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Effect of Combined Extracts of Acalypha australis, Andrographis paniculata, and Nigella sativa as Adjunctive Therapy on Fasting Blood Glucose: A Pilot Quasi-Experimental Study

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ABSTRACT: **Background:** This pilot study aimed to evaluate the effect of a combined extract of *Acalypha australis*, *Andrographis paniculata*, and *Nigella sativa* on fasting blood glucose levels in patients with type 2 diabetes mellitus. **Methods:** This study employed a quasi-experimental pretest–posttest control group design with repeated measurements over 30 days. Benodem (POM TR193337421) contained a combination of *Acalypha australis* (250 mg), *Andrographis paniculata* (200 mg), and *Nigella sativa* (100 mg) extracts per capsule. A total of 45 participants were equally allocated into three groups: a control group receiving metformin 500 mg twice daily, intervention group 1 receiving Benodem 3 × 2 capsules/day (3,300 mg/day) plus metformin, and intervention group 2 receiving Benodem 2 × 2 capsules/day (2,200 mg/day) plus metformin. **Results:** Baseline fasting blood glucose levels were 244 ± 58.8 mg/dL in the control group, 320 ± 56.8 mg/dL in intervention group 1, and 204 ± 37.8 mg/dL in intervention group 2. After 30 days, only the intervention groups showed significant reductions ($p < 0.001$), with the largest decrease in intervention group 1 at 153 mg/dL, followed by intervention group 2 at 72.9 mg/dL. The Kruskal–Wallis test indicated an overall between-group difference in week-4 change ($p < 0.001$); however, baseline imbalance and the non-randomized design mean that these findings should be interpreted as preliminary. **Conclusions:** The herbal combination may serve as a promising complementary therapy for improving fasting blood glucose control, although larger, long-term studies are needed to confirm its efficacy and safety.

1. INTRODUCTION

Type 2 diabetes mellitus is a chronic metabolic disorder characterized by blood glucose levels above the normal range and is influenced by both modifiable and non-modifiable risk factors.[1] According to the International Diabetes Federation, approximately 589 million adults aged 20–79 years were living with diabetes worldwide in 2024, and this number is projected to increase to 853 million by 2050. In Indonesia, diabetes remains a major public health concern, with approximately 20.426 million adults living with diabetes in 2024 and a projected increase to 28.584 million by 2050.[2] The 2023 Indonesian Health Survey also reported that diabetes prevalence continues to increase across Indonesian provinces, including South Sulawesi.[3] In South Sulawesi, Makassar City recorded the highest number of diabetes cases in 2024.[4]

Type 2 diabetes mellitus is closely associated with lifestyle, dietary patterns, insulin resistance, impaired insulin secretion, oxidative stress, and disturbances in glucose metabolism, making long-term and comprehensive management necessary.[5,17] In addition to pharmacological therapy, medicinal plants continue to be widely used by communities because they are commonly perceived as natural alternatives or complementary treatments for disease prevention and management.[6] Herbal medicine has also gained increasing attention as a complementary therapy for diabetes because bioactive compounds found in medicinal plants may act through various antidiabetic mechanisms, including improving insulin activity, inhibiting carbohydrate-digesting enzymes, reducing oxidative stress, and supporting glucose homeostasis.[9]

Andrographis paniculata contains andrographolide and other bioactive compounds that may contribute to blood glucose reduction by improving glucose utilization, stimulating insulin secretion, and inhibiting carbohydrate-digesting enzymes such as alpha-glucosidase and alpha-amylase.[8] *Nigella sativa* has also been reported to possess antidiabetic, antioxidant, hypoglycemic, insulin-regulating, and glucose-homeostasis-promoting properties.[9] Meanwhile, experimental research on *Acalypha* species has demonstrated their potential to reduce blood glucose levels.[10] These plants may therefore offer complementary mechanisms in diabetes management because each contains different bioactive compounds that may influence different aspects of hyperglycemia. Such a combination is theoretically relevant because type 2 diabetes mellitus involves multiple interconnected metabolic disturbances rather than a single pathological mechanism. Although previous studies have demonstrated the antihyperglycemic effects of *Acalypha* species, *Andrographis paniculata*, and *Nigella sativa* individually, clinical evidence concerning their combined administration in patients with type 2 diabetes mellitus remains limited. Therefore, evaluating the combined use of *Acalypha australis*, *Andrographis paniculata*, and *Nigella sativa* is important to determine whether these herbs may provide additional benefits as complementary therapy for blood glucose control in patients with type 2 diabetes mellitus.

The rationale for combining these three plants rests on their potentially complementary antihyperglycemic actions: *Andrographis paniculata* has been associated with glucose utilization and carbohydrate-digesting enzyme inhibition, *Nigella sativa* with insulin regulation and antioxidant activity, and *Acalypha* species with glucose-lowering effects in experimental models.[8–10] However, evidence specific to *Acalypha australis* remains limited, and clinical evidence for the combined use of these extracts with metformin is scarce. This pilot study provides preliminary clinical data on a BPOM-registered combination product. The two daily dose regimens (2,200 and 3,300 mg/day) were compared as study intervention levels to explore whether changes in fasting blood glucose differed by dose; this study was not designed to establish an optimal or generally recommended dose.

This study was conducted among subjects with blood glucose levels ranging from 200 to 550 mg/dL and a diabetes duration of two to five years. Fasting blood glucose levels were measured five times using a glucometer to observe short-term changes during the intervention period. This approach was selected to assess changes in blood glucose occurring during a relatively short intervention, whereas HbA1c represents average glycemic levels over a longer period.[22] The study included three groups: a control group receiving metformin 500 mg twice daily; an intervention group receiving metformin combined with mixed extracts of *Acalypha australis*, *Andrographis paniculata*, and *Nigella sativa* at 2,200 mg/day; and another intervention group receiving the same combination at 3,300 mg/day. Therefore, this study aimed to analyze the effect of consuming mixed extracts of *Acalypha australis*, *Andrographis paniculata*, and *Nigella sativa* on blood glucose reduction in subjects with type 2 diabetes mellitus.

2. MATERIALS AND METHODS

2.1 Research Design

This study employed a quasi-experimental pretest–posttest control-group design with repeated measurements. The study was conducted in Makassar City, South Sulawesi, Indonesia, from October 15 to November 30, 2025. Participants were allocated into three groups, each consisting of 15 participants. The control group received metformin 500 mg twice daily. Intervention Group 1 received metformin 500 mg twice daily combined with Benodem 550 mg, administered at six capsules per day (3,300 mg/day), whereas Intervention Group 2 received metformin 500 mg twice daily combined with Benodem 550 mg, administered at four capsules per day (2,200 mg/day). The intervention was administered for 30 days. Fasting blood glucose (FBG) levels were measured at five assessment points: baseline and four subsequent weekly follow-ups. This repeated-measurement approach enabled the evaluation of changes in FBG levels throughout the intervention period and comparisons among the three treatment groups. The study design is illustrated in Figure 1.

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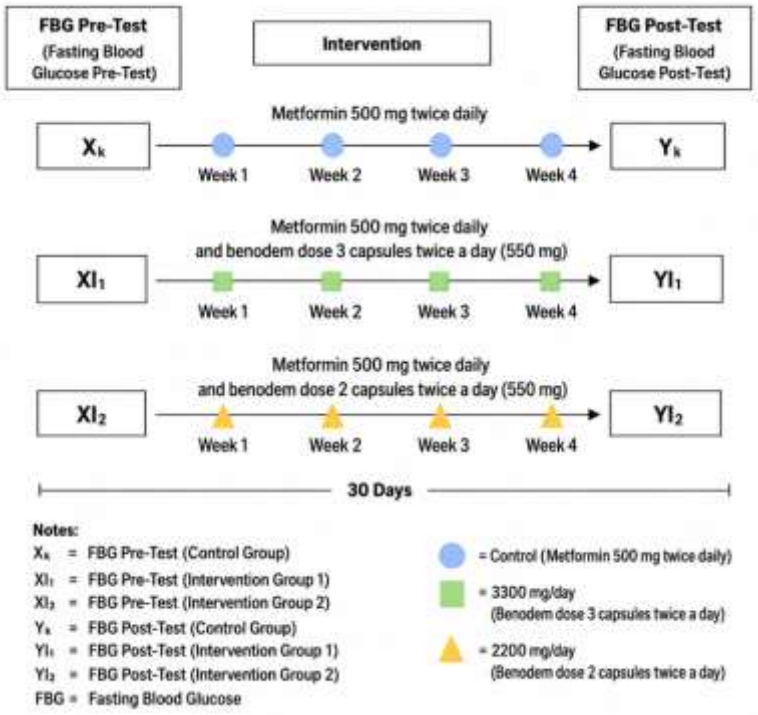


Figure 1. Study design.

2.2 Population and Sample

The study population consisted of patients with type 2 diabetes mellitus (T2DM) in Makassar City, South Sulawesi, Indonesia. Eligible participants were adults aged 35–65 years with a physician-confirmed diagnosis of T2DM, a disease duration of 2–5 years, and screening random blood glucose levels ranging from 200 to 550 mg/dL. Patients receiving insulin therapy, using other herbal products, pregnant women, and individuals with known allergies to any of the herbal extracts included in the study formulation were excluded. The sample size was determined using the Lemeshow formula for comparing two independent means. The minimum required sample size was calculated before participant recruitment, resulting in a total of 45 participants. These participants were allocated equally into three groups: one control group and two intervention groups, with 15 participants in each group. A consecutive sampling technique, classified as non-probability sampling, was employed to recruit eligible participants until the required sample size was achieved. In accordance with the quasi-experimental design, group allocation was non-randomized and followed the order of participant enrollment. Therefore, participants were assigned to the control or intervention groups without random allocation, which may have resulted in differences in baseline characteristics among the groups.

2.3 Operational Definitions

Table 1. Operational definitions of the study variables

Variable	Operational definition	Measuring instrument	Measurement result
Blood glucose level	Amount of glucose in the blood at a given time, expressed in mg/dL or mmol/L and measured before and after the intervention.	EasyTouch GCU glucometer, lancet, glucose test strip, and alcohol swab.	Blood glucose level before and after the intervention.
Benodem supplementation (mixed extracts)	Administration of a dry extract mixture of Acalypha australis, Andrographis paniculata, and Nigella sativa as the hard-capsule product Benodem for 30 days, together with metformin.	One Benodem capsule contains 550 mg of mixed extract: Acalypha australis 250 mg, Andrographis paniculata 200 mg, and Nigella sativa 100 mg.	Intervention 1: metformin 500 mg twice daily plus Benodem 550 mg, six capsules/day (3,300 mg/day). Intervention 2: metformin 500 mg twice daily plus Benodem 550 mg, four

			capsules/day (2,200 mg/day).
Treatment adherence	Level of adherence of patients with diabetes mellitus to the recommended treatment.	Medication adherence assessed using the MMAS-8 and weekly pill counts.	Low adherence = 0–5 Moderate adherence = 6–7 High adherence = 8
Metformin	Oral antidiabetic drug used as standard therapy for patients with type 2 diabetes mellitus, in tablet form.	500 mg twice daily; pill count at each weekly visit.	Compliance with metformin consumption during the intervention period.

Table 1 provides a clear explanation of each variable, including its indicators, measurement methods, and criteria used for data collection and analysis.

2.4 Data Collection and Instruments

Data collection comprised participant recruitment, eligibility screening, baseline assessment, intervention administration, weekly monitoring, final assessment, and medication adherence evaluation. Screening data included random blood glucose levels, while baseline and follow-up assessments included fasting blood glucose measurements. Demographic and anthropometric characteristics were also collected, including age, sex, body weight, height, and waist circumference. Medication adherence was evaluated using the Morisky Medication Adherence Scale-8 (MMAS-8) after the 30-day intervention period, supplemented by weekly pill counts. Fasting blood glucose measurements were performed by four trained health workers using EasyTouch GCU glucometers. Measurements were conducted at five assessment points, consisting of the baseline measurement and four subsequent weekly follow-ups. The same type of measurement instrument was used throughout the study to maintain consistency in glucose assessment. The intervention product was Benodem, a hard herbal capsule containing 550 mg of combined extracts of *Acalypha australis*, *Andrographis paniculata*, and *Nigella sativa*. Each capsule contained 250 mg of *Acalypha australis*, 200 mg of *Andrographis paniculata*, and 100 mg of *Nigella sativa*. The product was registered with the Indonesian Food and Drug Authority (BPOM) under registration number POM TR193337421 on July 31, 2024. It was manufactured by PT Elanazma Prima Int, Bekasi, Indonesia, and distributed by PT Berkah Amanah Selalu, South Bekasi, Indonesia. Data were subsequently entered, checked, and analyzed using JAMOVI version 2.7.5.

2.5 Safety Monitoring

The study product, Benodem, was registered with the Indonesian Food and Drug Authority (BPOM) under registration number POM TR193337421, as indicated in the product information. During the 30-day intervention period, participants had access to a general practitioner for consultation regarding the use of the herbal formulation alongside metformin. According to the study team's records, no adverse effects were reported by participants during the intervention period. However, the available study documentation did not specify the use of a standardized adverse-event assessment checklist, a predefined hypoglycemia threshold, or systematic laboratory monitoring of liver and kidney function. Consequently, the absence of reported adverse effects should not be interpreted as definitive evidence of the safety of the combined formulation. These limitations are important when interpreting the safety findings and should be addressed in future studies through systematic adverse-event monitoring and appropriate clinical assessments.

2.6 Data Analysis

Data were entered, checked for completeness, and analyzed using JAMOVI version 2.7.5. Data screening included checking for data-entry errors and potential outliers. Descriptive statistics were used to summarize participant characteristics and fasting blood glucose measurements, including means, standard deviations, minimum and maximum values, and frequencies, as appropriate. The normality of continuous data was assessed using the Shapiro–Wilk test. Because some variables did not meet the assumption of normality, non-parametric statistical tests were applied. Within-group differences in fasting blood glucose between baseline and week four were evaluated using the Wilcoxon signed-rank test. Changes across all five assessment points were examined using the Friedman test to assess repeated measurements within each group. Between-group differences in fasting blood glucose changes were assessed using the Kruskal–Wallis test. Changes in fasting blood glucose (ΔFBG) were calculated as the week-four value minus the baseline value:

$$\Delta FBG = FBG \text{ at week } 4 - FBG \text{ at baseline}$$

Accordingly, negative ΔFBG values indicated reductions in fasting blood glucose levels, whereas positive values indicated increases. Baseline categorical characteristics were compared among the three groups using Fisher's exact test. Pairwise post hoc comparisons using Dunn's test with Bonferroni correction were not available in the current statistical analysis output and were therefore not reported. Considering the differences in baseline fasting blood glucose levels among the study groups, percentage changes were also calculated descriptively using the group mean baseline and week-four values according to the following formula:

Percentage reduction (%) = [(Baseline mean FBG − Week-4 mean FBG) / Baseline mean FBG] × 100

These percentage changes were used to describe the magnitude of observed reductions within each group. They were not adjusted estimates of treatment effects. No baseline-adjusted analysis, such as analysis of covariance (ANCOVA), was performed. Therefore, between-group findings were interpreted cautiously, considering the non-randomized allocation and potential influence of baseline differences. Statistical significance was determined using a two-sided p-value of less than 0.05.

3. RESULTS AND DISCUSSION

3.1 Characteristics of Respondents

Table 2. Distribution of respondent characteristics by study group

Characteristic	Category	Control, n (%)	Intervention 1, n (%)	Intervention 2, n (%)	p-value
Age	Adult (30–59 years)	11 (73.3)	14 (93.3)	13 (86.7)	0.463
	Elderly (≥60 years)	4 (26.7)	1 (6.7)	2 (13.3)	
Sex	Male	1 (6.7)	0 (0.0)	3 (20.0)	0.302
	Female	14 (93.3)	15 (100.0)	12 (80.0)	
Body mass index (BMI)	<18.5 kg/m², underweight	0 (0.0)	2 (13.3)	0 (0.0)	0.507
	18.5–22.9 kg/m², normal	4 (26.7)	3 (20.0)	2 (13.3)	
	≥23.0 kg/m², overweight/obese	11 (73.3)	10 (66.7)	13 (86.7)	
Waist circumference	Normal	1 (6.7)	2 (13.3)	1 (6.7)	1.000
	Central obesity	14 (93.3)	13 (86.7)	14 (93.3)	

Note. Normal waist circumference was defined as <90 cm in men and <80 cm in women, while central obesity was defined as ≥90 cm in men and ≥80 cm in women.

Table 2 presents the characteristics of the 45 participants who completed the study, with 15 participants in each group. Overall, most participants were adults aged 30–59 years (84.4%), while 15.6% were aged ≥60 years. Female participants predominated (91.1%), whereas male participants accounted for 8.9%. Regarding BMI, 75.6% of participants had a BMI of ≥23.0 kg/m², indicating that most were classified as overweight or obese. Furthermore, 91.1% of participants had central obesity based on waist circumference criteria. No statistically significant differences were observed among the three groups in terms of age ($p = 0.463$), sex ($p = 0.302$), BMI category ($p = 0.507$), or waist circumference ($p = 1.000$). These findings indicate that the groups had comparable demographic and anthropometric characteristics, although this comparability does not necessarily extend to baseline fasting blood glucose levels.

3.2 Effect of Age and Sex on Changes in Fasting Blood Glucose

Table 3. Mann–Whitney test of changes in fasting blood glucose (FBG) by age category

Variable	Statistical test	Test statistic	p-value
ΔFBG week 4–week 0 (mg/dL)	Mann–Whitney U	95.0	0.240

Natural Resources for Human Health
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Table 4. Mann–Whitney test of changes in FBG by sex

Variable	Statistical test	Test statistic	p-value
ΔFBG week 4–week 0 (mg/dL)	Mann–Whitney U	69.0	0.618

The Mann–Whitney U test was used to examine whether changes in fasting blood glucose (ΔFBG) differed by age category and sex. No significant difference in ΔFBG was observed between participants aged 30–59 years and those aged ≥60 years (U = 95.0, p = 0.240). The comparison by sex was also not statistically significant (Table 4). These subgroup analyses should be interpreted cautiously because the number of male participants was small.

3.3 Medication Adherence

Table 5. Morisky Medication Adherence Scale (MMAS-8) score of respondents

Variable	n	Mean ± SD	Median	Minimum–maximum
MMAS-8 score	45	7.80 ± 0.405	8	7–8

Note. MMAS-8 = eight-item Morisky Medication Adherence Scale; SD = standard deviation.

Medication adherence was assessed using the eight-item Morisky Medication Adherence Scale (MMAS-8). As presented in Table 5, the mean adherence score was 7.80 ± 0.405, with a median of 8 and a range of 7–8. Overall, 36 participants (80.0%) demonstrated high medication adherence (MMAS-8 score = 8), while nine participants (20.0%) demonstrated moderate adherence (MMAS-8 score = 7). No participants were classified as having low medication adherence.

3.4 Effect of Benodem Supplementation on Weekly Fasting Blood Glucose Levels

Table 6. Shapiro–Wilk normality test results for fasting blood glucose levels by study group

FBG measurement	Control, p-value	Intervention 1, p-value	Intervention 2, p-value
Week 0	0.008*	0.310	0.013*
Week 1	0.028*	0.413	0.469
Week 2	0.070	0.402	0.483
Week 3	0.391	0.401	0.614
Week 4	0.858	0.589	0.655

Note. *p < 0.05 indicates that the data were not normally distributed.

The Shapiro–Wilk test indicated that several fasting blood glucose measurements deviated from a normal distribution, particularly at baseline and week 1 in the control group and at baseline in Intervention Group 2 (Table 6). Given these findings, non-parametric statistical methods were used to evaluate within-group changes and between-group differences.

Table 7. Changes in fasting blood glucose levels across measurement times and between study groups

Group	Week 0, mean ± SD	Week 1, mean ± SD	Week 2, mean ± SD	Week 3, mean ± SD	Week 4, mean ± SD	ΔFBG week 4–week 0, mean ± SD	Friedman test (p-value)
Control	244 ± 58.8	226 ± 77.5	244 ± 113.6	242 ± 103.0	244 ± 94.4	−0.0667 ± 71.1	0.892
Intervention 1	320 ± 56.8	260 ± 64.6	229 ± 56.0	225 ± 75.3	168 ± 46.0	−152.5333 ± 64.1	<0.001
Intervention 2	204 ± 37.8	183 ± 37.6	172 ± 43.3	154 ± 36.4	131 ± 32.1	−72.8667 ± 34.2	<0.001
Kruskal–Wallis p-value between groups	**<0.001**	**0.004**	**0.021**	**0.007**	**<0.001**	**<0.001**	**—**

Note. Values are presented as mean ± standard deviation. FBG = fasting blood glucose; SD = standard deviation.

Weekly fasting blood glucose measurements for all study groups are presented in Table 7 and Figure 2. At baseline, all participants had fasting blood glucose levels above the diagnostic threshold for diabetes mellitus. Baseline FBG differed significantly among the three groups (Kruskal–Wallis, p < 0.001). Intervention Group 1 had the highest mean baseline FBG (320 ± 56.8 mg/dL), followed by the control group (244 ± 58.8 mg/dL) and Intervention Group 2 (204 ± 37.8 mg/dL).

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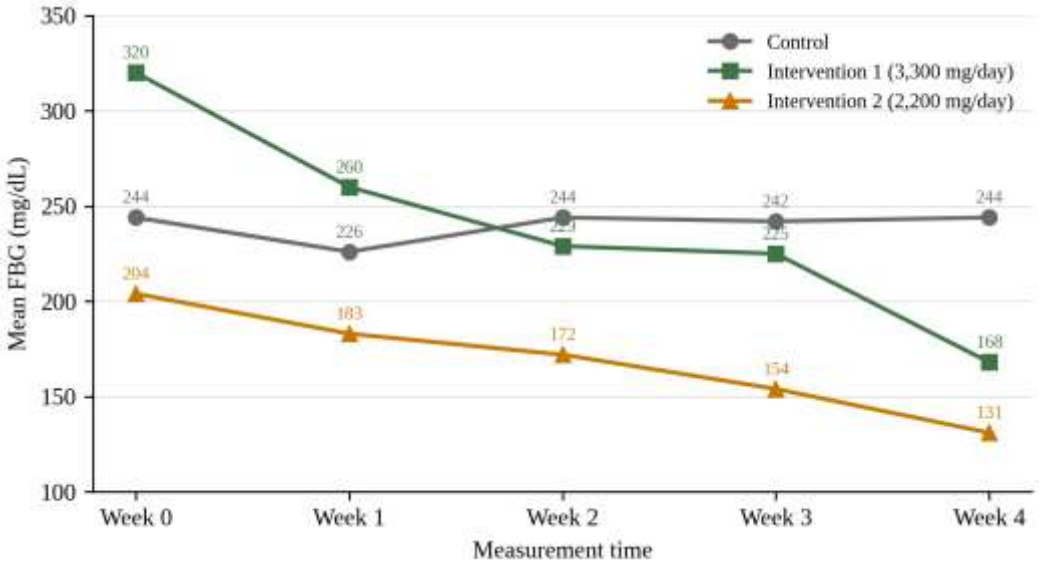


Figure 2. Mean fasting blood glucose (FBG) levels of the control, intervention 1, and intervention 2 groups from baseline to week 4.

During the intervention, different patterns of fasting blood glucose changes were observed. Intervention Group 1 demonstrated a decline in mean FBG from 320 ± 56.8 mg/dL at baseline to 260 ± 64.6 mg/dL in week 1, 229 ± 56.0 mg/dL in week 2, 225 ± 75.3 mg/dL in week 3, and 168 ± 46.0 mg/dL in week 4. Intervention Group 2 also demonstrated a progressive reduction, from 204 ± 37.8 mg/dL at baseline to 183 ± 37.6 mg/dL, 172 ± 43.3 mg/dL, 154 ± 36.4 mg/dL, and 131 ± 32.1 mg/dL across weeks 1–4, respectively. In contrast, the control group showed relatively small fluctuations, with mean FBG values ranging from 226 to 244 mg/dL.The mean changes from baseline to week four also varied among the groups. Intervention Group 1 demonstrated the largest mean reduction (ΔFBG = −152.5 ± 64.1 mg/dL), followed by Intervention Group 2 (ΔFBG = −72.9 ± 34.2 mg/dL). The control group showed almost no overall change (ΔFBG = −0.1 ± 71.1 mg/dL). The Friedman test indicated significant changes across the five measurement points in both intervention groups ($p < 0.001$ for each), whereas no statistically significant change was observed in the control group ($p = 0.892$). The Kruskal–Wallis test also indicated significant overall differences among the three groups at the individual measurement points and in week-four ΔFBG ($p < 0.001$ for ΔFBG).

3.5 Descriptive Change in Fasting Blood Glucose

Table 8. Descriptive percentage change in fasting blood glucose from baseline to week 4

Study group	Baseline FBG mean (mg/dL)	Week 4 FBG mean (mg/dL)	Mean change (mg/dL)	Descriptive reduction (%)
Control	244	244	−0.1	0.0
Intervention 1 (3,300 mg/day)	320	168	−152.5	47.5
Intervention 2 (2,200 mg/day)	204	131	−72.9	35.8

Table 8 presents the descriptive percentage changes in fasting blood glucose between baseline and week four. The control group demonstrated an almost unchanged mean FBG level, corresponding to a descriptive reduction of 0.0%. In comparison, Intervention Group 1 showed a descriptive reduction of 47.5%, while Intervention Group 2 showed a reduction of 35.8%. These percentages were calculated from group mean values and represent unadjusted descriptive changes rather than estimates of treatment effects. The observed differences should therefore be interpreted cautiously, particularly considering the significant baseline imbalance among the groups. The overall Kruskal–Wallis test indicated significant differences in week-four ΔFBG among the three groups ($p < 0.001$). However, specific pairwise differences were not established because appropriate post hoc comparisons were unavailable in the current analysis output.

Natural Resources for Human Health
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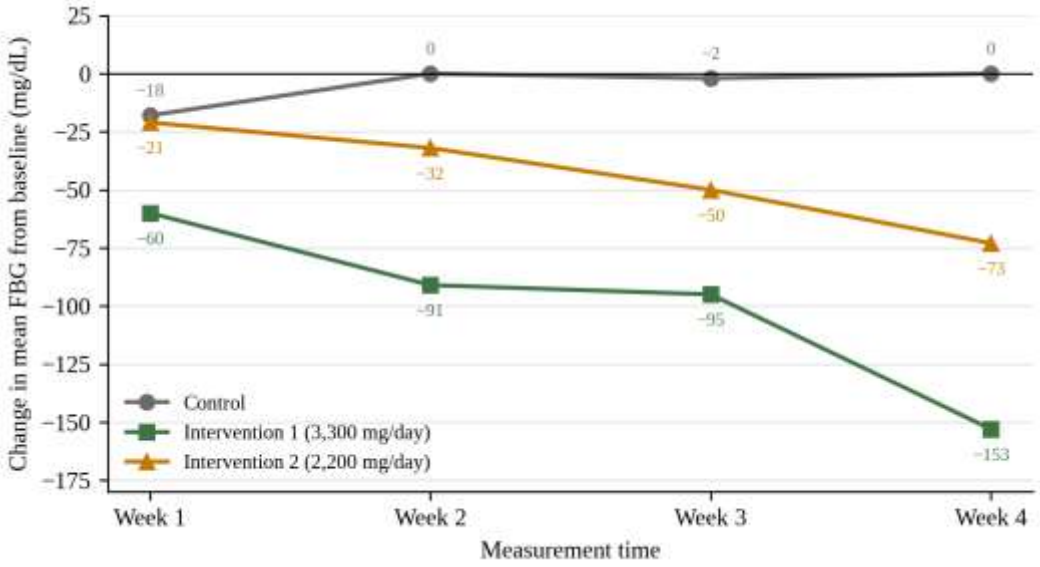


Figure 3. Changes in mean fasting blood glucose from baseline.

Figure 3 illustrates the changes in mean fasting blood glucose relative to baseline across the five assessment points. The control group showed small and inconsistent changes, with reductions of 18 mg/dL in week 1, no change in week 2, a reduction of 2 mg/dL in week 3, and no overall change in week 4. Intervention Group 1 demonstrated reductions of 60, 91, 95, and 153 mg/dL across weeks 1–4, respectively. Intervention Group 2 showed corresponding reductions of 21, 32, 50, and 73 mg/dL. Overall, the descriptive patterns showed greater reductions in both Benodem-treated groups than in the control group, with the largest reduction observed in Intervention Group 1. Nevertheless, these findings represent observed changes and should not be interpreted as definitive evidence of a causal treatment effect.

3.6 Safety and Adverse Events

Safety findings were based on information provided by the study team. No adverse effects were reported by participants during the 30-day intervention period. Participants also had access to a general practitioner for consultation regarding product use. However, the available study records did not provide group-specific adverse-event counts, documented hypoglycemic episodes, discontinuations due to adverse events, or systematic liver and kidney function results. Therefore, the absence of reported adverse effects should not be interpreted as confirmation that no adverse events occurred or as definitive evidence of the safety of the intervention.

3.7 Discussion

The present study demonstrated reductions in fasting blood glucose (FBG) levels in both groups receiving adjunctive Benodem supplementation alongside metformin over the 30-day intervention period. Type 2 diabetes mellitus is commonly found among adults and is closely associated with metabolic and lifestyle-related risk factors, including unhealthy dietary patterns, low physical activity, overweight, obesity, and increasing age.[12-14] The predominance of female respondents in this study may be associated with biological factors, including hormonal changes, pregnancy history, menopause, and body fat distribution, which may influence insulin resistance. However, previous studies have shown that sex is not always significantly associated with fasting blood glucose levels among patients with type 2 diabetes mellitus.[13,14] Consistent with this, the present study found no statistically significant differences in FBG changes according to age or sex, although the limited number of male participants requires cautious interpretation.

Most respondents in this study had a BMI of ≥23.0 kg/m² (75.6%), while 91.1% had central obesity. These findings indicate a high metabolic risk among the study participants. Increased adiposity and central obesity are strongly associated with the development of insulin resistance through mechanisms involving chronic inflammation, adipokine imbalance, increased circulating free fatty acids, and reduced insulin sensitivity.[15,6] Therefore, interventions that may improve insulin sensitivity, inhibit glucose absorption, and reduce oxidative stress are relevant for further investigation.

At baseline, all study groups exhibited poor glycemic control, with fasting blood glucose levels above the recommended therapeutic target for patients with type 2 diabetes mellitus.[11] During the four-week intervention, both Benodem-treated groups demonstrated progressive reductions in mean FBG, whereas the control group showed relatively stable values. Medication adherence was generally good, with a mean Morisky Medication Adherence Scale-8 score of 7.80. Most respondents (80.0%) demonstrated high adherence, while 20.0% demonstrated moderate adherence. This level of adherence may have been supported by daily medication reminders provided by the enumerators. Good adherence is important because diabetes management depends on consistent medication use and compliance with the prescribed treatment regimen.

The magnitude of FBG reduction differed between the intervention groups. Intervention Group 1, which received Benodem 3,300 mg/day alongside metformin, demonstrated a mean reduction of approximately 152.5 mg/dL, whereas Intervention Group 2, which received Benodem 2,200 mg/day, showed a reduction of approximately 72.9 mg/dL. In contrast, the control group demonstrated almost no overall change. The Friedman test indicated significant changes across the five measurement points in both intervention groups ($p < 0.001$), whereas no significant change was observed in the control group ($p = 0.892$). The Kruskal–Wallis test also indicated an overall difference in week-four FBG changes among the three groups ($p < 0.001$). However, because appropriate post hoc comparisons were unavailable, specific pairwise differences cannot be established. Therefore, the greater reduction observed in the higher-dose group represents a descriptive pattern rather than confirmed evidence of a dose-dependent treatment effect.

Benodem contains a combination of *Acalypha australis*, *Andrographis paniculata*, and *Nigella sativa* extracts, which may act through several potential antihyperglycemic mechanisms. These mechanisms may include improving insulin sensitivity, inhibiting glucose absorption, reducing hepatic glucose production, supporting pancreatic β-cell function, and producing antioxidant and anti-inflammatory effects. The present findings are consistent with previous studies indicating that *Nigella sativa* may contribute to reductions in blood glucose levels when administered alone or in combination with conventional antidiabetic therapy.[18,19] Experimental evidence has also demonstrated the glucose-lowering potential of *Acalypha* species, although the available study evaluated *Acalypha indica* rather than *Acalypha australis*.[10] These findings support further investigation into the potential benefits of combining herbal extracts with different mechanisms of action alongside conventional treatment. Nevertheless, the individual contributions and possible synergistic effects of the three extracts have not been established.[17]

Regarding safety, the study product was registered with BPOM, and participants had access to a general practitioner for consultation during the intervention. According to the study team's records, no adverse effects were reported during the 30-day intervention. Nevertheless, product registration alone does not establish the safety of co-administration with conventional antidiabetic drugs. The present study did not systematically evaluate herb–drug interactions or include documented laboratory monitoring of liver and kidney function. Therefore, the absence of reported adverse effects should not be interpreted as definitive evidence of safety. Further studies are needed to evaluate potential interactions and systematically assess the safety of this herbal combination when administered alongside metformin.

An important consideration is the baseline imbalance in fasting blood glucose among the groups (control: 244 ± 58.8 mg/dL; Intervention Group 1: 320 ± 56.8 mg/dL; Intervention Group 2: 204 ± 37.8 mg/dL; $p < 0.001$), which may have resulted from allocation based on enrollment order rather than randomization. Based on group mean values, FBG decreased by approximately 0.0% in the control group, 47.5% in Intervention Group 1, and 35.8% in Intervention Group 2 between baseline and week four. These percentages represent descriptive, unadjusted changes rather than adjusted treatment effects. The larger absolute reduction in Intervention Group 1 may partly reflect its higher baseline glucose level and potential regression toward the mean. Consequently, the observed between-group differences should be interpreted cautiously and considered preliminary.

3.8 Limitations

This study has several limitations. First, participants were allocated according to the order of enrollment rather than randomization, and neither a placebo control nor blinding was employed, potentially introducing selection and performance bias. Second, the sample size was small (n = 45) and predominantly female (91.1%), limiting the generalizability of the findings. Third, the intervention period was relatively short (30 days), and glycemic control was assessed using capillary fasting glucose measurements with a glucometer, without HbA1c or other laboratory-based glycemic markers. Fourth, systematic laboratory assessments of liver and kidney function and potential herb–drug interactions were not documented in the available study records. Fifth, dietary intake and physical activity were not systematically measured or controlled. Sixth, baseline differences in fasting blood glucose among the groups and the absence of baseline-adjusted analysis may have influenced the observed treatment differences. Seventh, the absence of appropriate post hoc comparisons limited the identification of specific between-

group differences. Finally, the product was evaluated only as a fixed combination, making it difficult to determine the individual contribution of each extract or establish potential synergistic effects. Larger randomized, placebo-controlled trials with longer follow-up, HbA1c measurements, appropriate baseline-adjusted analyses, and systematic safety monitoring are needed to confirm the potential benefits and safety of this herbal formulation.

4. CONCLUSION

This pilot quasi-experimental study found that fasting blood glucose decreased over 30 days among participants who received Benodem in addition to metformin, with a larger descriptive reduction in the 3,300 mg/day group than in the 2,200 mg/day group. The control group showed little overall change. Because the groups differed significantly in baseline fasting blood glucose and allocation was not randomized, these findings are preliminary and do not establish a causal or dose-dependent effect. Appropriate pairwise reanalysis and larger randomized controlled trials with longer follow-up, HbA1c assessment, and systematic safety monitoring are needed before conclusions about efficacy and safety can be made.

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AUTHOR CONTRIBUTIONS

Azura: Conceptualization, Methodology, Formal Analysis, Writing—Original Draft.

Dian Sidik Arsyad: Conceptualization, Methodology, Investigation, Formal Analysis, Writing—Original Draft.

Andi Zulkifli: Investigation, Data Collection.

Healthy Hidayanty: Formal Analysis, Interpretation of Results.

Stang: Formal Analysis, Interpretation of Results.

All authors reviewed the results and approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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ETHICS STATEMENT

This study received ethical approval from the Health Research Ethics Committee of Hasanuddin University (No. 2168/UN4.14.1/TP.01.02/2025)

DATA AVAILABILITY STATEMENT

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

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