

## Research Milestones

Below is a brief summary of key research studies and review articles. The first section includes published human studies and animal safety studies conducted on Teavigo green tea extract, the second section includes supporting scientific studies on green tea extract and EGCG in general, and the third section contains articles that review past research on green tea.

### Teavigo Studies

- 2011 -- An 8-week animal study was conducted to examine the effects of a dentrifice containing green tea catechins on gingival oxidative stress and periodontal inflammation. Researchers concluded that adding green tea catechins to a dentrifice may contribute to prevention of periodontal inflammation by decreasing gingival oxidative stress and expression of pro-inflammatory cytokines. (“Supplementation of Green Tea Catechins in Dentrifices Suppresses Gingival Oxidative Stress and Periodontal Inflammation.” T Maruyama, T Tomofuji, et al, *Archives of Oral Biology* (2011); (56) 48-53.)
- 2008 -- A double-blind, placebo-controlled, parallel study was conducted on 88 male subjects classified as either overweight or obese in order to investigate the effect of EGCG on insulin resistance and associated metabolic risk factors in humans. Subjects were randomly assigned to take 400 mg capsules of EGCG (in the form of Teavigo) or placebo twice daily for 8 weeks. Oral glucose tolerance testing and measurement of metabolic risk factors was conducted pre- and post-intervention. EGCG had no effect on insulin sensitivity, insulin secretion or glucose tolerance, but did reduce diastolic blood pressure. Results suggest that regular intake of EGCG had no effect on insulin resistance, but did result in a modest reduction in diastolic blood pressure. (“Effects of Dietary Supplementation with Green Tea Polyphenol Epigallocatechin-3-Gallate on Insulin Resistance and Associated Metabolic Risk Factors: Randomized Controlled Trial.” AL Brown, J Lane et al, *British Journal of Nutrition* (2009); 101(6) 886-894.)
- 2007 -- A double-blind, placebo-controlled, parallel study was conducted on 38 overweight or obese female subjects to evaluate the metabolic effects of EGCG when combined with a program of regular aerobic exercise. Subjects took 150 mg of EGCG (in the form of Teavigo) or placebo twice daily for 12 weeks. Results showed that body composition parameters were reduced in both groups, with no difference between EGCG and placebo. EGCG significantly decreased resting heart rate and reduced plasma glucose in subjects with impaired glucose tolerance. (“Can EGCG Reduce Abdominal Fat in Obese Subjects?” AM Hill, AM Coates, et al, *Journal of the American College of Nutrition* (2007); 26(4) 396S-402S.)
- 2007 -- A double-blind, placebo-controlled, crossover pilot study was conducted on six overweight men. Subjects were given 300 mg EGCG (in the form of Teavigo) per day for two days. Fasting and changes in energy expenditure following a meal were assessed, along with substrate oxidation. Resting energy expenditure did not differ significantly between EGCG and placebo treatments. During the first postprandial monitoring phase, respiratory quotient values were significantly lower with EGCG compared to the placebo. Results suggest that EGCG alone has the potential to increase fat oxidation in men and may contribute to the anti-obesity effects of green tea. (“The Effects of Epigallocatechin-3-Gallate on Thermogenesis and Fat Oxidation in Obese Men: A Pilot Study.” M Boschmann and F Thielecke *Journal of the American College of Nutrition* (2007); 26(4) 389S-395S.)

- 2007** -- A double-blind, placebo-controlled, crossover study was conducted on 42 male subjects with coronary artery disease to examine the effects of EGCG on endothelial function. Researchers measured brachial artery flow-mediated dilation by vascular ultrasound at six time points: prior to treatment with EGCG (in the form of Teavigo) or placebo, two hours after an initial dose of EGCG (300 mg) or placebo, and after two weeks of treatment with EGCG (150 mg twice daily) or placebo. Based on study results, researchers concluded that EGCG acutely improves endothelial function in humans with coronary artery disease. (“Acute EGCG Supplementation Reverses Endothelial Dysfunction in Patients with Coronary Artery Disease.” ME Widlansky, NM Hamburg, et al, *Journal of the American College of Nutrition* (2007); 26(2) 95-102.)
- 2006** -- A three-part animal study was conducted to determine the safety of EGCG (in the form of Teavigo). In Part 1 of the study, the genotoxic potential of EGCG was evaluated based on oral administration and intravenous injection, and results showed the EGCG extract is not genotoxic. In Part 2 of the study, the dermal, acute and short-term toxicity of EGCG (in the form of Teavigo) was evaluated. Topical, oral and dietary administration was conducted at various dosages, and from these studies a no-observed adverse effect level of 500 mg EGCG preparation/kg/day was established. In Part 3 of the study, the potential effects of EGCG (in the form of Teavigo) on a fetus were evaluated. EGCG preparations were administered to pregnant rats during organogenesis and development in order to determine safety. The study determined the no-observed adverse effect level to be 200 mg/kg/day EGCG preparation. (“Safety Studies on Epigallocatechin Gallate (EGCG) Preparations. Part 1: Genotoxicity; Part 2: Dermal, Acute and Short-Term Toxicity Studies; Part 3: Teratogenicity and Reproductive Toxicity Studies in Rats.” RA Isbrucker et al, *Food and Chemical Toxicology* (2006); 44 626-661.)

### Green Tea Extract/EGCG Studies

- 2010** -- Researchers analyzed cross-sectional data from the Ohsaki Cohort 2006 study. Usable self-administered questionnaires about green tea consumption and tooth loss were returned from 25,078 people aged 40-64. Multivariate logistic regression analysis was used to calculate odds ratios for tooth loss using 3 cut-off points of 10, 20, and 25 teeth relative to each category of green tea consumption. Findings indicate an association of green tea consumption with decreased odds for tooth loss. (“Association Between Green Tea Consumption and Tooth Loss: Cross-Sectional Results from the Ohsaki Cohort 2006 Study.” Y Koyama, S Kuriyama, et al, *Preventive Medicine* (2010)
- 2009** -- This study investigated the epidemiologic relationship between the intake of green tea and periodontal disease. A total of 940 Japanese men aged 49 to 59 were given health examinations with probing depth, clinical attachment loss, and bleeding on probing used as periodontal parameters. The intake of green tea was defined as the number of cups per day in a self-administered questionnaire. Results showed a modest inverse association between the intake of green tea and periodontal disease. (“Relationship Between Intake of Green Tea and Periodontal Disease.” M Kushiya, Y Shimazaki, et al, *Journal of Periodontology* (2009); 80(3) 372-377.)
- 2008** -- A crossover study of 15 male subjects investigated whether green tea powder reduces volatile sulfur compounds (VSCs) in mouth air, and compared its effectiveness with that of other foods which are claimed to control halitosis. The study concluded that green tea was very effective in reducing oral malodor temporarily because of its disinfectant and deodorant activities, whereas other foods were not effective. (“Effect of Green Tea on Volatile Sulfur Compounds in Mouth Air.” P Lodhia, K Yaegaki, et al, *Journal of Nutritional Science and Vitaminology* (2008); 54: 89-94.)

- 2008** -- Two studies were conducted, both with a counter-balanced crossover design. In study A, 12 healthy men performed 30-minutes of exercise at 60% maximal oxygen consumption before and after supplementation. In study B, 11 healthy men took an oral-glucose-tolerance test before and after supplementation. In the 24-hour period before the experimental trials, participants ingested three capsules containing either green tea extract or placebo. Average fat oxidation rates were 17% higher after ingestion of green tea extract than after ingestion of placebo. Moreover, the contribution of fat oxidation to total energy expenditure was also significantly higher, by a similar percentage, after green tea extract supplementation. The insulin area under the curve decreased in both the green tea extract and placebo trials, and there was a concomitant increase of 13% in insulin sensitivity. (“Green Tea Extract Ingestion, Fat Oxidation, and Glucose Tolerance in Healthy Humans.” MC Venables, C J Hulston, et al, *American Journal of Clinical Nutrition* (2008); 87(3) 778-84.)
- 2007** -- In a 12-week, double-blind parallel multi-center trial, 240 Japanese women and men with visceral fat-type obesity ingested green tea containing 583 mg of catechins (catechin group) or 96 mg of catechin (control group) per day. The continuous ingestion of GTE high in catechins led to a reduction in body fat, systolic blood pressure (SBP), and LDL cholesterol, suggesting that the ingestion of such an extract contributes to a decrease in obesity and cardiovascular disease risks. (“A Green Tea Extract High in Catechins Reduces Body Fat and Cardiovascular Risks in Humans.” T Nagao, T Hase, et al, *Obesity* (2007); 15(6) 1473-1483.)
- 2007** -- The randomized, controlled study concluded that green tea capsules in a dosage of 100 mg/day EGCG can increase energy expenditure and fat oxidation in obese Thai subjects in a 12-week period. The effects of green tea on weight reduction in a long term study are needed. (“Effectiveness of Green Tea on Weight Reduction in Obese Thais: A Randomized, Controlled Study.” P Auvichayapat, M Prapochanung, et al, *Physiology & Behavior* 2007.)
- 2006** -- A study of 15 subjects was conducted to examine the inhibition of acid production from dental plaque and mutans streptococci by EGCG. The effect of EGCG solution on dental plaque pH was investigated. Subjects rinsed their mouths with 2 mg/ml EGCG solution and then, after 30-minute interval, rinsed their mouths with 10% sucrose. The pH values of plaque samples from 15 subjects were significantly higher after treatment with catechin than after treatment with water. Study results suggest that EGCG is effective in reducing acid production in dental plaque and mutans streptococci. (“Inhibition of Acid Production in Dental Plaque Bacteria by Green Tea Catechins.” M Hirasawa, K Takada, et al, *Caries Research* (2006); 40: 265-270.)
- 2006** -- In a randomized, placebo-controlled trial of thirty-four Chinese women with polycystic ovary syndrome, (PCOS), the body weight of the green tea group decreased by a non-significant 2.4% after treatment; whereas the body weight, body mass index, (BMI), and body fat content of the control group were significantly higher after three months. There were no differences in any of the hormone levels measured in either group. The biochemical profiles of the two groups were also similar, except that there was a small, but significant rise in triglyceride level in the green tea group. Fewer patients in the green tea group remained amenorrhoeic, but this was not significantly different from the control group. (“Effects of Chinese Green Tea on Weight, and Hormonal and Biochemical Profiles in Obese Patients with Polycystic Ovary Syndrome—a Randomized, Placebo-Controlled Trial.” C Chan, M Koo, et al, *Journal of the Society for Gynecologic Investigation* (2006); 13(1) 63-68.)
- 2006** -- In a double-blind study, 97 women and 98 men in three parallel groups were assigned to consume 1) three bottles of placebo drink (control group), 2) two bottles of catechin-containing drink, and one bottle of placebo drink (low dose group), or 3) three bottles of catechin-containing drink (high dose

group), per day at meal times for 12 weeks. Compared to 0 week, consumption of two or three bottles of catechin-containing drink results in significant decrease in body weight and BMI at 8 and 12, or 4, 8 and 12 weeks, respectively. Body weight and BMI were significantly decreased in both catechin groups compared with control group from 4 to 12 weeks. The measurements of abdominal fat areas indicated significant reduction of total fat area and visceral fat area in both catechin groups compared with the control group at 12 weeks. Results suggest that consumption of a catechin-containing drink may be useful for the prevention of obesity-related disorders. ("Tea Catechins with a Galloyl Moiety Reduce Body Weight and Fat." O Kajimoto, Y Kajimoto, et al, *Journal of Health Sciences* 2006.)

- 2005** -- A placebo-controlled study of 14 men concluded that fat utilization for energy expenditure under both sedentary and exercising conditions was significantly increased by the combination of regular exercise and tea catechins intake compared to that by exercise alone. ("Effects of Combination of Regular Exercise and Tea Catechins Intake on Energy Expenditure in humans." N Ota, S Soga, et al, *Journal of Health Sciences* (2005); 51(2) 233-236.)
- 2005** -- A 12-week, double-blind study was performed on 38 male subjects, after a two-week diet run-in period. Subjects were divided into two groups with similar BMI and waist circumference distributions, then they were given either one bottle oolong tea per day containing 690 mg catechins (green tea extract group), or one bottle oolong tea per day containing 22 mg catechins (control group). Results showed that body weight, BMI, waist circumference, body fat mass, and subcutaneous fat area were significantly lower in the green tea extract group than in the control group. Changes in the concentrations of malondialdehyde-modified LDL were positively associated with changes in body fat mass and total fat area in the green tea extract group. ("Ingestion of a Tea Rich in Catechins Leads to a Reduction in Body Fat and Malondialdehyde-Modified LDL in Men." T Nagao, Y Komine, et al, *American Journal of Clinical Nutrition* (2005); 81(1) 122-9.)
- 2004** -- A double-blind, placebo-controlled study was conducted on 36 male subjects to assess the safety, tolerability, and plasma-kinetic behavior of EGCG. Subjects received ten days of repeated dosing with either oral EGCG in one dose of 200, 400, or 800 mg daily, or placebo. Results show that ten days' repeated administration of oral doses of EGCG of up to 800 mg per day were found to be safe and very well tolerated. ("Plasma-Kinetic Characteristics of Purified and Isolated Green Tea Catechin Epigallocatechin Gallate (EGCG) After 10 Days Repeated Dosing in Healthy Volunteers." U Ullmann, J Haller, et al, *International Journal for Vitamin & Nutrition Research* (2004); 74(4) 269-78.)
- 2003** -- A double-blind, placebo-controlled study was conducted on 60 male volunteers to assess the safety, tolerability and plasma-kinetic behavior of single oral doses of EGCG under fasting conditions. Subjects received either EGCG in single doses of 50 mg, 100 mg, 200 mg, 400 mg, 800 mg or 1600 mg, or placebo. Results indicate that single oral doses of EGCG up to 1600 mg were safe and very well tolerated. ("A Single Ascending Dose Study of Epigallocatechin Gallate in Healthy Volunteers." U Ullmann, J Haller, et al, *Journal of International Medical Research* (2003); 31 88-101.)
- 2002** -- A 26-week, double-blind study of 43 men and 37 women was conducted to determine the effect of catechins on body fat in humans. After a two-week run-in period, subjects were randomized into two groups for a 12-week test beverage ingestion period and a 12-week washout period. Catechins were taken as 340 mL of a green tea-like beverage. Two groups were used in the study, consisting of a control group (126 mg of catechins and 81 mg of caffeine per bottle) and a catechins group (588 mg of catechins and 83 mg of caffeine per bottle). Results showed that ingestion of catechins at a dose of 588 mg/day for 12 weeks reduces abdominal fat, particularly visceral fat in men and subcutaneous fat in women, and helps to prevent and improve obesity. ("Reduction of Body Fat in Humans by Long-Term Ingestion of Catechins." T Tsuchida, H Itakura, et al, *Progress in Medicine* (2002); 9(22) 2189-2203.)

- 2001** -- A study was conducted on 23 male subjects who ranged from normal weight to obese based on body mass index. Subjects were given either a low dose (118.5 mg) or a high dose (483 mg) of tea catechins for 12 weeks. The effects were evaluated after four and 12 weeks. At the high dose, body weight, body mass index, waist circumference, body fat ratio, and abdominal fat and serum concentrations of total cholesterol, glucose, insulin and PAI-1 at 12 weeks were significantly lower than at baseline. At the low dose, only body weight, BMI and serum insulin concentration changed. In the obese subjects, the decrease in the BMI was significantly great in those who took the high dose. ("Anti-Obesity Effects of Tea Catechins in Humans." T Hase, Y Komine, et al, *Journal of Oleo Science* (2001); 50(7) 599-605.)
- 2000** -- A double-blind, placebo-controlled study was conducted for four weeks on 47 subjects to investigate how green tea catechins and polyphenols in the form of green tea dragées may influence the inflammatory behavior of the gingiva. While in the verum group a distinct improvement in both approximal plaque index and sulcus bleeding index values could be stated, slight worsening of the values were determined for the placebo group. Results indicate that the oral application of green tea catechins and polyphenols might have a positive influence on the inflammatory reaction of periodontal structures. ("The Effect of Sugar-Free Green Tea Chew Candies on the Degree of Inflammation of the Gingiva." T Krahwinkel, B Willershausen, *European Journal of Medical Research* (2000); 5: 463-467.)
- 1999** -- A study was conducted on 10 male subjects to determine whether a green tea extract could increase 24 hour energy expenditure (EE) and fat oxidation. Twenty-four hour EE, the respiratory quotient (RQ), and the urinary excretion of nitrogen and catecholamines were measured in a respiratory chamber in each subject. On three separate occasions, subjects were randomly assigned among three treatments: green tea extract (50 mg caffeine and 90 mg epigallocatechin gallate), caffeine (50 mg), and placebo, which they ingested at breakfast, lunch and dinner. Results indicated that green tea has thermogenic properties and promotes fat oxidation beyond that explained by its caffeine content per se, and that it may play a role in the control of body composition via sympathetic activation of thermogenesis, fat oxidation, or both. ("Efficacy of a green tea extract rich in catechin polyphenols and caffeine in increasing 24-h energy expenditure and fat oxidation in humans." AG Dulloo, C Duret, et al, *American Journal of Clinical Nutrition* (1999); 70(6) 1040-1045.)

### Research Review Articles

- 2009** -- The authors provide a comprehensive overview of the human studies addressing the potential benefits of green tea catechins on the metabolic syndrome. Based on past research, the authors conclude that green tea, when consumed on a daily basis, supports health. There is conclusive evidence from in vitro and animal studies which provide the concepts for underlying functional mechanisms of green tea catechins and their biological actions. An increasing number of human studies have explored the effects of green tea catechins on the major metabolic syndrome conditions such as obesity, type-2 diabetes and cardiovascular risk factors. The number of human studies in this field is still limited. However, the majority of human epidemiological and intervention studies demonstrate beneficial effects of green tea or green tea extracts, rich in EGCG on weight management, glucose control and cardiovascular risk factors. The optimal dose has not yet been established. The authors conclude that the current body of evidence in humans warrants further attention, and well-controlled long-term human studies would help to fully understand the protective effects of green tea catechins on parameters related to the metabolic syndrome. ("The Potential Role of Green Tea Catechins in the Prevention of the Metabolic Syndrome – A Review." F Thielecke and M Boschmann, *Phytochemistry* (2009))

- 2006** -- The authors conclude that the strong antioxidant potential of catechins such as EGCG are thoroughly demonstrated in vitro and in animal studies. In addition, catechins possess antimutagenic, antidiabetic, anti-inflammatory, antibacterial and antiviral properties. The authors highlight recent human studies that suggest green tea may contribute to a reduced risk of cardiovascular disease and cancer. They conclude that although research of green tea is very promising, future studies considering dietetic, environmental and lifestyle factors are necessary to better understand its role in maintaining health. ("Beneficial Effects of Green Tea – A Review." C Cabrera, R Artacho, et al, *Journal of the American College of Nutrition* (2006); 25(2) 79-99.)
- 1996** -- This study was designed to evaluate the deodorizing reactions of EGCg, the main polyphenol in green tea, and to determine whether EGCg would chemically react with CH<sub>3</sub>SH to give new products. The non-volatile reaction products were purified and identified. They were found to be EGCg derivatives carrying methylthio and/or a methylsulphinyl groups on the B ring. ("Green Tea to Cure Bad Breath. The Role of Polyphenols Clarified." H Yasuda and T Arakawa, *Polyphénols Actualités* (1996); (15) 4-7.)