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REVIEWS: CURRENT TOPICS

Physiological effects of epigallocatechin-3-gallate (EGCG) on energy expenditure for prospective fat oxidation in humans: A systematic review and meta-analysis

Mahendra P. Kapoor, PhD[a,*], Masaaki Sugita, PhD[b], Yoshitaka Fukuzawa, MD, PhD[c], Tsutomu Okubo, PhD[a]

[a]Nutrition Division, Taiyo Kagaku Co. Ltd., Research & Development, 1-3 Takaramachi, Yokkaichi, Mie 510-0844, Japan
[b]Faculty of Education, University of Mie, 1577 Kurimamachiya cho, Tsu City, Mie 514 8507, Japan
[c]Department of Internal Medicine, Aichi Medical University, 21 Karimata, Yakazo, Nagakute-cho, Aichi-gun, Aichi 480-1195, Japan

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Abstract

Green tea catechins (GTCs) are known to improve fat oxidation (FOX) during fasted, rested and exercise conditions wherein epigallocatechin-3-gallate (EGCG) is thought to be the most pharmacologically active and has been studied extensively. From the available data of randomized controlled trials (RCTs) on EGCG, we carried out a systematic review and meta-analysis to elucidate whether EGCG consumption indeed increase energy expenditure (EE) and promote FOX. A systematic review of the literature was conducted using electronic databases (PubMed, Embase, Cochrane Library, CINAHL, JICST, JSTPLUS, and JMEDPLUS and others) and eight RCTs were included. RCTs were reviewed using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and methodological quality was assessed. After data extraction, results were aggregated using fixed- and random-effect approaches and expressed to quantify the relationship between the dose of EGCG for respiratory quotient (RQ), EE and rate of FOX to compare the EGCG and placebo treatments. The meta-analysis results of verities of studies in terms of dose and length of duration revealed that EGCG supplementation provided significant mean difference (MD) when compared with placebo for RQ [MD: −0.02; 95% confidence intervals (95% CI), −0.04 to 0.00; I^2=67%; P=.01] and EE [MD: 158.05 kJ/day; 95% CI, 4.72 to 311.38; I^2=0%; P=.04] in fixed-effect approach. Changes in FOX did not reach the level of statistical significance. Meta-analyses of EGCG influence on the body mass index, waist circumference and total body fat mass (TBFM) were also examined and their impact on the promotion of FOX is reported. Effect of EGCG doses was also systematically reviewed. Finding showed that EGCG intake moderately accelerates EE and reduces RQ. The analyses revealed that the EGCG resulted in difference in RQ and EE but the effect on the other measures of energy metabolism was relatively mild. Possibly, EGCG alone has the potential to increase metabolic rate at 300 mg dose. Collectively, the outcome supports the findings that EGCG has an effect on metabolic parameters. However, the large prospective trials are needed to confirm the findings.

Keywords: Catechins; Epigallocatechin-3-gallate; Energy expenditure; Fat oxidation; Respiratory quotient

1. Introduction

The naturally occurring compound epigallocatechin-3-gallate (EGCG) is the major potent polyphenolic constituent [1,2] and most abundant (representing 50%–80%) of the total catechins content [3–6] found in green tea (*Camellia sinensis* L. Kuntze) leaves. EGCG has been extensively studied and is believed to be a potent nutraceutical, responsible for a number of health benefits especially cancer chemopreventive, antidiabetic, antiangiogenic and antimutagenic properties including hypocholesterolemic, antibacterial and antiaging activity [7,8]. EGCG has shown health-promoting effects through different pathways such as anti-inflammatory and antiatherogenic activities [9,10], nitric oxide synthase gene expression activity [11], and sympathetic nervous system activity as well as eliciting an amyloid protein remodeling activity [12–14]. However, more researches are needed to identify molecular targets and assess the role of EGCG in health outcomes.

Obesity is directly connected to serious diseases such as cardiovascular disease, diabetes type 2 and others. [15,16]. Therefore, prevention of obesity has become an important issue in recent years, especially in developed countries. Research and development are in progress around the world to discover functional nutraceuticals to help in preventing obesity, but no decisive compound has yet to emerge [17,18]. Lately, it has also been suggested that EGCG has a thermogenic effect, with the potential to increase energy expenditure (EE) and promote fat oxidation (FOX) that could lead to weight loss. The EGCG-induced weight loss approaches may include, but are not limited to, the mechanisms of suppression/inhibition of fat absorption, promotion of FOX and combustion/utilization, and promotion of energy consumption *via* inhibition of catechol-*o*-methyl-transferase [6,19–22]. Recently, Mähler et al. [23] tested the hypothesis that EGCG improves energy metabolism and metabolic capacity at rest and during exercise in patients with multiple sclerosis. They found that there was no overall significant effect of EGCG on FOX when all

* Corresponding author.
E-mail address: mkapoor@taiyokagaku.co.jp (M.P. Kapoor).

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subjects were combined. However, they did observe an interaction at least in men, that EGCG treatment in multiple sclerosis patients improves muscle metabolism during exercise. Several human studies have investigated the effect of green tea catechins (GTCs) including EGCG on the biomarkers of exercise performance; however, additional research is usually recommended to compete the documentation about EGCG's influence on energy metabolism and athletic performance in general population [24,25]. It has been reported that EGCG consumption influences respiratory quotient (RQ) and EE *in vivo* [26,27]. Changing energy balance in the negative direction by increasing EE and/or decreasing energy intake may confer a metabolic advantage that contributes to greater FOX that leads to a weight loss, wherein resting EE represents the amount of calories required for a 24-h period by the body during a nonactive period. The EE can be measured indirectly with a metabolic cart by the analysis of metaphysis of respired gases (*i.e.*, O_2 uptake VO_2; CO_2 output VCO_2). The RQ represents the ratio of carbon dioxide exhaled to the amount of oxygen consumed by the individual (VCO_2/VO_2). RQ is useful in interpreting the results of the EE. The purpose of this systematic review and meta-analysis is to perform a comprehensive assessment of these known issues related to fat metabolism during the use of EGCG. Therefore, based on the preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [28,29], we have compiled this systematic review and meta-analysis of available studies to signify the clinical relevance of EGCG supplementation on EE leading to body FOX.

2. Materials and methods

2.1. Outlines of retrieval enforcement methods

Relevant clinical studies of the effect of EGCG on EE for anticipated FOX in human were identified in two stages. Agreeing to the quality of reporting of meta-analysis, MEDLINE (PubMed, http://pubmed.gov), National Library of Medicine Database, Embase, Cochrane Library and CINAHL Database were employed for English language publications, wherein a systematic computerized literature search was performed from January 1995 up to September 2015 (*i.e.*, 20 years) dealing with EGCG effects on amelioration of FOX to promote weight loss. JST (JICST, JSTPLUS and JMEDPLUS) database was searched for retrieval of related Japanese literature, with no restrictions in time. Suitable identical keywords were set up for all the search engines. The text keywords *green tea extract*, *green tea catechin* and *EGCG* of main domain were paired with following subdomain words: *fat oxidation*, *obesity*, *weight loss*, *weight management*, *metabolic syndrome or energy expenditure.* Additionally, the references from the retrieved clinical trial articles or any review articles were manually investigated to further identify possible additional relevant studies. An additional search methodology was further applied as a single search designed on the basis of keywords to look for the word in abstract or word in chemical name. The following keywords were used for the further citations search in all search engines as *epigallocatechin gallate*, *epigallocatechin3-gallate*, *epigallocatechin-3-gallate*, *epigallocatechin-3-o-gallate*, *epigallocatechol-gallate* or *galloylepigallocatechin*. The search was restricted to reports of clinical trials in adult humans. Limitations were set up for original papers and short communications, whereas preliminary drafts were excluded. Further, the limitations were narrowed to search the citation only in the medical, biological sciences, food sciences and food industry-related areas, and therein only published studies were considered. The Japanese citations retrieved through an identical search strategy were subjected to identification procedure along with English language citations under the already set inclusion and exclusion criteria. Finally, the search results were reported in accordance with the guidelines provided in the PRISMA statement [28].

2.2. Study selection procedure

Well-defined inclusion and exclusion criteria were used for the selected studies. The included studies were required to: (i) be a clinical trial; (ii) be a study that investigated the association between the intake of EGCG and weight management related parameters only (no combination with other dietary polyphenols nor other catechins); (iii) be a randomized trial or controlled intervention study; (iv) be a parallel or crossover or pretest/posttest design study; (v) be a trial of any duration with either single or chronic doses of EGCG intake; (vi) be a direct comparison of active EGCG ingredient *vs.* placebo or high *vs.* low dosage of EGCG; (vii) be a study with a trial quality greater than or equal to 3 points judged by jaded score [30]; (viii) be a study reporting at least one of the following parameter: FOX, EE and RQ or possibly body mass index (BMI), waist circumference (WC), body mass/weight or body fat mass; (ix) be a study of adult human participants; (x) be a study with reasonable tolerable dosages of EGCG either as regular beverage or tablets or capsule; and (xi) be a study approved by the authorized institutions.

Studies were excluded when they did not meet any of the aforementioned criteria and in event of no original data, or duplication of another published report, or subjects had suffered from any chronic diseases unlike otherwise stated [31,32].

2.3. Data extraction

To ensure that variation was not caused by systematic errors in study design or execution, two independent researchers (M.P.K. and M.S.) assessed the quality of articles according to the prescribed selection criteria and finally data were extracted for statistical analysis. In case of discrepancy an arbitration was sought within authors (Y.K. and T.O.) to resolve any specific issues with pointed discussions. The pertinent data regarding general background information about the studies were extracted. That data include, first name of author, year of publication, study design, formulation used, participant information, dosages, study duration, main diagnoses, study outcomes and related explanations (see Table 1).

2.4. Data retrieval and statistical analyses

Data were analyzed for meta-analysis using Review Manager Software (RevMan, version 5.3; http://ims.cochrane.org/revman) provided by Cochrane collaboration. Statistical analysis was completed following the guidelines in the Cochrane handbook for systematic reviews of interventions [32]. The net changes in each of the study parameters that were estimated from baseline and follow-up means (M) and standard deviations (S.D.s) were used to calculate the pooled effect. When S.D.s were not directly available, their values were calculated from standard errors, 95% confidence intervals (95% CIs) or *P* values. The percent changes in mean and S.D. values were entirely excluded when we extracted data for the meta-analysis. Weighted mean differences (MDs) with corresponding 95% CIs were calculated for continuous/dichotomous outcomes of net changes in the effective values for continuous data [32–34]. The I^2 statistic that measures the extent of variability across trials was examined for heterogeneity between randomized controlled trials (RCTs) with its degree of freedom *P* value. Data were pooled using fixed-effect model. In case of significant heterogeneity, results were further confirmed by using the random-effect model [33]. The χ^2 test with a *P* value of <.10 and values of I^2>50 indicated a significant heterogeneity; however, to display clarity of the information on data analysis, we have provided the results calculated from both fixed- and random-effect models, using restricted maximum-likelihood estimation to estimate heterogeneity in the effect size [35,36]. A two-tailed *P*<.05 was considered statistically significant. Similarly, the previously defined subgroup analyses were performed to estimate the possible source of heterogeneity among the studies using other related study parameters. Publication bias was addressed with funnel plots including assessing the risk of bias domain for each selected study according to standards of the Cochrane collaboration guidelines: concealment of allocation, sequence generation, blinding issues related to participants, personal, outcome assessors and data analyst and others, incomplete outcome data, selective outcome reporting and additional sources of bias [32,36]. The concerned items were classified as adequate, yes, inadequate no or unknown/unclear (Table 2). Secondary factors on the primary outcomes were evaluated and the defined subgroup analyses were performed where necessary. In addition, the Jaded score [30] was also ascribed to assess the quality of the included RCTs. The RCTs scored 1 point for each area addressed in the study design, preferably randomization, blinding reporting of withdrawals, allocation of concealment and random numbers generation, with possible scores of between 0 and 5 depending on the quality of the RCTs, wherein the higher number represented a better quality of RCTs [28].

3. Results

3.1. Results of retrieved literature

The number of retrieved English language citations for further comprehensive investigations searched using aforementioned, paired combinations is listed in Table 1. The complete schematic flow diagram of selected clinical studies is illustrated in Fig. 1. The initial search resulted in a total of 2163 relevant English language citations and 415 Japanese language citations. After primary screening of titles and abstracts, 1492 duplicate citations were excluded. Of the 1086 nonduplicate citations retrieved through the adopted search strategy, 109 potentially relevant citations met the primary inclusion criteria and were selected for secondary evaluation. Further, the 102 citations were excluded during the secondary screening/evaluation and due to incomplete information despite author contact. The remaining 7 eligible citations [24,26,27,37–40] were considered for this systematic review and meta-analysis and 1 additional citation [25] was identified for inclusion through a manual cross-reference search of available