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Research Article

# THE EFFECT OF DHAWALSAN-1 *(CURANGA FEL-TERRAE* [LOUR.]) EXTRACT VERSUS METFORMIN ON THE METABOLIC AND INFLAMMATORY CHARACTERISTICS OF PATIENTS WITH NEWLY DIAGNOSED TYPE 2 DIABETES MELLITUS

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**ABSTRACT**

**Objectives:** The prevalence of Type 2 diabetes mellitus (T2DM) continues to rise at an exponential rate around the world as well as in South-East Asia regions. This study compared the effect of metformin and dhawalsan-1 (*Curanga fel-terrae* [Lour.]) extract on metabolic and inflammatory characteristics in patients with newly diagnosed T2DM.

**Methods:** In this preliminary study, consecutive sampling was used to select 24 newly diagnosed T2DM subjects to be randomly assigned into two groups: One group received metformin 3 × 500 mg/day and another group received dhawalsan-1 extract 2 × 100 mg/day, in a double-blind fashion. Clinical characteristics of the patients were assessed before and after the 12-week treatment period.

**Results:** After the 12-week treatment, in metformin group, a significant decrease was noted in waist circumference (p=0.005), fasting plasma glucose (FPG; p=0.017), glycosylated hemoglobin (HbA1c) (p=0.021), and homeostasis model of assessment of β-cell function (HOMA-B; p=0.020). In dhawalsan-1 group, a significant decrease was noted in FPG (p=0.012), HbA1c (p=0.006), and HOMA-insulin resistance (p=0.033), and a significant increase was noted in adiponectin (p=0.008). No significant differences were found between metformin and dhawalsan-1 group in any measured clinical characteristic after 12 weeks.

**Conclusions:** This preliminary study indicated that dhawalsan-1 (*C. fel-terrae* [Lour.]) extract was effective in improving metabolic characteristics and significantly increased adiponectin levels in patients with newly diagnosed T2DM. The improvement also seemed to be comparable with that of metformin. Yet, Further larger studies are required to confirm these promising results.

**Keywords:** Type 2 diabetes mellitus, Metformin, Dhawalsan-1 (*Curanga fel-terrae* [Lour.]).

## INTRODUCTION

The prevalence and incidence of Type 2 diabetes mellitus (T2DM) continue to rise. The worldwide prevalence of diabetes for all age groups was estimated as 2.8% in 2000 and is predicted to reach 4.4% in 2030 [1]. Data from the Indonesian National Basic Health Research Survey (Riskesdas) in 2007 found a diabetes prevalence of 5.7%, of which more than 70% were undiagnosed cases [2]. Glucose control remains a major focus in the management of patients with T2DM. Studies have conclusively determined that reducing hyperglycemia decreases the onset and progression of microvascular complications [3].

Guidelines from the American Diabetes Association (ADA)/European Association for the Study of Diabetes and the American Association of Clinical Endocrinologists/American College of Endocrinology recommend metformin as the first choice of single or combination therapy for patients with T2DM [4]. Metformin treatment is well-tolerated, produces substantial reductions in glycosylated hemoglobin (HbA1c) without causing hypoglycemia or body weight gain, cardioprotective, and can be combined with other medications for T2DM [5]. Metformin can also reduce the expression of inflammatory markers such as intracellular adhesion molecule-1, vascular cell adhesion molecule-1, and C-reactive protein (CRP) in certain patients [6].

According to a study by the World Health Organization, over 80% of the world's population depends on biological resources for their primary healthcare needs. The use of traditional medicines in Indonesia has a history of several thousands of years, long before the advent of modern drug discovery, as illustrated in a relief painting from the Borobudur temple and in medicinal plant recipes written on palm leaves from Bali, dating from about AD 991 to 1026 [7]. Medicinal plants, used to treat diabetic conditions, are of considerable interest and a number of plants show varying degrees of hypoglycemic and antihyperglycemic activities [8]. Indeed, ethnobotanical studies of traditional herbal remedies used for diabetes have identified more than 1200 species of plants with hypoglycemic activity [9].

*Curanga fel-terrae* (Lour.); also known as *Picria fel-terrae* (Lour) Merr; *Caranga amara* Vahl; *Curanga melissifolia A.* Juss*; Curanga torenioides* Steud; *Gratiola amara* (Vahl.) Roxb belongs to the family *Scrophulariaceae* and grows in many countries in Asia including China, India, Philippines, Malaysia, Myanmar, and Indonesia. In Indonesia, *C. fel-terrae* (Lour.) spreads on the islands of Sumatra, Java, Borneo, and Maluku [10]. The plant is also known by different names throughout Indonesia including ai laun nyin (Ambon), kekurang (Maluku), mempedu tanah (Malay), papaita (Ternate), parang raiding (Minahasa), tamah raheut (Sunda) [10], and puguntano in Tiga Lingga village, Dairi (North Sumatra Province), where its leaves were used empirically as a diabetes medication. In Southern China, *C. fel-terrae* (Lour.) has been used as a traditional medicine for about 200 years in the treatment of fever, herpes infection, cancer, and inflammation [11]. A study in mice with alloxan-induced diabetes demonstrated that blood glucose levels were reduced by 44.47% after a 10-day treatment with n-hexane-extracted puguntano (*C. fel-terrae* [Lour.]) [12]. The current study was the first clinical study aimed to scientifically investigate the antidiabetic and anti-inflammatory properties of the ethanolic extract of *C. fel-terrae* (Lour.) in newly diagnosed Type-2 diabetes. The purpose of the current preliminary study was to compare the effect of a 12-week treatment of

metformin and dhawalsan-1 (*C. fel-terrae* [Lour.]) extract on metabolic and inflammatory characteristics in patients with newly diagnosed T2DM.

## METHODS

### Subjects

This study was conducted between July 2015 and November 2015 at the endocrinology-metabolic outpatient clinic of H. Adam Malik Hospital, with the Ethical approval of the local Research Ethics Commission. Consecutive random sampling was used to select newly diagnosed T2DM subjects, and the study was double-blind to the assigned treatment. Subjects were provided with information about the study and those agreeing to participate gave written informed consent. Patients were assigned to receive metformin capsules (3 × 500 mg/day) or dhawalsan-1 (*C. fel-terrae* [Lour.]) extract capsules (2 × 100 mg/day) with titrated dose for 12 weeks. T2DM was diagnosed using ADA criteria [13] and Perkeni [14].

An anamnestic interview was performed to obtain information on age, gender, T2DM, smoking habit, family disease, hypertension, and previous laboratory tests. Body height, body weight, body mass index (BMI), and waist circumference (WC) were recorded. The following inclusion criteria were used: Male and female individuals, age >17 years and newly diagnosed T2DM. Exclusion criteria were T1DM, anemia (male; Hb <120 g/L and female; Hb <110 g/L), hypertension (blood pressure >140/90 mmHg), impaired liver and kidney function, severe infection, stress or secondary hyperglycemia, and drop-out.

### Study products

Metformin used as the comparator drug in this study was one manufactured by PT. Hexpharm Jaya Laboratories, Indonesia. Dhawalsan-1 (*C. fel-terrae* [Lour.]) extract was produced by the percolation method using 70% ethanol [15]. The extract capsules were prepared by the Faculty of Pharmacy of North Sumatra University, Medan, Indonesia.

### Biochemical analysis

Biochemical analysis of blood samples was carried out at baseline and after 12 weeks by the standard methods [16]. Blood glucose was measured with a photometric AutoAnalyzer (Modular P 800), HbA1c was measured by HPLC methods, adiponectin was measured by ELISA (Daichi), high-sensitivity CRP (hs-CRP) was measured by an immunoturbidimetric assay (Architect i System, Abbott Laboratories), insulin was measured by an immunochemiluminescent method (Siemens Diagnostic). The homeostasis model of assessment-insulin resistance (HOMA-IR and HOMA-B assessment was determined by standard formula [17].

### Statistical analysis

Data are expressed as mean±standard deviation. The difference between means before and after treatment was determined within group by Student's paired t-test. For comparisons between groups, independent (unpaired) Student's t-test was used. All data were analyzed using the Statistical Program SPSS version 22.0. A level of significance (α) of 0.05 was used in the study.

## RESULTS

The baseline characteristics of subjects in the study are shown in Table 1. Baseline values of all measured parameters were comparable between the metformin and dhawalsan-1 (*C. fel-terrae* [Lour.]) groups. The results of the main parameters in both groups after the 12-week treatment period are shown in Table 2. In the metformin group, a significant decrease from baseline was noted in WC (p=0.005), fasting plasma glucose (FPG; p=0.017), HbA1c (p=0.021), and HOMA-B (p=0.02). In the dhawalsan-1 (*C. fel-terrae* [Lour.]) group, a significant decrease from baseline was noted in FPG (p=0.012), HbA1c (p=0.006), and HOMA-IR (p=0.033), and a significant increase was noted in adiponectin (p=0.008). No significant differences were found between the metformin and dhawalsan-1 (*C. fel-terrae* [Lour.]) groups in any measured parameters after 12 weeks. No hypoglycemic symptoms were reported in either group, and no worsening of liver or renal function was noted in the dhawalsan-1 (*C. fel-terrae* [Lour.]) extract group upon completion. The liver and renal functions after 12 weeks of treatment with dhawalsan-1 (*C. fel-terrae* [Lour.]) are shown in Table 3.

**Table 1: Baseline characteristics of subjects**

| Variable | Mean±SD (n=12) | | p value |
|---|---|---|---|
| | Metformin group | Dhawalsan-1 group | |
| Age (years) | 52.7±5.5 | 55.5±4.5 | 0.197 |
| Weight (kg) | 64.1±4.7 | 62.1±9.9 | 0.545 |
| BMI (kg/m$^2$) | 25.5±2.2 | 25.1±3.6 | 0.732 |
| WC (cm) | 95.5±4.2 | 94.2±3.7 | 0.446 |
| FPG (mmol/L) | 9.79±3.62 | 12.39±6.59 | 0.251 |
| 2h-PPG (mmol/L) | 14.01±5.08 | 16.72±8.69 | 0.469 |
| HbA1c (%) | 9.2±1.7 | 9.6±3.3 | 0.551 |
| HOMA-IR | 3.1±3.1 | 3.7±2.2 | 0.550 |
| HOMA-B (%) | 31.2±19.7 | 25.9±17.4 | 0.487 |
| TG (mmol/L) | 1.92±0.50 | 1.94±1.17 | 0.949 |
| HDL-C (mmol/L) | 1.07±0.20 | 1.17±0.20 | 0.239 |
| LDL-C (mmol/L) | 3.54±0.97 | 3.23±1.11 | 0.477 |
| hs-CRP (mg/L) | 3.6±2.7 | 2.7±2.6 | 0.466 |
| Adiponectin (µg/dL) | 4.3±2.3 | 4.3±1.7 | 0.912 |

Data are expressed in mean±SD. Categorical data are expressed in a number of subjects (n) and percentage (%). BMI: Body mass index, WC: Waist circumference, FPG: Fasting blood glucose, PPG: Postprandial blood glucose, HbA1c: Glycosylated hemoglobin, HOMA-IR: Homeostasis model assessment of insulin resistance, HOMA-B: Homeostasis model assessment of β-cell function, TG: Triglycerides, HDL-C: High-density lipoprotein-cholesterol, LDL-C: Low-density lipoprotein-cholesterol, hs-CRP: High-sensitivity C-reactive protein, SD: Standard deviation

## DISCUSSION

### Glycemic control

Metformin is regarded as an antihyperglycemic agent because it lowers blood glucose concentrations in T2DM without causing overt hypoglycemia. Metformin is also often referred to as an insulin sensitizer leading to an improvement in insulin resistance and a reduction in the plasma fasting insulin level. The improvement in insulin sensitivity by metformin could be ascribed to its positive effects on insulin receptor expression and tyrosine kinase activity [18]. Metformin may also exert its beneficial metabolic actions in part through the modulation of multiple components of the incretin axis [19].

Several secondary metabolites have been identified in ethanol extracts of *C. fel-terrae* (Lour.) leaves such as glycosides [20,21], flavonoids [22], saponins [23], and terpenoids [24]. Mechanistically, saponins inhibit the absorption of glucose [25] whereas flavonoids act as antioxidants to protect pancreatic β-cells from oxidative stress [26]. Furthermore, tannins stimulate glucose uptake by increasing insulin sensitivity and also inhibit adipogenesis [27].

In the present study, we found that the therapy with metformin and dhawalsan-1 (*C. fel-terrae* [Lour.]) extract for 12 weeks were equally effective in improving glycemic control (FPG and HbA1c). Metformin decreased FPG and HbA1c by 2.22 mmol/L and 1.1%, respectively, and dhawalsan-1 (*C. fel-terrae* [Lour.]) decreased FPG and HbA1c by 3.33 mmol/L and 1.5%, respectively. This finding was consistent with that of previous studies. A study by Sherifali *et al*. showed that most oral antidiabetic agents lowered HbA1c levels by 0.5-1.25% whereas thiazolidinediones and sulfonylureas lowered HbA1c levels by ~1.0-1.25% [28]. The observation from the United Kingdom Prospective Diabetes Study also reported that metformin is as effective as sulfonylureas in controlling blood glucose levels in overweight patients with T2DM [29]. Metformin is also effective in normal weight

**Table 2: Changes in the metabolic and inflammatory parameters before and after study**

| Variable | Metformin group (n=12) | | | Dhawalsan-1 group (n=12) | | | p value[c] |
|---|---|---|---|---|---|---|---|
| | Before mean±SD | After mean±SD | p value[a] | Before mean±SD | After mean±SD | p value[b] | |
| Weight (kg) | 64.1±4.7 | 63.7±4.7 | 0.095 | 62.2±9.9 | 61.5±9.6 | 0.089 | 0.336 |
| BMI (kg/m$^2$) | 25.5±2.1 | 25.3±2.0 | 0.071 | 25.1±3.6 | 24.8±3.4 | 0.066 | 0.325 |
| WC (cm) | 95.5±4.1 | 94.8±3.9 | 0.005* | 94.2±3.7 | 93.8±3.4 | 0.137 | 0.422 |
| FPG (mmol/L) | 9.79±3.62 | 7.72±2.65 | 0.017* | 12.39±6.59 | 9.19±3.78 | 0.012* | 0.413 |
| 2h-PPG (mmol/L) | 14.01±5.08 | 15.65±5.32 | 0.457 | 16.72±8.69 | 15.33±5.41 | 0.480 | 0.298 |
| HbA1c (%) | 9.2±1.7 | 8.1±1.5 | 0.021* | 9.6±3.2 | 8.1±2.0 | 0.006* | 0.581 |
| HOMA-IR | 3.0±3.1 | 2.8±2.2 | 0.689 | 3.7±2.2 | 2.1±1.2 | 0.033* | 0.257 |
| HOMA-B (%) | 31.2±19.7 | 58.3±32.4 | 0.020* | 25.9±17.4 | 32.5±22.5 | 0.262 | 0.093 |
| TG (mmol/L) | 1.92±0.50 | 1.78±0.72 | 0.287 | 1.94±1.17 | 1.94±1.03 | 0.937 | 0.753 |
| HDL-C (mmol/L) | 1.07±0.20 | 1.12±0.18 | 0.168 | 1.17±0.20 | 1.20±0.20 | 0.507 | 0.333 |
| LDL-C (mmol/L) | 3.54±0.97 | 3.56±1.13 | 0.970 | 3.23±1.11 | 3.14±1.03 | 0.707 | 0.921 |
| hs-CRP (mg/L) | 3.6±2.7 | 2.4±1.2 | 0.369 | 2.7±2.6 | 1.3±08 | 0.055 | 0.780 |
| Adiponectin (µg/dL) | 4.3±2.3 | 4.2±2.4 | 0.878 | 4.3±1.8 | 5.1±2.2 | 0.008* | 0.174 |

Categorical data are expressed in number of subjects (n) and percentage (%), [a]Difference between the baseline and 12-week follow-up surveys in the metformin group, based on a dependent *t*-test, [b]Difference between the baseline and 12-week follow-up surveys in the dhawalsan-1group, based on a dependent *t*-test, [c]Δ Difference between the metformin group and dhawalsan-1 group after the 12-week follow-up surveys, based on an independent t-test, *Significant. BMI: Body mass index, WC: Waist circumference, FBG: Fasting blood glucose, PPG: Postprandial blood glucose, HbA1c: Glycosylated hemoglobin, HOMA-IR: Homeostasis model assessment of insulin resistance, HOMA-B: Homeostasis model assessment of β-cell function, TG: Triglycerides, HDL-C: High-density lipoprotein-cholesterol, LDL-C: Low-density lipoprotein-cholesterol, hs-CRP: High-sensitivity C-reactive protein, SD: Standard deviation

**Table 3: Liver and renal functions after 12 weeks study of dhawalsan-1 (*C. fel-terrae* [Lour.])**

| Variable | Mean±SD | | p value |
|---|---|---|---|
| | Before | After | |
| SGOT (U/L) | 21.3±7.3 | 23.0±7.6 | 0.220 |
| SGPT (U/L) | 25.4±14.6 | 28.2±14.4 | 0.593 |
| Phosphatase alkali (U/L) | 77.9±21.2 | 70.2±25.6 | 0.937 |
| Ureum (mmol/L) | 7.57±2.78 | 8.75±2.00 | 0.142 |
| Creatinine (µmol/L) | 53.04±17.68 | 61.88±17.68 | 0.112 |

SD: Standard deviation, SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamate pyruvate transaminase, *C. fel-terrae: Curanga fel-terrae*, SD: Standard deviation

patients [30]. In a clinical trial, metformin was shown to decrease FPG by 3.3-3.9 mmol/L (60-70 mg/dL) and HbAc1 by 1-2% [31].

**Inflammation parameters**

Hyperglycemia is associated with an increase in serum CRP levels [32]. Several studies reveal that hs-CRP remains a significant predictor of diabetes risk even after adjusting for BMI, family history of DM, smoking, and other factors [33]. In the present study, a trend toward a decrease in hs-CRP was observed in the metformin and dhawalsan-1 (*C. fel-terrae* [Lour.]) groups after 12 weeks. This finding is consistent with the positive effect of metformin on inflammation markers in patients with impaired glucose tolerance and T2DM in one study [34] but not in another study [35].

Adiponectin, produced almost exclusively in adipose tissue, is an insulin-sensitizing hormone with antiapoptotic and anti-inflammatory effects. Adiponectin levels are significantly decreased in obesity and T2DM [36] and may negatively modulate the process of atherogenesis [37]. In line with our study results, a former study by Fisman and Tenenbaum showed that antidiabetic agents such as glitazones and glimepiride were able to improve adiponectin concentration [38]. In the present study, patients treated with dhawalsan-1 (*C. fel-terrae* [Lour.]) had significantly higher adiponectin levels than those treated with metformin. Based on this result, dhawalsan-1 (*C. fel-terrae* [Lour.]) may have specific anti-inflammatory properties and might prevent cardiovascular disease.

**Lipid profile**

An improvement in lipid profiles was observed with both metformin and dhawalsan-1 (*C. fel-terrae* [Lour.]) as measured by a decrease in triglycerides (TGs) and low-density lipoprotein-cholesterol and a trend toward an increase high-density lipoprotein-cholesterol (HDL-C) although these changes were not significant. The beneficial effects of metformin on lipid profile are contentious [39]. Whereas one study reported a reduction only in total cholesterol (TC) levels [40]; another study reported a reduction of both TC and TG, with an increase of HDL-C [41], and the third study showed no changes in lipid profile [42].

The strength of the study is that this was the first study to evaluate the effect of dhawalsan-1 (*C. fel-terrae* [Lour.]) on metabolic and inflammatory characteristics in patients with newly diagnosed T2DM. Large, long-term prospective studies are needed to determine the optimal dose and the potential for combination therapy with other oral hypoglycemic agents for T2DM.

## CONCLUSION

This preliminary study indicated that dhawalsan-1 (*C. fel-terrae* [Lour.]) extract was effective in improving metabolic characteristics and significantly increased adiponectin levels in patients with newly diagnosed T2DM. The improvement also seemed to be comparable with that of metformin. Yet, further larger studies are required to confirm these promising results.

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