Effectiveness and Safety of DLBS3233 in Newly Diagnosed Type 2 Diabetes Mellitus: A 12-week Clinical Trial

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ABSTRACT

Background: *DLBS3233, recognized as an agent enhancing insulin sensitivity, has exhibited promise as a therapeutic option for addressing type 2 diabetes mellitus (T2DM). This study aimed to evaluate the effectiveness and safety of DLBS3233, a natural compound, in individuals newly diagnosed with T2DM.* **Methods:** *A 12-week double-blind, randomized, placebo-controlled clinical trial was conducted with 104 eligible participants. They were assigned to receive DLBS3233 or a placebo along with lifestyle modifications. Various metabolic parameters, including fasting and post-meal plasma glucose levels at two hours, fasting insulin level, HOMA-IR, adiponectin level, lipid profile, superoxide dismutase (SOD) activity, GLUT-4 concentrations, and body weight measurements, were assessed at baseline, Week 6, and Week 12. Safety parameters assessment will include vital signs, liver function, renal function and adverse event.* **Results:** *Participants exhibited similar demographic characteristics in both groups. While no significant changes were noted in fasting plasma glucose and most other parameters, the DLBS3233 group significantly reduced 2-hour postprandial glucose at Week 12 (p = 0.026). There were no substantial differences in A1c levels, fasting insulin, insulin resistance, adiponectin levels, or lipid profiles between the two groups at any point in time. Safety parameters, including blood pressure, liver enzymes, heart rate, gamma GT, and serum creatinine, remained comparable between the groups.* **Conclusion:** *DLBS3233 showed potential for improving postprandial glucose control in newly diagnosed T2DM individuals. Although significant changes were limited, the study suggests that DLBS3233 could enhance glycemic regulation. The safety evaluation indicated no adverse effects on vital parameters. Further research with larger samples and more prolonged duration is warranted to comprehensively explore DLBS3233's potential in T2DM management.*

Keywords*: Type 2 Diabetes Mellitus, DLBS3233, Insulin sensitivity, clinical trial.*

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a prevalent metabolic disorder characterized by hyperglycemia and impaired insulin secretion.[1] Constituting over 90% of diabetes cases, T2DM arises predominantly from pancreatic β-cell dysfunction, leading to suboptimal insulin secretion and peripheral insulin resistance.[2] The pivotal roles of insulin in glucose homeostasis underscore the critical nature of

these mechanisms; any disturbances therein may precipitate metabolic irregularities and the onset of T2DM.[1,3]

The underlying processes of T2DM encompass complex molecular pathways concerning insulin production, secretion, and detection, along with subsequent impacts on insulin-sensitive organs.[1,4] Disruption of these intricate pathways can yield insufficient insulin secretion by pancreatic β-cells and diminished reactivity of target tissues to insulin.[1,4] Consequently, the equilibrium of glucose within the body is disturbed, culminating in sustained hyperglycemia.[1,4]

Management of T2DM encompasses alterations in lifestyle factors, including diet and physical activity, alongside medical interventions.[2,5] Medications to counter diabetes, like metformin and glucagon-like peptide-1 receptor analogs, are frequently recommended to enhance glycemic management in T2DM.[2,6] Nevertheless, a demand exists for innovative treatment strategies that can address the fundamental pathophysiological processes intrinsic to T2DM.

DLBS3233, recognized as an agent enhancing insulin sensitivity, has exhibited promise as a therapeutic option for addressing T2DM.[7] Originating from *Cinnamomum burmannii* and *Lagerstroemia speciosa*, DLBS3233 is a bioactive component that can mitigate insulin resistance in individuals with impaired glucose tolerance.[8] DLBS3233 displays potential as a prospective therapeutic choice for addressing T2DM. Several studies have explored DLBS3233 in various conditions, including T2DM polycystic ovary syndrome (PCOs), and pre-diabetes, with outcomes ranging from glycemic control and lipid profile to inflammatory/anti-inflammatory cytokine parameters. However, effects of DLBS3233 were inconsistent in these studies[8–10].

The primary outcome of this study is the reduction in HbA1c levels from baseline to Week 12. HbA1c serves as a standard marker for long-term glycemic control and reflects the average plasma glucose concentration over the preceding 8-12 weeks. Secondary outcomes include the reduction in fasting plasma glucose (FPG) and 2-hour postprandial glucose (2h-PG) levels at Weeks 6 and 12, improvement in insulin sensitivity (HOMA-IR), changes in adiponectin levels, lipid profiles (LDL, HDL, total cholesterol, triglycerides), GLUT-4 and the antioxidant enzyme activity of SOD. Safety parameters such as vital signs, liver and renal functions, and any adverse events are also monitored throughout the study.

The examination of adiponectin, GLUT4, and SOD parameters in this study aims to explore their roles and effects in the context of T2DM management[1]. Adiponectin is critical for regulating glucose levels and fatty acid breakdown, with higher levels associated with improved insulin sensitivity and anti-inflammatory effects[2]. GLUT4, a glucose transporter in adipose tissues and striated muscles, is crucial for glucose uptake and homeostasis, helping to understand DLBS3233's impact on insulin signalling[3]. SOD (Superoxide Dismutase), an antioxidant enzyme, mitigates oxidative stress, a contributing factor in T2DM pathophysiology, providing insights into DLBS3233's potential to reduce oxidative stress[4].

The study focuses on newly diagnosed T2DM patients to investigate the initial impact of DLBS3233 on metabolic parameters without the confounding effects of previous treatments. Newly diagnosed patients present a unique opportunity to observe the direct physiological and biochemical changes induced by the intervention. The rationale for selecting this population lies in their typically untreated status, allowing for a clearer assessment of the efficacy and safety of DLBS3233. This contrasts with populations with established diabetes who may have developed medication resistance, altered metabolic states due to long-term hyperglycemia, or complications from prolonged disease duration, which can confound study results .

METHODS

Trial Design

A clinical study was conducted to assess the effectiveness and safety of DLBS3233 in improving metabolic control among recently diagnosed patients with type 2 diabetes. The

study followed a two-arm, double-blind, parallel, randomized, and placebo-controlled design. This study was conducted in Ambokembang and Pekajangan villages, Pekalongan City, Central Java, Indonesia, from April to June 2014The therapy lasted for 12 weeks, and various parameters were measured to evaluate the efficacy and safety of DLBS3233. These parameters included A1c level, fasting and post-meal plasma glucose levels at two hours, fasting insulin level, HOMA-IR, adiponectin level, lipid profile, SOD activity, GLUT-4 concentrations and body weight. The steering committee planned and supervised the trial in collaboration with the sponsor, Dexa Medica Group. The committee was responsible for the trial's implementation, data analysis, and overall management. Before the commencement of the study, the study protocol received ethical clearance from the Independent Ethics Committee of Diponegoro University/Dr. Kariadi Hospital Semarang (No.338/EC/FK-RSDK/2014).

Participants

The research subjects were obtained from a study population totaling 1814 individuals, consisting of 1214 subjects from Pekajangan Village and 600 subjects from Ambokembang Village. The selection of research subjects was done through consecutive sampling. All subjects in the population underwent screening using a high-risk DM group form with at least two risk factors plus GDP (glucometer ≥ 110), followed by an oral glucose tolerance test (OGTT). Screening results identified 385 subjects. In the next step, these 385 subjects underwent OGTT. Subjects who met the criteria for a DM diagnosis were included in the study.

Participant eligibility criteria for this study adhere to the following parameters: adults aged 18 to 60 years irrespective of gender, excluding healthy volunteers. Inclusion criteria necessitate a minimum body mass index (BMI) of 18.5 kg/m² and newly diagnosed T2DM, as defined by an FPG level of ≥ 126 mg/dL or 2h-PG level of ≥ 200 mg/dL or A1c of ≥ 6.5%) with no prior T2DM history. Moreover, participants must exhibit FPG levels not exceeding 183 mg/dL; hemoglobin levels equal to or greater than 10.0 g/dL, serum alanine transaminase (ALT) levels within 2.5 times the upper limit of normal, and serum creatinine levels below 1.5 times the upper limit of normal. Characteristics of participants will be collected such as history of hypertension, dyslipidemia (triglyceride >150 mg/dl, HDL <40 mg/dL for male and <50 mg/dL),central obesity (Weight Circumference > 90 cm for male or > 80 cm for female) and BMI (Normal 18.5-22.9, Overweight and obese >23)[11–13].

Exclusion criteria encompass females of childbearing potential, individuals presenting with symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or other symptomatic ischemic arterial diseases requiring medical intervention. Uncontrolled hypertension, characterized by systolic blood pressure (SBP) above 160 mmHg or diastolic blood pressure (DBP) above 100 mmHg, is also an exclusionary factor. Furthermore, individuals with a history of renal or liver disease, any clinical evidence of malignancies, exacerbation of chronic illnesses, severe and acute infections, complicated infections, current administration of systemic corticosteroids or herbal (alternative) medicines, or recent participation in another intervention trial within 30 days before screening are ineligible for participation in the study.

In the subsequent final phase, 104 eligible respondents who conformed to the predetermined inclusion and exclusion criteria were meticulously selected for participation. Subsequently, these participants underwent a randomized block allocation into two distinct cohorts: the intervention group (administered with DLBS 3233) and the placebo group with 52 participants in each group.

Interventions

The study involved two groups with a 1:1 allocation ratio. One group received 100 mg of DLBS3233 once daily for 12 weeks, while the other group received a matching placebo. Both groups also received initial education on lifestyle modifications, which included dietary advice and exercise recommendations. Participants underwent clinical and physical examinations at the beginning and end of the study. All participants provided written informed consent before randomization. Both groups followed the same protocol, including the lifestyle

modification education, throughout the 12-week study period.

Subjects came to the clinic (study site) at Week 6 and Week 12 as follow-up visits. During the informed consent process, subjects had already been informed that they would have to come to the clinic for follow-up visits (study evaluation) at Week 6 (ie. 6 weeks after study treatment initiation) and Week 12 (ie. 12 weeks after study treatment initiation). They had also been informed to fast for 10-12 hours prior to the blood sampling in the clinic. During their enrollment, subjects were also reminded by phone call (by the Investigator team) at least 1-day prior to the Visits, to remind them to fast and the day after to come to the clinic for follow-up.

There were no regular visits to the subjects' houses during the study conduct. In order to ensure the compliance with the study protocol, at Baseline and each Visit, the Investigator team always reminded the subjects regarding the importance of the adherence to treatment. Further, the left-over study products with the packaging were collected from each of the study subjects and then counted by the Investigator at each Visit but the Baseline. Subjects were regarded as adequately taking the study medication when they took at least 80% of the whole 12 week-regimen of the study medication.

Primary Outcome

The primary outcome of this study was the reduction in HbA1c levels from baseline to Week 12, serving as a standard marker for long-term glycemic control and reflecting the average plasma glucose concentration over the preceding 8-12 weeks

Secondary Outcome

The secondary outcome measures include reducing venous fasting plasma glucose (FPG) and 2-hour postprandial glucose (2h-PG) levels at Week 6 and Week 12 of treatment. The response rate, expressed as the percentage of subjects with FPG < 110 mg/dL or a reduction of at least 10% in FPG level from baseline to Week 12, will also be assessed. Changes in fasting insulin level, HOMA-IR (Homeostatic Model Assessment of Insulin Resistance), adiponectin level, lipid profile (including LDL-cholesterol, HDL-cholesterol, total cholesterol, and triglyceride levels), GLUT-4, SOD enzyme activity, GLUT-4 concentration, and body weight will be measured from baseline to Week 12.

Safety Outcome

Safety outcome were evaluated with the following parameters: vital signs (blood pressure, heart rate, and respiratory rate), liver function (serum ALT, AST, and γ-glutamyl transferase levels), renal function (serum creatinine level). Adverse events will also be evaluated at specific intervals throughout the 12-week study period.

SOD enzyme activity is measured using K-ASSAY SOD Activity Kit (Kamiya Biomedical Company). GLUT-4 serum is measured using ELISA methods from Elabscience Biotechnology kit. Adiponectin is measured using Human Adiponectin ELISA Kit from Prointech. HOMA-IR was calculated with the following formula based on original study by Matthews et al[14].

Score = (Fasting insulin, uIU/mL)*(Fasting glucose, mg/dL) / 405

Sample Size

Minimum sample size was calculated with the assumption of 5% type I error and statistical power of 80%, with minimum significant difference of 0.5% ± 0.8% HbA1c between groups. Minimum sample size was calculated to be 42 subjects per group. An anticipated drop-out rate of 20% was used, and thus a total of 104 subjects (52 subjects in each group) was required to enroll in the study. For secondary outcomes such as fasting plasma glucose (FPG), 2-hour postprandial glucose (2h-PG), insulin sensitivity (HOMA-IR), adiponectin levels, lipid profiles, and SOD activity, similar statistical parameters were used to ensure adequate power to detect clinically meaningful differences.

Specifically, for FPG and 2h-PG, an effect size of 10 mg/dL and 20 mg/dL, respectively, with a standard deviation of 15 mg/dL and 30 mg/dL, resulted in a required sample size of 23 subjects per group after adjusting for a 20% drop-out rate. For HOMA-IR, with an effect size of 0.5 units and a standard deviation of 0.75 units, the required sample size was 23 subjects per group.

For adiponectin levels, with an effect size of 1 µg/mL and a standard deviation of 1.5 µg/mL, the sample size was also 23 subjects per group. Lipid profiles, assuming similar effect sizes and standard deviations across parameters, required a sample size of 23 subjects per group. Lastly, for SOD activity, with an effect size of 1 unit/mL and a standard deviation of 1.5 units/mL, the sample size was determined to be 23 subjects per group.

Randomization

Randomization and blinding code were prepared and performed by Dexa Medica using the permuted 4-block allocation and Table of Random numbers. The treatment provided was an herbal phytopharmaceutical combination of *Lagerstroemia speciosa* and *Cinnamomum burmanii* (DLBS 3233) obtained from a local distributor. The dosage administered was 100 mg orally once daily for 12 weeks. The placebo group received 100 mg of starch powder orally once daily for 12 weeks. Both groups also received lifestyle education (diet and exercise). The placebo drug contained starch powder placed inside capsules with the same shape, size, and color as the DLBS 3233 capsules. All packaging and labeling of the study products were prepared by Dexa Medica. The placebo (dummy) DLBS3233 capsules were also prepared by Dexa Medica and made identical in appearance and packaging with the active DLBS3233 capsules. The treatment sequence data were placed in sealed envelopes and remained unopened until the study was completed.

Statistical Analysis

Demographic information is presented through frequency distributions for categorical data and summarized using either the mean or median for numerical data. The assessment of outcome data involves comparing values at baseline and after follow-up. The distribution of outcome variables will be examined, and if it follows a normal distribution, an unpaired t-test will be utilized. In cases of non-normal distribution, the Mann-Whitney test will be employed. All statistical computations were conducted using SPSS Software (version 21.0). Significance was determined at a threshold of $P<0.05$.

RESULTS

Participants Flow

A total of 1814 participants were screened for eligibility criteria; 104 met the eligibility criteria. Participants were randomly assigned to receive DLBS 3233 or a matching placebo in a 1:1 allocation ratio. During follow-up, 17 from both the DLBS 3233 group and placebo group were unable to be contacted or were damaged in blood samples due to improper storage during transport. The final analysis included 35 and 35 participants from the DLBS 3233 group and placebo group that met the compliance criteria (**Figure 1**). There are no statistically significant differences in the demographic and clinical characteristics of the two groups (**Table 1**).

Efficacy Outcome

Fasting plasma glucose levels were observed at baseline, Week 6, and Week 12, revealing no statistically significant disparities between the DLBS3233 and placebo cohorts (**Figure 1**). However, it is worth noting that the DLBS3233 group exhibited a significant decrease in 2-hour postprandial glucose levels at Week 12 ($p = 0.026$), whereas the placebo group's levels remained relatively unchanged (**Figure 2**). Various additional metrics, encompassing A1c levels, fasting insulin concentrations, the homeostatic model assessment for insulin resistance (HOMA-IR), adiponectin concentrations, HDL cholesterol, LDL cholesterol, total cholesterol, triglycerides, and the ratio of total cholesterol to HDL cholesterol, displayed no statistically significant differences between the two groups at baseline, Week 6, or Week 12. These observations are presented in **Table 2**.

Regarding the 2-hour postprandial plasma glucose, adjustments from baseline to Week 6 revealed differences of -16.88 mg/dL for the Placebo group and -36.72 mg/dL for the DLBS3233 group ($p = 0.097$). Furthermore, differences from baseline to Week 12 were -8.61 mg/dL for the Placebo group and -45.11 mg/dL for the DLBS3233 group ($p = 0.024$). On the other hand, A1c levels experienced minimal shifts, manifesting differences of -0.25% for the Placebo group and -0.54% for the DLBS3233 group from baseline to Week 12 ($p = 0.644$).

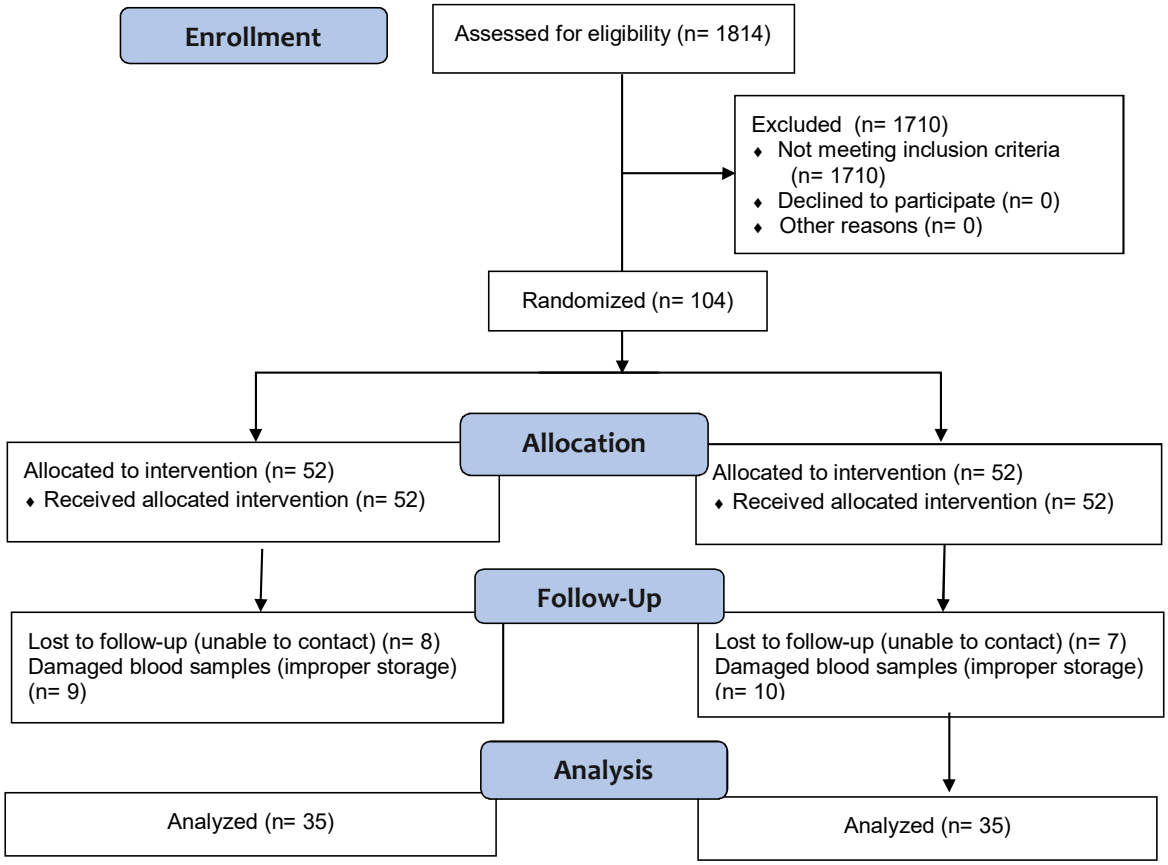

Figure 1. CONSORT 2010 Flow Diagram.

Table 1. Characteristics of Participants at Baseline.

Characteristics	Placebo (N=35)	DLBS 3233 (N=35)
Age	53.26 ± 6.13	50.51 ± 6.90
Sex		
Male (%)	8 (22.9)	4 (11.4)
Female (%)	27 (77.1)	31 (88.6)
History of Hypertension (%)	7 (20.0)	6 (17.1)
Dyslipidemia (%)	2 (5.7)	5 (14.3)
Central Obesity** (%)	24 (68.6)	26 (74.3)
Body Mass Index		
Normal (%)	12 (34.3)	11 (31.4)
Overweight and Obese (%)	23 (65.7)	24 (68.6)

** Weight Circumference > 90 cm (male) or > 80 cm (female)

Modest fluctuations were discerned in fasting insulin levels from baseline to Week 12, registering an increment of 1.54 mIU/mL in the Placebo group and 0.57 mIU/mL in the DLBS3233 group (p = 0.413). The HOMA-IR values, indicative of insulin resistance, exhibited marginal variations from baseline to Week 12, displaying an augmentation of 0.53 in the Placebo group and a reduction of -0.05 in the DLBS3233 group (p = 0.454).

Furthermore, analysis of other parameters, including adiponectin, HDL cholesterol, LDL cholesterol, total cholesterol, triglycerides, and the ratio of total cholesterol to HDL cholesterol, SOD, and GLUT-4 unveiled subtle deviations from baseline to Week 12 with no statistical significance.

Table 2. Metabolic Parameters at Baseline, after 6 and 12 weeks.

Variables	Placebo (n = 35)		DLBS3233 (n = 35)		p between groups
	Mean	SD	Mean	SD	
Fasting plasma glucose at Week 6 (mg/dL)	120.64	40.93	110.95	36.41	0.180
Fasting plasma glucose at Week 12 (mg/dL)	125.26	76.17	106.08	36.46	0.257
2-hr post prandial glucose at Week 6 (mg/dL)	174.61	78.61	153.74	64.10	0.219
2-hr post prandial glucose at Week 12 (mg/dL)	189.21	93.89	144.58	68.75	0.026
A1c at Week 12 (%)	6.79	1.43	6.40	1.12	0.388
Fasting Insulin at Week 12 (mIU/mL)	14.40	13.30	13.97	7.00	0.172
HOMA-IR calculation at Week 12	4.58	5.40	3.65	2.40	0.373
Adiponectin at Week 12 (µg/mL)	6.38	4.23	7.55	4.26	0.167
HDL cholesterol at Week 12 (mg/dL)	53.94	13.60	54.58	13.53	0.973
LDL cholesterol at Week 12 (mg/dL)	145.53	39.41	138.50	28.95	0.554
Total cholesterol at Week 12 (mg/dL)	221.47	46.91	212.00	36.92	0.804
Triglycerides at Week 12 (mg/dL)	146.24	73.04	126.42	52.95	0.481
Ratio Total Chol to HDL at Week 12	4.39	1.52	4.05	1.01	0.308
SOD Activity at Week 12	5.4	1.4	6.1	1.3	0.033
GLUT-4 baseline at Week 12 (U/ml)	21.0	9.9	21.5	10.2	0.823

Safety Outcome

During the initial assessment, no statistically significant distinctions were noted in any safety parameters between the DLBS3233 and placebo cohorts. As the study progressed to Week 12, the two groups had no substantial changes in systolic blood pressure, diastolic blood pressure, SGPT, SGOT, gamma GT, and serum creatinine levels. This information is presented in **Table 3**.

Notably, a notable trend concerning heart rate was identified, wherein marginal reductions were evident in both the placebo and DLBS3233 groups from baseline to Week 12. However, these observed changes did not attain statistical significance.

Table 3. Safety parameters at baseline and after 12 weeks.

Variables	Placebo (n = 35)		DLBS3233 (n = 35)		p between groups
	Mean	SD	Mean	SD	
Systolic Blood pressure at baseline (mmHg)	134.10	18.46	133.78	17.28	0.945
Systolic blood pressure at Week 12 (mmHg)	130.81	14.98	129.25	13.66	0.650
Diastolic blood pressure at baseline (mmHg)	82.56	6.77	82.44	8.23	0.983
Diastolic blood pressure at Week 12 (mmHg)	81.89	7.01	81.25	6.48	0.668
Heart rate of baseline (per minute)	83.95	7.26	84.83	5.90	0.473
Heart rate at Week 12 (per minute)	81.73	5.17	83.15	4.83	0.284
SGPT at baseline (U/L)	22.31	12.45	22.24	13.71	0.855
SGPT at Week 12 (U/L)	20.51	10.49	20.63	7.92	0.530
SGOT at baseline (U/L)	20.44	6.83	20.03	7.40	0.709
SGOT at Week 12 (U/L)	19.85	6.19	19.88	4.43	0.523
Gamma GT at baseline (U/L)	29.28	19.23	28.43	17.04	0.914
Gamma GT at Week 12 (U/L)	27.79	16.71	27.80	15.69	0.837
Serum Creatinine at baseline (mg/dL)	0.69	0.20	0.63	0.13	0.232
Serum Creatinine at Week 12 (mg/dL)	0.71	0.19	0.66	0.15	0.270

DISCUSSION

This study presents several novel aspects. Firstly, it is the first experimental study conducted in a high-prevalence diabetes area, implementing strict screening involving over 1800 participants, but only a small portion meeting eligibility criteria and completing the study. Secondly, it explores the potential role of antioxidants such as SOD and the inflammatory mechanism through GLUT4 regulation in glycemic control, which has not been comprehensively explored in similar populations.

Following the analysis of our study results, we observed a significant reduction in 2-hour postprandial glucose levels in the DLBS3233 group at Week 12 compared to the placebo group ($p = 0.026$). This finding indicates the potential efficacy of DLBS3233 in enhancing postprandial glycemic control in newly diagnosed T2DM patients. However, other parameters, including fasting plasma glucose, HbA1c levels, insulin sensitivity (HOMA-IR), and adiponectin levels, did not show significant differences between the two groups. The power calculation for the primary outcome was based on detecting a 0.5% difference in HbA1c levels with 80% power and a 5% type I error, resulting in a required sample size of 42 subjects per group. This study enrolled 104 participants to account for a 20% dropout rate, ensuring adequate power to detect meaningful differences in secondary outcomes such as FPG, 2h-PG, insulin sensitivity, and lipid profiles.

DLBS3233 represents a standardized blend comprising extracts from *Lagerstroemia speciosa* and *Cinnamomum burmannii*.[15] It has been the subject of research due to its potential as an enhancer of insulin sensitivity in individuals with type 2 diabetes mellitus.[15] Numerous investigations have delved into the operational mechanisms of DLBS3233, along with its impacts on glucose absorption, insulin signaling, and lipid profile.

Effects of DLBS3233 in controlling blood glucose levels were studied in an in-vivo study in an insulin-resistant rat model of the Wistar strain.[16] Treatment with DLBS3233 at the dose of 9 mg/Kg BW for two weeks showed a significantly decreased random blood glucose (BG) level by 29.64%, postprandial BG (PPBG) by 30.62%, and fasting BG (FBG) by 31.41%, from each respective baseline.[16] The results showed that the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index from the Insulin Resistant Group was more than 5-fold higher than the Control and then decreased after being treated with DLBS3233.[16]

Our investigation found no notable variations in metabolic parameters, except for 2-hour postprandial plasma glucose levels. The significant reduction in 2-hour postprandial glucose in the DLBS3233 group might be influenced by factors such as anthropometry and caloric intake. Despite no significant differences in adiponectin, GLUT-4, and SOD levels, variations in body weight, BMI, and dietary adherence could have played a role. Future studies should include detailed assessments of anthropometric changes and caloric intake to better understand their potential mediating effects on glycemic control.

This study is among the first to explore how DLBS3233 affects the activity of the SOD enzyme. SOD is a natural antioxidant that protects cells from reactive oxygen species (ROS). Previous studies have observed a decrease in SOD activity and other antioxidants in people with T2DM.[17,18] DLBS3233 works by reducing TNF-α, which lowers free fatty acids (FFA), ROS, PKC-ε, and PKC-θ, along with serine phosphorylation. Simultaneously, it increases tyrosine phosphorylation, helping to alleviate insulin resistance.[8] Our study found an increase in SOD activity in the DLBS3233 group. However, there is no significant difference compared to the placebo group.

An in vitro study conducted by Tandrasasmita et al. demonstrated that DLBS3233 prompted heightened phosphorylation at the tyrosine residue of the insulin receptor substrate, culminating in an amplified insulin signaling pathway.[15] This property was concomitant with an elevation in the expression of peroxisome proliferator-activated receptor gamma (PPARγ) and glucose transporter 4 (GLUT4), genes linked with augmented insulin sensitivity and enhanced glucose uptake.[15] However, in the present study, both the DLBS3233 group and the placebo group

exhibited increased GLUT4 expression, yet the difference between the two groups was not statistically significant.

Previous studies have explored the roles of SOD, GLUT-4, and adiponectin in diabetes management. SOD, an antioxidant enzyme, reduces oxidative stress, a key factor in T2DM pathophysiology. Studies have shown decreased SOD activity in T2DM patients, suggesting that enhancing SOD activity could improve glycemic control[4]. Similarly, GLUT-4 is crucial for glucose uptake in insulin-sensitive tissues, and its upregulation is associated with improved insulin sensitivity[19]. Adiponectin, a hormone involved in glucose regulation and fatty acid oxidation, has been linked to better insulin sensitivity and anti-inflammatory effects[20]. Our study included these variables to investigate their potential contributions to the observed effects of DLBS3233. Although no significant differences were found, the trends observed warrant further investigation.

The analysis of efficacy outcomes in our study provided a number of insights into the effects of DLBS3233 compared to the placebo. Initial fasting plasma glucose levels at baseline, Week 6, and Week 12 exhibited no significant differences between the two groups. Intriguingly, the DLBS3233 group showcased a notable reduction in 2-hour postprandial glucose levels at Week 12, while the placebo group did not demonstrate significant changes. Other parameters, including A1c levels, fasting insulin, insulin resistance (HOMA-R), adiponectin levels, HDL and LDL cholesterol, total cholesterol, triglycerides, and the ratio of total cholesterol to HDL cholesterol, remained consistent across baseline, Week 6, and Week 12.

In a similar study by Manaf et al. involving individuals with prediabetes, parallel findings emerged.[8] The outcomes underscored the promising effectiveness of DLBS3233 in augmenting insulin sensitivity.[8] The reduction in HOMA-IR was notably more pronounced in the DLBS3233 group when contrasted with the placebo group.[8] Furthermore, consistent enhancements in first- and second-phase insulin secretion and the oral disposition index were consistently noted in the DLBS3233-administered group.[8]

In contrast to our investigation, which primarily employs DLBS3233 as the sole agent for glycemic control, a study conducted by Tjokroprawiro et al. reveals DLBS3233's potential as an additional treatment for individuals with type-2 diabetes mellitus who have inadequate control with standard oral antidiabetic medications.[9] The study showcases a notable decrease in HbA1c levels, indicating enhanced control of blood glucose.[9] This discrepancy may be attributed to differences in study design, population characteristics, or the duration of treatment. Tjokroprawiro's study included participants with more advanced diabetes and used DLBS3233 in conjunction with other antidiabetic medications, whereas our study focused on newly diagnosed T2DM patients and employed DLBS3233 as a monotherapy. Additionally, variations in adherence to lifestyle modifications and dietary intake could have influenced the outcomes. Furthermore, the enhancements noted in fasting and postprandial glucose levels, insulin sensitivity, lipid profile, and adiponectin levels highlight DLBS3233's capacity to positively impact glucose and lipid metabolism within this particular patient group.[9]

Conversely, an additional investigation conducted by Hidayat et al. in a cohort of women with polycystic ovary syndrome (PCOS) produced different outcomes.[10] This study, involving PCOS women, indicates that DLBS3233, either alone or in conjunction with metformin, did not yield significant alterations in fasting plasma glucose, high-density lipoprotein (HDL), triglyceride levels, or other safety markers.[10] Despite the absence of substantial improvements in insulin resistance, the study underscores the safety and tolerability of DLBS3233 in subjects with PCOS.[10]

Additionally, the analysis of safety parameters accentuated the comparable trends exhibited by the DLBS3233 and placebo cohorts in terms of systolic and diastolic blood pressure, liver enzymes (SGPT and SGOT), gamma GT, and serum creatinine levels both at the outset and by Week 12. Remarkably, both groups demonstrated reductions in heart rate; however, these alterations did not attain

statistical significance. This outcome aligns with the observations from the Phase 1 clinical investigation conducted by Tjandrawinata et al., which underscores the safety of DLBS3233.[21] This study demonstrates that even at various administered doses, DLBS3233 does not trigger hypoglycemic events in healthy participants with normal blood glucose levels.[21] The study confirmed that DLBS3233 does not induce hypoglycemia in healthy individuals even at varying doses and does not adversely affect liver and kidney function.[21] Consistent safety profiles were noted in other investigations into DLBS3233.[8–10]

Our safety assessments align with those conducted in prior studies. Considering DLBS3233 as a novel alternative, its complete toxicity profile remains unclear. Hence, our study incorporates a comprehensive evaluation of vital signs, liver function, and renal function to thoroughly assess potential toxicity. Notably, hypoglycemic events were not specifically investigated in our study. However, previous research has demonstrated the absence of such events even in healthy individuals[8,21]. Consequently, we assume that DLBS3233 is safe for individuals with T2DM.

The study's limitations should be taken into account while interpreting the findings. The relatively small sample size could restrict the generalizability of the results. Therefore, careful interpretation is needed to extrapolate the outcomes to a broader population. Moreover, the study's duration was confined to a 12-week timeframe, potentially neglecting sustained impacts and prolonged safety considerations that may arise during extended treatment durations. The strict exclusion criteria might have impeded the inclusion of individuals with commonly associated type 2 diabetes comorbidities, limiting the sample's representativeness. The study's focus on specific villages geographically might limit the applicability of the results in more heterogeneous populations. Despite the double-blind design, the possibility of a placebo effect should not be entirely dismissed.

Addressing these limitations, future investigations could encompass a more diverse participant pool from various regions, explore the prolonged effects of DLBS3233 in lengthier studies, and undertake comparative analyses with other established diabetes treatments either in combination or as a sole agent. Future research should incorporate detailed evaluations of caloric intake and anthropometric changes, which are potent mediators of glycemic control. Monitoring dietary intake and body composition changes will provide more comprehensive insights into how these factors interact with DLBS3233 treatment and contribute to glycemic outcomes. Such studies could help identify specific subgroups of T2DM patients who may benefit most from DLBS3233 therapy.

CONCLUSION

In this study, DLBS3233 exhibited promising outcomes in terms of glycemic regulation, as highlighted by a noteworthy decrease in 2-hour postprandial glucose levels at Week 12 compared to the placebo group ($p = 0.026$). Nevertheless, no significant variations were observed in fasting plasma glucose, A1c levels, insulin concentrations, insulin resistance (HOMA-IR), and other metabolic indicators between the DLBS3233 and placebo cohorts at baseline, Week 6, and Week 12. These results suggest a potential advantage of DLBS3233 in enhancing postprandial glucose control. Moreover, in evaluating safety parameters, consistent patterns were observed in systolic and diastolic blood pressure, liver enzyme levels, heart rate, gamma GT, and serum creatinine levels across both study groups. While reductions in heart rate were noted, they did not reach statistical significance. These findings provide valuable insights into the glycemic and safety impacts of DLBS3233, paving the way for further explorations in this area.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper. The research was funded by PT. Dexa Medica and the authors affirm that this funding did not influence the design, conduct, or interpretation of the study.

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REFERENCES

1. Galicia-Garcia U, Benito-Vicente A, Jebari S, et al. Pathophysiology of type 2 diabetes mellitus. Int J Mol Sci. 2020;21(17):6275.
2. Zhang X, Jiang H, Ma X, Wu H. Increased serum level and impaired response to glucose fluctuation of asprosin is associated with type 2 diabetes mellitus. J Diabetes Investig. 2020;11(2):349–55.
3. Rahman MS, Hossain KS, Das S, et al. Role of insulin in health and disease: An update. Int J Mol Sci. 2021;22(12):6403.
4. Yaribeygi H, Sathyapalan T, Atkin SL, Sahebkar A. Molecular mechanisms linking oxidative stress and diabetes mellitus. Oxid Med Cell Longev. 2020;2020:e8609213.
5. Standards of Care in Diabetes.A bridged for primary care providers, clinical diabetes. American Diabetes Association. 2023 [Internet]. [cited 2023 Nov 23]. Available from: https://diabetesjournals.org/clinical/article/41/1/4/148029/Standards-of-Care-in-Diabetes-2023-Abridged-for
6. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2022;45(11):2753–86.
7. Permadi W, Hestiantoro A, Ritonga MA, et al. Administration of cinnamon and lagersroemia speciosa extract on lipid profile of polycystic ovarian syndrome women with high body mass index. J Hum Reprod Sci. 2021;14(1):16.
8. Manaf A, Tjandrawinata RR, Malinda D. Insulin sensitizer in prediabetes: a clinical study with DLBS3233, a combined bioactive fraction of Cinnamomum burmanii and Lagerstroemia speciosa. Drug Des Devel Ther. 2016;10:1279–89.
9. Tjokroprawiro A, Murtiwi S, Tjandrawinata RR. DLBS3233, a combined bioactive fraction of Cinnamomum burmanii and Lagerstroemia speciosa, in type-2 diabetes mellitus patients inadequately controlled by metformin and other oral antidiabetic agents. J Complement Integr Med. 2016;13(4):413–20.
10. Hidayat ST, Mulyantoro I, Damas S, Tjandrawinata RR. The effect and safety assessment of metformin and DLBS3233 (A bioactive fraction of Lagerstroemia speciosa and Cinnamomum burmannii) on improving metabolic parameters in women with polycystic ovary syndrome. Int J Womens Health. 2023;15:971–85.
11. Waist circumference and waist-hip ratio: report of a WHO expert consultation [Internet]. [cited 2024 Jul 11]. Available from: https://www.who.int/publications/i/item/9789241501491
12. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet Lond Engl. 2004;363(9403):157–63.
13. Alberti KGMM, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120(16):1640–5.
14. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412–9.
15. Tandrasasmita OM, Wulan DD, Nailufar F, Sinambela J, Tjandrawinata RR. Glucose-lowering effect of DLBS3233 is mediated through phosphorylation of tyrosine and upregulation of PPARγ and GLUT4 expression. Int J Gen Med. 2011;4:345–57.
16. Nailufar F, Tandrasasmita OM, Tjandrawinata RR. DLBS3233 increases glucose uptake by mediating upregulation of PPARγ and PPARδ expression. Biomed Prev Nutr. 2011;1(2):71–8.
17. Kumawat M, Sharma TK, Singh I, et al. Antioxidant enzymes and lipid peroxidation in type 2 diabetes mellitus patients with and without nephropathy. North Am J Med Sci. 2013;5(3):213–9.
18. Bhatia S, Shukla R, Venkata Madhu S, Kaur Gambhir J, Madhava Prabhu K. Antioxidant status, lipid peroxidation and nitric oxide end products in patients of type 2 diabetes mellitus with nephropathy. Clin Biochem. 2003;36(7):557–62.
19. Leto D, Saltiel AR. Regulation of glucose transport by insulin: traffic control of GLUT4. Nat Rev Mol Cell Biol. 2012;13(6):383–96.
20. Achari AE, Jain SK. Adiponectin, a therapeutic target for obesity, diabetes, and endothelial dysfunction. Int J Mol Sci. 2017;18(6):1321.
21. Tjandrawinata RR, Suastika K, Nofiarny D. DLBS3233 extract, a novel insulin sensitizer with negligible risk of hypoglycemia: A phase-I study. Int J Diabetes Metab. 2019;20(1):13–12.