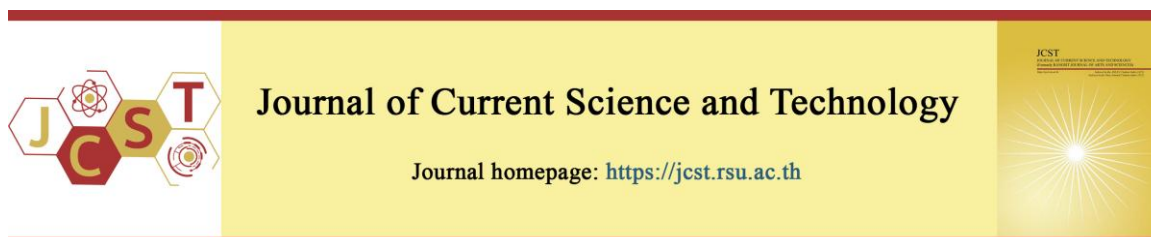


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Safety and Dose-Related Glycemic Signals of a *Gymnema inodorum*-Based Beverage in Type 2 Diabetes: An Open-Label Randomized Pilot Study

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Abstract

Gymnema inodorum is a popular traditional remedy for diabetes, yet clinical safety data for multi-herb beverages combined with metformin remain limited. This 12-week, open-label, randomized pilot study compared two daily doses of a *G. inodorum*–mulberry–chamomile beverage in adults with recently diagnosed type 2 diabetes mellitus (≤ 6 months since diagnosis) receiving stable metformin monotherapy. Thirty-two T2DM patients receiving metformin were assigned to consume the beverage at 150 mL/day (Group A) or 300 mL/day (Group B). The primary outcomes assessed safety markers, including hematology and hepatic and renal function. Secondary outcomes included fasting blood glucose (FBG), HbA1C, and oral glucose tolerance test (OGTT) indices. The beverage was generally well tolerated over 12 weeks; liver enzymes and serum creatinine remained stable in both groups. BUN changed differently between groups ($p = 0.007$), decreasing slightly in Group A but increasing in Group B. FBG changed by -6.21 mg/dL in Group A and $+22.25$ mg/dL in Group B (between-group $p = 0.014$), whereas HbA1C changed by $+0.23\%$ in Group A and $+0.42\%$ in Group B, with no significant between-group difference ($p = 0.230$). OGTT glucose exposure increased within both groups (Group A: tAUC $+12,821$ and iAUC $+12,209$; Group B: tAUC $+15,504$ and iAUC $+12,651$), with no significant between-group difference. These findings indicate short-term tolerability but do not demonstrate improved dynamic glucose tolerance; the lower dose showed a more favorable glycemic trend than the higher dose in this small non-placebo pilot. However, this observation is hypothesis-generating and should not be interpreted as a clinical recommendation.

Keywords: type 2 diabetes mellitus, *Gymnema inodorum*, safety, glycemic control, randomized clinical trial, herbal beverage

1. Introduction

Type 2 diabetes mellitus (T2DM) poses a rapidly expanding global health burden, with prevalence projected to rise significantly by 2050

(Magliano et al., 2021). The disease is characterized by chronic hyperglycemia and is associated with severe long-term microvascular and macrovascular complications (Zheng et al., 2018). Although

management relies on lifestyle modification and pharmacotherapy, many patients fail to achieve optimal glycemic targets or experience drug-related adverse effects, leading to the widespread use of complementary plant-based remedies alongside prescribed drugs.

Bioactive botanicals may complement conventional therapy via mechanisms such as the inhibition of carbohydrate-digesting enzymes and enhancement of insulin sensitivity (Ota & Ulrih, 2017). Herbal teas offer a culturally acceptable adjunctive option (Xu et al., 2020). In northern Thailand, *Gymnema inodorum* (Chiang-Da) is a popular traditional remedy for managing diabetes. A prior quasi-experimental study of *G. inodorum* tea in type 2 diabetes reported no significant changes in fasting blood sugar, HbA1C, lipid profile, AST, ALT, or serum creatinine over short-term use, indicating short-term tolerability but not established glycemic efficacy (Bespinyowong et al., 2013). Although *G. inodorum* is the principal botanical in the present formulation, the additional components may also influence glycemic interpretation and safety. Human studies of mulberry (*Morus alba*) suggest potential postprandial glucose-lowering effects, plausibly related to α -glucosidase inhibition, while a 12-week double-blind trial in T2DM reported limited broader metabolic effects but no major safety concern (Hwang et al., 2016; Taghizadeh et al., 2022). Chamomile has also shown modest glycemic or metabolic benefits in T2DM in clinical studies and systematic review data, although the evidence remains heterogeneous and insufficient for firm clinical recommendations (Hajizadeh-Sharafabad et al., 2020; Kaseb et al., 2018; Rafraf et al., 2015). Because all participants in the present study were receiving metformin, potential herb–drug interactions were also relevant a priori. Although direct clinical data for this specific beverage–metformin combination are lacking, herb–drug interactions are a recognized concern in diabetes care, and metformin disposition involves transporter-mediated pathways that may be susceptible to interaction; therefore, any dose-related differences observed in this pilot should be interpreted cautiously and as hypothesis-generating rather than mechanistically established (Gupta et al., 2017; Stage et al., 2015).

Detailed assessments of safety and dynamic glycemic indices (e.g., OGTT-derived AUCs) for such combined formulations are often lacking (Phanjaroen et al., 2024; Zhang et al., 2022a). To our knowledge, no clinical study has evaluated this ready-to-drink three-herb formulation in metformin-treated adults

with early T2DM while simultaneously examining dose-related safety signals and OGTT-derived dynamic glucose exposure.

2. Objectives

1) To evaluate the short-term safety of a *Gymnema inodorum*-based beverage in adults with early type 2 diabetes mellitus (T2DM) who are receiving metformin monotherapy.

2) To explore dose-related metabolic signals, including changes in fasting blood glucose (FBG), 2-hour postprandial glucose, HbA1C, OGTT-derived glucose exposure (total AUC and incremental AUC), fasting insulin, and insulin-derived indices.

3. Materials and Methods

3.1 Tools and Materials

The investigational product was a ready-to-drink beverage formulated from finely ground herbal powders: 85% *Gymnema inodorum* (Chiang Da) leaves, 10% mulberry (*Morus alba*) leaves, and 5% chamomile (*Matricaria chamomilla*) flowers. Each 150 mL bottle contained 2 g of the blend dissolved in purified water.

3.2 Study Design

This 12-week, open-label, randomized pilot trial evaluated the safety and metabolic effects of the beverage in adults with type 2 diabetes mellitus (T2DM). Because this was a pilot dose-comparison study intended to identify short-term safety signals and to inform dose selection for a subsequent definitive trial, two active dose levels were compared, and no placebo or no beverage control group was included. The study protocol was approved by the Human Experimentation Committee at the Research Institute for Health Sciences, Chiang Mai University (Code: 18/65) and registered in the Thai Clinical Trials Registry (TCTR20251031005). All participants provided written informed consent.

3.3 Participants

Eligible participants were adults aged 25 – 60 years diagnosed with T2DM within the previous six months at Ban Mae Ka Subdistrict Health Promoting Hospital, Chiang Mai. Inclusion criteria were FBG $\geq$ 126 mg/dL, HbA1C $\geq$ 6.5%, and stable metformin monotherapy. Exclusion criteria included insulin use, recent herbal supplement use, pregnancy/lactation, chronic liver/kidney disease, malignancy, or anticoagulant use.

3.4 Sample Size

This was a pilot clinical trial designed primarily to assess feasibility, short-term safety signals, and preliminary dose-related trends rather than to provide definitive between-group efficacy testing. A historical planning value was derived from a previous study, which reported an assumed fasting blood glucose difference of 28 mg/dL and a pooled variance of 1355.23 for planning purposes, corresponding to an approximate standardized effect size of 0.76 and a required sample size of 14.74 participants per group at one-sided $\alpha = 0.05$ and 80% power (Bespinyowong et al., 2013). Allowing for approximately 10% attrition, 16 participants were enrolled per group (total $n = 32$). This historical calculation was used as a pragmatic planning aid and the present pilot was not powered for confirmatory between-group inference.

3.5 Intervention and Assessment

Participants were assigned in a 1:1 ratio using simple randomization with a color-coded ball-draw method, and the allocation sequence was concealed through the use of opaque containers, preventing the prediction of group assignments. Participants then received either one bottle (150 mL/day; Group A) or two bottles (300 mL/day; Group B) of the Chiang-Da-based beverage once daily before breakfast for 12 consecutive weeks. The two dose levels were selected pragmatically to compare one-bottle/day (150 mL/day) versus two-bottles/day (300 mL/day) administration of the same ready-to-drink formulation and thereby obtain an initial short-term dose range for safety and signal detection in a pilot study. In addition, the study was not based on prior human pharmacokinetic dose-finding data. Adherence was monitored using returned bottle counts; however, the adherence rate was not formally quantified. At each visit, fasting blood samples were collected for glycemic indices (FBG, insulin, and HbA1C) and safety profiles (CBC and liver/kidney function). Anthropometrics and vital signs were recorded. Adverse events were monitored via weekly calls. Participants were instructed to maintain their usual diet, physical activity, and metformin regimen during the study; however, formal dietary records, physical activity logs, and objective metformin adherence measures were not collected. Laboratory tests were performed at the Faculty of Associated Medical Sciences, Chiang.

3.6 Outcomes Assessment

The primary outcome was product safety. Safety was evaluated based on changes in liver

enzymes (AST and ALT), kidney function (BUN and serum creatinine), and hematologic profile (CBC). Secondary outcomes included changes in fasting blood glucose (FBG), oral glucose tolerance test (OGTT) levels, glycated hemoglobin (HbA1C), fasting insulin, insulin indices (HOMA-IR, HOMA-S, and HOMA- β), and anthropometric parameters. OGTT levels were monitored using a portable glucometer (Accu-Chek Guide, Roche Diabetes Care GmbH, Mannheim, Germany), Oral glucose tolerance testing was performed after an overnight fast with a standard 75-g oral glucose load, and glucose values were recorded at 0, 15, 30, 60, and 120 min. Total AUC and incremental AUC were calculated using the trapezoidal rule (Zubair & Launico, 2025), glycated hemoglobin (HbA1C), Fasting insulin was measured using an ELISA kit (Elabscience Biotechnology Inc., Cat. No. E-UNEL-H0101, Houston, TX, USA). The raw data exported from the microplate reader in pg/mL were converted to standard clinical units (μ IU/mL) using the established conversion factor (1μ IU/mL = 34.7 pg/mL) before the calculation of insulin indices (Knopp et al., 2019). According to the manufacturer, the assay range was 0.78–50 μ IU/mL. Moreover, insulin indices (HOMA-IR, HOMA-S, and HOMA- β) were calculated (Yoon, 2020). Because absolute fasting insulin concentrations were high relative to routine clinical immunoassay values, insulin-derived indices (HOMA-IR, HOMA-S, and HOMA- β) were interpreted as exploratory within-study measures rather than stand-alone clinical estimates.

3.7 Statistical Analysis

Data are presented as mean $\pm$ SD or number (%). Between-group comparisons of change scores were performed using Welch's t-test for approximately normally distributed variables and Mann-Whitney U test for non-normally distributed variables. Within-group changes were assessed using the paired t-test or Wilcoxon signed-rank test, as appropriate. Because this pilot trial included multiple secondary endpoints and was not powered for confirmatory efficacy testing, p -values for secondary outcomes are reported as nominal and hypothesis-generating. No outcome data were missing; therefore, no imputation was performed. All randomized participants were included in the analysis as allocated. A p -value < 0.05 was considered statistically significant. Analyses were performed using GraphPad Prism version 9 (GraphPad Software, San Diego, CA, USA).

4. Results

A total of 44 individuals were screened for eligibility. However, 12 participants were excluded, with 8 not meeting the inclusion criteria and 4 declining to participate. No participant was excluded for other reasons. After screening, 32 eligible participants were enrolled and randomized into two groups (16 participants per group). All participants received their assigned interventions according to group allocation. During the 12-week intervention period, no participants discontinued the intervention or were lost to follow-up for the primary outcomes. Therefore, data from all 32 participants were included in the final analysis. Overall, the trial achieved 100% retention and compliance with the study protocol, and

no participants were excluded from the analysis (Figure 1).

4.1 Participant Characteristics at Baseline

A total of 32 adults with type 2 diabetes were equally randomized into Group A and Group B. Baseline demographic characteristics, including age and gender distribution, were comparable between the two groups. Similarly, there were no significant differences in baseline glycemic control markers (FBG and HbA1C), anthropometric measurements (BMI, waist and hip circumference, and waist/ hip ratio), or vital signs (blood pressure and heart rate) (Table 1).

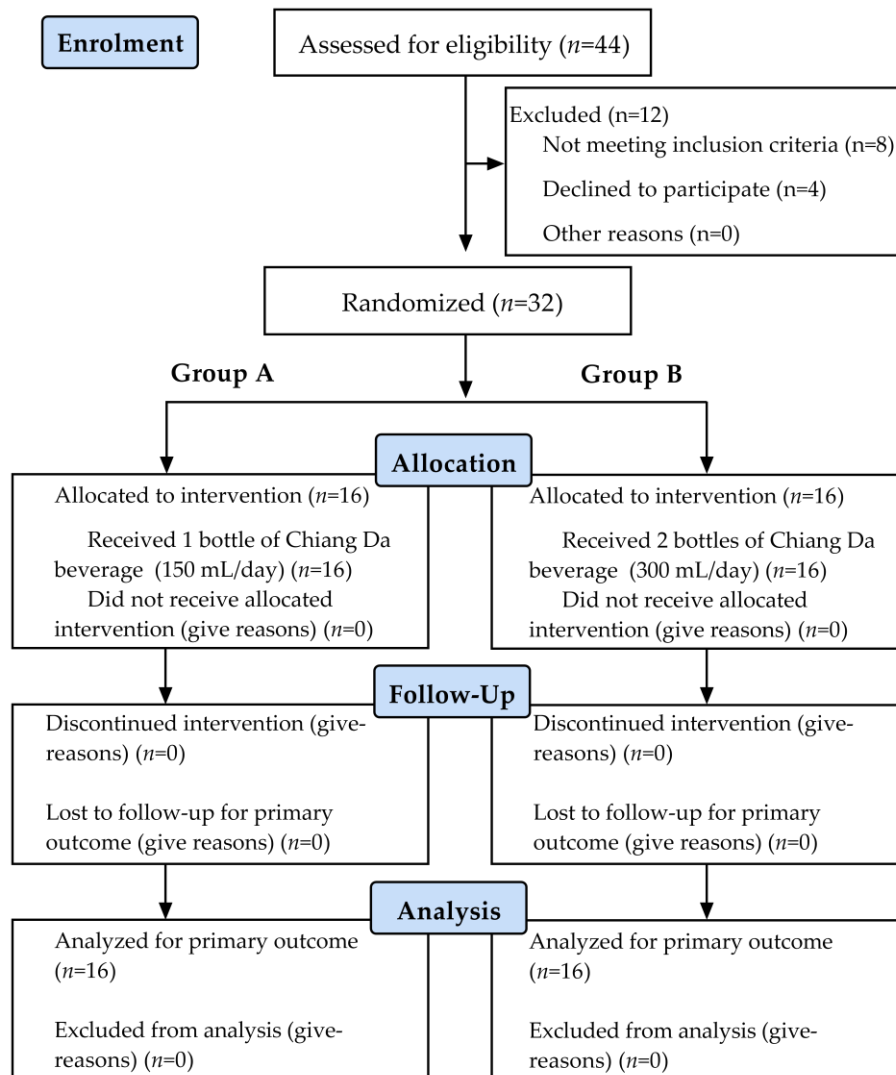


Figure 1 CONSORT diagram showing the study flow

Table 1 Baseline characteristics of the study participants^a

Parameters	Group A (n=16)	Group B (n=16)	p-Value ^b
Sex (Male/ Female)	7/ 9	5/ 11	0.233
Age (years)	59.50 ± 4.88	57.44 ± 10.24	0.372
FBG (mg/dL)	143.90 ± 25.15	156.20 ± 31.22	0.116
HbA1C	6.86 ± 1.52	7.56 ± 1.12	0.077
BMI (kg/m ²)	27.09 ± 4.79	24.31 ± 3.58	0.071
Waist circumference (cm)	89.79 ± 11.58	82.41 ± 10.46	0.068
Hip circumference (cm)	96.32 ± 9.68	92.69 ± 8.49	0.134
Waist/ Hip Ratio	0.92 ± 0.05	0.88 ± 0.06	0.071
SYS (mmHg)	144.70 ± 15.43	145.00 ± 22.99	0.484
DIA (mmHg)	84.71 ± 5.22	80.75 ± 11.05	0.104
HR (bpm)	92.08 ± 12.71	86.75 ± 16.39	0.157

Abbreviations: FBG, fasting blood glucose; HbA1C, glycated hemoglobin; SYS, systolic blood pressure; DIA, diastolic blood pressure; HR, heart rate. ^aData are presented as numbers or mean ± standard deviation (Mean ± SD). ^bBetween-group comparisons were analyzed using the independent t-test (Welch's test) for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. The chi-square test was applied to compare sex proportions between groups. Statistical significance was set at $p < 0.05$ with a 95% confidence interval (95% CI).

4.2 Anthropometry and Vital Signs Over 12 Weeks

Over 12 weeks, body weight and BMI showed no significant differences between groups. However, hip circumference decreased significantly in Group B compared with Group A ($p = 0.009$), leading to a significant between-group difference in waist-to-hip ratio ($p = 0.033$). Blood pressure and heart rate trended downward in both groups without significant between-group differences (Table 2).

4.3 Safety Laboratory Parameters

Complete blood count values (WBC, RBC, hemoglobin, hematocrit, MCV, MCH, MCHC, and platelet count) and leukocyte differentials (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) did not differ significantly between groups at any time, and average values remained within normal laboratory ranges before and after the intervention. For renal function, serum creatinine did not differ between groups ($p = 0.338$). Blood urea nitrogen (BUN) decreased slightly in Group A (12.71 ± 3.06 to 12.66 ± 2.20 mg/dL) and increased in Group B (13.53 ± 6.24 to 16.55 ± 9.00 mg/dL), yielding a significant between-group difference in change ($p = 0.007$) as shown in Table 2. Liver enzymes (AST and ALT) tended to decrease in Group A and decreased slightly in Group B, with no significant between-group differences ($p = 0.120$ and $p = 0.310$, respectively) as shown in Table 2.

4.4 Glycemic Control and β -cell Function Indices

Fasting blood glucose decreased modestly in Group A (143.90 ± 25.15 to 137.70 ± 21.56 mg/dL;

mean change -6.21 mg/dL) but increased in Group B (156.20 ± 31.22 to 178.40 ± 63.68 mg/dL; mean change $+22.25$ mg/dL), with a significant difference between groups ($p = 0.014$) as shown in Figure 2a–2b. HbA1C did not differ significantly between groups ($p = 0.230$) as shown in Figure 2c–2d. Fasting insulin decreased in both groups (-2.80 μ IU/mL in Group A and -5.49 μ IU/mL in Group B), and the between-group difference in change was significant ($p = 0.016$) as shown in Table 3. HOMA-IR decreased in both groups without a significant difference between groups ($p = 0.358$) as shown in Table 3. HOMA-S increased in both groups, with a significant difference between groups ($p < 0.001$) as shown in Table 3. HOMA- β decreased in both groups, with significant difference between groups ($p = 0.025$) as shown in Table 3.

4.5 Oral glucose tolerance test

A notable finding was that both groups showed increased OGTT glucose exposure after the intervention, with significant within-group increases in both total AUC and incremental AUC, indicating that dynamic post-load glucose handling did not improve at either dose over 12 weeks, as shown in Figure 3b–3d. For tAUC, Group A increased from $17,781.00 \pm 3,298.00$ to $30,603.00 \pm 6,343.00$ (mean difference = $12,821.00$; 95% CI: $7,155.00$ to $18,488.00$), while Group B increased from $23,448.00 \pm 4,790.00$ to $38,953.00 \pm 8,548.00$ (mean difference = $15,504.00$; 95% CI: $9,838.00$ to $21,171.00$), with no significant difference between groups ($p = 0.097$).

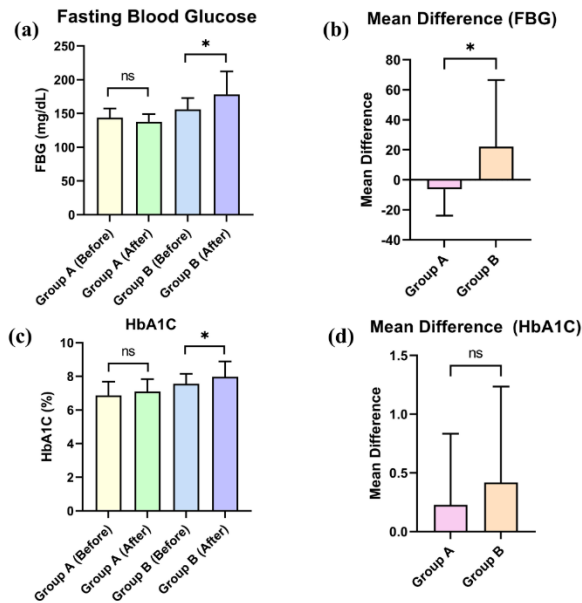


Figure 2 Clinical effects of 12-week consumption of the test product on changes in fasting blood glucose levels (FBG) and glycated hemoglobin (HbA1C) in participants ($n = 32$). (a) illustrates the comparison of mean FBG values before and after consuming the test product in Group A and Group B. (b) demonstrates the mean differences in FBG between participants in Group A and those in Group B. (c) illustrates the comparison of mean HbA1C values before and after consuming the test product in Group A and Group B. (d) demonstrates the mean differences in HbA1C between participants in Group A and those in Group B

^{ns} indicates no statistically significant difference in mean values between the two groups at $p < 0.05$.

* indicates a statistically significant difference in mean values between the two groups at $p < 0.05$

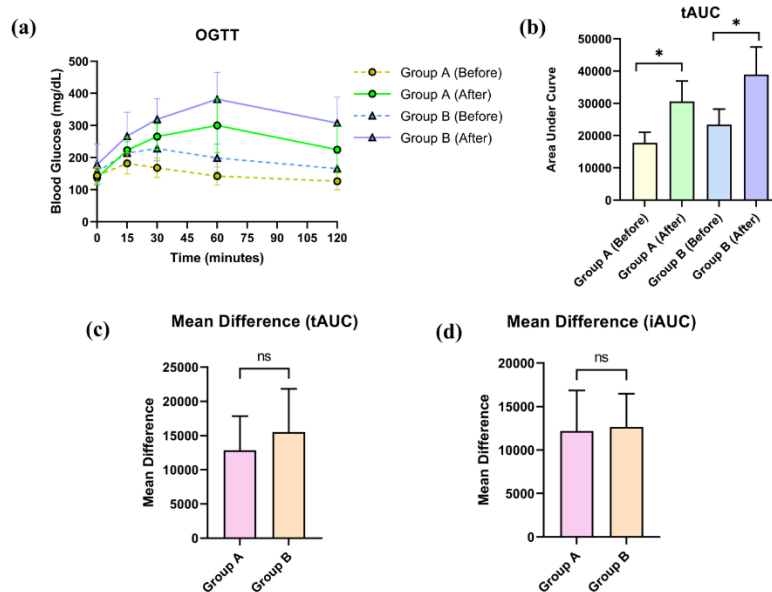


Figure 3 Clinical effects of 12-week consumption of the test product on oral glucose tolerance test (OGTT) responses in participants ($n = 32$). (a) illustrates blood glucose concentrations during OGTT before and after consumption of the test product in Group A and Group B. (b) demonstrates the mean values of the total area under the curve (tAUC) for OGTT in each group. (c) illustrates the mean differences in tAUC between participants in Group A and those in Group B. (d) demonstrates the mean differences in iAUC between participants in Group A and those in Group B

^{ns} indicates no statistically significant difference in mean values between the two groups at $p < 0.05$

* indicates a statistically significant difference in mean values between the two groups at $p < 0.05$

Table 2 Physical, Physiological, Liver, and Renal Parameters^a.

Parameters	Group A (n = 16)					Group B (n = 16)					p-Value ^d
	Before	After	p-Value ^b	Mean Difference	95% CI of Diff.	Before	After	p-Value ^c	Mean Difference	95% CI of Diff.	
Weight (kg)	64.36 ± 12.87	65.37 ± 13.25	<0.001 [†]	1.01	−7.08, 9.10	58.40 ± 7.46	58.97 ± 7.44	0.029 [†]	0.56	−6.21, 7.33	0.089
BMI (kg/m ²)	27.09 ± 4.80	27.51 ± 4.90	<0.001 [†]	0.41	−2.55, 3.38	24.31 ± 3.58	24.54 ± 3.48	0.040 [†]	0.22	−2.34, 2.79	0.091
Waist circumference (cm)	89.79 ± 11.58	91.47 ± 11.87	<0.007 [†]	1.68	−6.28, 9.64	82.41 ± 10.46	84.76 ± 8.90	0.061	2.36	−5.61, 10.32	0.334
Hip circumference (cm)	96.32 ± 9.68	97.03 ± 10.43	0.214	0.71	−6.55, 7.98	92.69 ± 8.50	90.72 ± 7.90	0.003 [†]	−1.97	−9.23, 5.29	0.009*
Waist/ Hip Ratio	0.92 ± 0.06	0.94 ± 0.06	0.147	0.01	−0.04, 0.06	0.88 ± 0.06	0.93 ± 0.06	0.004 [†]	0.05	−0.005, 0.09	0.033*
SYS (mmHg)	144.70 ± 15.43	142.40 ± 12.76	0.164	−2.29	−17.63, 13.06	145.00 ± 22.99	138.30 ± 21.32	0.028 [†]	−6.69	−22.03, 8.66	0.136
DIA (mmHg)	84.71 ± 5.22	83.08 ± 5.62	0.020 [†]	−1.64	−8.50, 5.23	80.75 ± 11.05	78.69 ± 11.42	0.115	−2.06	−8.93, 4.80	0.409
HR (bpm)	92.08 ± 12.71	84.21 ± 13.66	0.003 [†]	−7.86	−21.31, 5.58	86.75 ± 16.39	84.38 ± 15.67	0.163	−2.38	−15.82, 11.07	0.060
Hepatic Function											
AST (U/L)	33.79 ± 10.26	30.14 ± 7.14	0.003 [†]	−3.65	−22.65, 15.35	40.06 ± 32.84	39.56 ± 33.29	0.173	−0.50	−19.50, 18.50	0.120
ALT (U/L)	28.79 ± 12.95	25.14 ± 6.79	0.019 [†]	−3.65	−24.45, 17.15	43.31 ± 39.42	38.50 ± 34.10	0.017 [†]	−4.81	−25.61, 15.98	0.310
Renal Function											
BUN (mg/dL)	12.71 ± 3.06	12.66 ± 2.20	0.363	−0.04	−4.27, 4.18	13.53 ± 6.24	16.55 ± 9.00	0.001 [†]	3.02	−1.20, 7.24	0.007*
Serum Creatinine (mg/dL)	0.76 ± 0.20	0.78 ± 0.20	0.204	0.01	−1.20, 1.24	1.60 ± 2.58	1.02 ± 0.60	0.365	−0.58	−1.80, 0.64	0.338

Abbreviations: SYS, systolic blood pressure; DIA, diastolic blood pressure; HR, heart rate.

^aData are presented as mean ± standard deviation (mean ± SD), n = 16.

^bp-values represent the difference within Group A, analyzed using the Wilcoxon matched-pairs signed-rank test (nonparametric, paired) or paired t-test (parametric).

^cp-values represent the difference within Group B, analyzed using the Wilcoxon matched pairs signed rank test (nonparametric, paired) or Paired t-test (parametric).

^dp-values represent the mean differences between Group A and Group B, analyzed using the Mann–Whitney test (nonparametric, unpaired) or Welch’s t-test (parametric).

[†](p < 0.05) indicates a statistically significant difference within groups of participants.

* (p < 0.05) indicates a statistically significant difference between the two groups of participants

Table 3 Changes in Pancreatic β-Cell Function^a

Parameters	Group A (n= 16)					Group B (n = 16)					p-Value ^d
	Before	After	p-Value ^b	Mean Difference	95% CI of Diff.	Before	After	p-Value ^c	Mean Difference	95% CI of Diff.	
Fasting Insulin (μIU/ml)	9.49 ± 1.91	6.69 ± 2.52	0.014 [†]	−2.80	−5.50, −0.10	17.50 ± 4.59	12.00 ± 3.41	<0.001 [†]	−5.49	−8.19, −2.80	0.016*
HOMA-IR	3.34 ± 0.75	2.29 ± 0.98	0.014 [†]	−1.04	−2.23, 0.14	6.66 ± 1.92	5.08 ± 1.63	<0.001 [†]	−1.59	−2.78, −0.40	0.358
HOMA-S	0.32 ± 0.07	0.49 ± 0.15	<0.001 [†]	0.18	0.08, 0.26	0.16 ± 0.04	0.22 ± 0.09	<0.001 [†]	0.06	−0.03, 0.14	<0.001*
HOMA-β (%)	46.84 ± 19.00	33.62 ± 12.27	0.003 [†]	−13.22	−39.22, 12.78	76.45 ± 36.48	51.87 ± 38.19	0.003 [†]	−24.59	−50.59, 1.42	0.025*

Abbreviations: HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; HOMA-S, Homeostatic Model Assessment for Insulin Sensitivity; HOMA-β (%), Homeostatic Model Assessment of β-Cell Function.

^aData are presented as mean ± standard deviation (mean ± SD), n = 16.

^bp-values represent the difference within Group A, analyzed using the Wilcoxon matched pairs signed rank test (nonparametric, paired) or Paired t-test (parametric).

^cp-values represent the difference within Group B, analyzed using the Wilcoxon matched pairs signed rank test (nonparametric, paired) or Paired t-test (parametric).

^dp-values represent the mean differences between Group A and Group B, analyzed using the Mann–Whitney test (nonparametric, unpaired) or Welch’s t-test (parametric).

[†](p < 0.05) indicates a statistically significant difference within groups of participants.

* (p < 0.05) indicates a statistically significant difference between the two groups of participant

For iAUC, Group A rose from $1,930.00 \pm 592.70$ to $14,138.00 \pm 4,954.00$ (mean difference = 12,209.00; 95% CI: 9,209.00 to 15,208.00) and Group B rose from $4,890.00 \pm 1,729.00$ to $17,540.00 \pm 3,655.00$ (mean difference = 12,651.00; 95% CI: 9,651.00 to 15,650.00), with no significant difference between groups ($p = 0.386$). In addition, the between-group differences in AUC change were not statistically significant. Thus, neither dose improved post-load glucose handling over 12 weeks. Changes in glucose concentration at each time point are shown in Figure 3a.

5. Discussion

This 12-week pilot randomized trial evaluated the feasibility and metabolic impact of a ready-to-drink herbal beverage (Chiang-Da–mulberry–chamomile) as an adjunct to metformin therapy in adults with recently diagnosed T2DM. Chiang-Da (*Gymnema inodorum*) and mulberry (*Morus alba*) leaves contain strong antidiabetic compounds, such as gymnemic acid (Haideri et al., 2024; Phanjaroen et al., 2024) and 1-deoxynojirimycin (DNJ) (Fongsodsri et al., 2022), which may be responsible for the hypoglycemic effects of the beverage. The main findings indicate that the beverage was generally well tolerated at both 150 mL/day and 300 mL/day, with no clinically meaningful adverse changes in hematology, liver enzymes, or serum creatinine (Permsuwan & Deerochanawong, 2025). However, dynamic glucose tolerance did not improve, as OGTT glucose exposure (tAUC and iAUC) increased over 12 weeks in both groups. Importantly, glycemic trends differed by dose, with the higher-dose group showing a less favorable pattern (higher fasting glucose and 120-min OGTT glucose) than the lower-dose group. Given the absence of placebo control, these findings primarily inform safety and dose selection rather than efficacy.

Anthropometric and blood pressure outcomes remained largely stable over 12 weeks. Both groups showed small, non-significant increases in body weight and BMI. Although the between-group differences in hip circumference and waist-to-hip ratio reached statistical significance, the absolute magnitudes were small and likely of limited clinical relevance. Resting blood pressure and heart rate trended downward without significant group differences. This aligns with prior evidence that short-term herbal tea interventions often show modest or neutral anthropometric effects (Kumar et al., 2023; Majeed et al., 2021).

Safety laboratory markers supported short-term tolerability. Complete blood counts and liver enzymes (AST, ALT) showed no significant changes or toxicity signals (Alasvand Zarasvand et al., 2025; Zhang et al., 2022a). AST and ALT did not increase in either group, or were the between-group differences significant. In the context of stable hematology and serum creatinine, this pattern does not suggest hepatocellular toxicity over 12 weeks. At the same time, because the study was small and not designed to test hepatoprotective efficacy, the modest downward trends in aminotransferases should not be overinterpreted as hepatic benefit. This cautious interpretation is directionally consistent with prior short-term human studies in related herbal contexts, which also did not identify major hepatic safety concerns (Bespinyowong et al., 2013; Hajizadeh-Sharafabad et al., 2020; Taghizadeh et al., 2022). A dose-related difference was observed in BUN (decreased in Group A, increased in Group B). The isolated increase in BUN in the higher-dose group (Group B), without a corresponding increase in serum creatinine, suggests a nonspecific signal rather than clear evidence of intrinsic renal toxicity. Potential explanations include prerenal factors such as differences in hydration status and dietary protein intake, altered nitrogen metabolism, or other unmeasured influences. Additionally, a transporter-mediated interaction affecting metformin exposure remains hypothetical and cannot be established from the present data. Because specific variables such as fluid intake, daily protein consumption, cystatin C, eGFR trends, or tubular injury biomarkers were not assessed, we interpreted the BUN finding as a monitoring signal that warrants attention in future studies rather than as proof of renal harm.

Regarding glycemic control, Group A demonstrated a modest reduction in fasting blood glucose (-6.21 mg/dL), whereas Group B showed an increase ($+22.25$ mg/dL) ($p < 0.05$). The lower dose showed a more favorable glycemic trend within this pilot dataset. The increasing fasting glucose trend in Group B may have several non-mutually exclusive explanations, including random baseline imbalance, uncontrolled diet or physical activity, natural disease progression during follow-up, or dose-dependent herb–herb or herb–metformin interactions affecting glucose handling. Because the present study was small, open-label, and non-placebo-controlled, these possibilities should be interpreted as hypotheses rather than established mechanisms. HbA1C did not

change significantly, which is reasonable given the short duration and near-target baseline values (Cuschieri, 2019; Davies et al., 2022; Magliano et al., 2021). Fasting insulin decreased in both groups. However, because insulin was measured using a research ELISA platform and commercial insulin immunoassays are not fully harmonized across assays, insulin-derived indices should be interpreted as exploratory and with caution. Crucially, Group A maintained lower fasting glucose and a smaller increase in 120-min OGTT glucose than Group B, reinforcing a more favorable profile for the lower dose (Kumar et al., 2023; Nayebi et al., 2020; Zhang et al., 2022b).

A notable finding was the increase in both tAUC and iAUC after 12 weeks in both dose groups. Because these within-group changes were large and their confidence intervals did not cross zero, the present data do not support improved dynamic glucose tolerance at either dose. This finding is clinically important and is now discussed with the same level of prominence as the BUN divergence. Although the differences between groups in AUC change were not significant, the within-group worsening is clinically relevant and should not be understated. In the absence of a placebo group, we cannot determine whether this pattern reflects the beverage, background disease progression, behavioral variation, or a combination of these factors.

Comparisons with earlier work help contextualize these findings. Although previous studies of *G. inodorum* and *G. lactiferum* teas reported improved FBG and HbA1C (Bespinyowong et al., 2013; Karthigesu et al., 2024; Alasvand Zarasvand et al., 2025), our higher-dose group showed a worsening trend. This apparent non-linear dose-response relationship might be explained by higher herbal exposure interfering with metformin absorption or altering gastrointestinal carbohydrate handling (An et al., 2020; Karthigesu et al., 2024; Alasvand Zarasvand et al., 2025). Additionally, the larger fluid volume (300 mL) in Group B may have influenced gastric emptying. Furthermore, baseline imbalances (higher initial FBG in Group B) could have predisposed this group to greater glycemic drift. Moreover, dietary intake, physical activity, and ongoing metformin adherence were not formally quantified during follow-up, and these uncontrolled concomitant factors may have influenced both fasting and post-load glycemic outcomes.

Key strengths of this study include the use of a culturally familiar intervention, the inclusion of diabetic patients receiving metformin monotherapy, and a high level of participant adherence. However, limitations include the small sample size, the open-label design without a placebo control, and the lack of strict control over dietary intake and physical activity. Moreover, the sample-size planning relied on historical assumptions rather than a definitive between-group effect estimate for the current two-dose comparison, and the present study should therefore be interpreted as a pilot signal-generating trial rather than a powered comparative efficacy trial. The 12-week follow-up was chosen to assess short-term tolerability and preliminary metabolic signals. In addition, without a placebo/no-beverage arm, we cannot exclude the possibility that some of the glycemic worsening, particularly in the higher-dose group, reflects the natural trajectory of recently diagnosed T2DM rather than a beverage-specific effect. Additionally, portable glucometers used for OGTT have a known variance of ± 10 –15%. However, to ensure internal validity, we used identical devices and strip lots for all measurements within each subject. Although absolute AUC values should be interpreted with this margin in mind, the comparative glycemic trends between the two dose groups remain statistically robust. Furthermore, the study evaluated multiple secondary outcomes without prespecified multiplicity adjustment; therefore, nominal *p*-values for secondary endpoints should be interpreted cautiously because the probability of false-positive findings is increased. Future studies should prioritize larger, longer placebo-controlled trials to determine durability and efficacy and whether the combination with mulberry and chamomile confers additive or synergistic benefits beyond Chiang-Da alone. Incorporating continuous glucose monitoring could better capture daily glycemic variability (Beck et al., 2019; Davies et al., 2022; LeRoith, 2002).

6. Conclusion

This pilot randomized trial demonstrates that a ready-to-drink mixed *Gymnema inodorum*–mulberry–chamomile beverage is generally safe and well tolerated as an adjunct to metformin in adults with early T2DM. Over 12 weeks, routine safety profiles (hematology, liver enzymes, and serum creatinine) remained stable. However, a dose-dependent divergence in BUN, decreasing in the lower-dose group (150 mL) but increasing in the higher-dose

group (300 mL), suggests that renal monitoring is advisable for higher intakes. Dynamic glucose tolerance did not improve in either group, and post-load glucose exposure increased over 12 weeks in both dose groups. Accordingly, the present findings should be regarded as hypothesis-generating only and cannot support a clinical recommendation without confirmation in a larger placebo-controlled trial.

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8. Abbreviations

Abbreviation	Full Term
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CI	Confidence Interval
DIA	Diastolic Blood Pressure
DNJ	1-Deoxynojirimycin
ELISA	Enzyme-Linked Immunosorbent Assay
FBG	Fasting Blood Glucose
HbA1C	Glycated Hemoglobin
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
HOMA-S	Homeostatic Model Assessment for Insulin Sensitivity
HOMA-β	Homeostatic Model Assessment of β-Cell Function
HR	Heart Rate

Abbreviation Full Term

iAUC	Incremental Area Under the Curve
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
OGTT	Oral Glucose Tolerance Test
RBC	Red Blood Cell
SD	Standard Deviation
SYS	Systolic Blood Pressure
tAUC	Total Area Under the Curve
T2DM	Type 2 Diabetes Mellitus
WBC	White Blood Cell

9. CRediT Statement

Wiritphon Khiaolaongam: Conceptualization, Methodology, Software, Formal Analysis, Investigation, Data Curation, Writing - Original Draft, Visualization.

Kongsak Boonyapranai: Conceptualization, Methodology, Validation, Investigation, Writing - Review & Editing.

Pornsiri Pitchakarn: Validation, Resources, Writing - Review & Editing.

Pennapa Chonpathompikunlert: Validation, Writing - Review & Editing.

Sakaewan Ounjaijean: Conceptualization, Methodology, Validation, Investigation, Data Curation, Writing - Review & Editing, Supervision, Project Administration, Funding Acquisition.

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