

Administration of Cinnamon and *Lagersroemia speciosa* Extract on Lipid Profile of Polycystic Ovarian Syndrome Women with High Body Mass Index

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ABSTRACT

Background: Hyperinsulinemia, a common feature in PCOS, have been found to contribute to metabolic disturbance, such as dyslipidaemia and diabetes mellitus type 2. Oral anti-diabetic medications have been prescribed to alleviate this effect. We sought to find whether DLBS3233, an insulin sensitizer, could alleviate dyslipidaemia in women with PCOS with high BMI. **Aim:** This study aimed to investigate the effect of DLBS3233, an herbal combination of *C burmanii* and *L spesiosa* extract, on lipid profile, insulin resistance, and free testosterone of women with PCOS with high BMI. **Study Setting and Design:** This was a controlled trial conducted in Dr. Cipto Mangunkusumo Hospital, Jakarta, and Dr Hasan Sadikin Hospital, Bandung, Indonesia. **Materials and Methods:** A controlled trial was conducted on 62 volunteers diagnosed with PCOS according to Rotterdam criteria and exhibited insulin resistance as signified by HOMA-IR > 2.0; baseline lipid profile (LDL, HDL, Triglyceride and Total cholesterol) and free testosterone concentration were obtained. Participants were given 100 mg of DLBS3233 in the morning, and volunteers were followed up monthly, with laboratory tests conducted at the third and sixth months. Data were analysed through intention-to-treat analysis, separating high BMI (≥ 25 kg/m²) subjects. **Statistical Analysis:** Repeated-measures model. **Results:** DLBS3233 improved lipid profile and insulin sensitivity by reducing triglycerides, HOMA-IR, and free testosterone in subjects with high BMI. Limitations and Implications: The current study does not compare the effect of DLBS3233 with a control group. A larger study with a proper control group would have to be conducted to have more conclusive results. **Conclusion:** This study showed that DLBS3233 holds promise as a novel therapy to improve lipid profile for women with PCOS.

KEYWORDS: DLBS3233, high body mass index, polycystic ovarian syndrome

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a common endocrine disorder in reproductive-age women, characterized by oligo- or anovulation, clinical and biochemical features of hyperandrogenism, such as hirsutism, acne, and alopecia, and polycystic ovaries.^[1,2] Insulin resistance, thought to be the result of genetic predisposition and environmental factors, is also a common feature in PCOS.^[3]

Obesity is found in approximately half of all PCOS cases^[3] and, along with insulin resistance, appeared to exacerbate hyperandrogenemia by way of hyperinsulinemia and an

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increased dehydroepiandrosterone synthesis.^[3] Although the former is independent of the latter, hyperinsulinemia may contribute to the development of metabolic morbidities, such as dyslipidemia and diabetes mellitus type 2,^[4] which in turn may contribute to obesity. Given the role of insulin resistance in PCOS, insulin sensitizer such as metformin had been used to alleviate the symptoms of PCOS and induce ovulation. Metformin, a biguanide, is also able to affect lipid metabolism through several pathways: (a) the activation of AMP-activated protein kinase, which suppressed lipogenesis, and (b) by increasing insulin-mediated glucose uptake in the visceral fat, reducing lipolysis.^[5] While the evidence is inconclusive, metformin was repeatedly shown to increase high-density lipoprotein cholesterol (HDL-C) and decrease total cholesterol (TC), low-density lipoprotein (LDL), and triglyceride (TG) level in women with normo- and overweight women with PCOS.^[6] However, other randomized controlled trials of metformin administration in obese women with PCOS did not find significant effects on serum TC, LDL, and HDL, and few reported decreased TG level in obese women with PCOS.^[6] As such, the effects of metformin in PCOS appear to differ according to the baseline metabolic status of the women.

Research on thiazolidinediones (TZDs), a selective ligand on the peroxisome proliferator-activated receptor-gamma (PPAR- γ), is scarce: a 2012 meta-analysis of the effect of TZDs on hyperinsulinemia and fasting glucose in PCOS yielded eight studies.^[7] In their meta-analysis, Du *et al.* found that TZDs were effective in improving fasting insulin and reducing fasting blood glucose level.^[7] However, a recent meta-analysis by Xu *et al.* showed no difference in the improvement of homeostatic model assessment of insulin resistance (HOMA-IR) score between metformin and pioglitazone.^[8] There is also concern regarding the side effects of certain TZDs, such as the hepatotoxic effect of troglitazone or the association between rosiglitazone with cardiovascular adverse effects.^[6] To date, metformin remains the main choice of ISA to use in PCOS, with TZD available for use as a second-line option.

DLBS3233 is a bioactive fraction of *Cinnamon burmannii* and *Lagerstroemia speciosa*, which had been shown to improve insulin resistance in patients with impaired glucose tolerance.^[9] Previously, Cao *et al.* (2010) had demonstrated that cinnamon polyphenol upregulated the activity of insulin-regulated glucose transporter 4 (GLUT4), as well as regulating the expression of insulin-signaling gene expression in mouse adipocytes.^[10] *L. speciosa* exhibited glucose uptake-inducing activity in adipocytes.^[11,12] The herbal

combination of *C. burmannii* and *L. speciosa* in DLBS3233 had been shown to improve adiponectin and reduce LDL and TC in type 2 diabetes mellitus patients inadequately controlled by metformin.^[13]

To date, there had only been one study reporting the effect of DLBS3233 in women with PCOS, where insulin resistance is a common feature. A recent study by Wiweko and Susanto reported that the administration of DLBS3233 on women with PCOS significantly decreased serum anti-Mullerian hormone (AMH) and body mass index (BMI),^[14] implying that it may be used as an adjuvant or an alternative therapeutic option to reduce cardiometabolic risk in women with PCOS. Given the findings stated above, we aim to investigate the effect of DLBS3233 on lipid profile, free testosterone, and HOMA-IR in obese with PCOS.

METHODS

Subjects and study design

This was a clinical study conducted between March 2013 and March 2018 in Yasmin Clinic, Dr Cipto Mangunkusumo Hospital Jakarta, and Aster Clinic, Hasan Sadikin Hospital Bandung. This study protocol was approved by Faculty of Medicine, Universitas Indonesia, and Faculty of Medicine, Universitas Padjadjaran under registry number 605/H2.F1/ETIK/2012. Sixty-two patients were enrolled by a consecutive sampling method. Inclusion criteria for the study were as follows: female; aged 18–40 years and diagnosed with PCOS as confirmed by two of the Rotterdam criteria; exhibited insulin resistance as defined by baseline HOMA-IR of >2.00 following the results of previous studies on women with PCOS;^[15,16] and gave written and verbal consent to participate. Women who are pregnant, lactating, diagnosed with Cushing's syndrome, congenital adrenal hyperplasia, uncontrolled thyroid disease, diabetes mellitus, and impaired renal and liver function were excluded. Women were divided into high and lower BMI groups based on the WHO BMI cutoff (≥ 25 kg/m²)^[17] and were given DLBS3233, 100 mg daily in the morning. Sample size was previously calculated by power calculation and resulted in 62 patients.

In brief, DLBS3233 (Dexa Laboratories of Biomolecular Sciences, PT Dexa Medica, Indonesia) is a bioactive fraction derived from *C. burmannii* and *L. speciosa*. Details of preparation, extraction as well as the phytochemical characterization of DLBS3233 were as previously described.^[18] DLBS3233 was pharmaceutically formulated in oral capsules, each of which contains 100 mg of the bioactive fraction.

Participants were followed up monthly and laboratory tests were performed at 3- and 6-month

time point to evaluate the primary and secondary endpoints of interest: An improvement in lipid profile markers (reduced TC, LDL, TG, and increased HDL), reduced HOMA-IR, and free testosterone.

The assays used for direct measurement of those parameters in plasma samples were cholesterol oxidase-phenol and 4-aminophenazone (PAP) for TC; homogeneous assays for LDL- and HDL-cholesterol; glycerol-3-phosphate oxidase-PAP for TG; glucose oxidase-PAP for glucose; immunochemiluminescence for insulin; and electrochemiluminescence for free testosterone.

Statistical analysis

A repeated-measures model was applied for the analysis of the primary and secondary endpoints as they are continuous outcomes with more than one measurement. Direct estimates of the treatment effect at specific times were obtained using a model with intercept and time variables. An unstructured correlation model was chosen when there are relatively few repeated measurements per participant. This likelihood-based analysis is considered valid under the assumption of missing data mechanism missing at random.

RESULTS

Of 62 patients enrolled, 10 were excluded due to pregnancy and one was excluded due to an adverse event. Of the remaining 52 available for intention-to-treat analysis, 44 (84.6%) had BMI ≥ 25 kg/m² and 8 (15.4%) had lower BMI than 25 kg/m². The distribution of baseline characteristics is presented in Table 1.

Effect on lipid profile

Among PCOS women with high BMI, there was no significant difference in LDL, HDL, and TC across time points compared to baseline. There was a significant decrease in TG concentration at 3 months (139.81 and 121.66, $P < 0.05$) [Table 2], however, it increased at 6-month time point. A significant decrease in HDL was found at 3-month time point, however, it returned to baseline level at 6 months of treatment. We observed a decreasing trend in the concentration of TC compared to baseline in 3 and 6 months, however, the difference was not statistically significant (193.81 and 191 and 189.02, respectively; $P = 0.395$ at 3 months and 0.219 at 6 months).

Effect on homeostatic model assessment of insulin resistance

Among PCOS women with high BMI, there was a significant decrease in homeostatic model assessment of insulin resistance at 3-month time point (4.5 and 3.82, $P < 0.05$). At 6 months, we observed a nonsignificant decrease (4.5 and 3.64, $P > 0.05$).

Table 1: Baseline characteristics

Variable (mean±SE)	Value (n=44)
Age	28.5±3.78
BMI	31.9±4.09
Body fat	43.02±6.93
LDL (mg/dL)	137.88±28.46
HDL (mg/dL)	42.35±8.44
Total cholesterol (mg/dL)	194.37±33.8
Triglycerides (mg/dL)	194.37±33.8
Free testosterone (%)	7.75±6.12
HOMA-IR	4.5±3.5

HOMA-IR=Homeostatic model assessment of insulin resistance, LDL=Low-density lipoprotein, HDL=High-density lipoprotein, BMI=Body mass index, SE=Standard error

Table 2: Lipid profile, homeostatic model assessment of insulin resistance, and free testosterone profile

Variable	Value (n=44), mean (SD)	P value versus baseline
LDL (mg/dL)		
3 months	135.01 (30.77)	NS
6 months	134.04 (30.38)	NS
HDL (mg/dL)		
3 months	42.13 (7.95)	NS
6 months	42.44 (7.56)	NS
Total cholesterol (mg/dL)		
3 months	191 (34.36)	NS
6 months	189.02 (37.07)	NS
Triglycerides (mg/dL)		
3 months	121.66 (41.65)	<0.05*
6 months	123.2 (76.74)	NS
HOMA-IR		
3 months	3.82 (2.42)	<0.05*
6 months	3.64 (2.11)	NS
Free testosterone (%)		
6 months	6.25 (4.31)	<0.05*

*Significance is determined at $p < 0.05$. HOMA-IR=Homeostatic model assessment of insulin resistance, LDL=Low-density lipoprotein, HDL=High-density lipoprotein, NS=Not significant, SD=Standard deviation

Effect on free testosterone

A significant decrease in free testosterone was found among with PCOS women with high BMI in 6-month time (7.75% and 6.25%, $P < 0.05$).

DISCUSSION

A higher baseline level of TGs, free testosterone, and HOMA-IR was observed in our PCOS patients with high BMI, which was significantly reduced following administration of DLBS3233. HOMA-IR was reduced significantly ($P < 0.05$), however, the decline was not statistically significant at 6 months. Free testosterone was significantly reduced, which could be explained by the higher HOMA-IR among these participants, implying a

more severe insulin resistance: hyperinsulinemia reduces sex hormone-binding globulin, and resulted in increased sex steroid hormones.^[19,20]

As shown by Tandrasasmita *et al.*, DLBS3233 increases glucose uptake in insulin-resistant adipocytes by the activation of genes regulating insulin signaling, such as PPAR- γ , GLUT4, Akt, and phosphatidylinositol 3-kinase (PI3K).^[18] In a similar study, they demonstrated that DLBS3233 upregulated the expression of GLUT4 in 3T3 fibroblast Swiss albino cells by twofold, higher than that of pioglitazone and insulin.^[18] Therefore, DLBS3233, in part, shares its mechanism with TZDs, as both acted through activation of PPAR- γ . In a study of women with PCOS who were resistant to metformin, pioglitazone was able to improve HDL concentration, while Sangeeta showed that pioglitazone significantly reduced TC, very-low-density lipoprotein (VLDL), and HOMA-IR, along with an insignificant reduction of testosterone levels.^[21,22] These data agreed with the result of our study, which may be explained by the shared mechanism of action between pioglitazone and DLBS3233.

PPAR- γ is highly expressed in the adipose tissue and regulates the expression of adiponectin. Adiponectin is a 30 kDa protein produced mainly by the adipose tissue, although recent studies have also shown the production of adiponectin by liver parenchyma cells, myocytes, and placental tissue.^[23] Adiponectin interacts with resistin, a peptide hormone with opposite mechanism to adiponectin, in the regulation of glucose and lipid metabolism.^[24] Jonas *et al.* have shown that visceral and subcutaneous adiponectin level was lower in obese individuals compared to nonobese individuals, whereas resistin is expressed at the highest level in the subcutaneous tissue of obese individuals.^[24] In a mouse model of elevated adiponectin, Qiao *et al.* showed that adiponectin was responsible in increasing skeletal muscle lipoprotein lipase, which consequently increases VLDL metabolism and decreases plasma TG level.^[25] In the previous study by Tandrasasmita *et al.*, it was also demonstrated that DLBS3233 upregulated adiponectin, with the opposite effect to resistin.^[18] Taken together, the result of the current study is largely in line with what is known regarding the preclinical mechanism of DLBS3233: DLBS3233 appeared to decrease TG in women with high BMI through the activation of PPAR- γ , in turn affecting adiponectin and VLDL metabolism.

Insulin-stimulated transporter GLUT4 plays a major role in maintaining glucose homeostasis. Once insulin binds to the receptor, it starts a reaction involving lipid kinase PI3K, which activates serine/threonine kinase Akt and activates the expression of GLUT4 in the

plasma membrane.^[18] Previous result by Tandrasasmita *et al.* demonstrated significantly increased expression of GLUT4 as well as enhanced Akt expression in mice adipocytes, implying the ability to improve insulin sensitivity.^[18] Our data support these results, as proven by a significant decrease in HOMA-IR in PCOS women with high BMI. This study is limited by the lack of comparison with gold standard medications, such as metformin. Future research could consider comparing metformin and DLBS to see how both interventions perform.

CONCLUSION

Our study had shown that DLBS3233 could improve lipid profile and insulin sensitivity for women with PCOS, particularly in those with high BMI. In the future, larger, double-blinded trials could be conducted to further confirm the impact of DLBS3233.

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Conflicts of interest

There are no conflicts of interest.

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