated a reduction in serum malondialdehyde in alloxan-induced diabetic mice, particularly at the 2 g/100 mL dose. That study supports the possibility that Kawa gambir reduces oxidative stress, which is relevant because oxidative stress is closely linked to β-cell injury and diabetic dyslipidemia. Nevertheless, the earlier study did not assess LDL or other lipid parameters directly. Accordingly, it should be interpreted as indirect mechanistic support rather than direct confirmation of the LDL-lowering effect observed in the present experiment. This distinction is

important because improvement in oxidative stress markers does not necessarily translate proportionally into improvement in serum LDL, and outcome differences between studies may also reflect differences in species, intervention duration, and biochemical endpoints.[5,12,17]

Among the three Kawa gambir treatment groups, P2 had the lowest mean LDL level numerically. This may suggest that 2 g/100 mL provided the most favorable biological window in this dataset. However, this finding should not be overinterpreted. The post hoc results did not demonstrate statistically significant differences among P1, P2, P3, and MET. Therefore, it is more accurate to state that P2 showed the lowest average LDL level numerically, rather than claiming that it was definitively the optimal dose. The pattern may indicate a non-linear rather than strictly dose-proportional response. One possible explanation is that catechin-related effects on oxidative stress reduction, hepatic cholesterol synthesis, and intestinal cholesterol handling may reach partial saturation, so increasing the dose beyond a certain threshold does not yield proportional LDL reduction. Another possibility is that higher-concentration infusions contain a more complex phytochemical matrix that does not increase the bioavailable LDL-lowering fraction in a linear manner. The fact that the previous Ansori study also found the 2 g/100 mL dose to be favorable strengthens this interpretation, although that study evaluated MDA rather than LDL.[7,12,22]

Overall, the main statistical interpretation of the present study is that Kawa gambir lowered LDL relative to the untreated diabetic control and produced LDL values comparable to metformin, while no statistically significant differences were observed among the active treatment groups. These findings support the potential of Kawa gambir as a natural antidyslipidemic agent in experimental diabetes, but they do not support a definitive claim that one Kawa gambir dose was superior to the others. Several limitations should be acknowledged. First, this study used a post-test-only design for LDL, so baseline lipid comparability across groups was not directly demonstrated. Second, LDL was estimated indirectly using the Friedewald formula and not measured directly. Third, the sample size was relatively small, which may have limited the power to detect between-treatment differences. Fourth, mechanistic biomarkers such as MDA, insulin, HMG-CoA reductase activity, and LDL receptor expression were not measured in the same experiment. Therefore, the proposed mechanisms should be interpreted as biologically plausible rather than conclusively proven.[7,12,15]

## 5. CONCLUSION

Alloxan induction successfully established a diabetic rat model. Kawa gambir leaf infusion significantly reduced serum LDL levels compared with the untreated diabetic control group. Among the tested doses, 2 g/100 mL showed the lowest mean LDL level and the most favorable numerical effect. The LDL-lowering effect of Kawa gambir was comparable to metformin, as no significant differences were observed between the treatment groups and the metformin group. These findings suggest that Kawa gambir leaves have potential as a natural antidyslipidemic agent in diabetic dyslipidemia.

## 6. LIMITATION

The study is limited in that the evaluation of LDL was performed at the conclusion of the study, thereby preventing the assessment of any rise in serum LDL

## 7. ACKNOWLEDGMENTS

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