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

Some benefits on cognition, vascular health, and cholesterol have been observed in people, but the magnitude of effects appears to be small and short-lived.

Neuroprotective Benefit: Some cognitive benefits are seen in Down syndrome patients, but long-term studies are lacking in healthy adults.

Aging and related health concerns: EGCG lowers total and LDL cholesterol in humans and extends lifespan in rats and worms, but many studies examining its effects on weight loss, blood pressure, and cancer have shown null effects.

Safety: EGCG supplements are considered safe for most people when taken at recommended doses, but high doses have been associated with slightly elevated liver enzymes.

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 four major tea catechins are epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG), and epicatechin (EC). 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 from 1999 to 2012 [3]. EGCG is a popular supplement for its purported cardioprotective, neuroprotective, and anti-cancer effects. 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.

Neuroprotective Benefit: Some cognitive benefits are seen in Down syndrome patients, but long-term studies are lacking in healthy adults.

Types of evidence:
- 4 double-blind randomized clinical trials, 1 in AD patients, 1 in Down Syndrome patients, 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 [4; 5]. In a pilot study of 29 patients with Down syndrome, EGCG (9 mg/day) for 3 months significantly improved episodic memory [5]. 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 RCT 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 [4]. 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 RCT 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 [6], which are associated with relaxation, arousal/focused attention, and quiet wakefulness, respectively [7]. These results are consistent with anecdotal accounts that green tea is relaxing and alerting. In another double-blind RCT 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 [8].

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 RCT of 48 people with AD 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 [9]. 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 [10], 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) [11; 12].

In AD mouse models, EGCG treatment (10-50 mg/kg/day) resulted in many benefits: improved cognitive function [13; 14], improved psychomotor coordination [15], reduction of both soluble and insoluble Aβ levels in the cortex and hippocampus [14], reduction of phospho-tau [14], improved AChE activity [13], and improved measures of oxidative stress (glutathione peroxidase activity, nitric oxide metabolites, and reactive oxygen species) [13].

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 [16]. 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 [17].

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 [18]. 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 [19]. 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 in humans and extends lifespan in rats and worms, but many studies examining its effects on weight loss, blood pressure, and cancer have shown null effects.

Types of evidence:
- 0 meta-analyses or systematic reviews
- 11 randomized controlled trials (3 on cholesterol, 1 on vascular function, 1 on prostate cancer rate, 1 on cardiovascular function, 4 on weight loss, and 1 in diabetes patients)
- 2 other clinical trials, 1 on ovarian cancer recurrence and 1 in diabetes patients
- Numerous laboratory studies
- 2 review articles

Weight/Fat: LITTLE/NO BENEFIT. 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[20]. These changes are unlikely to be clinically significant. In a double-blind RCT 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 [21]. Similar negative results were observed in another double-blind RCT of 78 obese women receiving 12 weeks of green tea extract (~900 mg EGCG/day) [22].

Cholesterol: BENEFIT. In a large double-blind RCT of 1,075 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 (-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) [23]. 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 [22]. Other studies have shown an absence of EGCG effects on cholesterol levels [21].

Vascular function: BENEFIT. A double-blind RCT of 42 patients with coronary artery disease reported that EGCG (300 mg/day) acutely improves endothelial function via enhancement of nitric oxide status [24]. 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) [25]. However, other clinical trials have shown a lack of change in blood pressure [20; 26].

Blood glucose/Insulin: LITTLE/NO BENEFIT. In a double-blind RCT 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 [27]. 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 [25]. Similar negative results were obtained from a double-blind RCT of 83 obese women that tested the effects of EGCG in combination with an energy-restricted diet [21]. 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 [28].

Cancer: LITTLE/NO BENEFIT. 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 [29]. 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.

In cultures of breast cancer and leukemia cells, EGCG reduced cellular proliferation and induced apoptosis via antioxidant and epigenetic modulation [30]. EGCG effects varied by cell and cancer type.

Lifespan: BENEFIT. 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 [31]. 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* [32].

Safety: EGCG supplements are considered safe for most people when taken at recommended doses, but high doses have been associated with slightly elevated liver enzymes.

Types of evidence:
- 2 Cochrane meta-analyses based on 14 and 11 RCTs 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 RCT examining the effects of green tea
- 1 systematic review based on 4 RCTs 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 RCTs 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 [33]. In another Cochrane meta-analysis based on 11 RCTs 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 [34]. In another Cochrane meta-analysis based mostly on observational studies (27 case-control studies, 23 cohort studies, and 1 RCT) 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) [35].

Clinical trials on EGCG: A systematic review based on 4 RCTs 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 [36]. Based on these analyses, liver-related adverse events with green tea extracts are expected to be rare. In a large double-blind RCT of 1,075 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 [37]. In a smaller double-blind RCT of 83 obese women, EGCG treatment (300 mg/day) for 12 weeks did not cause any adverse effects on liver function biomarkers [21]. Liver-related adverse events may be more common at higher doses. Other common side effects of EGCG supplementation included nausea [29; 37].

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 [6; 21; 24]. Labdoor.com has a top 10 list of green tea supplements, based on label accuracy, purity, contaminants (lead and arsenic), and safety.

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). 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) [38], along with vitamins A, B-complex, C, E, K, and trace minerals.

Factors that increase EGCG bioavailability include: cool and dry storage, fasting conditions, albumin, soft water, vitamin C, fish oil, and piperine [39]. 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: A clinical trial is testing whether a brain health supplement (BBG-1001) that contains green tea extract, turmeric, fish oil, and vitamin D can slow cognitive decline in people with mild cognitive impairment (NCT02741804). This study is scheduled to be completed in May 2019. This study has not started recruiting participants yet. Outstanding questions include the extent of blood-brain-barrier permeability and the optimal dose of EGCG for neuroprotection.

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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10

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