Recent Study of Turmeric in Combination with Garlic as Antidiabetic Agent

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Abstract

The aim of this study was to compare efficacy and safety of Allium Curcuma with glibenclamide in type-2 diabetes mellitus with or without dyslipidemia. Thirty five patients were recruited and randomized into 2 groups for 14 weeks treatment and assessment. One group received study drug, three times two capsules containing 200 mg turmeric and 200 mg allium extract per day. The other group received 1 capsule of 5 mg glibenclamide as standard drug per day. After 14 weeks of treatment patients with allium curcuma treatment showed significant decreased in fasting blood glucose (192.76 versus 141.71 mg/dL) and 2 hours post-prandial blood glucose (295.35 versus 204.35 mg/dL). HbA1C level was also significantly decreased (10.41 versus 8.09). No difference was found in blood pressure, hematology profile, liver and kidney function of both groups. In conclusion, allium curcuma has potential to be used as antidiabetic agent.

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1. Introduction

Globally, there is a growing prevalence of type-2 diabetes mellitus. WHO estimates that more than 180 million people worldwide have impaired glucose tolerance. It is predicted that the number of worldwide diabetes cases might increase from 171 million in 2000 to 366 million in 20301. The prevalence of diabetes mellitus in adults

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worldwide was estimated to be 5.4% in 2025. The major increase will be in the developing countries (170% increase) while developed countries the increase will be 42%. Hence, it was predicted that by the year 2025, 75% of diabetes population reside in the developing countries.

Many herbal compounds have been used throughout the world for diabetes. Among others, turmeric (Curcuma longa L.) and garlic (Allium sativum L.) have been shown to have hypoglycemic action and therefore both are used for diabetes treatment. A. sativum L., commonly known as garlic, has been used for medicinal purpose. When garlic cloves are crushed or disrupted, allinase enzyme which present in garlic (A. sativum) will act on alliin to produce allicin, the principal bioactive compound in garlic. Turmeric, the rhizome of Curcuma longa, is also spice and medicinal plant used in some Asian countries. Curcuminoids are the main component in Curcuma species responsible for their major biological effects. Curcumin, predominantly contained in curcuminoids, has a wide range of pharmacological effects including reduction of blood cholesterol and glucose levels, and other medicinal effects.

Innovation in antidiabetic agents, oral antihyperglycaemic agents as well as insulin preparation, developed robustly nowadays. However, the “back to nature” (herbal) medicines are frequently considered to be less toxic than the synthetic drugs since they have commonly few adverse reactions. Combination of extract garlic and turmeric (Allium Curcuma) has been proven pre-clinically and clinically as antidiabetic agent. Our study on animal even showed that combination of both substances gives synergistic effect compared to their individual usage. Antidiabetic dose ranging clinical study of Allium Curcuma has been done previously and resulted the optimum dose of Allium Curcuma 2.4 g. Here we conduct a study to compare efficacy and safety of Allium Curcuma with oral antihyperglycaemic agent Glibenclamide in type-2 diabetes mellitus patients, with or without dyslipidemia.

### Nomenclature

| Acronym | Description |
|---------|-------------|
| WHO | World Health Organization |
| HSH | Hasan Sadikin Hospital |
| LDL | Low Density Lipoprotein |
| BMI | Body Mass Index |
| AST | Aspartate Transaminase |
| ALT | Alanin Transaminase |
| ECG | Electrocardiogram |
| HDL | High Density Lipoprotein |
| PT | Prothrombin Time |
| APTT | Activated Partial Thromboplastin Time |
| INR | International Normalized Ratio |
| 2HPP | 2 Hours Post-Prandial |
| AC group | Allium Curcuma Group |
| Hb1AC | Glycosylated hemoglobin |
| DM | Diabetes Mellitus |
| PPAR-γ | Peroxisome Proliferator-Activated Receptor-γ |
| ACE | Angiotensin Converting Enzyme |
| FBG | Fasting Blood Glucose |
| 2HPP BG | 2 Hours Post-Prandial Blood Glucose |

### 2. Experiments

This is a double blind, parallel, randomized control trial conducted in 14 weeks. The study protocol was approved by Ethics Committee on Research in Human, Hasan Sadikin Hospital (HSH), Bandung, Indonesia. Written informed consent was obtained from each patient before any procedure was performed. This clinical study was conducted...
according to Good Clinical Practice Procedure and in accordance with precepts established by the Declaration of Helsinki in 1974.

2.1. Subjects

Male or female patients with type-2 diabetes mellitus aged more than 35 years old, who had random blood glucose level ≥200 mg/dL, fasting blood glucose level ≥126 mg/dL with or without dyslipidemia (total cholesterol >200 mg/dL and LDL >130 mg/dL) were recruited.

Table 1. Baseline data of the patients (n=29)

| Parameters            | AC                        | Glibenclamide          | p value |
|-----------------------|---------------------------|------------------------|---------|
| Demography            |                           |                        |         |
| Age (years)           | 53.12 ± 2.11              | 52.83 ± 2.26           | 0.929   |
| Weight (kg)           | 62.53 ± 2.46              | 57.21 ± 2.88           | 0.173   |
| BMI (kg/m²)           | 25.80 ± 1.05              | 24.70 ± 1.43           | 0.53    |
| Blood pressure        |                           |                        |         |
| Systole (mmHg)        | 126.56 ± 3.19             | 124.25 ± 5.54          | 0.704   |
| Diastole (mmHg)       | 81.25 ± 1.25              | 81.08 ± 2.77           | 0.953   |
| Diabetic parameters   |                           |                        |         |
| Fasting glucose (mg/dL)| 192.76 ± 14.59            | 250.33 ± 14.55         | 0.012*  |
| 2 hours PP glucose (mg/dL)| 295.35 ± 18.58         | 374.83 ± 28.63         | 0.022*  |
| HbA1C (%)             | 10.41 ± 0.64              | 11.86 ± 0.53           | 0.104   |
| Insulin (pmol/L)      | 56.89 ± 14.40             | 59.98 ± 17.83          | 0.894   |
| Haematology           |                           |                        |         |
| Haemoglobin (g/dL)    | 14.53 ± 0.44              | 14.52 ± 0.48           | 0.990   |
| Leukocyte (10³/mm³)   | 8.07 ± 0.72               | 7.81 ± 0.50            | 0.771   |
| Thrombocyte (10³/mm³) | 271.73 ± 21.45            | 267.33 ± 14.19         | 0.864   |
| Haematocrite (%)      | 42.92 ± 1.19              | 41.92 ± 1.19           | 0.558   |
| Blood coagulation parameters | 12.66 ± 0.16                | 12.73 ± 0.18           | 0.785   |
| PT (second)           | 29.17 ± 0.99              | 29.38 ± 0.72           | 0.857   |
| APTT (second)         | 0.94 ± 0.01               | 0.94 ± 0.01            | 0.902   |
| Lipid profile         |                           |                        |         |
| Total cholesterol (mg/dL)| 238.06 ± 8.25            | 235.67 ± 7.66          | 0.84    |
| HDL (mg/dL)           | 46.35 ± 2.23              | 44.25 ± 2.82           | 0.559   |
| LDL (mg/dL)           | 156.59 ± 8.66             | 150.45 ± 7.33          | 0.623   |
| Triglyceride (mg/dL)  | 162.82 ± 13.74            | 202.08 ± 33.35         | 0.294   |
| Liver function        |                           |                        |         |
| AST (U/L)             | 24.77 ± 2.57              | 23.83 ± 3.17           | 0.819   |
| ALT (U/L)             | 22.92 ± 3.28              | 27.42 ± 3.10           | 0.332   |
| Kidney function       |                           |                        |         |
| Ureum (mg/dL)         | 23.46 ± 1.77              | 27.08 ± 1.57           | 0.168   |
| Creatinine (mg/dL)    | 0.84 ± 0.05               | 0.78 ± 0.08            | 0.506   |

Note: All baseline data was measured on week 0; except blood coagulation parameters, liver function, kidney function, insulin and HbA1C were on week 2. * statistically significant difference (p<0.05)

The recruited patients must have never received oral hypoglycaemic agent or insulin prior this study and were willing to sign informed consent. Patients with type-1 diabetes mellitus or patients who previously received antidiabetic therapy, steroid or oral contraception; patients with renal and liver failure; patients with ketoacidosis complication, diabetic ulcer or gangrene; pregnant and lactating women, were excluded. Patients’ baseline characteristic was shown in Table 1.
2.2. Preparation of study drugs

Study drug (Allium Curcuma) was 400 mg capsule contains 200 mg of turmeric ethanolic extract and 200 mg of garlic aqueous extract. Standard drug was 5 mg Glibenclamide (produced by Indofarma, Pte. Ltd., Indonesia).

2.3. Study Design

Patients were assigned in a run-in phase for two weeks before the treatment. During run-in phase they were regularly doing diet and exercise. Demographic data, daily habits, such as cigarette smoking and alcohol consumption, medical history, and body mass index (BMI) were recorded at the first visit. After the run-in phase, patients were screened again for the blood glucose level and lipid profiles based on the inclusion criteria. Patients who failed to improve their blood glucose and lipid profile were divided subject into two groups, i.e. AC group and glibenclamide group. AC group received 2.4 g Allium Curcumacapsules administered astwo times three capsules per day (morning and evening) after meal. Glibenclamide group also received two times three capsules per day however at morning after breakfast they consumed one capsule contain 5 mg Glibenclamide plus two capsules contains placebo and at evening after dinner they consumed three placebo capsules. Subjects were still encouraged to continuediet and exercise.

Subjects were evaluated every two weeks for 12 weeks. Anamnesis and physical examination were done every visit including signs and symptoms, adverse events, any concomitant medication, and clinical improvement. Fasting blood glucose, 2 hours post-prandial (2HPP) blood glucose, lipid profile examination were done every two weeks from week-0 to week-14. HbA1C, fasting insulin, liver function, renal function, complete hematology, urine, and heart function examination were done in week-2 and week-14. Complete examinations were not done on week-0 because patients still had possibility to be excluded if blood glucose level became normal after 2 weeks run-in phase. Safety and quality of life evaluation were done by anamnesis on every visit. Study flowchart is shown in Fig. 1.

2.4. Measurement of blood glucose, lipid profile, and other haematological parameters

These following measurements were done during each visit: fasting blood glucose level, 2 hours post-prandial glucose level, HbA1C, fasting insulin level, lipid profile (total cholesterol, HDL, LDL and triglyceride); hematology parameters including hematocrit, hemoglobin, leukocyte and thrombocyte; PT, APTT and INR; renal function (ureum and creatinine); heart function (ECG); liver function (AST and ALT); symptoms and signs, adverse events, and physical examinations (body mass index and blood pressure). All clinical tests were done in Hasan Sadikin Hospital.

2.5. Statistical Method and Data Analysis

Data results were analyzed by general linear model repeated measure method to determine the differences in intra-group and intergroup from week 0 to week 14. Baseline characteristics were evaluated by independent t-test and proportion test was analyzed by chi square method.

Blood glucose profile and body mass index from week to week were analyzed per-protocol in order to reveal maximal therapeutic efficacy whereas for parameter analysis, supporting laboratory examination and adverse events were analyzed per intent-to-treat to get complete information.
3. Results and Discussion

3.1. Demographic Characteristic of the Patients

Thirty six type-2 diabetes mellitus patients were eligible and recruited for this study. After randomization, 17 patients were in AC group and 12 patients in glibenclamide group. Demographic data and laboratory parameters (Table 1) showed a comparable profile between both groups, except fasting blood glucose and 2HPP blood glucose levels (p<0.05).
3.2. Fasting Blood Glucose and 2 Hours Post-Prandial Blood Glucose Levels

The intra-group analysis of fasting blood glucose and 2 hours postprandial (2HP P) blood glucose levels during the study showed a significant decrease (p<0.05), but there was no significant difference in inter-group analysis (p=0.529) (Table 2, Fig. 2 and 3).

Table 2. Fasting and 2 hour post-prandial blood glucose levels on week 0 - 14.

| Week | Fasting Glucose Levels (mg/dL) | 2 HPP Blood Glucose (mg/dL) |
|------|-------------------------------|-----------------------------|
|      | AC (n=17)                     | Glibenclamide (n=12)        | AC (n=17)                     | Glibenclamide (n=12)        |
| 0    | 192.76 ± 14.59                | 250.33 ± 14.55              | 295.35 ± 18.58               | 374.83 ± 28.63              |
| 2    | 157.53 ± 8.51                 | 221.08 ± 18.03              | 231.29 ± 12.17               | 334.75 ± 27.53              |
| 4    | 154.41 ± 9.04                 | 133.25 ± 8.69               | 241.59 ± 15.40               | 204.75 ± 18.10              |
| 6    | 148.88 ± 10.52                | 130.33 ± 11.86              | 228.41 ± 14.82               | 212.25 ± 18.08              |
| 8    | 140.47 ± 11.69                | 121.67 ± 6.13               | 214.59 ± 12.99               | 210.67 ± 18.43              |
| 10   | 141.53 ± 12.19                | 128.92 ± 9.92               | 201.06 ± 18.14               | 208.45 ± 16.30              |
| 12   | 139.65 ± 12.01                | 143.75 ± 17.47              | 212.29 ± 14.47               | 246.60 ± 22.01              |
| 14   | 141.71 ± 9.67                 | 154.50 ± 24.06              | 204.35 ± 11.11               | 228.83 ± 21.71              |

| Intra-group p value | 0.028* | 0.003* | 0.019* | 0.020* |
| Inter-group p value | 0.529  | 0.061  |

Note: * statistically significant (p<0.05)

The blood glucose levels of the patients were also grouped, based on Indonesian Endocrinologist Association criteria, into poor, moderate, and good (Table 3). After 14 weeks treatment, percentages of patients in AC group with good and moderate 2HP P blood glucose profile increased from 0% of both categories to 11.8% (good) and 17.6% (moderate). While in Glibenclamide group, these percentages were also increasing from 0% in both categories to 8.3% (good) and 25% (moderate). The percentage of subjects with poor postprandial glucose in week 14 was equal in both groups, i.e. 70.6% in AC group versus 66.7% in Glibenclamide group. The percentage of patients in AC group with good and moderate fasting blood glucose level after 14 weeks of treatment increased from 0% to 5.9 % in good category and from 11.8% to 17.6 % in moderate category. In Glibenclamide group, these percentages increased from 0% to 16.7 % in good category and from 0% to 33.3 % in moderate category. The percentage of subject with poor fasting blood glucose levels after 14 weeks of treatment in AC group was 76.5% and 50% in the Glibenclamide group. Although it was observed a shift from poor 2HP P and fasting blood glucose levels into moderate or good categories, the differences were not statistically significant (Table 3). Therefore, AC treatment has shown a comparable result as Glibenclamide.

As shown in Figure 2 and 3, the decrease of fasting and 2HP P blood glucose levels in AC and Glibenclamide groups showed similar trend at week 4-14 of treatment. All sulphonylureas are well absorbed and their peak plasma concentration is reached in 2-4 hours\textsuperscript{11}. On the contrary, garlic and turmeric preparation decreases blood glucose slowly by increasing sensitivity to insulin\textsuperscript{12-14}. The mechanism of turmeric as antidiabetic is through PPAR-\(\gamma\) (peroxisome proliferator-activated receptor-\(\gamma\)) activation. Activated PPAR-\(\gamma\) regulates transcription of responsive gene to insulin that involve in producing, transporting and using glucose with the result are lower blood glucose and hyperinsulinemia\textsuperscript{15}.
Insulin is a regulator of glucose level. Garlic could reduce blood glucose by two mechanisms, i.e. by promoting insulin secretion and by increasing sensitivity to insulin. As cited El-Demerdash reported, garlic can combine with cysteine-like compound and enhance serum insulin. Garlic can also increase insulin secretion from pancreatic beta cells or release the bound-insulin. Despite the insulin secretagogue property of garlic, in this study the fasting insulin level was reduced in AC group. Fasting insulin level has been considered as one of insulin resistance surrogate markers. Insulin sensitivity and insulin secretion are inversely related, therefore when insulin sensitivity is increased then insulin secretion is reduced. Thus in this study, decrease of fasting insulin level in AC group indicated that Allium Curcuma might play a role in lowering insulin resistance.

### 3.3. HbA1C and Insulin

HbA1C and insulin examinations were done before and week 2 and week 14 after treatment. There was a decrease in insulin level at week 14 compared to week 2 in AC and Glibenclamide groups, but the decrease in AC group was greater than in Glibenclamide group (9.26 pmol/L versus 0.304 pmol/L) (Table 4).
Fig. 3. Two hours post-prandial blood glucose profile during study.

Table 4. HbA1C and insulin levels on week 2 and week 14

|                        | Week 2 X ± SEM | Week 14 X ± SEM | Delta X ± SEM | Intra-group p value | Inter-group p value |
|------------------------|----------------|-----------------|---------------|---------------------|---------------------|
| HbA1c (%)              |                |                 |               |                     |                     |
| AC (n=15)              | 10.41 ± 0.64   | 8.09 ± 0.37     | -2.33 ± 0.47  | 0.000*              | 0.368               |
| Glibenclamide (n=12)   | 11.86 ± 0.53   | 7.86 ± 0.45     | -4.00 ± 0.36  | 0.000*              |                     |
| Insulin (pmol/L)       |                |                 |               |                     |                     |
| AC (n=15)              | 56.89 ± 14.40  | 47.64 ± 12.34   | -9.26 ± 7.68  | 0.153               | 0.711               |
| Glibenclamide (n=12)   | 59.98 ± 17.83  | 59.68 ± 14.05   | -0.30 ± 10.13 | 0.675               |                     |

Note: * statistically significant difference (p<0.050)

We grouped the subjects based on criteria for HbA1C control for DM treatment into poor, moderate, and good categories. It was found that there was no significant difference between both treatment groups (p=0.368) (Table 5), although the decrease of HbA1C level in both AC and Glibenclamide groups before and week 14 after treatment were significant (p=0.000) (Table 4).

Allium and curcumin are also known to have antiglycation effect that prevents the progressive of type-2 DM complication\(^{14,18}\). Glycosylated hemoglobin (HbA1c) was measured in this study as a marker of long-term glycemic control and long-term complications of diabetes\(^ {17}\) and showed significant decreases in both AC and Glibenclamide groups. The HbA1c decrease did not significantly differ between two groups indicating a comparable glycemic control of Allium Curcuma and standard drug, Glibenclamide.

3.4. Body Mass Index (BMI)

Body mass index (BMI) is an indicator to determine overweight or obesity level on adults. To prevent chronic complications of DM, patients have also to control their nutrition status as depicted by the BMI. The body weight (Table 7) and BMI status (Table 6 and Figure 4) of patients in Glibenclamide group showed significant increases during the study (p=0.015 and p=0.034, respectively). On contrary, body weight and BMI decreased was observed
in AC group although the decrease of BMI was not statistically significant (p=0.068) while the body weight decrease was significant (p=0.006).

Table 5. Patient proportion based on HbA1C control criteria

| Criteria          | Week 0 | Week 14 |
|-------------------|--------|---------|
|                   | AC     | Glibenclamide | AC     | Glibenclamide |
| Good (< 6.5%)     | 0 (0%) | 0 (0%)    | 0 (0 %) | 3 (25%)       |
| Moderate (6.5-8%) | 3 (20%)| 0 (0%)    | 8 (53.3 %) | 5 (41.7%) |
| Bad (>8%)         | 12 (80%)| 12 (100%) | 7 (46.7%) | 4 (33.3%)     |

Inter-group p value 0.156 0.121

Table 6. Body mass index profile

| Week | BMI (kg/m²) |
|------|-------------|
|      | AC (n=17)   | Glibenclamide (n=12) |
|      |             |                      |
| 0    | 25.80 ± 1.05 | 24.70 ± 1.43         |
| 2    | 25.39 ± 1.01 | 24.65 ± 1.38         |
| 4    | 25.55 ± 1.01 | 25.19 ± 1.43         |
| 6    | 25.48 ± 1.05 | 25.46 ± 1.47         |
| 8    | 25.18 ± 0.95 | 25.52 ± 1.47         |
| 10   | 25.43 ± 1.03 | 25.48 ± 1.41         |
| 12   | 25.27 ± 1.00 | 25.60 ± 1.37         |
| 14   | 24.77 ± 1.00 | 25.54 ± 1.40         |

Inter-group p value 0.068 0.034* 0.705

Note: * statistically significant difference

Increased body weight and BMI in Glibenclamide group was possibly because increase of insulin secretion by Glibenclamide. Higher insulin level will increase glucose transfer to cells and prevent lipolysis which leads to more body fat and eventually higher body weight that in turn is related to insulin resistance. Insulin sensitivity will decrease 30-40% in people with 35-40% increase of body weight. Obesity will also increase the risk of cardiovascular complication. Interestingly, Allium Curcuma administration did not increase body weight. Even Longquan Yu and Hiramitsu Suzuki reported that feeding mice with food containing 1% allium or curcuma for 90 days will lower body weight compared to baseline data. Curcumin supplementation could increase fatty acid oxidation and decrease fatty acid esterification which led to adipose tissue catabolism. Loss of body weight would in turn decrease the insulin resistance.

3.5. Hematology Parameters

Blood profiles in both AC and Glibenclamide group were in normal range. Glibenclamide nor extract combination of AC did not alter hematology profile. The ALT and AST in AC group showed a significant decreased (p=0.048 and p=0.007, respectively), while it was observed slight increase of ALT and AST levels in Glibenclamide group (p=0.091 and p=0.228, respectively). The levels of ureum and creatinin showed slight increases but there were no significant differences between both AC and Glibenclamide group (p>0.05) and there were still in normal limits (Table 7).
3.6. Other Supporting Parameters

Lipid profiles of patients in AC group showed a significant total cholesterol decrease (p=0.045) and also slight decreases of triglyceride and LDL levels, while in Glibenclamide group total cholesterol and LDL levels decreased significantly (p<0.001). The HDL levels in both groups showed no changes. Observation on blood pressure showed that there were no significant changes on blood pressure profile of AC or Glibenclamide treatment groups during the study (Table 7).

Table 7. Other supporting parameters among ITT patients

| Parameters                  | Treatment Group | n   | Before treatment | After treatment | p      | p*     |
|-----------------------------|-----------------|-----|------------------|----------------|--------|--------|
| Demography                  |                 |     |                  |                |        |        |
| Weight (kg)                 | AC              | 20  | 61.85 ± 2.12     | 60.33 ± 1.99   | 0.008* | 0.269  |
|                             | Glibenclamide   | 16  | 56.59 ± 2.50     | 58.38 ± 2.59   | 0.015* | 0.224  |
| Systole (mmHg)              | AC              | 18  | 128.06 ± 3.86    | 126.06 ± 3.43  | 0.545  | 0.256  |
|                             | Glibenclamide   | 16  | 120.69 ± 4.50    | 121.56 ± 3.91  | 0.855  | 0.555  |
| Diastole (mmHg)             | AC              | 18  | 81.67 ± 1.21     | 81.06 ± 2.12   | 0.77   | 0.173  |
|                             | Glibenclamide   | 16  | 78.94 ± 2.34     | 77.75 ± 1.75   | 0.628  | 0.032  |
| Hematology                  |                 |     |                  |                |        |        |
| Hemoglobin (g/dL)           | AC              | 13  | 14.26 ± 0.48     | 13.48 ± 0.46   | 0.109  | 0.614  |
|                             | Glibenclamide   | 15  | 14.35 ± 0.40     | 13.99 ± 0.58   | 0.509  | 0.106  |
| Leukocyte (/mm³)            | AC              | 13  | 8.06 ± 0.66      | 7.91 ± 0.50    | 0.698  | 0.781  |
|                             | Glibenclamide   | 15  | 7.75 ± 0.44      | 7.79 ± 0.68    | 0.916  | 0.916  |
| Thrombocyte (/mm³)          | AC              | 12  | 277.83 ± 20.51   | 262.83 ± 12.56 | 0.213  | 0.808  |
|                             | Glibenclamide   | 15  | 270.20 ± 12.16   | 259.93 ± 19.31 | 0.513  | 0.513  |
| Hematocrit (%)              | AC              | 13  | 42.62 ± 1.14     | 40.62 ± 1.20   | 0.101  | 0.991  |
|                             | Glibenclamide   | 15  | 41.73 ± 0.97     | 41.53 ± 1.78   | 0.901  | 0.901  |
| Lipid Profile               |                 |     |                  |                |        |        |
| Total Cholesterol (mg/dL)   | AC              | 20  | 240.15 ± 8.01    | 226.65 ± 7.95  | 0.045* | 0.004  |
|                             | Glibenclamide   | 16  | 234.38 ± 6.16    | 175.63 ± 6.45  | 0.000* | 0.000  |
| HDL (mg/dL)                 | AC              | 20  | 48.15 ± 2.45     | 48.35 ± 2.37   | 0.94   | 0.104  |
### Parameters

| Treatment Group | n   | Before treatment | After treatment | p<sup>a</sup> | p<sup>b</sup> |
|----------------|-----|-----------------|----------------|-------------|-------------|
| LDL (mg/dL)    |     |                 |                |             |             |
| Glibenclamide  | 16  | 43.75 ± 2.36    | 43.00 ± 2.37   | 0.756       |             |
| AC             | 20  | 151.70 ± 9.31   | 148.30 ± 6.71  | 0.687       | 0.011       |
| Glibenclamide  | 15  | 152.07 ± 5.87   | 96.60 ± 8.31   | 0.000*      |             |
| Triglyceride (mg/dL) |  |           |                |             |             |
| AC             | 20  | 179.10 ± 9.31   | 149.75 ± 12.00 | 0.195       | 0.3         |
| Glibenclamide  | 16  | 209.56 ± 30.64  | 186.25 ± 40.11 | 0.508       |             |

### Liver Function

| Treatment Group | n   | Before treatment | After treatment | p<sup>a</sup> | p<sup>b</sup> |
|----------------|-----|-----------------|----------------|-------------|-------------|
| AST (U/L)      | AC  | 24.43 ± 2.40    | 18.43 ± 1.22   | 0.007*      | 0.128       |
| Glibenclamide  | 16  | 23.06 ± 2.55    | 31.88 ± 5.20   | 0.228       |             |
| ALT (U/L)      | AC  | 22.50 ± 3.07    | 16.50 ± 1.56   | 0.048*      | 0.045*      |
| Glibenclamide  | 16  | 27.94 ± 3.04    | 43.38 ± 12.33  | 0.091       |             |

### Kidney Function

| Treatment Group | n   | Before treatment | After treatment | p<sup>a</sup> | p<sup>b</sup> |
|----------------|-----|-----------------|----------------|-------------|-------------|
| Ureum (mg/dL)  | AC  | 24.79 ± 2.10    | 27.71 ± 1.82   | 0.218       | 0.503       |
| Glibenclamide  | 16  | 26.56 ± 1.39    | 28.56 ± 1.73   | 0.37        |             |
| Creatinine (mg/dL) | |           |                |             |             |
| AC             | 15  | 0.85 ± 0.05     | 0.94 ± 0.11    | 0.441       | 0.481       |
| Glibenclamide  | 16  | 0.80 ± 0.06     | 0.86 ± 0.07    | 0.036*      |             |

### Clotting Blood Function

| Treatment Group | n   | Before treatment | After treatment | p<sup>a</sup> | p<sup>b</sup> |
|----------------|-----|-----------------|----------------|-------------|-------------|
| PT (second)    | AC  | 12.66 ± 0.16    | 12.82 ± 0.18   | 0.24        | 0.76        |
| Glibenclamide  | 13  | 12.74 ± 0.17    | 12.62 ± 0.16   | 0.577       |             |
| APTT (second)  | AC  | 29.17 ± 0.99    | 29.79 ± 0.66   | 0.393       | 0.642       |
| Glibenclamide  | 13  | 29.14 ± 0.70    | 30.78 ± 0.87   | 0.077       |             |
| INR            | AC  | 0.94 ± 0.01     | 0.95 ± 0.02    | 0.434       | 0.538       |
| Glibenclamide  | 13  | 0.94 ± 0.01     | 0.93 ± 0.01    | 0.65        |             |

Note: p<sup>a</sup>: intra-group p value; p<sup>b</sup>: inter-group p value. Baseline data is data on week 0, except blood coagulation function values, liver function, insulin and HbA1C were data on week 2. *: statistically significant difference (p<0.050). The decrease of lipid level on Glibenclamide group was caused by simvastatin drug used by 12 out of 16 subjects.

### 3.7. Adverse Events

Adverse events were considered to be related to Allium Curcuma or Glibenclamide when they have been reported elsewhere (Table 8). Seven out of 20 patients (35%) in AC group did not have any complaints at all during the trial. Few patients receiving AC drug complained about gastrointestinal disorders such as burn sensation on abdominal, gastric pain. Unpleasant breath and body odor that usually are the major complaints of garlic consuming were not reported in this study. It seemed that allium’s strong scent was covered by curcuma. In contrast, 15 out of 16 patients (93.8%) in Glibenclamide group have experienced adverse events. There were also not reported any drug interactions with the drugs consumed during the study by patients in AC group including analgesic (acetaminophen), anti-inflammatory, ACE inhibitor, and vitamins.

Lower AST and ALT values in the AC group might be due to hepatoprotector effect of *Allium Curcuma*. Study in animal showed that allicin in allium works as hepatoprotector and decrease AST and ALT levels in mice that had been induced by galactosamine<sup>21</sup> or by streptozotocin<sup>22</sup>. The hepatoprotector effect might also be related with antioxidant effect of garlic and turmeric<sup>19,23</sup>. It was reported that the S-allylcysteinsulfoxide contained in garlic could maintain the free radical levels<sup>16</sup> and curcumin could inhibit lipid peroxidation in diabetic animal model<sup>18</sup>.

The improvement on clinical symptoms in AC and Glibenclamide group was basically equal. When blood glucose levels were already within normal range, the diabetic classical symptoms were improved or even disappeared. Five subjects on AC group reported improvement of neuropathy symptoms such as paresthesia and tingling, and only 1 of 8 patients in Glibenclamide group was reporting the improvement. Improvement of polyuria was reported by 4 of 5 patients in AC group, and 1 of 5 patients in Glibenclamide group.
Table 8. Adverse events reported during the study

| Adverse events                     | AC treatment (n=20) | Glibenclamide treatment (n=16) |
|-----------------------------------|---------------------|--------------------------------|
|                                   | Grade   | N (%) | Relationship to treatment | Grade | N (%) | Relationship to treatment |
| Gastrointestinal tract            |         |       |                         |        |       |                         |
| Constipation                      | Mild     | 2(10) | Not related             | -      | -     | -                         |
| Nausea                            | Mild     | 2(10) | Not related        | Mild   | 1(6.3) | Possibly related          |
| Diarrhea                          | Mild     | 1(5)  | Not related           | Mild   | 1(6.3) | Not related             |
| Burn sensation on abdomen         | Mild-moderate | 2(10) | Possibly related | -      | -     | -                         |
| Gastric discomfort                | Mild     | 1(5)  | Possibly related      | Mild   | 1(6.3) | Possibly related          |
| Respiratory tract                 |         |       |                         |        |       |                         |
| Cough                             | Mild     | 2(10) | Not related           | Mild   | 1(6.3) | Not related             |
| Flu                               | Mild     | 2(10) | Not related           | Mild   | 1(6.3) | Not related             |
| Allergic reactions                |         |       |                         |        |       |                         |
| Itchy                             | Mild     | 2(10) | Not related           | Mild   | 1(6.3) | Not related             |
| Dyspnea (asthma)                  | Mild     | 1(5)  | Not related           | -      | -     | -                         |
| Central nervous system (CNS)      |         |       |                         |        |       |                         |
| Dizziness                         | Mild     | 3(15) | Not related           | Mild-moderate | 5(31.2) | Possibly related         |
| Musculoskeletal                   |         |       |                         |        |       |                         |
| Shoulder pain                     | Mild     | 1(5)  | Not related           | -      | -     | -                         |
| Tiredness                         | Mild     | 1(5)  | Not related           | -      | -     | -                         |
| Stiffness                         | Mild     | 3(15) | Not related           | -      | -     | -                         |
| Bone/muscle pain                  | Mild     | 1(5)  | Not related           | Mild-moderate | 2(12.5) | Possibly related         |
| Ocular system                     |         |       |                         |        |       |                         |
| Blurred vision                    | -       | -     | -                       | Mild-moderate | 2(12.5) | Not related             |
| Others                            |         |       |                         |        |       |                         |
| Urinary incontinence              | Mild     | 1(5)  | Not related           | -      | -     | -                         |
| Increased creatinine              | Moderate | 1(5)  | Not related           | -      | -     | -                         |
| Swollen feet                      | -       | -     | -                       | Mild   | 1(6.3) | Not related             |
| Hypoglycemia                      | -       | -     | -                       | Moderate | 2(12.5) | Related               |
| Palpitation                       | -       | -     | -                       | Mild   | 1(6.3) | Not related             |
| Increased ALT                     | -       | -     | -                       | Moderate | 2(12.5) | Not related         |

Notes: N = number of subjects

The increasing use of herbal medicines has raised the concern about the potency of herbal-drug interactions. Concurrent use of herbal remedies may augment or reduce the effect of several conventional drugs. Concomitant use of garlic and turmeric with anticoagulant/anti-platelet agents may increase bleeding tendency. Despite possible pharmacokinetic or pharmacodynamic interactions between Allium Curcuma and concurrent conventional drugs, including acetaminophen, aspirin, ACE inhibitor, theophylline, there was no observed symptom indicating drug interactions during this study. This suggested that the possible herbal-drug interactions of Allium Curcuma may not have major clinical significance, although a more detail data collection should be performed in the future to identify symptoms caused by toxicity or by the interactions.

4. Conclusion

This study demonstrated that the effect Allium Curcuma was comparable to Glibenclamide on decreasing blood glucose in type 2 DM patients. The administration of Allium Curcuma was well-tolerated and no drug interaction was reported during the trial.
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