Clinical Research

Additional benefit of higher dose green tea in lowering postprandial blood glucose

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ABSTRAK

Latar belakang: *Teh hijau mengandung katekin yang memiliki efek menghambat amilase, sukrosa, dan* sodium dependent glucose transporter *(SGLT) yang mengakibatkan penurunan kadar gula darah* postprandial *(GDP). Efek menguntungkan ini telah didemonstrasikan secara luas menggunakan teh hijau dosis biasa (DB). Penelitian ini bertujuan mempelajari efek penurunan yang lebih besar dari GDP dengan menggunakan teh hijau dosis tinggi (DT) pada remaja sehat.*

Metode: *24 subjek menerima larutan 100 mL dari seduhan 0,67 atau 3,33 gram teh hijau bersama dengan makanan uji. Gula darah puasa* postprandial *(GDPP) menit ke-30, ke-60, dan ke-120 diukur. Dilakukan* cross-over *setelah* wash out*. GDP dan* incremental area under the curve *(IAUC) dianalisis dengan uji T berpasangan. Kandungan katekin dalam teh diukur menggunakan* high-performance liquid chromatography *(HPLC).*

Hasil: *GDP kelompok DT lebih rendah dibanding DB (menit ke-60 = 113,70 ± 13,20 vs 124,16 ± 8,17 mg/dL, p = 0,005; menit ke-120 = 88,95 ± 6,13 vs 105,25 ± 13,85). IAUC kelompok DT juga ditemukan lebih rendah dibanding DB (2055,0 vs 3411,9 min. mg/dL, p < 0,001).*

Kesimpulan: *Efek tambahan yang menguntungkan dari penurunan GDPP dapat dicapai dengan menggunakan dosis teh hijau yang lebih tinggi. Oleh karena itu, penelitian ini merekomendasikan penggunaan dosis teh hijau yang lebih tinggi untuk kontrol gula darah* postprandial *yang lebih baik.*

ABSTRACT

Background: Green tea contains catechins that have inhibitory effects on amylase, sucrase, and sodium-dependent glucose transporter (SGLT) which result in lowering of postprandial blood glucose (PBG). This beneficial effect has been widely demonstrated using the usual dose (UD) of green tea preparation. Our study was aimed to explore futher lowering of PBG using high dose (HD) of green tea in healthy adolescents.

Methods: 24 subjects received 100 mL infusion of either 0.67 or 3.33 grams of green tea with test meal. Fasting, PBG at 30, 60, 120 minutes were measured. Subjects were cross-overed after wash out. PBG and its incremental area under the curve (IAUC) difference between groups were analyzed with paired T-test. Cathecin contents of tea were measured using high-performance liquid chromatography (HPLC).

Results: The PBG of HD group was lower compared to UD (at 60 minutes =113.70 ± 13.20 vs 124.16 ± 8.17 mg/dL, p = 0.005; at 120 minutes = 88.95 ± 6.13 vs 105.25 ± 13.85 mg/dL, p < 0.001). The IAUC of HD was also found to be lower compared to UD (2055.0 vs 3411.9 min.mg/dL, p < 0.001).

Conclusion: Additional benefit of lowering PBG can be achieved by using higher dose of green tea. This study recommends preparing higher dose of green tea drinks for better control of PBG.

Keywords: cathecin, green tea, postprandial blood glucose

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One of degenerative diseases with high prevalence according to International Diabetes Federation (IDF) is diabetes mellitus type two. Approximately five million people in Indonesia suffered from diabetes in year 2000, and 12 millions are predicted to have this condition by year 2025. World Health Organization (WHO) estimated that Indonesia will be one of ten countries with highest prevalence of diabetes in the world in 2025.[1]

The pathophysiology of diabetes type two is related to prolonged state of hyperglycemia, insulin resistance and deficiency of insulin production. Diabetes mellitus is defined if random blood glucose level is more than 200 mg/dL, or fasting glucose level more than 126 mg/dL, or both.[1,2] However, hyperglycemia alone may be found in diabetic or non-diabetic patients.[3,4] Prolonged state of hyperglycemia which carries a risk in developing diabetes in the future usually caused by unhealthy lifestyle due to high carbohydrate diet and sedentary lifestyle.[2]

Green tea contains high level of polyphenol substances (catechins) because green tea leaves undergo minimal fermentation process compared to black tea.[5] One of its active substances, epigallocatechin gallate (EGCG), was known with its beneficial effects as hypocholesterolemic,[6] antibacteria,[7] and antioxidant,[8,9] with minimal side effects.[10]

The role of green tea catechins in maintaining normal blood glucose level (euglycemia) is achieved via inhibitory activity of amylase, sucrase, and sodium-dependent glucose transporter (SGLT),[11] as well as enhancing activity of tyrosine phophorilase enzyme,[12] which enhances insulin secretion. The secretion of insulin, with its roles in glycogen synthesis and decreasing gluconeogenic enzyme such as phosphoenol pyruvate carboxy kinase (PEPCK) and glucose-6-phosphatase (G-6-P),[13,14] also maintained by catechins through its antioxidant effect of preventing liver and pancreatic beta cells damage caused by free radicals.[10] Nagao, et al[15] reported that EGCG could cause a decrease in HbA_{1c} and improve sensitivity of insulin. A study by Tsuneki, et al[16] in healthy subjects showed that green tea could lower blood glucose level compared with water. Meanwhile, Josic, et al[17] and Ryu, et al[18] did not find any positive effect of green tea in lowering blood glucose levels.

Until now, the optimal dose of green tea catechins suggested in lowering postprandial blood glucose (PBG) elevation has been varied; however, some studies showed that the dose of green tea catechin which yields beneficial effect starting from 84 mg of EGCG. This is equivalent to 176 mg of total green tea catechin as reported by Babu, et al[19] which showed that 48–55 % of green tea catechins occurred as EGCG. This can be obtained by infusing green tea in boiling water for three minutes.[15,16,20] The beneficial effect has been widely demonstrated using the usual dose of green tea consumption by drinking two small cups of regular strength tea (0.67 gram of green tea infused in 100 mL of boiling water). This study was aimed to explore potential further lowering of PBG by using higher dose of green tea (3.33 grams of green tea infused in 100 mL of boiling water) in healthy adolescents. As the catechin content of Indonesian green tea might be different from tea from other countries,[10] we hope that our study can be extrapolated to other population using different tea. In addition, we also analyzed the catechin content of tea used in this study.

METHODS

This study was a randomized, double-blind, cross over design clinical trial. It was held from May until June 2014 and the protocol of this study has been approved by Medical Ethics Committee of University of Indonesia (No. 320/H2.F1/ETIK/2014). The subjects were healthy female nursing students at Muhammadiyah Tangerang University aged 19-24 years with normal body mass index (BMI) of 18.5-22.9 kg/m^2, [21] systolic blood pressure < 120 mmHg and diastolic blood pressure < 80 mm Hg,[22] random blood glucose 200 mg/dL,[1,23] and provided written informed consent. Exclusion criteria were history of degenerative diseases such as diabetes mellitus, cardiovascular, renal or liver diseases, smokers, use of antioxidant supplements in the last two weeks, symptom of gastritis after consumption of tea, and pregnancy or lactation. Subjects who were sick during the study, refused to finish the study, consumed EGCG supplements or food contain catechins during wash-out period, and could not complete the tasks, were dropped out from this study.

The study was carried out in two separate days with three days wash out period. Subjects were

randomly divided into two groups. Each group received 100 mL solution prepared from infusion of either 0.67 gram of green tea (usual dose group, UD) or 3.33 grams (high dose group, HD) in boiling water. The infusion time in both groups was three minutes. We analyzed the catechin content of the drinks using high performance liquid chromatography (HPLC) which was done by Saraswanti Indo Genetech Bogor. The UD drinks contain 66.52 mg of green tea catechins, and the HD drinks contain 369.14 mg. All subjects consumed high carbohydrate diet consisting of two slices of white bread[24] and 3 grams of sucrose within 10 minutes time period after drinking green tea. Total calories from meal given to subjects were 212 kcal (39 g carbohydrate, 6 g protein and 3 g fat).

Fasting, as well as PBG at 30, 60, and 120 minutes were measured in every subjects using Accu-Chek® finger prick blood test. Every subjects were then cross-overed, thus, subjects who have received UD solution would be given HD solution after three days of wash out period, and vice-versa. The drinks were provided using indistinguishable, covered cups prepared by a third party, and both the subjects and data collector were not aware of every subject's group designation until data analysis has been done. Data were analyzed using Statistical Package for Social Science (SPSS) version 20 and Microsoft Office 2013 Data Analysis Tools. PBG and its incremental area under the curve (IAUC) difference between the groups were analyzed with paired t-test, and tolerability of high dose green tea among subjects were also explored. The result was considered statistically significant using p value cutoff of <0.05.

Table 1. Demographic characteristics of subjects

Parameters	Mean ± SD
Age (years)	20.1 ± 0.4
BMI (kg/m^2)	20.37 ± 1.40
Systolic BP (mmHg)	107.91 ± 9.65
Diastolic BP (mmHg)	69.16 ± 7.17

RESULTS

All 24 subjects completed this study. The demographic characteristics of the subjects are depicted in Table 1.

Table 2 shows fasting and postprandial blood glucose, as well as its IAUC value in the UD and HD groups.

There was no statistically significant difference of fasting blood glucose between groups. The PBG at 30 minutes of HD was lower than UD, although the difference was not statistically significant. The PBG at 60 and 120 minutes of HD group were lower than those of UD group. Altogether, those receiving higher dose of green tea exhibited lower IAUC of postprandial blood glucose level compared to usual dose.

All subjects finished drinking the tea prepared, although 16 subjects (66.7%) complained bitter taste while consuming HD drinks. No subjects complained of palpitations, excessive diuresis, nausea and gastritis while receiving UD and HD of green tea. The HPLC results were as follows: drinks from the UD group- (prepared by infusing 0.67 gram of green tea) contain 66.52 mg of green tea catechins, and drinks from HD group- contain 369.14 mg of green tea catechins.

Table 2. Fasting and postprandial blood glucose levels following usual dose and high dose of green tea consumption and its IAUC value

Blood glucose	Usual Dose (n = 24)	High Dose (n = 24)	p
Fasting (mg/dL)	88.04 ± 5.98	90.04 ± 5.92	0.164
30 min (mg/dL)	130.37 ± 12.40	124.12 ± 15.41	0.070
60 min (mg/dL)	124.16 ± 8.17	113.70 ± 13.20	0.005
120 min (mg/dL)	105.25 ± 13.85	88.95 ± 6.13	< 0.001
IAUC (min.mg/dL)	3411.87 ± 802.21	2055.00 ± 979.75	< 0.001

IAUC = incremental area under the curve

DISCUSSION

Green tea's beneficial anti-hyperglycemic effects occurred both in the short- and long-term timeframe. When taken with meal, green tea exhibits protective effect by shortening the duration of hyperglycemia and reducing overall elevation of postprandial blood glucose above the baseline or fasting level.[11-14] Secondly, the antioxidant effects of habitual green tea drinking yields protective effect from free radical damage of pancreatic beta cell.[9,10] Several studies showed that green tea effect in lowering blood glucose levels depends on its catechins content per drinks consumed and drinking frequency.[16,17,25,26] This study focused on the short-term protective effect of green tea drinking, examined the additional postprandial blood glucose (PBG) lowering effect by increasing the dose taken at mealtime.

The subjects in this study were healthy adolescents aged 19-24 years and all of them were female. It was considered that carbohydrate metabolism was not impaired in young population, except in diabetes mellitus type 1 patients.[27] Basu, et al[28] also indicated that women have higher sensitivity of insulin compared with men, possibly due to hormonal factor, as estrogen and progesterone affects tissue responses to glucose and gut motility.[29] Although the result of this study might not be able to be extrapolated to male and older population, the homogeneity of subjects does minimize the bias of this study.

The fasting blood glucose levels of all subjects were considered within normal limits, and the blood glucose levels at 30 minutes reached almost two times the fasting level which indicates first and second stage of insulin secretion.[29,30] Higher insulin secretion at second stage leads to a decrease in blood glucose levels at 60 minutes and further lowering at 120 minutes. Thus, the data of PBG in both HD and UD groups were considered within normal bounds of physiological insulin secretion in controlling blood glucose following a meal.[30,31]

As expected of the good cross over study, the fasting blood glucose level did not differ significantly between the groups (UD = 88.04 ± 5.98, HD = 90.04 ± 5.92; p = 0.164) because the subjects themselves exposed to the two different treatment, thus eliminating individual variation between groups in non-cross over studies. Furthermore, the subjects were not permitted to consume green tea and other food sources of catechins during wash out period. The PBG at minutes 30 also did not differ between the HD and UD groups, implying the role of green tea catechins in the later period of PBG elevation rather than in the early period, by inducing salivary a amylase bond to hydrogen complex interaction[13] and inhibiting the activity of pancreatic a amylase.[32,33] Other study conducted by Kobayashi, et al[11] showed that EGC and EGCG can inhibit the activity of SGLT-1 which lead to decreased absorption of carbohydrate. The same results were also reported by Snoussi, et al[34].

The PBG at 60 and 120 minutes were found to be lower in the HD group compared to UD group and the differences were statistically significant. The PBG were 8.42% lower at minutes 60 and 15.49% lower at minutes 120 in the HD group compared to UD group. The mechanism involved at these point of time related to an increase in glucose uptake into cells by increasing insulin secretion.[35] Babu, et al[36] in animal study found that green tea catechins could stimulate glucose uptake by increasing insulin secretion, inhibiting glucose transporter type four system, and decreasing gene expression that control gluconeogenesis mechanism. Other study conducted by Sheperd, et al[37] also agrees with this finding. The total/cumulative effect of the benefit of HD of green tea over UD in this study can be evaluated by comparing overall elevation of postprandial blood glucose following the same test meal using incremental area under the curve (IAUC) of PBG. The IAUC in the HD group was 2055.00 ± 979.75 min.mg/dL, or 39.8%, which was significantly lower than the UD group (3411.87 ± 802.21 min.mg/dL, $p < 0.001$) suggesting the HD yields overall additional benefit in postprandial blood glucose control over UD.

Regarding the return of postprandial blood glucose level to its baseline or fasting value, we found that the return at minutes 120 was observed in 14 subjects (58.3%) from the HD group but only observed in two subjects (8.3%) from the UD group. During the two hour period, no subjects in either groups have exhibited symptoms of hypoglycemia or have PBG value lower than 70 mg/dL.

Of interesting note was our finding related to the time of return of postprandial glucose elevation to baseline or fasting level. Only 8.3% subjects receiving UD of green tea have their PBG returned to baseline level at minutes 120, while greater proportions of subjects (58.3%) receiving HD of green tea have achieved baseline levels at minutes 120. These findings suggest that drinking higher dose of green tea together with meals could somehow offset the risk of developing diabetes mellitus type two if done consistently, because prolonged state of hyperglycemia is an independent risk factor of type two diabetes mellitus.[2] Although the meal used in this study contains fewer calories than meals typically consumed during lunch or dinner, the use of higher calorie meals could be evaluated in future studies. These findings could also be explored in future studies using higher dose of green tea to determine the ceiling dose of green tea that further increase of dose could not yield additional benefits.

The side effects reported in this study were only related to the taste of drinks prepared from HD of green tea, certainly, this could not be avoided because the bitterness of the drinks would increase when infusing greater amount of tea. Longer term studies by evaluating whether this taste preference would change should be studied to make our recommendations of using HD more acceptable to the public. As we found no negative short term effects of drinking HD of green tea reported and that the safety of higher quantity of green tea drinking in the long term has already been established[38] the HD of green tea preparation could be recommended.

In conclusion, the additional benefit of lowering postprandial blood glucose can be achieved by using higher dose of green tea. Thus, we recommend preparing green tea drinks by infusing at least 3.33 grams of green tea in boiling water for 3 minutes as a better alternative to usual preparation of 0.67 gram for better control of PBG elevations following high carbohydrate meals.

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Conflict of interest

The authors affirm no conflict of interest in this study.

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