

RESEARCH STUDY

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Antihyperglycemic Effects of Combined Ethanolic Extracts of Cocor Bebek (*Kalanchoe pinnata*) and Lidah Buaya (*Aloe vera*) in Alloxan-Induced Mice

Efek Antihiperqlikemik Kombinasi Ekstrak Etanol Cocor Bebek (*Kalanchoe pinnata*) dan Lidah Buaya (*Aloe vera*) pada Mencit yang Diinduksi Aloksan

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ABSTRACT

Background: Hyperglycemia is a hallmark of diabetes mellitus and contributes significantly to the development of systemic complications. Plant-based antihyperglycemic agents have gained increasing attention as alternative therapies due to their bioactive compounds and relatively low side effects. However, evidence on the combined effects of *Kalanchoe pinnata* (cocor bebek) and *Aloe vera* (lidah buaya) remains limited.

Objectives: This study aimed to evaluate the glucose-lowering effects of combined ethanolic extracts of *Kalanchoe pinnata* and *Aloe vera* leaves in alloxan-induced hyperglycemic mice.

Methods: Leaves were dried, powdered, and extracted with 96% ethanol via maceration, followed by filtration, evaporation, and freeze-drying. A total of 25 male mice were randomly divided into five groups (n=5 per group): negative control, positive control (glibenclamide), and three treatment groups receiving combined extracts at doses of 200, 400, and 800 mg/kg body weight. Hyperglycemia was induced using alloxan (150 mg/kg BW), and mice were considered hyperglycemic when blood glucose exceeded 176 mg/dL. Blood glucose levels were measured at 0, 30, 60, and 90 minutes post-treatment.

Results: Minimal glucose reduction was observed in the negative control group (1.64-3.63%), while the positive control showed the greatest decrease (29.81-59.28%). The treatment groups demonstrated a dose-dependent effect, with reductions of 17.61%, 24.52%, and 32.80% at doses of 200, 400, and 800 mg/kg BW, respectively. Statistical analysis showed significant differences among groups ($p < 0.001$) and between doses ($p = 0.016$).

Conclusions: These findings suggest that combined extracts of *Kalanchoe pinnata* and *Aloe vera* exhibit significant antihyperglycemic activity in alloxan-induced mice.

INTRODUCTION

Diabetes mellitus remains a serious health problem worldwide, affecting people in both developed and developing countries. One important issue is that many cases are still not diagnosed. In 2021, about 44.7% of adults with diabetes did not know they had the disease, with higher proportions reported in regions such as Southeast Asia¹. In Indonesia, the prevalence of diabetes has stayed relatively high over the past decade. It increased from 10.7% in 2013 to 11.8% in 2018, and then slightly decreased to 11.3% in 2023². This condition is often associated with prolonged hyperglycemia, which contributes to various systemic complications. Overall,

diabetes continues to be an ongoing public health concern in Indonesia.

According to the 2023 Indonesian Health Survey (SKI), the prevalence of diabetes based on a doctor's diagnosis is 1.7% across all age groups. However, when blood glucose measurements are used (fasting ≥ 126 mg/dL or 2-hour post-load ≥ 200 mg/dL), the prevalence increases substantially to 11.7% among individuals aged 15 years and above. This creates a striking 9.5-percentage-point gap between clinically diagnosed cases and undiagnosed cases detected through laboratory testing, highlighting how many people live with diabetes without knowing it. These findings underscore that

diabetes in Indonesia is not only widespread but also substantially underdiagnosed, making early detection and effective treatment strategies critically important³.

Diabetes mellitus (DM) is now being reported more frequently in children and adolescents, which raises concern about the need for interventions that are safe, effective, and easy to access⁴. This condition is a chronic metabolic disorder caused by either inadequate insulin production or reduced insulin sensitivity, leading to sustained high blood glucose levels. Prolonged hyperglycemia is strongly associated with the development of complications such as neuropathy, nephropathy, retinopathy, and cardiovascular disorders⁵.

While pharmacological therapies such as insulin and synthetic oral antidiabetic drugs remain the cornerstone of treatment, many patients experience side effects. Limited accessibility and reduced efficacy over time also present significant challenges⁶. These limitations have stimulated growing interest in herbal-based antihyperglycemic agents that are safe, affordable, and culturally acceptable, especially in settings where traditional medicine is widely practiced.

One medicinal plant of growing interest is *Kalanchoe pinnata* (Cocor Bebek). This plant contains bioactive compounds, including phenolics compounds, flavonoids, and terpenoids, which are associated with antioxidant, and anti-inflammatory properties, as well as potential antidiabetic activities^{7,8}. A recent study demonstrated that *K. pinnata* extracts can inhibit carbohydrate-digesting enzymes such as α -glucosidase and α -amylase, with effects similar to the standard drug acarbose, suggesting a role in reducing glucose absorption⁹. Furthermore, compounds such as epigallocatechin gallate (EGCG), kaempferol, quercetin, and apigenin, may help improve blood glucose control, reduce oxidative stress, and enhance insulin sensitivity, supporting their potential relevance in metabolic research^{10,11}.

Similarly, *Aloe vera* has been widely explored for its antihyperglycemic effects. Its gel and leaf extracts contain polysaccharides, tannins, alkaloids, flavonoids, and anthraquinones, which contribute to antioxidant and glucose-lowering effects¹²⁻¹⁵. Traditionally used in complementary medicine to manage diabetes mellitus, *Aloe vera* has demonstrated multiple biological effects in experimental models, including antihyperglycemic, anti-inflammatory, antioxidant, and antihyperlipidemic activities. Studies using streptozotocin-induced diabetic models have shown that *Aloe vera* may improve glucose metabolism and support overall metabolic function¹⁶.

Several animal studies have reported reductions in blood glucose following administration of *A. vera* extract. Chemical analyses also identify bioactive compounds that may enhance insulin secretion or protect pancreatic β -cells from oxidative damage^{17,18}. Safety evaluations further show that *A. vera* extracts can provide pancreatic protection without causing major toxicity¹⁹.

While *Kalanchoe pinnata* and *Aloe vera* have each been studied individually, research on their combined effects remains limited, especially using ethanol extracts tested in alloxan-induced animal models. Studying them in combination is important because their combined

effects may provide additive or enhanced antihyperglycemic activity compared with individual extracts. Without in vivo evidence, its antihyperglycemic effects remain insufficiently investigated. This study aims to evaluate the antihyperglycemic effect of combined ethanol extracts of *Kalanchoe pinnata* and *Aloe vera* leaves in alloxan-induced mice, and to compare their effectiveness with that of each extract administered individually.

METHODS

This study employed an experimental design using a pre- and post-test with a control group approach. Male white mice (*Mus musculus*) were used as the experimental animals, and diabetes was induced using alloxan. The independent variable was the combination extract of *Kalanchoe pinnata* (cocor bebek) and *Aloe vera* at various dose concentrations. The dependent variable was the blood glucose level of mice, while the controlled variables included the type of experimental animal, extraction procedures, and the in vivo antidiabetic testing protocol. All experimental procedures adhered to institutional ethical guidelines and received approval from the Ethics Committee of Poltekkes Kemenkes Jambi (Approval No. LB.02.06/2/429/2025).

In this study, *Kalanchoe pinnata* leaves and *Aloe vera* leaves were identified through organoleptic examination and compared with the standards listed in *Materia Medika Indonesia*²⁰ and the *Indonesian Herbal Pharmacopoeia* (3rd Edition)²¹. Fresh leaves of both plants were dried under direct sunlight for 3–5 days to reduce moisture content and prevent microbial growth. After drying, the leaves were powdered and sieved using a 40-mesh sieve to obtain a uniform particle size.

Male white mice (*Mus musculus*), aged approximately 6-8 weeks and weighing 20-30 g, were used in this study. The animals were housed under standard laboratory conditions and had free access to standard feed and water ad libitum. The mice were acclimatized for 7 days with free access to food and water. On day 8, they were fasted for approximately 12 hours, with water allowed. Body weights were recorded, and fasting blood glucose levels were measured²².

Alloxan induction solution was prepared by dissolving alloxan monohydrate at a dose of 150 mg/kg BW, a concentration considered effective for producing stable, long-term hyperglycemia, in 10 mL of 0.9% NaCl physiological solution. Physiological saline was used to maintain pH stability and minimize rapid alloxan degradation. The prepared solution was administered intraperitoneally, enabling rapid absorption through the peritoneal blood vessels into systemic circulation, where alloxan selectively destroys pancreatic β -cells. The injection volume was standardized at 0.2 mL for each 20 g mouse, equivalent to approximately 3 mg of alloxan per mouse. For a total of 25 mice, the prepared volume was increased to 10 mL to ensure adequate supply. After alloxan administration, mice were monitored. After 3 days, blood glucose was measured again to confirm hyperglycemia. Mice were considered successfully diabetic when their post-induction blood glucose levels exceeded 176 mg/dL. Hyperglycemic mice were then

randomly assigned to five groups, each consisting of five mice.

The extract suspensions for the test groups were prepared using a 1:1 (w/w) mixture of *Kalanchoe pinnata* and *Aloe vera* extracts. The appropriate amounts of the combined extract were weighed to achieve doses of 200 mg/kg BW, 400 mg/kg BW, and 800 mg/kg BW, and each was suspended in 0.5% Na-CMC to obtain a uniform preparation with a final administration volume of 0.2 mL per 20 g mouse.

A 0.5% Na-CMC suspension was prepared by sprinkling 0.5 g of Na-CMC into 20 mL of hot water in a mortar, allowing it to swell, and triturating the mixture until a uniform gel formed. The suspension was then gradually diluted with distilled water to a final volume of 100 mL. The glibenclamide suspension was prepared by

pulverizing a 5 mg tablet into a fine powder, calculating the mouse dosage using the standard human-to-mouse conversion factor ($5 \text{ mg} \times 0.0026$), resulting in an equivalent dose of 0.013 mg for a 20 g mouse, and then dispersing the powder in the 0.5% Na-CMC vehicle to obtain a final administration volume of 0.2 mL per mouse

The extracts were prepared using maceration. Powdered simplicia of *K. pinnata* and *A. vera* were weighed and placed in separate maceration bottles at a 1:10 ratio of material to 96% ethanol. Samples were soaked for 5 days, stirred 3 times daily, and filtered through filter paper. The filtrates were concentrated using a vacuum rotary evaporator at 60°C until thick extracts were obtained. Extract yield (%) was calculated using:

$$\text{Extract yield (\%)} = \frac{\text{Weight of extract}}{\text{Weight of dried simplicia}} \times 100\%.$$

The major secondary metabolites in the extract are determined by phytochemical screening. Flavonoids were detected by adding magnesium powder and 2N HCl to the sample, then heating and adding amyl alcohol; a red-to-orange color in the amyl alcohol layer indicated a positive reaction. Phenols were identified by placing the sample on a spot plate and adding FeCl_3 , producing a black, purple, or green coloration when positive. Saponins were tested by heating the sample in a water bath and vigorously shaking, which resulted in the formation of a stable foam confirming their presence. Alkaloids were identified by treating the sample with ammonia and chloroform, adding 2N HCl to the filtrate, and then applying Dragendorff reagent, which yields a brick-red precipitate if alkaloids are present. Steroids and triterpenoids were tested by mixing the sample with

acetic anhydride and concentrated H_2SO_4 ; a greenish-blue color indicated steroids, while a red to purple color suggested triterpenoids. Tannins were detected by adding 2N HCl to the sample, heating it, and adding amyl alcohol; a red-orange coloration indicated a positive result.

Mice were acclimatized for seven days with unrestricted access to food and water. On day 8, they were fasted for ± 12 hours, with water allowed. Body weights were then recorded, followed by measurement of fasting blood glucose levels. Alloxan was then administered intraperitoneally. After 3 days, blood glucose was measured again to confirm hyperglycemia. Hyperglycemic mice were subsequently randomized into five groups, with five animals per group.

Table 1. Experimental Groups and Treatment Regimens in Alloxan-Induced Mice

Group	Treatment
Negative control	Alloxan + Na-CMC 0.5%
Positive control	Alloxan + Na-CMC 0.5% + glibenclamide
Extract 200 mg/kg	Alloxan + extract 200 mg/kg
Extract 400 mg/kg	Alloxan + extract 400 mg/kg
Extract 800 mg/kg	Alloxan + extract 800 mg/kg

Blood glucose levels were measured at 30, 60, and 90 minutes after treatment²³ using a Nesco MultiCheck® glucometer (Nesco, Korea). The mouse tail was cleaned with an alcohol swab, punctured with a

sterile needle, the first drop discarded, and the next drop applied to the test strip. Changes in blood glucose were analyzed using the Kruskal-Wallis test with statistical significance defined at $p < 0.05$ (95% confidence interval).

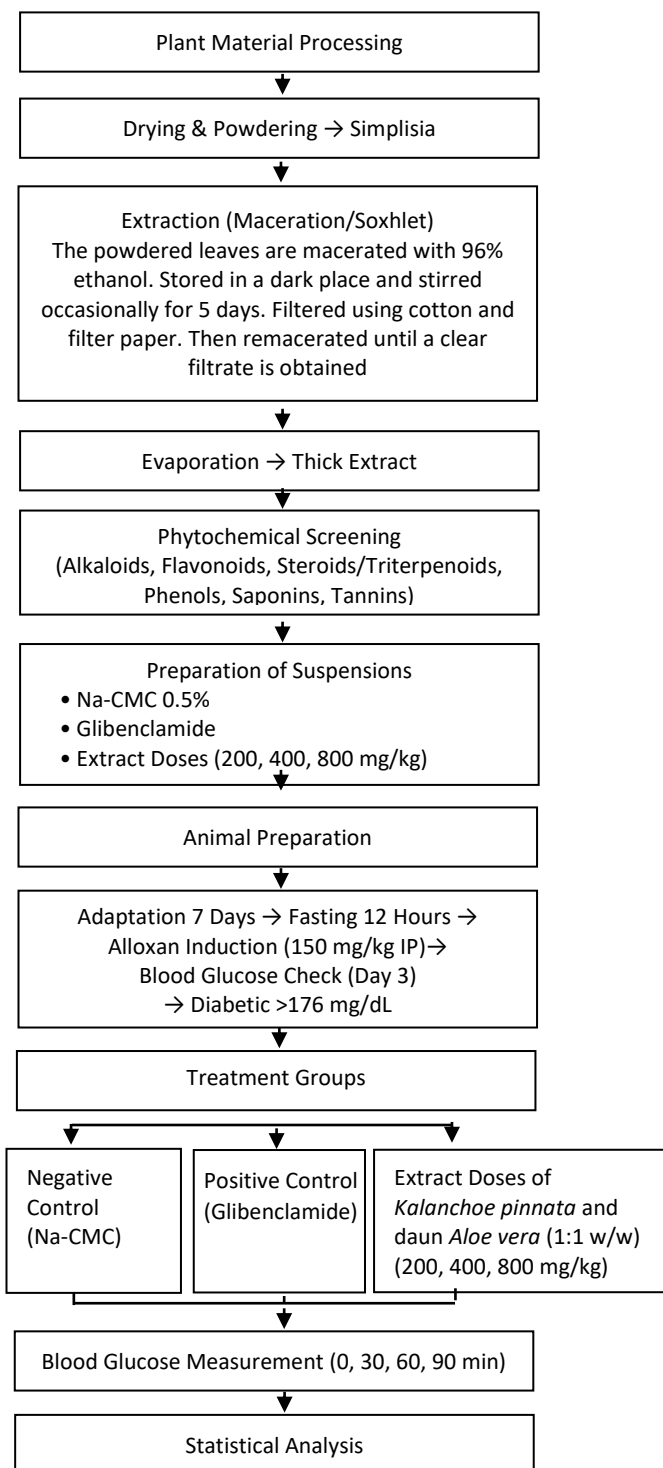


Figure 1. Flowchart diagram

RESULTS AND DISCUSSIONS

Phytochemical screening was conducted to determine the main bioactive compounds in the ethanolic extracts of *Kalanchoe pinnata* and *Aloe vera* leaves. This analysis helps explain their potential biological activities, including antihyperglycemic effects. Compounds such as phenolics, flavonoids, terpenoids, and alkaloids are widely associated with antioxidant activity and glucose regulation. The findings of the phytochemical screening are presented in Table 2.

According to the phytochemical screening presented in Table 2, both *Kalanchoe pinnata* and *Aloe vera* extracts contain some bioactive compounds. These include phenols, flavonoids, some alkaloids, and saponins. There are also tannins, terpenoids, steroids, and triterpenoids. These compounds are known for their antioxidant activity, which helps reduce oxidative stress. This mechanism also suggests they may have potential antihyperglycemic effects.

Table 2. Phytochemical Screening Results of *Kalanchoe pinnata* and *Aloe vera* Leaf Extracts

Test	Reagent	<i>Kalanchoe pinnata</i> Extract	<i>Aloe vera</i> Extract
Phenols	Sample + FeCl ₃	(+) Black coloration	(+) Brown-black coloration
Terpenoids	Liebermann–Burchard (conc. H ₂ SO ₄)	(+) Reddish-brown color	(+) Reddish-brown color
Alkaloids	Dragendorff	(+) Brick-red precipitate	(+) Brick-red precipitate
	Bouchardat	(+) Brown precipitate	(+) Brown precipitate
Saponins	Sample + hot water (vertical shaking)	(+) Stable foam lasting 5 minutes	(+) Stable foam lasting 5 minutes
Flavonoids	Sample + Mg + HCl (heated) + amyl alcohol	(+) Red to orange color in the middle layer	(+) Orange-red color in the middle layer
Tannins	FeCl ₃	(+) Greenish-black color	(+) Greenish-black color
Steroids	Liebermann–Burchard (acetic anhydride + H ₂ SO ₄)	(+) Orange color	(+) Orange color
Triterpenoids	Liebermann–Burchard (acetic anhydride + H ₂ SO ₄)	(+) Orange color	(+) Orange color

Blood glucose levels were measured in mice across five experimental groups, including a negative control, a positive control receiving glibenclamide, and three treatment groups given extract doses of 200, 400, and 800 mg/kg body weight. Measurements were obtained at baseline (fasting), four days after alloxan induction, and at 30, 60, and 90 minutes following

treatment administration. Given the short duration of post-treatment observation, this study primarily reflects an acute glycemic response rather than a long-term intervention effect. The descriptive statistics (Mean and SD) for each group at all time points are presented in Table 3.

Table 3: Blood glucose levels (mg/dL) at different time points in all treatment groups (mean ± SD)

Group	Fasting	Day 4 After Alloxan	30 min After Treatment	60 min After Treatment	90 min After Treatment
Negative Control	83.8 (27.34)	181.4 (3.51)	178.4 (2.19)	176.8 (2.39)	174.8 (2.17)
Positive Control (Glibenclamide)	88.0 (9.03)	218.8 (30.28)	151.2 (6.65)	129.4 (13.72)	88.2 (6.61)
Dose I (200 mg/kg BW)	86.2 (17.92)	200.4 (7.70)	192.0 (6.52)	179.8 (9.31)	165.0 (8.28)
Dose II (400 mg/kg BW)	73.6 (6.43)	205.2 (17.63)	187.2 (25.17)	170.2 (20.43)	154.8 (14.81)
Dose III (800 mg/kg BW)	94.2 (23.06)	213.0 (10.37)	180.4 (22.67)	163.6 (21.04)	143.2 (26.23)

This study demonstrates distinct differences in blood glucose responses among treatment groups following alloxan induction. As expected, the negative control group showed consistently elevated glucose levels after induction, with only minimal decreases over time, indicating that Na-CMC 0.5% had no antihyperglycemic effect.

In contrast, the positive control group receiving glibenclamide exhibited a substantial reduction in glucose levels beginning as early as 30 minutes after treatment, with glucose values continuing to decline through the 90-minute measurement. This confirms the efficacy of glibenclamide as a standard antidiabetic agent in lowering post-induction hyperglycemia. The extract-treated groups showed varying degrees of antihyperglycemic activity. The 200 mg/kg dose produced moderate glucose reductions from 30 to 90 minutes,

although the levels remained higher than those of the positive control. The 400 mg/kg dose demonstrated a similar pattern, with slightly greater reductions than the 200 mg/kg dose, suggesting a dose-dependent improvement in activity. Interestingly, the 800 mg/kg dose produced the most notable decrease among the extract groups, with glucose levels declining steadily across all post-treatment time points.

Despite this improvement, its effect remained less potent than that of glibenclamide, particularly by the 90-minute mark. Overall, the findings indicate that the extract possesses antihyperglycemic potential, likely increasing with dose. However, none of the tested doses matched the pronounced glucose-lowering effect of glibenclamide.

Table 4. Percentage of Blood Glucose Reduction Compared to Day-4 Hyperglycemic Baseline After Alloxan Induction in Mice

Treatment	Blood Glucose Reduction (%)			*p- value
	30 minutes	60 minutes	90 minutes	
Negative Control	1.64	2.53	3.63	
Positive Control (Glibenclamide)	29.81	40.22	59.28	<0.001
Dose I (200 mg/kg BW)	4.18	10.26	17.61	0.016
Dose II (400 mg/kg BW)	9.19	17.14	24,52	
Dose III (800 mg/kg BW)	15.39	23.25	32.80	

* Kruskal-Wallis test

This study demonstrated that the combined extract of *Kalanchoe pinnata* and *Aloe vera* possesses antihyperglycemic activity in alloxan-induced hyperglycemic mice. Blood glucose reduction was calculated relative to the Day-4 post-alloxan baseline, at which point all mice had reached a stable hyperglycemic state. The percentage reductions observed across treatment groups differed markedly, as confirmed by the Kruskal–Wallis analysis ($p < 0.001$). Furthermore, comparison among the three extract doses alone also revealed significant variation ($p = 0.016$), indicating a dose-dependent effect.

The positive control, glibenclamide, produced the highest glucose reduction at 30, 60, and 90 minutes. This result was expected because glibenclamide, a sulfonylurea agent, is known to stimulate pancreatic β -cells to release insulin^{24,25}. The minimal reduction observed in the negative control group confirms that spontaneous glucose decline does not occur in alloxan-induced hyperglycemia and underscores the model's validity.

Among the experimental groups, Dose III (800 mg/kg BW) showed the greatest percentage reduction in glucose, followed by Dose II (400 mg/kg BW) and Dose I (200 mg/kg BW). This pattern indicates a dose-response relationship, suggesting that higher concentrations of the combined extract provide greater antihyperglycemic action. A similar dose-dependent response has been reported in previous studies assessing the antidiabetic activity of *Kalanchoe pinnata* or *Aloe vera* individually^{26,27}. These plants are rich in bioactive compounds such as flavonoids, alkaloids, tannins, saponins, and polysaccharides, which have been associated with glucose-lowering effects^{13,14,27,28}.

Several mechanisms may explain the antihyperglycemic activity observed in this study. From a nutritional perspective, these bioactive compounds are dietary phytochemicals with potential applications in functional foods. Flavonoids and polyphenols in *K. pinnata* may enhance insulin sensitivity and protect pancreatic β -cells from oxidative damage induced by alloxan-generated reactive oxygen species^{29–31}. Meanwhile, *Aloe vera* contains acemannan and other polysaccharides that have been shown to improve glucose metabolism, delay carbohydrate absorption, and enhance peripheral glucose uptake^{12,32,33}. The combination of both plants likely produces complementary effects. It supports the concept of food synergy, in which multiple phytochemicals could contribute to glycemic control through different mechanisms.

Comparable findings have been reported in previous animal studies. *Aloe vera* extracts improved

glucose tolerance and reduced fasting glucose levels in both alloxan- and streptozotocin-induced diabetic models¹⁶. Similarly, *Kalanchoe pinnata* extracts have demonstrated protective effects on pancreatic tissues and improved glycemic control^{11,27}.

This study is consistent with these findings. It suggests that the combined extract may exert its effect through complementary mechanisms, antioxidant activity, pancreatic protection, and improved peripheral glucose utilization. Although the highest extract dose did not surpass glibenclamide at all time points, its natural origin and potential safety profile suggest that it could serve as a functional dietary adjunct for managing mild hyperglycemia. This is particularly relevant for nutritional strategies aimed at preventing or delaying the progression of type 2 diabetes, in which plant-based bioactive compounds can complement lifestyle and dietary interventions. Overall, these results support the potential of *K. pinnata* and *Aloe vera* as functional food ingredients or nutraceuticals³⁴.

However, the extract's natural origin and potential safety profile make it a promising adjunctive therapy or alternative for mild hyperglycemia. Overall, the study supports the antihyperglycemic potential of *Kalanchoe pinnata* and *Aloe vera* extract, especially at higher doses. The dose-dependent effect and consistency with earlier research suggest that further investigation, including chronic administration and mechanistic studies, is warranted to better understand the therapeutic potential of this combination.

This study has several limitations that should be considered. The sample size was relatively small, and the short observation period reflects only an acute glycemic response rather than long-term effects. In addition, the assessment was limited to blood glucose levels; other metabolic parameters were not evaluated, and the proposed mechanisms were not directly investigated. Future research should explore chronic administration, optimal dosing, and human clinical trials, and include more comprehensive outcome measures to better assess efficacy and safety. Furthermore, incorporation into palatable food products may help evaluate acceptability and support the development of plant-based dietary strategies for glycemic management and diabetes prevention.

CONCLUSIONS

The combined extract of *Kalanchoe pinnata* and *Aloe vera* demonstrated antihyperglycemic activity in alloxan-induced mice, with reductions in blood glucose levels that depended on the dose. The highest dose showed the greatest effect, although it remained lower than that of the standard drug. These findings suggest

that the combined extract may have potential as a natural antihyperglycemic agent. However, further studies are needed to confirm its efficacy, safety, and underlying mechanisms.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

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AUTHOR CONTRIBUTIONS

A: conceptual, funding acquisition, supervision, project administration, resources, writing, review & editing; H: methodology, investigation, data curation, formal analysis, validation, ; KTF: investigation, data curation, visualization, software, writing original draft, writing review & editing.

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