Original Article

Decaffeinated green tea polyphenols supplementation had no adverse health effects in girls with obesity: a randomized controlled trial

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Background and Objectives: While the health promoting effects of green tea polyphenols have been identified among adult, research on children is scarce probably due to safety concerns about caffeine. This study aims to evaluate the safety of decaffeinated green tea polyphenols (DGTP) supplementation in girls with obesity and lay the foundation for its application in children population. **Methods and Study Design:** This 12-week randomized, double-blinded, parallel-controlled trial was performed among 62 girls with obesity aged 6 to 10 years old. Participants were allocated to take 400 mg/d DGTP (DGTP group, n = 31) or isodose placebo (Control group, n = 31) at random. Anthropometric measurements and biochemical parameters including hepatic and renal function indicators, serum minerals concentrations, and routine blood parameters, were measured at baseline and the end of this trial. DGTP intake diary was required for each participant to record any abnormal reactions. **Results:** After the 12-week supplementation, compared to Control group, the uric acid concentration in DGTP group showed a significant decrease (-48.0 ± 83.2 vs -0.01 ± 69.1, μmol/L), within the normal range. Regarding other biochemical indicators, there were no significant differences in changed values between the two groups. Throughout the trial, no adverse effects were reported in either group. **Conclusions:** This study indicated that the supplementation of 400 mg/d DGTP for 12 weeks had no adverse health effects in girls with obesity, providing evidence for the DGTP adoption in children research.

Key Words: decaffeinated green tea polyphenols, safety, children, obesity, randomized controlled trial

INTRODUCTION

Tea is one of the most extensively used beverages and comes in various forms.[1] Green tea, as a nonfermented one, contains a wide range of chemical compounds.[2] The major active component accounting for the aroma and beneficial health effects of green tea is green tea polyphenols (GTP). And (-)-Epigallocatechin-3-gallate (EGCG) is the most abundant constituent of GTP with strong biological effects.[3,4]

As a natural medicinal food component, the health benefits of GTP have been widely studied in recent years. Numerous experimental studies have documented the properties of antioxidant, anticancer, anti-cardiovascular, and antiobesity.[5] The positive effects have been verified in various diseases in the adult population, including cardiovascular disease,[6] cancer,[7,8] and especially obesity.[9-11] Some clinical trials revealed the positive effects of GTP on fat mass decreasing,[9] plasma lipid concentration reduction,[10] and weight loss[11] in obese adults.

However, few trials to date focused on the health effects of GTP in children. Only one Japanese trial recruited 40 obese children to take green tea beverage daily for 24 weeks.[12] But the potential benefits of GTP on obesity and other diseases should not be ignored in children,

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since GTP is a natural functional food ingredient for promoting human health.[13]

The safety concerns of caffeine contained in GTP might be the main reason for few GTP interventions were conducted in children. It has been reported that caffeine causes adverse effects on the physical and mental health of children, including sleep difficulties,[14] adverse physiological responses like headache, stomachache, and slow heart rate,[15] and mental anxiety or depression.[16] Safety is the top priority in children's research, and the current separation and extraction technique can effectively remove caffeine contained in GTP. Thus, decaffeinated green tea polyphenols (DGTP) applied in children's research is more appropriate, which is also consentaneous by some nutritional experts.

Is it safe to use DGTP to intervene with children? This issue needs to be resolved so that future trials can use DGTP in children to study its health effects. Until now, there is no report about DGTP safety conducted on children. Therefore, this research aims to test the safety of DGTP intake, evaluate the potential risk, and explore a safe dosage of DGTP in children, thus laying the foundation for GTP to be used in children population.

METHODS

Study design and participants

Characteristics of the participants, the exclusion criteria, study design, and the trial profile were reported previously.[17] Briefly, 62 girls aged 6 to 10 years with body mass index (BMI) at the overweight or obesity threshold in China,[18] with no known severe systemic, hepatic, and renal diseases, enrolled in a 12-week randomized, double-blind, placebo-controlled trial of DGTP safety examination. Subjects were randomly assigned into 2 groups on a 1:1 ratio to take 400 mg DGTP (EGCG 50%) or placebos per day for 12 weeks. Randomization and allocation into 2 groups were done by a central randomization system implemented by the Research Department in Xinhua Hospital.

The potential risks of the trial have been informed to subjects and their custodians during the enrollment, and consent on paper was filled out by each subject. This research obtained the approval from Ethics Committee of Xinhua Hospital (Shanghai, China). Trial registration is Clinical Trials.gov NCT03628937.

Study procedure

Questionnaires were administered to participants at baseline regarding their demographics and lifestyles. Anthropometric measurements and biochemical parameters measurements were conducted twice at Week 0 and Week 12. Throughout the supplementation, the DGTP capsule intake diary was required to be recorded in detail by guardians and reported to the investigators. There was no withdrawal restriction during the study for any participant.

Assessment of DGTP safety

DGTP capsule intake diary

The daily capsule intake diary included (i) the time and amount of DGTP intake, (ii)swallowing adaption, (iii) sleep condition, (iv) any discomfort condition or adverse reaction, and (v) other medicine intakes. To monitor the health status of all subjects, the diaries were asked to report to the investigators through WeChat every day.

Biochemical parameters

Blood samples of 15 mL collections were performed in the morning after more than 12 hours of overnight fasting, to measure serum minerals concentrations, liver and kidney function indicators, and routine blood parameters. All biochemical tests were performed by technicians in clinical laboratories at Xinhua Hospital: (i) hepatic and renal function indicators were detected by Hitachi LABOSPECT 008 AS automatic biochemical analyzer, (ii) the serum minerals concentrations were measured by BH7100 S atomic absorption spectrometer, (iii) complete blood count was tested by Beckman Coulter LH 750 automatic blood analyzer.

Calculation of DGTP dosage

The DGTP dosage chosen to be tested was determined at the onset of the study. Referring to the reported 12-week GTP intervention research on body weight and metabolism in adults, GTP intake is about 500-700 mg/d (EGCG 270-350 mg/d). To ensure the safety of children enrolled, 600 mg/d (EGCG 50%) for adults was selected as the reference dosage, and the dosage applied in this trial was converted according to body weight. 40 kg was used as the average weight of overweight and obese children aged 6-10 years, and a female adult was supposed to be 160 cm high and weigh 65kg (body mass index $\geq$ 24 kg/m^2), thus the estimated dosage of DGTP in girls with obesity was 400 mg/d (EGCG 50%).

Production of DGTP capsules and placebos capsules

DGTP is slightly hygroscopic and susceptible to oxidative and browning under alkaline conditions, making them unsuitable for making into tablets. So, we decided to make it into capsules. According to the regulations related to the production and processing of capsules, only pharmaceutical products can be produced as hard capsules. As a nutrient supplement, DGTP is produced in the form of soft capsules. The manufacturing process of DGTP soft capsules is that DGTP is dissolved in soybean oil, forming a suspension to increase the stability of DGTP. The capsule shells are made from glycerin and beeswax, which are black to protect the activity of DGTP from light. Considering the actual swallowing ability of children, we chose soft capsules with a capacity of 500 mg. Each DGTP capsule contains 200 mg of DGTP and 300 mg of soybean oil. As for placebo capsules, the appearance, color, and smell were entirely identical to those of DGTP capsules, with only 200 mg of DGTP replaced by an equal dose of soybean oil.

DGTP raw materials (polyphenols 99%, Catechins 81%, EGCG 50%, caffeine < 0.5%) were bought from Chengdu WAGOTTBIO-TECH Co., Ltd. which is one of the largest tea extract manufacturers in China. The company responsible for DGTP soft capsules and placebo capsules processing is Liaocheng AOJIAN Biotechnology Co., Ltd. All the materials mentioned above have safety inspection reports.

Statistical analysis

Continuous variables are reported as the means ± SDs, while categorical variables are shown as numbers and percentages. Normality test was performed for measurement data. To detect differences between the two groups, we applied independent samples t-tests or Mann-Whitney U tests for continuous variables according to data normality and χ^2 tests for categorical variables. Paired-samples t-tests or Wilcoxon signed-rank tests were performed to compare differences between pre- and post-supplementation. Statistical analyses were done by SPSS version 26.0 software (SPSS Inc., Chicago, IL, USA). All *p* values were calculated based on two-sided tests and significance was determined at $p < 0.05$.

RESULTS

Sixty-two participants completed the study and were included in the analysis. The participant flowchart is shown in Figure 1. Their general characteristics were presented in Table 1, and no significant differences were found between the DGTP group and Control group.

Hepatic and renal function indicators were presented in Table 2. At baseline, the DGTP group had a lower glomerular filtration rate and higher serum creatinine than Control group. At the end of the trial, no significant differences were found between the two groups. Regarding the changed value of these indicators in 12 weeks, the uric acid (UA) concentration of subjects in the DGTP group had decreased significantly (-48.0 ± 83.2 vs -0.01 ± 69.1, μmol/L) compared to the Control group. As for the comparison of indicators before and after the trial in each group, alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transferase, and UA concentrations considerably reduced after supplementation in the DGTP group. While in the Control group, the alanine aminotransferase and γ-glutamyl transferase concentration significantly decreased after this 12-week trial. Although the concentrations of some indicators decreased after the 12-week experiment, they were all still within the normal physiological range.

For serum minerals results, there were no significant differences between the DGTP group and Control group at baseline, at Week 12, and in changed values. And when comparing pre- and post-trial concentrations, no significant changes were found within each group. (Table 3)

Table 4 illustrated that no significant differences were found in routine blood parameters between groups at baseline, after trial, and in change value. Regarding the 12-week changes within two groups, monocyte percentage and mean corpuscular volume levels of DGTP group showed a significant change, and white blood cell count and eosinophil percentage levels of Control group also changed significantly.

During the whole safety test procedure, no adverse reactions of sleep difficulty, mental anxiety, slow heart rate, or gastrointestinal discomfort were reported. Some participants reported that the capsules were slightly large, causing mild swallowing discomfort.

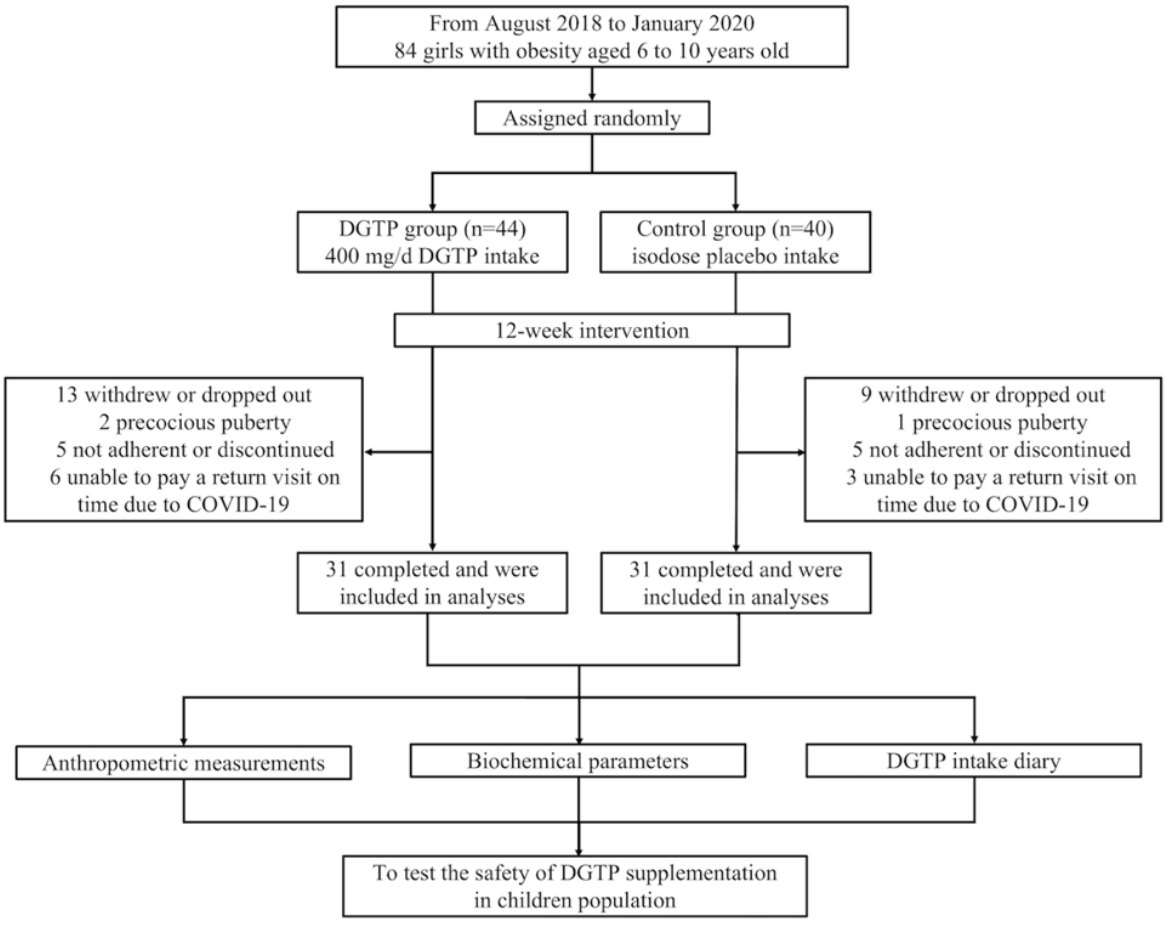

Figure 1. Participant flowchart

Table 1. General characteristics of participants

	DGT group (n=31)	Control group (n=31)
Age, y	8.1±1.3	8.4±1.2
Weekly physical activity, h	6.2±2.5	5.4±2.3
Sleep time		
< 8h/d	3 (10)	1 (3)
8-10h/d	27 (87)	29 (94)
>10h/d	0	1 (3)
Height at baseline, cm	137±7.5	139±8.4
Height at end of trial, cm	139±7.6	142±8.2
Height change, cm	2.3±0.9	2.4±0.9
Weight at baseline, kg	42.5±7.5	46.0±10.3
Weight at end of trial, kg	43.7±9.4	46.3±9.9
Weight change, kg	1.2±7.0	0.3±1.7
BMI at baseline, kg/m^2	22.6±2.9	23.5±3.3
BMI at end of trial, kg/m^2	21.9±2.7	22.8±2.9
BMI change, kg/m^2	-0.8±1.4	-0.7±1.4
SBP, mmHg	106±12.7	106±13.8
SBP at end of trial, mmHg	106±11.0	107±16.0
SBP change, mmHg	0.00±11.7	1.2±15.8
DBP, mmHg	72.2±20.3	66.8±10.8
DBP at end of trial, mmHg	71.0±12.4	70.2±14.1
DBP change, mmHg	-1.2±21.2	3.4±13.3

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; DGTP, decaffeinated green tea polyphenols

DISCUSSION

After 12 weeks DGTP safety test trial, the participants in the DGTP group showed no significant differences in serum minerals concentrations and routine blood parameters compared with those in the Control group. Only UA, one of the hepatic and renal function indicators, decreased significantly in the DGTP group compared to the Control group. All indicators in both groups were within the normal range. The result demonstrated that 400 mg/d DGTP (50% EGCG) intake for 12 weeks was a safe dosage in girls without any adverse effects, thus laying the foundation for DGTP application to children's research. As far as we know, it is the first randomized controlled research testing DGTP intake safety in children population.

DGTP contains no caffeine theoretically. However, due to current technical limitations, the DGTP capsules used in this study could only achieve a caffeine content of less than 0.5%, less than 1 mg per capsule. Even a single dose of 50 DGTP capsules can only reach the dose of caffeine in a cup of green tea (about 50 mg), which is far less than the safe dose of caffeine for children of 2.5 mg/kg.[19] Therefore, the effect of residual caffeine in DGTP capsules on the safety and results of the experiment was negligible.

It has been reported that repeated supplementation of GTP may lead plasma polyphenols concentrations to toxic concentrations in mice despite its low bioavailability.[20] However, the toxicology test on GTP has been developed well. Choosing a safe dosage of GTP for children can avoid acute and chronic toxicity. This study used a daily supplement dosage of 400 mg GTP for 12 weeks. According to the Toxnet website, this dosage is safe for children.

Liver injury caused by GTP and its constituents has been reported previously.[21,22] While recent studies have found that GTP supplementation ameliorated inflammation associated with acute liver injury by inhibiting NLRP3 inflammasome activation.[23] The supplementation dose is a key determinant of GTP effects on the liver. Our findings suggest that 400 mg/d GTP intake causes no adverse effects on liver function. Recent progress has shown that GTP might play a beneficial role in various kidney diseases.[24] Our experiment found no adverse effects of GTP on renal function indices and facilitated the reduction of UA, which is in line with this view.

There are some studies reported that GTP may form complexes with iron, zinc, and other minerals, thereby reducing the absorption of minerals and affecting the nutrition status.[25-27] However, some scholars deem that the low absorption rate is caused by other components in tea, such as tannic acid. And there is a related animal study revealed that GTP had no negative effects on minerals absorption even with the dosage of 200 mg/kg, which was much larger than the dosage of 400 mg/d GTP used in this study.[28] In this safety test trial, no significant changes or differences were observed in minerals concentrations between the DGTP group and the Control group before and after the trial.

There were no statistical differences between the DGTP group and the Control group in terms of height, weight, BMI, blood pressure, and the changes observed in these indicators before and after the intervention. This suggested that DGTP supplementation had no adverse effects on anthropometric parameters. Meta-analysis studies focusing on the effects of GTP on anthropometric measures in adults found that GTP had beneficial effects on body weight and blood pressure. However, these effects are significantly influenced by an array of factors, including health status, dietary habits, and physical activity.[29,30] When comparing the data before and after the intervention, it was observed that the height of girls with obesity in both groups increased significantly, and BMI both decreased significantly. This may be attributed to both groups receiving professional health education at the

Table 2. Comparison of hepatic and renal function indicators in two groups before and after trial

	DGTP group (n=31)			Control group (n=31)		
	Baseline	End of trial	Change	Baseline	End of trial	Change
ALT, U/L	25.6±15.5	18.9±11.9§	-6.76±12.4	24.7±16.6	19.5±13.5¶	-5.31±17.5
AST, U/L	27.7±6.98	25.0±5.18§	-2.72±5.20	26.6±5.93	24.0±8.20	-2.59±8.85
ALP, U/L	318±65.3	301±62.0	-16.6±44.6	320±84.3	325±88.0	5.66±60.4
GGT, U/L	17.9±6.15	13.9±4.25§	-4.04±5.51	17.96±7.40	15.1±4.84¶	-2.90±4.59
TBIL, μmol/L	9.56±3.18	9.50±4.21	-0.06±3.14	8.97±3.47	9.22±3.32	0.24±3.46
DBIL, μmo/L	3.04±1.40	2.93±1.42	-0.11±1.21	2.51±1.03	2.66±0.94	0.16±1.11
BUN, mmol/L	4.36±0.80	4.24±0.97	-0.12±0.79	4.63±1.00	4.58±0.86	-0.05±0.86
Scr, μmol/L	39.7±6.43	38.9±6.48	-0.81±6.29	35.0±6.49†	37.0±5.42	1.98±5.21
UA, μmol/L	376±91.1	327±54.0§	-48.0±83.2	336±61.1	336±68.9	-0.01±69.1‡
GFR, ml/min per1.75m^2	213±65.2	203±74.2	-9.26±61.6	258±45.2†	234±42.1	-24.3±45.5

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyl transferase; TBIL, total bilirubin; DBIL, direct bilirubin; BUN, blood urea nitrogen; Scr, serum creatinine; UA, uric acid; GFR, glomerular filtration rate

†Significantly different at baseline. ‡Significantly different in change value. §Statistically significant after trial within DGTP group. ¶Statistically significant after trial within Control group.

Table 3. Comparison of serum minerals concentrations in two groups before and after trial

	DGTP group (n=18)			Control group (n=16)		
	Baseline	End of trial	Change	Baseline	End of trial	Change
Cuprum, μmol/L	18.4±2.55	18.1±3.71	-0.53±3.38	17.6±3.29	17.0±2.56	-0.09±2.90
Zinc, μmol/L	12.3±1.91	13.1±2.52	1.20±2.59	12.2±2.70	12.6±1.34	0.68±2.12
Calcium, mmol/L	2.27±0.10	2.28±0.11	0.02±0.09	2.31±0.12	2.24±0.07	-0.06±0.14
Magnesium, mmol/L	0.90±0.05	0.91±0.04	0.01±0.06	0.90±0.03	0.90±0.02	0.00±0.04
Iron, μmol/L	22.9±6.46	24.3±5.84	2.46±10.6	22.0±6.46	25.2±7.65	4.48±9.78

Table 4. Comparison of routine blood parameters in two groups before and after trial

	DGTP group (n=31)			Control group (n=31)		
	Baseline	End of trial	Change	Baseline	End of trial	Change
WBC, 10^9/L	7.00±2.06	7.29±1.67	0.29±2.06	7.58±2.36	7.15±2.38‡	-0.43±2.08
NEUT, %	50.3±8.74	54.9±9.86	4.63±9.95	51.4±9.47	54.4±10.9	2.93±8.53
MONO, %	8.40±8.78	5.54±1.14†	-2.69±7.44	8.20±8.73	6.10±1.51	-2.10±8.33
LY, %	37.8±9.09	36.9±9.00	-0.93±10.1	37.5±10.2	36.3±9.74	-1.18±11.7
EO, %	2.45±1.67	2.17±1.83	-0.26±1.61	2.45±2.00	2.85±2.32‡	0.40±1.20
BASO, %	0.40±0.18	0.43±0.31	0.03±0.27	0.41±0.14	0.42±0.17	0.00±0.18
RBC, 10^{12}/L	4.85±0.25	4.77±0.28	-0.08±0.25	4.83±0.33	4.72±0.39	-0.12±0.37
HGB, g/L	137±5.29	135±7.08	-2.18±6.42	135±8.14	133±11.3	-2.67±11.1
MCV, fl	83.3±3.52	83.9±3.42†	0.59±3.55	111±146	83.2±2.63	-27.5±140
BPC, 10^9/L	290±45.7	290±44.1	0.18±43.5	321±70.0	303±77.2	-18.4±50.7

WBC, white blood cell count; NEUT, neutrophilic granulocyte percentage; MONO, monocyte percentage; LY, lymphocyte percentage; EO, eosinophil percentage; BASO, basophil percentage; RBC, red blood count; HGB, hemoglobin; MCV, mean corpuscular volume; BPC, blood platelet count

†Statistically significant after trial within DGTP group, ‡Statistically significant after trial within Control group.

time of enrollment, and continuing to receive dietary guidance during the intervention.

As the first randomized controlled study focused on DGTP safety in the children population, this research verified that 400 mg/d DGTP intake was safe for girls with obesity aged 6 to 10. It broadens the application of GTP from adult to children and lays the foundation for its use in children. However, there are some limitations in this trial. We should have applied a higher dosage and monitored more indicators to test the safety of DGTP intervention. But considering that the research subjects are children, the current dosage and indicators were chosen from an ethical point of view.

Taken together, this safety test trial demonstrated that 400 mg/d DGTP (50% EGCG) intake for 12 weeks had no adverse health effects in girls with obesity, which indicated DGTP safety and provided preliminary evidence for DGTP adoption in children research.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURES

The authors declare that they have no competing interests.

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