Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Epigallocatechin Gallate (EGCG)

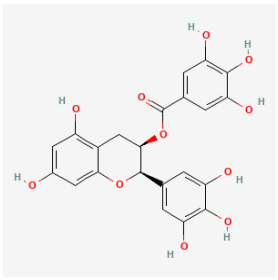
Evidence Summary

EGCG may lower total and LDL cholesterol and protect against respiratory infections such as influenza. High dose EGCG supplementation may increase liver enzymes.

Neuroprotective Benefit: Some cognitive benefits are seen with EGCG in Down syndrome patients. Two trials in multiple sclerosis failed to show benefit. Long-term cognitive effects of EGCG in healthy adults are unknown.

Aging and related health concerns: EGCG lowers total and LDL cholesterol and protects against influenza and other upper respiratory tract infections. Clinical trials in people with increased risk of cancer have not found preventive benefits of EGCG.

Safety: EGCG supplements are considered safe for most people when taking physiologic doses, but high doses have been associated with elevated liver enzymes.

Availability: OTC, present in green tea	**Dose**: not established; doses used in clinical trials varied widely; many studies have used doses between 300-400 mg daily, orally	**Chemical formula**: $C_{22}H_{18}O_{11}$ **MW**: 458.4  Source: PubChem
Half-life: 2-6 hours	**BBB**: penetrant	
Clinical trials: Clinical trials testing EGCG specifically (as opposed to green tea extract) have enrolled up to 122 patients.	**Observational studies**: No observational studies have examined EGCG intake specifically. Numerous large observational studies have examined green tea and green tea extract intake.	

What is it?

Green tea, white tea, and black tea are made from dried leaves of *Camellia sinensis*, a perennial evergreen shrub. About 30-40% of the dry weight of *Camellia sinensis* tea leaves is accounted for by catechins, which are antioxidants [1]. The 6 major tea catechins are epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG), and epicatechin (EC), gallocatechin, and catechin. Of these, EGCG is the most abundant and represents 50-80% of total catechins [2]. EGCG is the most prevalent catechin in dietary supplements and its use has increased among US adults [3]. EGCG is a popular supplement for its purported cardioprotective, neuroprotective, and anti-cancer effects. EGCG is a peroxynitrite scavenger that reduces free radicals [4]. It also acts as a chelator of iron and other metals. EGCG is abundant in green tea and white tea, but black tea contains significantly less EGCG, as it is oxidized to thearubigin and theaflavins during the fermentation process.

Green tea extract typically contains a significant amount of EGCG—most green tea extract supplements are roughly 50% EGCG (Examine.com).

Neuroprotective Benefit: Some cognitive benefits are seen with EGCG in Down syndrome patients. Two trials in multiple sclerosis failed to show benefit. Long-term cognitive effects of EGCG in healthy adults are unknown.

Types of evidence:

- 6 double-blind randomized clinical trials, 2 in multiple sclerosis, 1 in Alzheimer's disease, 1 in Down Syndrome, and 2 acute studies in healthy adults
- 1 pilot clinical study in people with Down Syndrome
- 9 laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

No human studies have evaluated whether EGCG can protect from cognitive decline.

Some positive effects of EGCG on cognitive function have been observed in people with Down syndrome, though the doses used were very low compared to other clinical studies [5; 6]. In a pilot study of 29 patients with Down syndrome, EGCG (9 mg/day) for 3 months significantly improved episodic memory [6]. The EGCG-treated group showed a higher percentage of correct answers in visual memory recognition compared to placebo and a trend for a benefit with EGCG was observed for working memory and psychomotor speed. In a phase II double-blind randomized controlled trial of 84 people with Down syndrome, EGCG (9 mg/day) treatment combined with cognitive training for 6 months was associated with significantly higher scores in visual recognition memory, inhibitory control, and adaptive behavior compared to the group receiving placebo with cognitive training [5]. No significant differences were seen in measures of social skills and quality of life. Phase 3 trials will be needed to assess and confirm long-term efficacy of EGCG and cognitive training in this population.

Effects of acute EGCG treatment have also been examined in healthy adults. In one double-blind randomized controlled trial of 31 healthy adults, EGCG treatment significantly increased calmness and reduced stress, and EGCG treatment was associated with a significant overall increase in alpha, beta, and theta activities [7], which are associated with relaxation, arousal/focused attention, and quiet wakefulness, respectively [8]. These results are consistent with anecdotal accounts that green tea is relaxing and alerting. In another double-blind randomized controlled trial in healthy adults, administration of 135 mg EGCG resulted in reduced cerebral blood flow in the frontal cortex compared

to placebo, but no significant differences were observed for cognitive performance or mood measures [9].

In a double-blind randomized controlled trial of 99 older adults with subjective cognitive decline or mild cognitive impairment, 2 grams of matcha daily (containing 170 mg of catechins and 48 mg of theanine) for 12 months significantly improved the social acuity score (p=0.028), as evaluated by the perception of facial emotions [10]. There was also a trend toward improvement in sleep quality (measured by change from baseline on the Pittsburgh Sleep Quality Index scores) with the matcha intervention compared to placebo (p=0.088). However, the primary outcomes, Montreal Cognitive Assessment (MoCA) or Alzheimer's Disease Cooperative Study Activity of Daily Living (ADCS-ADL) scores showed no significant changes with the matcha intervention compared to placebo. There were also no significant differences between matcha and placebo groups for reaction time, complex attention, cognitive flexibility, executive function, simple attention, ADCS-MCI-ADL, MMSE, ADAS-J cog, or Repeatable Battery for Assessment of Neuropsychological Status (RBANS).

Two clinical trials have been carried out in multiple sclerosis, both of which have shown a lack of benefit with EGCG. In a double-blind randomized controlled trial of 122 patients with relapsing-remitting multiple sclerosis, EGCG treatment (800 mg/day, orally) as an add-on to glatiramer acetate for 18 months did not significantly improve the primary outcome (proportion of patients without new hyperintense lesions) [11]. There were also no significant differences in other radiologic outcomes, including T2-weighted MRI lesion volume, T1-weighted MRI hypointense lesion number or volume, number of cumulative contrast-enhancing lesions, percent brain volume change, or clinical parameters (EDSS, MS functional composite, and annualized relapse rate). Pharmacologic analysis found wide-ranging plasma levels of EGCG. In a double-blind randomized controlled trial of 61 patients with progressive multiple sclerosis, EGCG treatment (up to 1200 mg daily, orally) for 36 months did not significantly improve the primary outcome, which was the rate of brain atrophy [12]. The rate of decrease in brain parenchymal fraction was 0.0092 ± 0.0152 in the EGCG group and -0.0078 ± 0.0159 in the placebo group. None of the secondary MRI and clinical endpoints (EDSS, CDP, MSFC, BDI, fatigue scores) showed significant group differences. In the EGCG-treated group, 18 of 27 patients (66.67%) were relapse-free during the study. In the placebo group, 20 of 28 patients (71.43%) were relapse-free during the study. In the open-label extension study, 17 patients from the EGCG group and 15 patients from the former placebo group were available for follow-up and at month 48, there were no significant differences in the rate of brain atrophy or any other clinical progression parameters.

Human research to suggest benefits to patients with dementia:

No human studies have tested the use of EGCG itself for dementia. In a double-blind randomized controlled trial of 48 people with Alzheimer's disease and 52 controls, consumption of an antioxidant beverage containing extracts of green tea (Suphenon 90LB) and apple (AF POMM 9050) for up to 8 months was associated with decreased biomarkers of oxidative stress [13]. The beverage prevented the decrease in total antioxidant status, but additional studies are needed to see whether the decrease in oxidative stress markers in AD patients correlates with improved cognitive status.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

EGCG is thought to promote neuroprotection by chelating transitional metals (iron and copper), inhibiting oxidative stress, and reducing inflammation [14], though much of the evidence comes from preclinical studies. *In vitro* and *in silico* studies have also shown that green tea polyphenols inhibit acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) [15; 16].

A review of the neuroprotective mechanisms of EGCG has summarized the preclinical evidence of EGCG, which included anti-inflammatory, antioxidant, anti-amyloid, autophagy-promoting, cholesterol metabolism-promoting, and anti-aging effects [4].

In mouse models of Alzheimer's disease, EGCG treatment (10-50 mg/kg/day) resulted in many benefits: improved cognitive function [17; 18], improved psychomotor coordination [19], reduction of both soluble and insoluble Aβ levels in the cortex and hippocampus [18], reduction of phospho-tau [18], reduced AChE activity [17], and improved measures of oxidative stress (glutathione peroxidase activity, nitric oxide metabolites, and reactive oxygen species) [17].

In a mouse model of accelerated aging (SAMP8), EGCG treatment (5-15 mg/kg/day) for 60 days rescued cognitive decline and reduced Aβ accumulation [20]. In a rat model of chronic unpredictable mild stress, EGCG treatment (25 mg/kg/day, i.p.) significantly improved memory performance, attenuated pathological abnormalities in the hippocampus, reduced Aβ levels, and restored autophagic flux [21].

Cognitive benefits were also observed in young rats that were treated with polyphenon E (63% EGCG, 11% EC, 6% EGC, and 6% ECG) mixed with water for 26 weeks [22]. Polyphenon E-treated rats had improved reference and working memory. They also had lower plasma concentration of lipid peroxides,

decreased reactive oxygen species in the hippocampus, and greater plasma ferric-reducing power compared to controls.

Doses used in rodent studies are comparable to those used in human clinical studies after accounting for differences in body surface area [23]. While a pharmacokinetic study in healthy volunteers has shown that a single dose of EGCG (up to 1600 mg) can result in micromolar plasma concentration (130-1392 ng/ml), outstanding questions include the extent of blood-brain-barrier permeability and the optimal doses of EGCG for neuroprotection in humans.

***APOE4 interactions**:* Unknown.

Aging and related health concerns: EGCG lowers total and LDL cholesterol and protects against influenza and other upper respiratory tract infections. Clinical trials in people with increased risk of cancer have not found preventive benefits of EGCG.

Types of evidence:

- 5 meta-analyses or systematic reviews
- 16 randomized controlled trials
- 2 other clinical trials, 1 on ovarian cancer recurrence and 1 in diabetes patients
- Numerous laboratory studies
- 2 review articles

Lifespan: EXTENDED IN RODENTS

Only preclinical data exist for lifespan studies. In male rats, EGCG treatment extended lifespan and delayed death on average by 8-12 weeks compared to the control group [24]. EGCG appeared to exert its protective effects by reducing liver and kidney damage and limiting age-associated inflammation and oxidative stress. EGCG inhibits NFκB signaling and activates the longevity factors FoxO3a and SIRT1. EGCG also extends lifespan in several strains of *C. elegans* [25].

Obesity/overweight: SMALL BENEFITS

In a randomized controlled trial of 70 overweight or obese men, consumption of decaffeinated green tea extract (~400 mg of EGCG, twice daily) was associated with a slight decrease in weight (by 0.64 kg),

whereas an increase in weight (by 0.53 kg) was observed in the placebo group[26]. These changes are unlikely to be clinically significant. In a double-blind randomized controlled trial of 83 obese women on energy-restricted diet, no significant differences in body weight, fat mass, or metabolism were observed with 12 weeks of EGCG (300 mg/day) treatment when compared to placebo [27]. Similar negative results were observed in another double-blind randomized controlled trial of 78 obese women receiving 12 weeks of green tea extract (~900 mg EGCG/day) [28].

In a 2023 meta-analysis of 11 randomized controlled trials including a total of 613 overweight/obese people, green tea catechin supplements (EGCG doses ranging from 208 to 857 mg daily, orally) for 6-16 weeks significantly decreased waist circumference (weighted mean difference [WMD]=-1.37 cm; 95% CI, -2.52 to -0.22 cm; p=0.019), but there were no significant effects on BMI [29].

Cholesterol: BENEFIT

In a large double-blind randomized controlled trial of 1075 postmenopausal women, supplementation with green tea extract (containing 843 mg of EGCG per day) for 1 year resulted in a significant reduction in circulating total cholesterol (-2.1% compared with 0.7% for placebo), LDL-cholesterol (-4.1% compared with 0.9%), and non-HDL cholesterol (-3.1% compared with 0.4%). There was no change in HDL concentration and a significant reduction in total cholesterol was observed only among women with high baseline total cholesterol levels (>200 mg/dl) [30]. In a double-blind randomized controlled trial of 78 obese women, consumption of green tea extract (~900 mg EGCG/day) for 12 weeks was also associated with a significant reduction in LDL and triglyceride and a marked increase in HDL, adiponectin, and ghrelin [28]. Other studies have shown an absence of EGCG effects on cholesterol levels [27].

In a 2023 meta-analysis of 11 randomized controlled trials including a total of 613 overweight/obese people, green tea catechin supplements (EGCG doses ranging from 208 to 857 mg daily, orally) for 6-16 weeks significantly increased HDL-cholesterol (weighted mean difference [WMD]=0.07 mmol/L; 95% CI, 0.01 to 0.14 mmol/L; p=0.031) and reduced triglyceride levels (WMD=-0.18 mmol/L; 95% CI, -0.35 to -0.02 mmol/L; p=0.032)[29].

In a 2023 meta-analysis of up to 55 randomized controlled trials, green tea extract supplementation (4 studies tested EGCG specifically) for 2-48 weeks significantly reduced total cholesterol (weighted mean difference [WMD]=-7.62; 95% CI, -10.51 to -4.73; p<0.001) and LDL-cholesterol (WMD=-5.80; 95% CI, -8.30 to -3.30; p<0.001), and significantly increased HDL-cholesterol (WMD=1.85; 95% CI, 0.87 to 2.84;

p=0.010)[31]. No significant effects were seen for triglycerides, though in subgroup analyses, significant reductions in triglycerides with green tea extract intervention were seen when both men and women were included in the study, when the duration of the intervention was longer than 12 weeks, when the dosage was less than 1000 mg/day, the baseline BMI was between 25-29.9 kg/m2, and when the baseline triglyceride levels were higher than 200 mg/dl. Randomized controlled trials included in the meta-analysis enrolled healthy people (29 studies) as well as people with type 2 diabetes (15 studies), liver disorders (3 studies), hypercholesterolemia (2 studies), overweight/obesity (3 studies), polycystic ovarian syndrome (2 studies), and others. Clinical trials were run in different countries including Australia, US, Iran, Brazil, UK, China, Spain, Japan, Taiwan, Lithuania, Poland, Netherlands, Finland, Pakistan, and Mexico.

Vascular function: BENEFIT

A double-blind randomized controlled trial of 42 patients with coronary artery disease reported that EGCG (300 mg/day) acutely improves endothelial function via enhancement of nitric oxide status [32]. However, these protective benefits disappear by 2 weeks of treatment.

Blood pressure: LITTLE/NO BENEFIT

In a randomized controlled trial of overweight or obese men, EGCG treatment (800 mg/day) for 8 weeks resulted in reduced diastolic blood pressure (mean change, -2.68 mmHg) [33]. However, other clinical trials have shown a lack of change in blood pressure [26; 34].

In a 2023 meta-analysis of 11 randomized controlled trials including a total of 613 overweight/obese people, green tea catechin supplements (EGCG doses ranging from 208 to 857 mg daily, orally) for 6-16 weeks did not significantly affect systolic or diastolic blood pressure [29].

In a 2023 meta-analysis of 28 randomized controlled trial arms, green tea extract supplementation (4 studies tested EGCG specifically) for 2-48 weeks significantly reduced diastolic blood pressure (WMD=-0.87; 95% CI, -1.45 to -0.29; p=0.003) [31]. Subgroup analyses indicated that a significant decrease in diastolic blood pressure was observed if the duration of intervention was ≤12 weeks, the dosage of supplementation was less than 1,000 mg/day, baseline values of diastolic blood pressure were more than 80 mmHg, and the baseline value of BMI was ≥ 30 kg/m2.

In a double-blind randomized controlled trial of 30 obese subjects, EGCG treatment (150 mg twice a day, orally) for 8 weeks significantly decreased systolic blood pressure, diastolic blood pressure, and mean arterial pressure ($p<0.05$ for all)[35]. EGCG treatment also increased the low-frequency (LF) to high-frequency power (HF) ratio (LF/HF ratio) ($p<0.05$), indicating a shift toward sympathetic dominance. It is not clear if this increase is a direct effect of EGCG as a sympathetic potentiator or an indirect compensatory response following blood pressure reduction.

Type 2 diabetes: LITTLE/NO BENEFIT

In a double-blind randomized controlled trial of 68 obese people with type 2 diabetes, 16 weeks of green tea extract (containing 856 mg of EGCG per day) treatment was associated with some benefits in metabolic measures including reduced HbA1C, HOMA-IR index, and insulin levels, and increased ghrelin levels [36]. More research is required to determine whether there are any clinical benefits in obese people with type 2 diabetes. Other studies have shown negative results. In a randomized controlled trial of overweight or obese men, EGCG treatment (800 mg/day) for 8 weeks had no effect on insulin sensitivity, insulin secretion, or glucose tolerance [33]. Similar negative results were obtained from a double-blind randomized controlled trial of 83 obese women that tested the effects of EGCG in combination with an energy-restricted diet [27]. While the clinical data are mixed, one of the ways in which EGCG may benefit diabetes patients is through inhibition of the S100A12-RAGE axis, which is thought to play a critical role in the progression of type 2 diabetes [37].

In a double-blind randomized controlled of 60 type 2 diabetes patients, EGCG treatment (300 mg/day, orally) for 2 months significantly decreased BMI, diastolic blood pressure, mean arterial pressure, and serum total cholesterol level compared with placebo in those who carried the risk A allele of the FTO (fat mass and obesity-associated; rs9939609) candidate gene associated with type 2 diabetes [38]. A gene-treatment interaction showed that those with the risk allele (AA or AT) showed a better response to EGCG than those without the risk allele.

In a 2023 meta-analysis of up to 55 randomized controlled trials, green tea extract supplementation (4 studies tested EGCG specifically) for 2-48 weeks significantly reduced fasting blood glucose (WMD=-1.67; 95% CI, -2.58 to -0.75; $p<0.001$) and HbA1c (WMD=-0.15; 95% CI, -0.26 to -0.04; $p=0.008$) but had no effects on fasting insulin or HOMA-IR [31]. In subgroup analyses, significant reductions in fasting blood glucose with green tea extract supplementation were observed when the baseline BMI was between 25-29.9 kg/m2, when studies included women only or men and women, when the duration of the intervention was longer than 12 weeks, when the dosage was less than 1000 mg/day, and when

baseline fasting blood sugar levels were less than 100 mg/dl. Subgroup analyses found that green tea extract supplementation significantly reduced HbA1c if the duration of intervention was ≤12 weeks, the dosage of supplementation was ≥1,000 mg/d, baseline values of HbA1c were less than 6.5%, male or both genders were involved, and the baseline value of BMI was ≥30 kg/m2.

Prostate cancer: UNCLEAR

In a randomized clinical trial of 97 men with elevated risk for prostate cancer (diagnosis of high-grade prostatic intraepithelial neoplasia [HGPIN] and/or atypical small acinar proliferation [ASAP]), daily Polyphenon E treatment (green tea catechins containing 400 mg of EGCG) for 1 year did not result in a significant reduction of prostate cancer cases [39]. However, a greater reduction of serum PSA was observed with Polyphenon E treatment compared to placebo. Also, in a secondary analysis, Polyphenon E treatment was associated with a lower rate of prostate cancer with ASAP diagnosis in men who were diagnosed with HGPIN without ASAP at baseline.

Colorectal cancer: LITTLE/NO BENEFIT

In a double-blind randomized controlled trial of 879 older people (50-80 years old) who have had ≥1 histologically confirmed colorectal adenoma(s) removed within 6 months, treatment with great tea extract (standardized to 150 mg of EGCG, twice daily, orally; Dr. LOGES + Co. GmbH/Winsen, Germany) for 3 years did not significantly affect the primary endpoint, which was presence of adenoma/colorectal cancer at the follow-up colonoscopy [40]. Adenomas are precursor lesions of colorectal cancers and removal of adenomas during colonoscopy reduces colorectal cancer incidence. The adenoma rate was 55.7% in the placebo and 51.1% in the green tea extract groups (p=0.16).

In a double-blind randomized controlled trial of 39 patients with prior colorectal advanced adenomas or cancers (and had ≥5 rectal aberrant crypt foci at a preregistration chromoendoscopy), green tea polyphenol treatment (Polyphenon E, 780 mg EGCG daily, orally) for 6 months did not significantly change percent reduction in rectal aberrant crypt foci number compared to placebo [41]. Adenoma recurrence rates at 6 months were similar between groups.

Breast cancer: UNCLEAR

In a randomized controlled trial of postmenopausal women at increased risk of breast cancer, green tea extract supplementation (including 843 mg of EGCG daily) for 12 months did not significantly change

percent mammographic density or absolute mammographic density [42]. However, in women between 50-55 years old, green tea extract supplementation significantly reduced percent mammographic density by 4.4% compared to placebo which showed a 1.02% increase (p=0.05). High mammographic density is an established risk factor for breast cancer.

In cultures of breast cancer and leukemia cells, EGCG reduced cellular proliferation and induced apoptosis via antioxidant and epigenetic modulation [43]. EGCG effects varied by cell and cancer type.

Upper respiratory infections: DECREASED

In a 2021 meta-analysis of 8 studies (5 randomized controlled trials and 3 cohort studies) including a total of 5048 participants, green tea catechins (via gargling, green tea catechin supplementation, or drinking green tea) showed significant effects on the prevention of influenza infection compared to the control group [44]. A meta-analysis of the 5 randomized controlled trials including 884 participants treated with green tea catechins (378-1500 mg EGCG per day) showed a statistically significant effect on the prevention of influenza infection compared to the control group (RR=0.67; p=0.005). A meta-analysis of the 3 cohort studies with 2,223 participants treated with green tea catechins showed statistically significant associations with lower influenza infection (RR=0.52; p=0.001). An analysis of 4 studies that tested green tea gargling (100 to 280 mg of EGCG per day) found a pooled RR of 0.70 (95% CI, 0.44 to 1.09, p=0.069). An analysis of 2 studies that tested green tea catechin capsules showed a significant effect in preventing influenza infection (RR=0.54; 95% CI, 0.26 to 1.13, p=0.003). Two studies tested green tea drinking (1-5 cups per day) which was associated with a significantly lower risk of influenza (RR=0.54, 95% CI, 0.37 to 0.80; p=0.002).

In a 2021 meta-analysis of 6 randomized controlled trials and 4 prospective cohort studies including a total of 3748 participants, tea gargling and tea catechins (all including EGCG) significantly prevented against upper respiratory tract infections (RR=0.74; 95% CI, 0.64 to 0.87)[45]. A significant preventive effect/association was observed in both randomized controlled trials (RR=0.79; 95% CI, 0.66 to 0.94) and in cohort studies (RR=0.67; 95% CI, 0.50 to 0.91), for influenza (RR=0.69; 95% CI, 0.58 to 0.84) and for acute upper respiratory tract infections (RR=0.78; 95% CI, 0.62 to 0.98). Tea and tea catechin consumption had an RR of 0.68 (95% CI, 0.52 to 0.87) and tea gargling had an RR of 0.83 (95% CI, 0.72 to 0.96).

Oxidative stress: DECREASED

In a 2024 meta-analysis of 10 randomized controlled trials, green tea extract supplementation (varied between 60 to 3000 mg/day) for 2-48 weeks significantly reduced an oxidative stress marker, malondialdehyde (MDA; WMD=-0.32 µmol/l; 95% CI, -0.46 to -0.19; p<0.001)[46]. Subgroup analysis showed that green tea extract supplementation significantly reduced MDA when doses were <1000 mg/day, doses were ≥ 1000 mg/day, in studies that enrolled women, in short-term studies under 12 weeks, and in people younger than 50 years old. A meta-analysis of 11 randomized controlled trials showed that green tea extract supplementation significantly increased total antioxidant capacity (TAC; WMD=0.10 mmol/l; 95% CI, 0.06 to 0.15, p<0.001). TAC was significantly increased in studies that enrolled men, short-term studies of under 12 weeks, and in people younger than 50 years old.

Inflammation: MIXED

In a 2024 meta-analysis of randomized controlled trials in people with metabolic syndrome and related disorders, green tea supplementation (green tea extract, green tea leaf powder, or EGCG) for 4 to 16 weeks significantly decreased blood TNF-α levels (-0.4293 pg/mL; 95% CI, -0.7821 to -0.0764; p=0.0171) but did not affect CRP and IL-6 levels [47]. Subgroup analysis showed that green tea supplementation in studies lasting ≤8 weeks significantly *increased* levels of CRP.

Safety: EGCG supplements are considered safe for most people when taking physiologic doses, but high doses have been associated with elevated liver enzymes.

Types of evidence:

- 2 Cochrane meta-analyses based on 14 and 11 randomized controlled trials examining the effects of green tea on weight loss and cardiovascular disease prevention, respectively
- 1 Cochrane meta-analysis based on 50 observational studies and 1 randomized controlled trial examining the effects of green tea
- 1 systematic review based on 4 randomized controlled trials testing the effects of EGCG
- 4 other clinical trials testing the effects of EGCG

Meta-analyses on green tea: There are 3 Cochrane meta-analyses that have included analysis of the safety profile of green tea, which did not examine EGCG specifically. A Cochrane meta-analysis based on 14 randomized controlled trials in overweight or obese adults (total of 703 subjects) reported that side effects from green tea consumption were mild and none of the serious adverse events observed were related to the intervention [48]. In another Cochrane meta-analysis based on 11 randomized controlled

trials in healthy adults and those at high risk of cardiovascular disease (total of 821 subjects), side effects were mild and no significant differences in adverse events were observed between green tea and placebo groups [49]. In another Cochrane meta-analysis based mostly on observational studies (27 case-control studies, 23 cohort studies, and 1 randomized controlled trial) that included a total of over 1.6 million subjects, green tea was judged to be safe at moderate and regular amounts (3 to 5 cups per day, up to 1200 ml/d) [50].

Clinical trials on EGCG: A systematic review based on 4 randomized controlled trials that examined the effects of relatively high doses of green tea extracts (containing 800-1600 mg of EGCG or 500 mg of green tea polyphenol) reported a few cases of liver enzyme elevation, but most of these cases were mild and there were no serious liver-related adverse events [51]. In a large double-blind randomized controlled trial of 1075 postmenopausal women, 843 mg of EGCG taken daily for 1 year was associated with a higher incidence of alanine aminotransferase (ALT) elevation, and 1.3% of women experienced ALT-related serious adverse events [52]. In a smaller double-blind randomized controlled trial of 83 obese women, EGCG treatment (300 mg/day) for 12 weeks did not cause any adverse effects on liver function biomarkers [27]. Liver-related adverse events may be more common at higher doses. Other common side effects of EGCG supplementation included nausea [39; 52].

In a double-blind randomized controlled trial of 122 patients with relapsing-remitting multiple sclerosis, EGCG treatment (800 mg/day, orally) for 18 months resulted in a wide range of EGCG plasma levels, but treatment was well tolerated with a similar incidence of mostly mild adverse events similar to the placebo group [11]. The most common adverse events were upper respiratory tract infections, gastrointestinal issues, and urinary tract infections. In the study, 17 patients in the EGCG group and 12 patients in the placebo group did not complete the study, which was due to personal reasons, changes in disease-modifying therapy, or noncompliance of study rules. In the EGCG group, 6 participants (10%) had a serious adverse event, and in the placebo group, 8 participants (13%) had a serious adverse event. None of the serious adverse events were considered related to the study drug. In the EGCG group, 1 participant had to stop the treatment because of elevated liver enzymes higher than 3-fold the upper limit of normal; elevated values normalized thereafter. One patient in each group discontinued due to stomach and digestion complaints.

In a double-blind randomized controlled trial of 61 patients with progressive multiple sclerosis, EGCG treatment (up to 1200 mg daily, orally) for 36 months resulted in adverse events that were mostly mild and occurred with a similar incidence to placebo [12]. One patient in the EGCG group had to stop treatment due to elevated aminotransferases (>3.5 times the upper limit of normal), which normalized

after seizing medication. The most common adverse events were flu-like infections, urinary tract infections, fractures and contusions after falling, and elevated liver enzymes, without statistical difference between groups. In the EGCG group, 2 patients reported partial intolerability to the study medication and discontinued the study, and 1 patient dropped out due to elevated aminotransferases. There were 11 participants (36.7%) in the EGCG group and 10 participants (32.3%) in the placebo group that had a serious adverse event, none of which were considered related to the study drug.

In a double-blind randomized controlled trial of 879 older people (50-80 years old) who have had ≥1 histologically confirmed colorectal adenoma(s) removed within 6 months, treatment with great tea extract (standardized to 150 mg of EGCG, twice daily, orally; Dr. LOGES + Co. GmbH/Winsen, Germany) for 3 years did not result in major differences in adverse events compared to placebo except for some differences in liver enzymes [40]. Elevations of transaminases were detectable in 0.5% of the participants in the run-in phase with 0.1% grade 3 elevations. During the randomized phase, there were more grade 1/2 elevations of alanine aminotransferase (2.9% vs 0.9%) and aspartate aminotransferase (2.7% vs 0.2%) in the green tea extract group compared to the placebo group.

In a double-blind randomized controlled trial of 39 patients with prior colorectal advanced adenomas or cancers, green tea polyphenol treatment (Polyphenon E, 780 mg EGCG daily, orally) for 6 months was well tolerated and adverse events did not differ compared to placebo [41]. One subject on placebo had two grade 3 adverse events (abdominal pain ad dyspepsia). One subject in the green tea polyphenol group had grade 2 hepatic transaminase elevations attributed to treatment. Stopping Polyphenon E treatment resulted in normalization of transaminase values.

Drug interactions: Three drugs are known to interact with green tea, but the interactions are judged to be minor and minimally clinically significant (drugs.com). The three drugs are warfarin (also known as Coumadin™ and Jantoven™), anisindione (or Miradon™), and dicumarol. Caffeine in green tea can also interact with some drugs (drugs.com).

Sources and dosing:

Clinical trials examining the effects of EGCG on cognitive function, cholesterol levels, blood pressure, and insulin resistance have used doses ranging from 9 to 1,200 mg per day, with many studies using 300-400 mg/day [7; 27; 32].

EGCG is also abundant in green tea. Sencha, the most common type of green tea in Japan, contains 40~60 mg of caffeine, 8~25 mg of L-theanine, and 25~60 mg of EGCG in a cup (200 mL), though levels of these compounds can vary widely depending on how much tea leaves is used and how it is brewed. Gyokuro, a type of green tea that is produced from shading the tea leaves, contains 240 mg of caffeine, 85 mg of L-theanine, and 86 mg of EGCG per cup. Matcha is powdered Japanese green tea often used in Japanese tea ceremony and contains 25 mg of caffeine, 36 mg of L-theanine, and 17-109 mg of EGCG per serving (80 ml) [53], along with vitamins A, B-complex, C, E, K, and trace minerals. Green tea extract typically contains a significant amount of EGCG—most green tea extract supplements are roughly 50% EGCG (Examine.com).

Factors that increase EGCG bioavailability include: cool and dry storage, fasting conditions, albumin, soft water, vitamin C, fish oil, and piperine [54]. Factors that decrease bioavailability include: air contact oxidation, gastrointestinal inactivation, calcium, magnesium, metals, catechol-O-methyltransferase (COMT; an enzyme that degrades dopamine, norepinephrine, and epinephrine) polymorphisms, sulfation, and glucuronidation.

Research underway:

The PENSA study is part of the World Wide FINGERS Initiative (BarcelonaBeta.org; [55]). PENSA is a randomized double-blind controlled clinical trial that is evaluating the efficacy of personalized multimodal lifestyle intervention combined with EGCG in slowing down cognitive decline and improving brain connectivity in 200 people with subjective cognitive decline who are APOE4 carriers [55]. There are 4 treatment arms: multimodal intervention + EGCG/placebo, or lifestyle recommendations + EGCG/placebo. The intervention is for 12 months. The EGCG intervention is 400 to 600 mg/day prior to meals, dissolved in 100 mL of water (Laboratoires Grand Fontaine based on FontUp product). The primary efficacy outcome is change in the composite score for cognitive performance measured with the Alzheimer's Disease Cooperative Study modified Preclinical Alzheimer Cognitive Composite (ADCS-PACC-plus; addition of the Interference score from the Stroop Color and Word Test and the Five Digit Test). Secondary efficacy outcomes are change in functional magnetic resonance imaging (fMRI) and structural neuronal connectivity (structural MRI) and safety of EGCG. A digital platform collects information on diet, mood, mental health, and activities related to the intervention. Continuous measures of physical activity, heart rate, and sleep quality are collected from an activity tracker (Fitbit, Charge 3).

Search terms:

Pubmed, Google: EGCG, green tea catechins

- + cognitive, + memory, + dementia, + meta-analysis, + systematic review, + ApoE4, + cancer, + cardiovascular, + diabetes, + lifespan, + safety

Clinicaltrials.gov: Green tea, EGCG, catechin

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