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Review

Nutraceuticals for body-weight management: The role of green tea catechins

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HIGHLIGHTS

- Beneficial effects of green tea catechin-caffeine mixture on body-weight management.
- Limitations: high caffeine intake, protein intake, COMT *Val108/158Met* polymorphism.
- Fat absorption and composition of the gut microbiota may play a role.

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ABSTRACT

Green tea catechins mixed with caffeine have been proposed as adjuvants for maintaining or enhancing energy expenditure and for increasing fat oxidation, in the context of prevention and treatment of obesity. These catechins-caffeine mixtures seem to counteract the decrease in metabolic rate that occurs during weight loss. Their effects are of particular importance during weight maintenance after weight loss. Other metabolic targets may be fat absorption and the gut microbiota composition, but these effects still need further investigation in combination with weight loss. Limitations for the effects of green tea catechins are moderating factors such as genetic predisposition related to COMT-activity, habitual caffeine intake, and ingestion combined with dietary protein.

In conclusion, a mixture of green tea catechins and caffeine has a beneficial effect on body-weight management, especially by sustained energy expenditure, fat oxidation, and preservation of fat free body-mass, after energy restriction induced body-weight loss, when taking the limitations into account.

Contents

1. Introduction

Overweight and obesity are the result of an imbalance between energy intake and energy expenditure [1, 2]. A negative energy balance is needed to produce weight loss and can be achieved by decreasing energy intake while energy expenditure is sustained [3, 4]. The prevention

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of the usual decline of energy expenditure during dieting by the use of thermogenic ingredients is of interest; especially because these ingredients do not contain energy themselves, yet stimulate energy expenditure. In this respect a green tea catechins-caffeine mixture appears to be relevant. Green tea is made from the leaves of the *Camellia sinensis* L. species of the Theaceae family; it is a non-oxidized, non-fermented product [5, 6]. It contains several polyphenolic components, particularly epicatechin, epicatechin gallate, epigallocatechin, and the most abundant and bioactive component, epigallocatechin-3-gallate (EGCG) [7]. Since these tea leaves have been processed the least, they contain the most catechins.

Caffeine, which is also present in tea, and which in most of the studies is present as a green tea catechin-caffeine mixture, possesses thermogenic effects and can stimulate fat oxidation, in part via sympathetic activation of peripheral tissues [8–11]. Green tea extracts containing caffeine and catechin polyphenols have been reported to have an effect on body weight [7, 12] and energy expenditure [12–14]. In the latter context, the thermogenic effect of a green tea catechins-caffeine mixture was shown to increase 24 h energy expenditure and fat oxidation, and such stimulation of metabolism was not observed with an equivalent amount of caffeine [13]. Green tea has thermogenic properties and promotes fat oxidation beyond that explained by its caffeine content per se. The thermogenic properties beyond those explained by the caffeine content may result from the catechins or via interactions between catechins and caffeine. However, some moderating factors limit the beneficial effects of green tea catechins-caffeine mixtures, which should be taken into account. Nonetheless, this mixture still is considered as a feasible weight-controlling ingredient.

2. Body weight management

Improved body-weight loss and body-weight maintenance over the long-term, using mixtures of green tea catechins and caffeine has been reported [12, 15–22]. In short-term studies, mainly the effects on energy expenditure and fat oxidation, which are important metabolic targets for body-weight management have been addressed [13]. Moreover, meta-analyses on short term as well as long-term studies showed the relevant beneficial effects of catechins and caffeine [15, 16, 19].

An example of these studies is a weight loss study resulting in a weight loss of 1.2 kg in 24 elderly subjects who consumed green tea during two months vs. no weight loss in the control group [20]. Furthermore, weight-maintenance studies have shown body-weight maintenance after body-weight loss induced by an energy-restricted diet, while consuming green tea catechins and caffeine mixtures [17, 21, 22]. In addition, a meta-analysis showed a significantly decreased body-weight or body-weight maintenance of ~1.31 kg (95% CI: −2.05, −0.57 kg; $I^2 = 94\%$), due to consumption of a green tea catechins caffeine mixture [16]. Moderating factors appeared to be ethnicity and habitual caffeine consumption. A following meta-analysis [19] showed that green tea catechins with caffeine decreased body-weight (−1.38 kg: 95% CI: −1.70, −1.06 kg; $I^2 = 0\%$), body mass index (BMI), and waist circumference compared with caffeine alone. Green tea catechins with caffeine consumption also decreased body weight (−0.44 kg: 95% CI: −0.72, −0.15 kg; $I^2 = 0\%$) when compared with a caffeine-free control. Importantly, studies that evaluated green tea catechins without concomitant caffeine administration did not show benefit on any of the assessed anthropometric endpoints, suggesting that the synergistic effect between catechins and caffeine is necessary for obtaining favorable effects on body weight management. However, a too high habitual caffeine intake (>300 mg/d) counteracts this effect [17]. In that respect weight gain in high-habitual consumers compared with low-habitual caffeine consumers after 12 week consumption of a green tea catechin caffeine mixture was observed [21]. This can be explained in the light of data analysis suggesting an apparent dose-response relationship between acute caffeine administration on 24 h energy expenditure, while the caffeine-catechin relationship to caffeine dose is shifted upwards [23].

Not only high habitual caffeine consumption, but also the matrix of foods or meals in general may influence its actions on energy metabolism. For instance, protein intake interferes with effects of green tea catechin caffeine mixtures in acute [24–29] as well as long term studies [30, 31]. A green tea catechin caffeine intake does not add synergistically to the beneficial effect of a high-protein diet during weight maintenance after weight loss, while protein intake alone as well as consumption of the green tea mixture showed beneficial effects based upon preservation of fat free body mass and sustained energy expenditure despite being in negative energy balance [30]. The inhibitory effect of protein, especially proline-rich caseins, on the effect of green tea catechins due to the formation of protein-polyphenol complexes that reduce the absorption or that produce metabolites without thermogenic actions [31–36] may cause this phenomenon. On the other hand, the bioavailability of catechins can be enhanced by ingestion in combination with sucrose and ascorbic acid [37].

Before addressing the moderating factor of ethnicity, likely being caused by genetic predisposition, the mechanisms of action will be reviewed.

3. Mechanisms of action

Catechins and caffeine separately and synergistically may affect energy expenditure, fat oxidation, and possibly fat absorption, with a potential impact on weight loss and weight maintenance [37, 38]. Catechins upregulate lipid-metabolizing enzymes via NF-κB (nuclear transcription factor κB) and thereby stimulate fat oxidation [39–41]. Tea catechins block nuclear transcription factor κB (NF-κB) activation by inhibiting the phosphorylation of IκB (inhibitor of κB) [40]. This action prevents NF-κB from inhibiting the peroxisome proliferator–activated receptors (PPARs) that are important transcription factors for lipid metabolism [41]. Thus, mRNA expression of lipid-metabolizing enzymes such as acyl-CoA oxidase and medium-chain acyl-CoA dehydrogenase (MCAD) is upregulated. The upregulation of acyl-CoA oxidase, a peroxisomal β-oxidation enzyme, and MCAD, a mitochondrial β-oxidation enzyme, in the liver [41] suggests β-oxidation activation followed by an increase in fat oxidation.

They also inhibit COMT (catechol-O-methyltransferase), leading to an increase in norepinephrine and adenyl cyclase, decreased glucose uptake, and enhanced lipolysis [14, 39].

Caffeine acts as an antagonist on adenosine, thereby diminishing the usual decrease in concentrations of norepinephrine. Phosphodiesterase is inhibited by caffeine, and protein kinase increases. Catechins also inhibit pancreatic and gastric lipases and attenuate fat emulsification, whereby fat absorption is decreased [14]. Taken together, the methylation of catechins by catechol-O-methyltransferase (COMT), and the inhibition of phosphodiesterase by caffeine appear to be the principal mechanisms behind the stimulating properties of a green tea catechins caffeine mixture [14]. The inhibition of both enzymes activates a signal cascade that stimulates the SNS (sympathetic nervous system); together with HSL (hormone-sensitive lipase) and upregulation of UCPs (uncoupling protein) this leads to increased energy expenditure and fat oxidation [14, 37, 38].

However, there has been criticism about whether COMT inhibition is of importance in the thermogenic effects of green tea catechins-caffeine [42]. Yet, more evidence for the role of COMT inhibition from in vivo studies in humans has appeared, namely from the studies on genetic polymorphism [43–45]. Subjects carrying the $COMT^H$ allele increased energy expenditure and fat-oxidation upon ingestion of green tea catechins vs. placebo, whereas $COMT^L$ allele carriers reacted similarly to green tea catechins and placebo ingestion. The differences in responses were due to the different responses on placebo ingestion, but similar responses to green tea catechins ingestion, pointing to different mechanisms. The different alleles of the functional COMT *Val108/158Met*

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polymorphism appear to play a role in the inter-individual variability for energy expenditure and fat oxidation after green tea catechins treatment [44].

4. Bioavailability of catechins

After ingestion, catechins are hydrolyzed by enzymes and colonic microflora, and during absorption, metabolites are produced by conjugation catalysed by phase II enzymes in the small intestine, enterocytes, and liver. Also conjugation via methylation, glucuronidation, and sulfation occurs. This decreases the hydrophilicity of catechins, promotes their excretion via bile and urine and improves their absorption via passive diffusion [46, 47]. Catechins are either incorporated in tissues or returned to the intestines, after circulation. Catechins can be excreted in the feces or further metabolized and reabsorbed via enterohepatic recycling in the intestine [48–50].

5. Dietary fat absorption

Catechins may inhibit pancreatic and gastric lipases and thus attenuate fat emulsification [51–58]. An increase in the excretion of lipids in the feces of 12 healthy subjects after a 10-d treatment with a catechin-rich beverage during a high-fat diet compared with a control beverage was observed in humans [59]. Consequently, catechins may limit the absorption of dietary fat. In this respect, fat absorption was assessed in sixty Caucasian men and women (BMI: 18–25 kg/m^2 or >25 kg/m^2 age: 18–50 years) in a randomized, placebo-controlled trial in which fecal energy content, fecal fat content, resting energy expenditure, respiratory quotient, body composition and physical activity were measured twice (baseline, vs. week 12). For 12 weeks, subjects consumed either green tea catechins mixed with caffeine (>0.56 g/d epigallocatechin-gallate + 0.28–0.45 g/d caffeine) or placebo capsules. Preceding the measurements, subjects recorded energy intake for four consecutive days and collected feces for three consecutive days. Here no significant differences between groups and no significant changes over time were observed for the measured variables and it was concluded that supplementation for 12 weeks in 60 men and women did not have a significant effect on fecal energy content, fecal fat content, resting energy expenditure, respiratory quotient, body composition [60].

6. Role of gut microbiota

In humans, the gut microbial composition differs between obese and lean individuals, with obese individuals having a decrease in Bacteriodetes [61, 62]. Moreover, obese people have a lower bacterial diversity than lean people [63, 64]. Furthermore, an increase in body weight of germ free mice occurred when fecal microbiota from obese people was transplanted into germ-free mice, while body weight did not increase in mice receiving microbiota from lean people [65]. This suggests that the gut microbiota of obese people is more efficient in extracting energy from the diet and to store this energy as fat, resulting in an increase in body weight [66, 67].

A possible role of tea catechins in body weight management has been suggested to be attributed to their effect on gut microbiota [66]. The gut microbiota metabolizes catechins and hydrolyzes them to promote absorption. Bacteriodetes are more capable of degrading glycans than Firmicutes, and they are less repressed by polyphenols, which may lead to a different composition of the gut microbiota [66]. The increase in energy expenditure might partly be attributed to the metabolic capacity of the gut microbiota. However, by decreasing fat absorption, catechins may decrease the energy content and thereby prevent a change in composition of the gut microbiota [66].

In this respect, a randomized placebo controlled trial examined whether green tea supplementation for 12 weeks induces changes in composition of the human gut microbiota in 58 Caucasian men and women (BMI 18–25 kg/m^2 or ≥25 kg/m^2), aged between 18 and 50 years [67]. For 12 weeks, subjects consumed either a green tea catechin-caffeine mixture (>0.56 g/d epigallocatechin-gallate + 0.28–0.45 g/d caffeine) or placebo capsules. Fecal samples were collected twice (baseline, week 12) for analyses of total bacterial profiles by means of IS-profiling (IS-pro), a 16S–23S interspacer (IS) region-based profiling method. No significant differences between treatment groups and no significant changes over time were observed for body composition. Analysis of the fecal samples in subjects receiving the green tea catechins-caffeine mixture or placebo showed similar bacterial diversity and community structures, indicating there were neither significant differences in composition of the gut microbiota between groups nor significant changes over time (baseline vs. week 12). Although, there were no significant differences between normal weight and overweight subjects in response to green tea, a reduced bacterial diversity in obese as compared to normal weight subjects was observed. It was concluded that supplementation for 12 weeks did not have a significant effect on composition of the gut microbiota. It is likely that green tea catechins only have beneficial effects on weight maintenance after weight loss [68], and these effects of catechins on body weight after a diet-induced weight loss may occur via a change in bacterial composition. This may as well be an explanation for the fact that no difference in bacterial composition was observed when subjects were in energy balance. In general, the gut microbial composition is quite stable in adults, therefore a change in body weight or extreme switches in dietary patterns may be needed to have a significant change in microbial composition [68].

7. Genetic predisposition

It may be that behind the seemingly moderating factor of ethnicity, a genetic predisposition for the efficacy of green tea catechins on energy metabolism is hidden, since interactions of different COMT polymorphisms are associated with ethnic origins. The *Val*(*108*/*158*)*Met* polymorphism, which replaces valine with methionine, changes COMT activity with an interindividual variability of ~3-fold. Asian populations appear to have a higher frequency of the thermo-stable, high-activity enzyme COMT^H allele (*Val*/*Val* polymorphism) than do white populations, who have a higher frequency of the thermo-labile, low-activity enzyme COMT^L allele (*Met*/*Met* polymorphism); half of the white population is homozygous for the COMT^L allele (25%) and the COMT^H allele (25%). The other 50% of this population is heterozygous (*Val*/*Met* polymorphism). This genotype may explain the difference in sensitivity to green tea catechin caffeine mixtures [43, 68, 69]. Experimentally it appeared that acute consumption of the green tea catechin mixture vs. placebo increased energy expenditure and fat oxidation in the COMT^H allele carriers, whereas no differences were observed in the COMT^L allele carriers [44]. However, different polymorphisms do not seem to have a large impact on the absorption and metabolism of catechins [45].

8. Summary and conclusion

Green tea catechins mixed with caffeine have been shown to have beneficial effects on body-weight management, especially on body-weight maintenance after energy restriction induced body-weight loss, based upon sustained energy expenditure, fat-oxidation, and preservation of fat free body-mass. Limitations of these effects are a too high habitual caffeine intake, a combination with protein intake, and a genetic predisposition by among others the COMT^L allele. These effects appear either during body-weight management after body-weight loss, or over the short term. Over the long term, hardly any effects have been shown without the application of energy restriction.

Effects via limited fat-absorption or effects on the gut microbial composition, assessed in energy balance, were not shown, which may be attributable to the lack of an energy restriction situation.

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Further studies on the mechanisms and efficacy of green tea catechins mixed with caffeine are required, with respect to their bioavailability and metabolism. Determination of the role of genetic predisposition is necessary, including more polymorphisms and haplotypes. A new area of research may be a possible relation between tea and sleep. The green tea mixture contains the amino acid L-theanine, which increases α-wave activity associated with being awake and mentally relaxed. Also stimulating effects on δ-waves, associated with deep sleep, and θ-waves, associated with light sleep, thereby perhaps affecting sleep quality [70] have been reported. The functional polymorphisms of COMT mentioned before also modulate sleep homeostasis due to their dopaminergic signaling [71]. Thus, investigations on the relation between tea and sleep are warranted.

In conclusion, a mixture of green tea catechins and caffeine has a beneficial effect on body-weight management, especially by sustained energy expenditure, fat oxidation, and preservation of fat free body-mass, after energy restriction induced body-weight loss, when taking the limitations into account.

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