HYPOGLYCEMIC EFFECT OF *TINOSPORA CRISPA* DRY POWDER IN OUTPATIENTS WITH METABOLIC SYNDROME AT KING CHULALONGKORN MEMORIAL HOSPITAL

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ABSTRACT: To determine the hypoglycemic effect of *Tinospora crispa* dry powder in patients with metabolic syndrome, a randomized double–blind placebo-controlled, crossover design was conducted at the outpatient internal medicine clinic at King Chulalongkorn Memorial Hospital during October 2008 to March 2009. Thirty-six patients who met the NCEP III criteria guideline for metabolic syndrome were included and randomly assigned to receive 250 mg *T. crispa* dry powder capsule or placebo twice a day for 2-months treatment period. It was found that patients who received *T. crispa* dry powder had significantly decreased fasting blood glucose level from the baseline (4.03 ± 11.35 mg/dl, p=0.027, median=4.00 mg/dl, n=36). Patients who received *T. crispa* for the first 2 months also had significantly reduced fasting blood glucose level which is statistically different from the baseline (6.29 ± 10.47 mg/dl, p=0.007, median=8.00 mg/dl, n=24). Adherence was assesses by the pill count method. The results showed that 91.6% of patients adhered to *T. crispa*. Seventy-two percent of the patients did not have significantly different calorie intake between the *T. crispa* and placebo groups. Also statistically, there was no significant difference in body weights between the T. crispa and placebo groups during the study period (p=0.920). An elevation of more than 3 times baseline levels of aspartate aminotransferase and alanine aminotransferase was found in 16.7% of the samples.

Keywords: *Tinospora crispa* dry powder, hypoglycemic effect, metabolic syndrome

INTRODUCTION: Metabolic syndrome is a constellation of interrelated risk factors of metabolic origin metabolic risk factors that appear to directly promote the development of atherosclerotic cardiovascular disease (ASCVD)[1)]. Patients with metabolic syndrome also are at increased risk for developing type 2 diabetes mellitus. The prevalence of metabolic syndrome in the Thai population using the National Cholesterol Education Program Adult Treatment Panel III criteria (NCEP III criteria)[2)] was 15-20%[3-6)] as high as those observed in developed countries[3)]. The sooner the diagnosis and management of metabolic syndrome the lower the risk of cardiovascular disease, the American Heart Association (AHA 2005)[2)] suggested the primary goal of clinical management in individuals with metabolic syndrome i.e., first-line therapy should be directed towards the major risk factors: LDL above normal level, hypertension, and diabetes. Prevention of type 2 diabetes mellitus is another important goal when it is not present in a person with metabolic syndrome. For individuals with established diabetes, risk factor management (obesity, physical inactivity, and atherogenic diet) must be intensified to diminish their higher risk for ASCVD. Although many studies have investigated that hypoglycemic drug i.e., metformin, thiazolidinediones and acarbose will lower the risk for diabetes mellitus in people with impair fasting glucose (IFG) or impaired glucose tolerance (IGT), except for a preliminary trial with acarbose, no clinical trial evidence is yet available to document that oral hypoglycemic agents will lessen risks for cardiovascular events. Moreover, neither metformin nor thiazolidinediones are recommended in this treatment solely for the purpose of preventing diabetes because their cost-effectiveness and long-term safety have not been documented[2)]. Another way for reducing blood glucose in metabolic syndrome patients was herbal medicine. *Tinospora crispa* or Borapet was a Thai traditional herbal long time ago. Ancient Thai medics widely used *T. crispa*

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stems as antipyretic agent[7] cardiotonic agent[8] and oral hypoglycemic agent[9]. Many studies have found that *T. crispa* reduced blood glucose by increasing insulin secretion[10-12]. Kongkathip *et al.*, has revealed that 0.125-0.5 g/kg (rat weight) *T. crispa* water extracts reduced blood glucose in diabetic rats, the same as 5 mg/kg (rat weight) glibenclamide. 0.125-0.5 g/kg (rat weight) *T. crispa* water extracts reduced 39.7-44.8% of blood glucose in 90 and/or 120 minute after oral glucose administration while glibenclamide reduced by 56.6-56.9%. Recommended *T. crispa* dry powder dose was 7.5-30 mg/kg (body weight)day had hypoglycemic effect like that of 5 mg/day glibenclamide[13]. There were 3 substances from *T. crispa* water extracts purification: substance A (in the process for patent application number 080 1005093), sodium nitrate and potassium lactate[14]. Kongkathip *et al.,* also found that 0.5 mg/kg (weight rat) substance A, sodium nitrate and potassium lactate reduced rat blood glucose 16.2%, 14.4%, and 6%, respectively after 120 minute oral glucose. In addition, 0.25 and 0.5 mg/kg(rat weight) reduced blood glucose in diabetic rats the same as 5 mg/kg glibenclamide. In this study we used substance A as an active ingredient (marker) for qualifying *T. crispa* dry powder. For studying hypoglycemic effect of *T. crispa* dry powder, we included metabolic syndrome patients who did not use oral hypoglycemic agents, to determine the quality of *T. crispa* dry powder and compared fasting blood glucose in the same person after receiving *T. crispa* dry powder and placebo. We also detected enzyme aspartate aminotransferase (AST) and alanine amino-transferase (ALT) every 2 months. The purpose of this study was to compare the hypoglycemic effect of 250 mg/capsule *T. crispa* by taking orally one dry powder capsule 30 minutes before meal twice daily and placebo in patients with metabolic syndrome.

DEFINITIONS:

Hypoglycemic effect

The ability of 250 mg/capsule *T. crispa* dry powder by taking orally 1 capsule 30 minutes before meal twice daily for 2 months to reduce fasting blood glucose compared to the placebo when administered in the same person.

Metabolic syndrome patients:

Patients who met NCEP III criteria (positive for any 3 of the 5 criteria) constitute diagnosis of metabolic syndrome

(1) Elevated waist circumference :
≥ 90 cm (36 inches) in men,
≥ 80 cm (32 inches) in women
(2) Elevated triglycerides ≥ 150 mg/dl
or on drug treatment for elevated triglycerides
(3) Reduced HDL < 40 mg/dl in men,
< 50 mg/dl in women
or on drug treatment for reduced HDL
(4) Elevated blood pressure ≥ 130/85 mmHg
or on antihypertensive drug treatment in a patient with a history of hypertension
(5) Elevated fasting glucose:
fasting blood glucose ≥ 100 mg/dl

MATERIALS AND METHODS: A randomized double–blind placebo-controlled, cross-over design was conducted at the outpatient internal medicine clinic of the King Chulalongkorn Memorial Hospital during October 2008 to March 2009. The experimental protocol has been approved by the ethics committee of Faculty of medicine Chulalongkorn University. A sample size was estimated according to the pilot study[15] that mean difference of fasting blood glucose between receiving *T.crispa* (1.26% dry weight substance A) and placebo was 10 mg/dl with type I error 5% and type II error 10%.

Thirty-six patients who met the NCEP III criteria guideline for metabolic syndrome and did not use oral hypoglycemic drug were selected and randomly assigned to receive 250 mg *T. crispa* dry powder capsule or placebo twice a day for 2-months treatment period. The quality of the *T. crispa* dry powder was confirmed by Kongkathip *et al.,* of the .Department of Chemistry, Faculty of Science, Kasetsart University, Bangkok. They found that *T. crispa* dry powder consists of 0.98% dry weight substance A (marker).

Descriptive statistics was used to describe basic demographic characteristics and inferential statistics was used to compare fasting blood glucose after the 2-months study *T. crispa* and placebo. Kolmogorov-Smirnov Test was used to

Table 1 Demographic characteristics of metabolic syndrome patients (n=36)

Variables	Patients (%)
Sex	
men	14 (38.9)
women	22 (61.1)
Age (year)	
41-50	3 (8.3)
51-60	8 (22.2)
61-70	15 (41.7)
71-80	7 (19.4)
≥ 81	3 (8.3)
Body mass index (kg/m^2)	
18.5-22.9	5 (13.9)
23.0-24.9	6 (16.7)
25.0-29.9	15 (41.7)
≥ 30.0	10 (27.8)
Waist circumference (person)	
normal	7 (19.4)
elevated*	29 (80.6)
Fasting blood glucose (mg/dl)	
100-109	14 (38.9)
≥ 110	22 (61.1)
Hemoglobin A_1C (%)	
4.5-5.7	7 (19.4)
5.8-6.9	25 (69.4)
7.0-8.3	4 (11.1)
Total cholesterol (mg/dl)	
< 200	23 (63.9)
≥ 200	13 (36.1)
Triglyceride (mg/dl)	
normal	17 (47.2)
elevated**	19 (52.8)
HDL (mg/dl)	
normal	16 (44.4)
reduced***	20 (55.6)
LDL (mg/dl)	
< 100	12 (33.3)
100-149	19 (52.8)
≥ 150	5 (13.9)
AST (unit/l)	
< 30	33 (91.7)
30-35	3 (8.3)
ALT (unit/l)	
< 30	25 (69.4)
30-38	11 (30.6)
Serum creatinine (mg/dl)	
< 1	25 (69.4)
1-1.2	11 (30.6)
Hypertension (person)	
yes	32 (88.9)
no	4 (11.1)
Dyslipidemia (person)	
yes	26 (72.2)
no	10 (27.8)
Cardiovascular disease (person)	
yes	8 (22.2)
no	28 (77.8)
Met NCEP III criteria (person)	
3 risk factors	6 (16.7)
4 risk factors	13 (36.1)
5 risk factors	17 (47.2)

* elevated waist cir.:
≥ 90 cm (36 inches) in men, ≥80 cm (32 inches in women
** elevated triglyceride:
elevated ≥ 150 mg/dl, normal < 150 mg/dl
*** reduced HDL: < 40 mgdl in men, < 50 mgdl in women

test the distribution of data. For normal distribution data, Paired t Test was used to compare data after treatment with *T. crispa* and placebo. In the case of non normal distribution, Wilcoxon Signed-Ranks Test was used for comparison. Adverse reaction monitoring was conducted by telephone monitoring during the study period and aspartate aminotransferase and alanine aminotransferase level was detected at baseline and after receiving *T.crispa* and placebo.

RESULTS AND DISCUSSION:

Demographic characteristics

Thirty-six patients who met the NCEP III criteria guideline for metabolic syndrome and did not use oral hypoglycemic drug had average age of 63.97 ± 9.86 years, average fasting blood glucose 116.08 ± 10.72 mg/dl. Table 1 shows the demographic characteristics of samples.

Comparison of baseline FBG, HbA_1C, TC, TG, HDL, LDL after 2 months receiving *T. crispa* (n=36).

Metabolic syndrome patients who met the NCEP III criteria guideline and did not use oral hypoglycemic drug were included and the baseline FBG, HbA_1C, TC, TG, HDL and LDL were determined. The subjects were randomly assigned to receive 250 mg *T. crispa* dry powder capsule or placebo twice a day for the 2 months treatment period. We repeated FBG, HbA_1C, TC, TG, HDL and LDL at 2^{nd} and 4^{th} months. Treatment was exchanged between in metabolic syndrome patients who finished the 2 months study period. Group 1 who were randomly assigned to receive 250 mg *T. crispa* dry powder capsule were given placebo while group 2 who took placebo were given *T.crispa* dry powder capsule.

As shown in Table 2, it was found that fasting blood glucose and triglyceride after *T.* crispa treatment for 2 months, were reduced and were of statistically significant difference from the baseline at α=0.05 (p=0.027 and p=0.017 respectively) and HDL after 2 months of *T.* crispa treatment were increased statistically different from the baseline at α=0.05 (p=0.024). This results are similar to those

Table 2 Comparison of baseline FBG, HbA_1C, TC, TG, HDL, LDL and after 2 months receiving *T. crispa* (n=36)

Variables	Baseline (n=36)	After 2 months *T. crispa* (n=36)	Average reduction (95 %CI, p-value)
FBG	116.08 ±1 0.72	112.06 ± 13.98	4.03 (0.19, 7.87) p=0.027*[a]
HbA_1C	6.33 ± 0.64	6.20 ± 0.55	0.13 (-0.03, 0.29) p=0.102 [a]
TC	190.22 ± 34.55	189.31 ± 33.91	0.92 (-11.05,12.89) p=0.877 [b]
TG	159.03 ± 66.69	135.78 ± 65.59	23.25 (4.37, 42.13) p=0.017*[b]
HDL	45.75 ± 8.60	48.03 ± 9.95	-2.28 (-4.24, -0.32) p=0.024*[b]
LDL	113.38 ± 31.82	114.11 ± 30.82	-0.73 (-11.83,10.36) p=0.894 [b]

* statistically significant difference at $p < 0.05$ [a] Wilcoxon Signed-Ranks Test [b] Paired t Test

Table 3 Comparing FBG, HbA_1C, TC, TG, HDL, LDL after 2 months receiving *T. crispa* and placebo (n=36)

Variables	After 2 months *T. crispa* (n=36)	After 2 months placebo (n=36)	Average reduction (95 %CI, p-value)
FBG	112.06 ± 13.98	111.69 ± 13.16	0.36 (-2.61, 3.34) p=0.807[a]
HbA_1C	6.20 ± 0.55	6.21 ± 0.59	-0.02 (-0.17, 0.14) p=0.829[b]
TC	189.31 ± 33.91	192.00 ± 33.06	-2.69 (-10.28, 4.89) p=0.475 [a]
TG	135.78 ± 65.59	129.11 ± 58.58	6.67 (-7.27, 20.60) p=0.338 [b]
HDL	48.03 ± 9.95	47.75 ± 11.84	0.28 (-1.99, 2.55) p=0.805 [b]
LDL	114.11 ± 30.82	118.49 ± 27.13	-4.38 (-10.95, 2.19) p=0.185 [a]

[a] Paired t Test [b] Wilcoxon Signed-Ranks Test

reported by Oomchoo Saiphet[16] that *T. crispa* water extracts reduced blood glucose and increased HDL in rat signi-ficantly compared with the control group. In addition, these findings agree with the previous study by Kongkathip *et al.*[13] that 0.125-0.5 g/kg (rat weight) *T. crispa* water extracts reduced 39.7-44.8% blood glucose in diabetic rat after 90 and/or 120 minute oral glucose dose. Although fasting blood glucose was reduced significantly after receiving *T. crispa* dry powder but the average difference in blood glucose (4 mg/dl) was less than that reported by Kongkathip *et al.*[13]. It is possible that *T. crispa* dry powder may have less hypoglycemic effect than *T. crispa* water extracts. The average difference in blood glucose (4 mg/dl) was also less than that of the pilot study[16] that *T. crispa* dry powder reduced fasting blood glucose to 10 mg/dl compared with the placebo in patients who met metabolic syndrome criteria.

There may be a suitable quantity of marker (substance A) that might effect the reduction of blood glucose. Because 0.98% dry weight substance A in this study was less than 1.26% dry weight substance A in the pilot study. Four mg/dl reduction of blood glucose was not clinically significant compared with the effects of hypoglycemic drugs[17]. Duration of treatment period (2 months) may be another cause that effected reduction of blood glucose. In addition, it is probable that the smallest *T. crispa* dry powder recommended dose (500 mg/day) also effected reduction of blood glucose.

Comparing FBG, HbA_1C, TC, TG, HDL, LDL after 2 months *T. crispa* and placebo treatment (n=36)

Table 3 shows that the average fasting blood glucose, triglyceride and HDL show no statistically significant differences between the *T. crispa* and placebo groups within the 2-months test period. These results are consistent with previous results that *T. crispa* significantly reduced fasting blood glucose as well as triglyceride and increased HDL with significant difference from the baseline. The adherence trait might effect fasting blood glucose, triglyceride and HDL because group 1 subjects who received *T. crispa* in the first 2-months exhibited the adherence trait more than the group 2 patients who received *T. crispa* in the second 2-months trial. Comparing fasting blood glucose, hemoglobin A_1C, total cholesterol, triglyceride, HDL, and LDL of group 1 and group 2 was shown in Table 4 and Table 5 respectively.

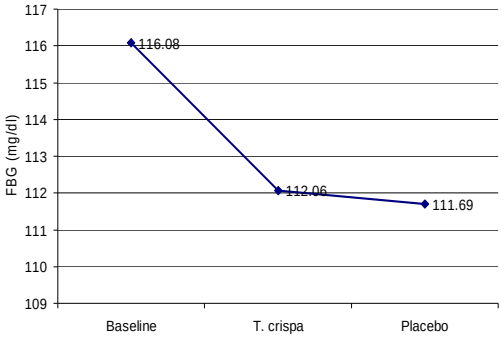

Figure 1 Average fasting blood glucose at baseline, after 2-months receiving *T. crispa* and after 2-months receiving placebo (n=36)

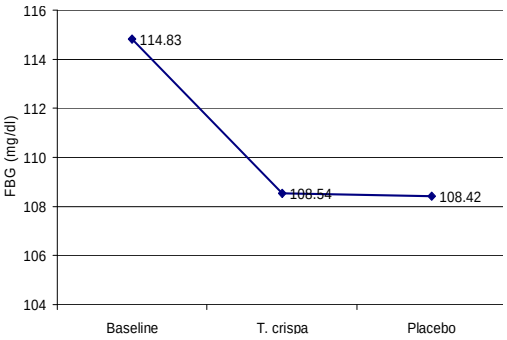

Figure 2 Average fasting blood glucose at baseline, after 2 months receiving T. crispa and after 2 months receiving placebo in group 1 (n=24)

Table 4 Comparing FBG, HbA_1C, TC, TG, HDL, LDL at baseline, after 2-months receiving *T. crispa* and placebo in group 1 (n=24)

Variables	**FBG**	**Average difference (95% CI, p-value)**
Baseline	114.83 ± 10.67	6.29 ± 10.47 (1.87, 10.71) p=0.007*[a]
After *T. crispa*	108.54 ± 12.56	
After placebo	108.42 ± 12.59	0.12 ± 9.10 (-3.72, 3.97) p=0.947[a]
Variables	**HbA_1C**	**Average difference (95% CI, p-value)**
Baseline	6.22 ± 0.52	0.13 ± 0.44 (-0.05, 0.32) p=0.151[a]
After *T. crispa*	6.09 ± 0.45	
After placebo	6.28 ± 0.56	-0.19 ± 0.41 (-0.36, -0.01) p=0.051[b]
Variables	**TC**	**Average difference (95% CI, p-value)**
Baseline	182.96 ± 34.29	-4.25 ± 34.81 (-18.95, 10.45) p=0.556[a]
After *T. crispa*	187.21 ± 31.64	
After placebo	186.13 ± 32.21	1.08 ± 24.16 (-9.12, 11.29) p=0.828[a]
Variables	**TG**	**Average difference (95% CI, p-value)**
Baseline	159.29 ± 74.06	21.62 ± 49.24 (0.83, 42.42) p=0.026*[b]
After *T. crispa*	137.67 ± 69.14	
After placebo	133.79 ± 68.04	3.88 ± 42.56 (-14.10, 21.85) p=0.659[b]
Variables	**HDL**	**Average difference (95% CI, p-value)**
Baseline	46.96 ± 9.18	-2.08 ± 5.97 (-4.60, 0.44) p=0.101[a]
After *T. crispa*	49.04 ± 10.06	
After placebo	47.08 ± 10.48	1.96 ± 5.01 (-0.16, 4.07) p=0.068[a]
Variables	**LDL**	**Average difference (95% CI, p-value)**
Baseline	106.11 ± 29.89	-4.52 ± 33.90 (-18.83, 9.80) p=0.520[a]
After *T. crispa*	110.63 ± 29.36	
After placebo	112.31 ± 24.60	-1.68 ± 22.17 (-11.05, 7.68) p=0.713[a]

***** statistically significant difference at $p < 0.05$ [a] Paired t Test [b] Wilcoxon Signed-Ranks Test

Figure 1 shows that after 2-months receiving *T. crispa* fasting blood glucose was reduced statistically significant from the baseline at α= 0.05. Average reduced 4.03 ± 11.35 mg/dl, 95% CI 0.19 to 7.87, median 4.00 mg/dl, p=0.027. But there was no significant difference between 2-months of receiving *T. crispa* and 2-months receiving placebo at α=0.05 (111.69 ± 13.16 mg/dl compared with 112.06 ± 13.98 mg/dl, p= 0.807). There may be adherence trait that might effect fasting blood glucose differently between group 1 and group 2 as presented in Table 6.

Comparison of FBG, HbA_1C, TC, TG, HDL, LDL with baseline, after 2-months receiving *T. crispa* and placebo in group 1 (n=24)

Table 4 and Figure 2 compare average fasting blood glucose with baseline. *T. crispa* fasting blood glucose was reduced statistically significant from the baseline at α=0.05 (108.54 ±1 2.56 mg/dl compared with 114.83 ± 10.67 mg/dl, average reduction = 6.29 ± 10.47 mg/dl, 95%CI 1.87 to 10.71, median 8.00 mg/dl, p=0.007). Reducing blood glucose in group 1 was higher than in all of the samples. But there was no significant

Table 5 Comparing FBG, HbA_1C, TC, TG, HDL, LDL at baseline, after 2 months receiving *T. crispa* and placebo in group 2 (n=12)

Variables	**FBG**	**Average difference (95% CI, p-value)**
Baseline	118.58 ± 10.83	0.33 ± 8.33 (-4.96, 5.62) p=0.892 [a]
After placebo	118.25 ± 12.22	
After *T. crispa*	119.08 ± 14.54	-0.83 ± 8.53 (-4.58, 6.25) p=0.741[a]
Variables	**HbA_1C**	**Average difference (95% CI, p-value)**
Baseline	6.54 ± 0.82	0.45 ± 0.52 (0.12, 0.78) p=0.012* [a]
After placebo	6.09 ± 0.67	
After *T. crispa*	6.42 ± 0.68	-0.32 ± 0.36 (0.10, 0.55) p=0.010* [a]
Variables	**TC**	**Average difference (95% CI, p-value)**
Baseline	204.75 ± 31.52	1.00 ± 32.91 (-19.91, 21.91) p=0.918 [a]
After placebo	203.75 ± 32.89	
After *T. crispa*	193.50 ± 39.20	10.25 ± 16.85 (-20.95, 0.45) p=0.059 [a]
Variables	**TG**	**Average difference (95% CI, p-value)**
Baseline	158.50 ± 51.79	38.75 ± 52.13 (5.63, 71.87) p=0.026* [a]
After placebo	119.75 ± 33.12	
After *T. crispa*	132.00 ± 60.60	-12.25 ± 39.49 (-12.84, 37.34) p=0.306 [a]
Variables	**HDL**	**Average difference (95% CI, p-value)**
Baseline	43.33 ± 7.05	-5.75 ± 11.45 (-13.02, 1.52) p=0.099 [b]
After placebo	49.80 ± 14.62	
After *T. crispa*	46.00 ± 9.83	3.08 ± 52.13 (-8.48, 2.32) p=0.222 [b]
Variables	**LDL**	**Average difference (95% CI, p-value)**
Baseline	127.92 ± 31.74	-2.93 ± 31.34 (-22.85, 16.98) p=0.752 [a]
After placebo	130.85 ± 28.73	
After *T. crispa*	121.08 ± 33.78	9.77 ± 11.14 (-16.85, -2.68) p=0.011* [a]

***** statistically significant difference at $p < 0.05$ [a] Paired t Test [b] Wilcoxon Signed-Ranks Test

Table 6 Adherence and leftover capsules of *T. crispa* and placebo in group 1 (n=24) and group 2 (n=12)

	Group 1 (n=24)	**Group 2 (n=12)**	**All patients (n=36)**
T. crispa			
Adherence* (person)	23 (95.8)	10 (83.3)	33 (91.7)
Average *T. crispa* capsules (%)	97.3 ± 5.8	90.5 ± 13.4	95.6 ± 8.6
Residual *T. crispa* capsules (capsules)	77	112	189
Placebo			
Adherence* (person)	19 (79.2)	7 (58.3)	26 (72.2)
Average placebo capsules (%)	112.9 ± 11.5	111.4 ± 9.5	112.4 ± 10.8
Residual placebo capsules (capsules)	170	103	273

*90% of *T. crispa* or placebo capsules was taken.

difference between 2 months receiving *T. crispa* and 2 months receiving placebo at α=0.05 (108.54 ± 12.56 mg/dl compared with 108.42 ± 12.59 mg/dl, p= 0.947).

Comparing FBG, HbA_1C, TC, TG, HDL, LDL at baseline, after 2 months receiving *T. crispa* and placebo in group 2 (n=12)

Table 5 compares average fasting blood glucose at baseline, after 2 months receiving *T. crispa* and placebo in group 2 in which patients were randomly assigned to receive placebo in the first 2 months. The results showed that fasting blood glucose was not significantly different at α=0.05 during the research period. Group 2 results were inconsistent with group 1 results that *T. crispa* reduced fasting blood glucose statistically significant from the baseline at α=0.05 compared with baseline.

The possibility that adherence might effect fasting blood glucose differently in group 1 and group 2 needs to be considered. Adherence analysis revealed that group 1 patients adhered more to the use of *T. crispa* than group 2 patients. We found that patients had more adherent trait in the first intermission (either *T. crispa* or placebo). As shown in Table 6 leftover capsules in the first 2 months was 180 capsules (77 capsules of *T. crispa* and 103 placebo) while 282 capsules were

unused in the second 2 months (112 *T. crispa* and 170 placebo capsules). It is probable that differences in adherence trait may cause difference in fasting blood glucose result.

Adherence analysis (n=36)

Adherence was assesses by pill count method. We used reference criteria that 90% of *T. crispa* was taken[18]. The results showed t because 91.6% of patients (n=36) adhered to *T. crispa*. The average capsules were 95.6 ± 8.6 (Table 6). Group 1 (n=24) in which patients were randomly assigned to receive *T. crispa* in the first 2 months had 95.8% adherence trait (97.3 ± 5.8 average capsules) while 83.3% adhered (90.5 ± 13.4 average capsules) in group 2 where patients were randomly assigned to receive placebo in the first 2 months. Unused capsule in the first 2 months was 180 capsules (77 capsules *T. crispa* and 103 capsules placebo) while 282 capsules in the second 2 months (112 capsules *T. crispa* and 170 capsules placebo). It is probable that difference adherence may cause different fasting blood glucose results. The order of the intermission could be another factor that effected the results because the patients had more adherence in the first than in the second intermission.

Comparing average body weight after receiving *T. crispa* and placebo (n=36)

As shown in Table 7, there was no statistically significant difference in the body weights between *T. crispa* and placebo groups during the study period (p=0.920).

Comparing calorie intake after receiving *T. crispa* and placebo (n=36)

Food intake record profiles were analyzed by formula from the Nutrition Division, Department of Health, Ministry of Public Health[19]. Paired t Test was used to comparing calorie intake during the administration of *T. crispa* and placebo in the same person. Table 8 shows that 7 patients (19.4%) had higher calorie intake when receiving *T. crispa* than placebo (significantly different at $\alpha = 0.05$ ($p<0.05$) while 3 patients (8.3%) had more calorie intake upon receiving placebo than *T. crispa* (significantly different at $\alpha=0.05$ ($p<0.05$). Seventy-two percent of the patients (26 persons) did not show significant differences in calorie intake between the *T. crispa* and placebo groups during the study period.

Table 7 Comparing average body weight after receiving *T. crispa* and placebo (n=36)

	Average body weight	Average difference (95% CI)
Baseline	68.69 ± 12.27	-0.13 ± 1.18 (-0.53, 0.27) p=0.516
After *T. crispa*	68.82 ± 12.32	
After placebo	68.83 ± 12.54	-0.02 ± 0.90 (-0.32, 0.29) p=0.920

Table 8 Comparing calorie intake after receiving *T. crispa* and placebo (n=36)

Calories intake person (%)	Group1 person (%)	Group2 person (%)	All patients
T. crispa > placebo	5 (13.9)	2 (5.6)	7 (19.4)
placebo > *T. crispa*	3 (8.3)	0 (0)	3 (8.3)
No change	16 (44.4)	10 (27.8)	26(72.2)

Table 9 Adverse reactions while receiving *T. crispa* and placebo (n=36)

Adverse reaction	During *T. crispa*	During placebo	p-value
Gastrointestinal			
ALT ≥ 3 times	6	1	< 0.001* [a]
AST ≥ 3 times	3	1	
Constipation	-	3	< 0.001* [a]
Flatulence	1	2	
Dry mouth	-	1	
Central nervous system			
dizziness	1	2	< 0.001* [a]
Cardiovascular			
Palpitation		1	
bradycardia		1	
Genitourinary			
uropenia		1	
Miscellaneous increase			
appetite	1	1	

Adverse reaction

Telephone monitoring was conducted among all patients during the study period. Table 9 shows that 16.7% (6 persons) of subjects had elevated aspartate aminotransferase and/or alanine aminotransferase, more than 3 times the baseline levels. Other adverse reactions while receiving *T. crispa* were flatulence, dizziness and increased appetite.

Chi-Square Test was used to compare the patients whose elevated aspartate aminotransferase and/or alanine aminotransferase while receiving *T. crispa* and placebo. The result revealed that during *T. crispa* period, there were more patients with elevated aspartate aminotransferase and/or alanine aminotransferase than the placebo period (significantly different at

α=0.05 p<0.001) 6 persons compared with 1 person.

No hepatitis, jaundice or any disorder symptom was found in patients with elevated aspartate aminotransferase and/or alanine aminotransferase. After 2 months follow up, 5 patients had normal aspartate aminotransferase and/or alanine aminotransferase. Only one patient with aspartate aminotransferase and/or alanine aminotransferase still had rising value after stopping *T. crispa*. In this case, antilipemic agent was stopped and hepatic ultrasound was conducted, then fatty liver was found. It might be that the cause of hepatic enzyme elevation was taking *T. crispa* with some drug, because when taking *T. crispa* was stopped, hepatic enzyme was almost reduced to the normal range. In addition, the possibility that co-drug therapy elevated aspartate aminotransferase and/or alanine aminotransferase needs to be considered. The results showed that all patients with elevated aspartate aminotransferase and/or alanine aminotransferase used antilipemic agent. Simvastatin was used in four patients and two patients used atorvastatin. Using statin may cause elevated aspartate aminotransferase and/or alanine aminotransferase. Using statin with *T. crispa* may be a risk factor for elevating aspartate aminotransferase and/or alanine aminotransferase.

CONCLUSIONS: From these overall results, we can conclude that receiving 250 mg twice a day *T. crispa* dry powder (0.98% dry weight marker A) for 2 months can reduced fasting blood glucose significantly from baseline. Although 16.7% of the samples had elevated aspartated aminotransferase and/or alanine aminotransferase more than 3 times the baseline levels but using T. crispa dry powder with statin may be a risk factor for elevated liver enzyme.

ACKNOWLEDGEMENTS: The authors are grateful to Faculty of Pharmaceutical Sciences, Chulalongkorn University for the financial support.

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