Review

Effects of Green Tea and EGCG on Cardiovascular and Metabolic Health

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Since ancient times green tea has been considered a health-promoting beverage. In recent years, scientists throughout the world have investigated the potential benefits of green tea and its most abundant catechin, epigallocatechin gallate (EGCG). The anti-cancer effects of green tea and EGCG were the focus of early research, and encouraging data from *in vitro,* animal model, and human studies have emerged. Due to the dominant role of cardiovascular disease and the dramatic rise of obesity and type 2 diabetes mellitus as major and interlinked healthcare problems, green tea and EGCG are increasingly being investigated in these areas. Dose-response relationships observed in several epidemiological studies have indicated that pronounced cardiovascular and metabolic health benefits can be obtained by regular consumption of 5–6 or more cups of green tea per day. Furthermore, intervention studies using similar amounts of green tea, containing 200–300 mg of EGCG, have demonstrated its usefulness for maintaining cardiovascular and metabolic health. Additionally, there are numerous *in vivo* studies demonstrating that green tea and EGCG exert cardiovascular and metabolic benefits in these model systems. Therefore, green tea and EGCG can be regarded as food components useful for the maintenance of cardiovascular and metabolic health. To prove the effectiveness for disease prevention or treatment, several multi-center, long-term clinical studies investigating the effects of one precisely-defined green tea product on cardiovascular and metabolic endpoints would be necessary. The aim of this manuscript is to provide an overview of the research investigating the effects of green tea and green tea catechins on cardiovascular and metabolic health.

Key teaching points:

- Initiatives to maintain and enhance cardiovascular and metabolic health of the general population involving proper nutrition and exercise are needed.
- Green tea is a beverage which has been consumed for centuries and is traditionally associated with various health benefits.
- Green tea is a rich source of polyphenols, especially of EGCG, the most abundant green tea catechin.
- Epidemiological and intervention studies indicate that consumption of 5–6 or more cups of green tea, containing 200–300 mg EGCG, per day may be beneficial for maintaining cardiovascular and metabolic health.
- Several large-scale, long-term, clinical studies with a defined green tea product, showing benefits for cardiovascular and metabolic endpoints, would be necessary to prove preventative and/or therapeutic effects of green tea.

INTRODUCTION

Public and private health initiatives are currently launching significant programs for the promotion of cardiovascular and metabolic health. At the same time, green tea consumption is increasingly being shown to be associated with enhanced cardiovascular and metabolic health. Green tea polyphenols and

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Abbreviations: EC = epicatechin, ECG = epicatechin gallate, EGC = epigallocatechin, EGCG = epigallocatechin gallate, GLUT1 = glucose transporter 1, GLUT4 = glucose transporter 4, GSH = reduced glutathione, HOMA = homeostatic model assessment, i.p. = intraperitoneal, i.v. = intravenous, NADPH = nicotinamide adenine dinucleotide phosphate (reduced form), NF-κB = nuclear factor-kappa B, NO = nitric oxide, oGTT = oral glucose tolerance test, PPARα = peroxisome proliferator activated receptor alpha, PPARδ = peroxisome proliferator activated receptor delta, PPARγ = peroxisome proliferator activated receptor gamma, PPARγ2 = peroxisome proliferator activated receptor gamma 2, SGLT1 = sodium/glucose co-transporter 1, STZ = streptozotocin, T2DM = type 2 diabetes mellitus, VEGF = vascular endothelial growth factor, WHO = World Health Organization. Vol. 26, No. 4

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especially the most abundant green tea catechin, epigallocatechin gallate (EGCG), are the subjects of increasing research interest. In recent years, the number of studies investigating the roles of green tea and EGCG has risen dramatically. The aim of this article is to review the existing scientific evidence for the effects of green tea and EGCG on cardiovascular and metabolic health. This manuscript focuses on studies in healthy and diseased human subjects as well as studies using *in vivo* models of cardiovascular and metabolic diseases. For detailed descriptions of the wealth of in vitro studies and of the proposed mechanisms of action of green tea and EGCG the interested reader is referred to other recently published review articles [1–5].

Cardiovascular and Metabolic Health - *Quo Vadis?*

Cardiovascular and metabolic diseases are the major causes of death and disability worldwide [6]. The economic burden on health care systems due to cardiovascular and metabolic diseases is tremendous. Ischemic heart disease and cerebrovascular disease are the leading causes of death and the number of deaths from these diseases are predicted to continue to grow in the coming years [7]. The age-standardized death rate for diabetes mellitus is projected to increase, whereas for most other diseases it will decrease. This statistic reflects the markedly increasing prevalence of obesity and diabetes mellitus. Furthermore, obesity and diabetes mellitus are increasingly diagnosed in younger individuals [8,9]. Importantly, metabolic and cardiovascular diseases are strongly interlinked, e.g., with the majority of people suffering from type 2 diabetes mellitus (T2DM) dying of cardiovascular disease [10,11]. Furthermore, 40–45% of patients admitted to hospital for acute myocardial infarction display impaired glucose tolerance or T2DM, and glucose concentration at admission predicts in-hospital mortality [12,13]. T2DM is a deadly disease, which, in the year 2000, was associated with approximately 2.9 million deaths worldwide [14]. It is estimated that T2DM is globally the fifth leading cause of death. Long-term complications in patients with T2DM include cardiovascular disease, blindness, neuronal damage, renal failure and diabetic foot disease. There are pronounced ethnic differences in the prevalence of both T2DM and diabetic complications [15,16]. Diabetic adults have a substantially higher risk of death, together with lower survival rates and lower life expectancy compared with non-diabetic adults [17]. The mortality and end-stage complications due to T2DM are thought to be markedly underestimated [18]. Furthermore, in some countries more than one fifth of the older population has either undiagnosed T2DM or impaired fasting glucose [19]. In patients undergoing coronary artery bypass surgery, the prevalence of T2DM may reach up to 35% [20]. Remarkably, more than 5% of such patients have undiagnosed T2DM and display significantly increased mortality and morbidity rates during perioperative and postoperative courses, compared with diagnosed diabetics and non-diabetics.

The worldwide prevalence of T2DM is predicted to increase in the coming years, reaching 300 million by 2025 [21]. In 2030, there will be approximately 366 million people suffering from T2DM [8]. In some areas, such as the Middle East, Asia and Africa, the number of patients with T2DM will double, placing enormous financial pressure on national health care systems. The increasing prevalence of diabetes is largely due to the rapid spread of obesity, which is considered to be the most important risk factor for T2DM [22–24]. In particular, transition countries, as well as developing countries, will experience substantial health care problems due to increased energy consumption and decreased physical activity [25].

The fact that risk factors for cardiovascular and metabolic diseases, such as insulin resistance, hypertriglyceridemia, and low plasma levels of high-density lipoprotein, often appear clustered in the same individual was first described almost 20 years ago [26]. Subsequently, the World Health Organization (WHO), the International Diabetes Federation (IDF) and the Adult Treatment Panel III (ATPIII) of the National Cholesterol Education Program (NCEP) developed definitions for this cluster of risk factors termed "metabolic syndrome" [27–29]. Briefly, the definitions are: WHO: insulin resistance (high homeostatic model assessment insulin resistance (HOMA-IR)) and/or impaired fasting glucose (110–125 mmol/L) plus at least 2 of the following factors: obesity (body mass index (BMI) >30 kg/m^2 and/or waist-to-hip ratio (WHR) >0.9 and >0.85 for men and women, respectively), dyslipidemia (high-density lipoprotein (HDL) cholesterol <0.35 and <0.40 mg/dL for men and women, respectively, and/or triglycerides >150 mg/dL), hypertension ($>140/90$ mmHg and/or antihypertensive medication), microalbuminuria (albumin/creatine ratio 25–250 mg/g); IDF: central obesity with waist circumference >94 and >80 cm for men and women, respectively, (values vary depending on ethnicity), plus at least 2 of the following factors: hypertriglyceridemia (>150 mg/dL or specific treatment), low HDL cholesterol (<40 and <50 mg/dL for men and women, respectively, or specific treatment), hypertension ($>130/85$ mmHg or treatment of previously diagnosed hypertension), impaired fasting glycemia (>100 mg/dL or previously diagnosed T2DM); NCEP: 3 or more of the following factors: abdominal obesity (>102 cm and >88 cm for men and women, respectively), hypertriglyceridemia (>150 mg/dL), low HDL cholesterol (<40 and <50 mg/dL for men and women, respectively), hypertension ($>130/85$ mmHg), impaired fasting glycemia (>110 mg/dL).

Even though the different definitions may characterize distinct subject populations they have one thing in common: The metabolic syndrome is associated with a markedly elevated risk of T2DM, cardiovascular disease incidence and mortality, as well as all-cause mortality [30,31].

Weight loss is known to significantly reduce incidence of T2DM and cardiovascular disease, decrease mortality rates, and may be a relatively cost effective method for increasing life-expectancy and quality-adjusted life-expectancy [32–34].

Lifestyle modifications, including moderately increased physical activity and decreased caloric intake, reduce the risk of developing T2DM by almost 60%, even though weight loss and the reduction of waist circumference were reported to be only 5–7% [35]. Therefore, the most important aspect in the prevention and treatment of T2DM is weight loss. Reduced caloric intake and increased physical activity are both effective and should ideally be combined for achieving weight loss [36–38].

Physical activity lowers age-adjusted mortality from cardiovascular disease, cancer and all causes, compared with inactivity, even after adjustment for other cardiovascular risk factors such as smoking, systolic blood pressure, cholesterol, BMI, diabetes and education [39]. Furthermore, physical activity is negatively associated with risk factors for cardiovascular disease, such as waist circumference, BMI, waist-hip-ratio and triglycerides, and is positively associated with HDL [40]. The beneficial effects of physical activity appear to be dose-related up to a threshold of 45 metabolic equivalents (METs), which is considered moderate physical activity.

Nutritional guidelines to reduce cardiovascular and metabolic disease risk include the reduction of saturated fat (<7% of total calories), trans fatty acids, and cholesterol (<200 mg) [41]. Carbohydrate intake should be limited to 60% of total calories or reduced to 50% in the presence of high triglycerides or low HDL cholesterol. Carbohydrate sources with a high-fiber content should be consumed in preference to refined carbohydrate sources. High intake of n-3 polyunsaturated fatty acids, derived from fatty fish or vegetable oils, is recommended to be part of a cardiovascular disease risk-reduction diet by the American Heart Association and the National Cholesterol Education Program [41]. Limiting sodium intake, ideally to <1.5 g/d (sodium chloride <3.8 g/d), significantly reduces blood pressure and thus reduces cardiovascular risk [42,43]. Increasing potassium intake has emerged as another dietary means to reduce blood pressure and the American Heart Association recommends increasing intake to approximately 4.7 g/d [43]. The consumption of a diet rich in fruits, vegetables and low-fat dairy products, with a reduced content of saturated and total fat (e.g. the Dietary Approaches to Stop Hypertension (DASH) eating plan), can have substantial positive effects on blood pressure and cardiovascular risk [44]. Intake of vitamins and antioxidants, such as vitamins B6 and B12, folic acid, ascorbic acid, α-tocopherol, β-carotene and selenium, have not consistently resulted in reduced risk of cardiovascular or metabolic diseases in controlled trials. Therefore, most organizations do not endorse intake above the current recommended dietary allowance (RDA).

Several herbal dietary supplements are promoted for their potential benefits on cardiovascular and metabolic health. However, the lack of standardization of the individual products and their formulations, as well as the limited amount of data from controlled efficacy and safety trials, currently prevent their widespread recommendation.

The aim of this manuscript is to provide an overview of the steadily increasing research investigating the effects of green tea and green tea catechins on cardiovascular and metabolic health, the two most prominent public health threats in today's society.

Green Tea

In Asia, green tea is a widely-consumed beverage and, for centuries, has been regarded to possess significant health-promoting effects [45]. The health-promoting effects of green tea are mainly attributed to its polyphenol content. Green tea is a rich source of polyphenols, especially flavanols and flavonols, which represent approximately 30% dry weight of the fresh leaf [45]. Catechins are the predominant flavanols and are mainly comprised of epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG), and epicatechin (EC) [46].

A large part of the research on green tea has focused on its effects related to the prevention of cancer, and encouraging knowledge regarding efficacy, safety and potential mechanisms of action has accumulated in this area [47–49]. Furthermore, the anti-inflammatory [50], anti-arthritic [51,52], anti-bacterial [53], anti-angiogenic [54,55], anti-oxidative [56,57], anti-viral [58,59] and neuroprotective effects [60] of green tea and isolated green tea constituents have been investigated. Recently, many of the aforementioned beneficial effects of green tea were attributed to its most abundant catechin, EGCG [61–67]. Emerging areas of significant research activities on green tea catechins include the effects on cardiovascular and metabolic health, which will be reviewed in the following sections.

EPIDEMIOLOGICAL STUDIES

Cardiovascular Health

In a recent prospective cohort study in 40,530 Japanese adults, the consumption of 5 or more cups of green tea per day was found to significantly reduce mortality due to all causes (−16% compared to subjects consuming less than 1 cup per day) and cardiovascular disease (−26%) [68]. Among cardiovascular diseases the strongest reduction in mortality was observed for stroke (−37%) and, in particular, for cerebral infarction (−51%). Importantly, the inverse relationship of green tea consumption and cardiovascular mortality was observed after adjusting for age, job status, education, body mass index, physical activity, history of hypertension, diabetes and gastric ulcers, smoking status, alcohol consumption, energy intake and consumption of rice, soybean products, meat, fish, dairy products, fruits, vegetables, oolong tea, black tea and coffee. Thus, the influence of differing lifestyle and nutrition between subjects consuming different amounts of green tea is expected to be minor, which makes the results very valuable for understanding the potential health benefits of green tea. Another important finding of the study was the apparent dose-response

relationship, e.g. the beneficial effects of green tea on cardiovascular disease mortality increased with increasing consumption of green tea.

In a case control study in Japanese subjects, the consumption of green tea was found to be inversely related to subarachnoid hemorrhage [69]. Daily consumption of 1 or more than 1 cup of green tea reduced the risk by 26% and 44%, respectively, compared with subjects not consuming green tea. The results of this study confirm the findings of the above-mentioned prospective cohort study, in which a risk reduction of 63% was observed for mortality due to subarachnoid hemorrhage in subjects consuming 3 or more cups of green tea per day [68]. Although this risk reduction did not reach the level of statistical significance in the prospective cohort study, considering the observations of these two studies together it appears that green tea may exerts a beneficial effect against subarachnoid hemorrhage.

The major risk factor for stroke and cardiovascular disease is hypertension. In a cross-sectional study of 1507 Chinese subjects, the role of habitual green tea consumption was investigated [70]. After adjustment for confounding factors, including BMI, lifestyle and diet, it was observed that daily consumption of 120–599 mL of green tea per day for at least one year reduced the risk of developing hypertension by 46%, compared to those subjects consuming less than 120 mL per day. Consuming more than 600 mL per day reduced the risk by 65%. These results provide one possible explanation for the reduced cardiovascular mortality associated with habitual green tea consumption.

In another recent study, the beneficial effects of a Japanese dietary pattern rich in soybean products, fish, seaweeds, vegetables, fruits and green tea was found to be associated with a lower mortality due to cardiovascular disease (−27%), suggesting that green tea consumption may be at least partly responsible for the observed beneficial effects of the Japanese diet [71]. However, this study also highlights the fact that the consumption of green tea can be associated with other dietary patterns and that careful adjustment for confounding factors is crucial for interpreting results of epidemiological studies.

In 512 Japanese subjects undergoing coronary angiography, Sasazuki et al. [72] observed a trend towards an inverse association between green tea consumption and coronary atherosclerosis. In a subgroup of 262 men, excluding those under dietary or drug treatment for T2DM, the risk of significant stenosis was reduced by 50% for subjects consuming 2–3 cups per day and by 60% for those consuming 4 or more cups per day, compared with a consumption of 1 cup per day or less.

Metabolic Health

In a retrospective cohort study among 17,413 adult Japanese subjects, a risk reduction for developing diabetes of 33% was found in subjects consuming 6 or more cups of green tea per day, compared to those consuming less than 1 cup per week [73]. In women, the majority of the study population, a strong dose-response relationship was observed with risk reductions of 21%, 34%, 39%, and 51% for subjects consuming 1–6 cups per week, 1–2 cups per day, 3–5 cups per day, and 6 or more cups per day, respectively.

In 2003, Wu et al. [74] reported the results of a cross-sectional study conducted with 1,210 subjects from Taiwan. Subjects with habitual consumption of tea for more than ten years were characterized by a lower percentage of total body fat, smaller waist circumference and decreased waist-to-hip ratio. Approximately 4% of the habitual tea drinkers consumed black tea and 96% consumed green or oolong tea, which contain higher amounts of catechins compared to black tea. However, the effect of the duration of tea consumption on obesity was stronger than the effect of the amount of tea consumed, thus not allowing conclusions to be drawn with respect to a dose-response relationship.

In summary, there is evidence from epidemiological studies that the habitual consumption of green tea is inversely associated with cardiovascular mortality, mortality due to stroke, the risk of developing hypertension and of diabetes, and with percent body fat and body fat distribution. These effects are especially prominent in subjects consuming 5 or more cups of green tea per day.

INTERVENTION STUDIES

Endothelial Dysfunction

In an open, uncontrolled study, the effects of green tea consumption on flow-mediated dilation were investigated in 20 chronic smokers [75]. Consumption of 8 g powdered green tea per day for 2 weeks significantly enhanced flow-mediated dilation and the number of circulating endothelial progenitor cells. These results led the authors to suggest that green tea consumption may prevent future cardiovascular events in smokers. Similar results were obtained in a cross-over study, in which the acute effects of green tea consumption on forearm blood flow were investigated in smokers [76]. The consumption of 400 mL green tea (~247 mg EGCG in ~692 mg total catechins per day) enhanced forearm blood flow and reduced the urinary concentration of 8-iso-prostaglandin-$F_{2\alpha}$, a marker of oxidative stress. In a randomized, double blind, placebo-controlled, cross-over study in 42 subjects with endothelial dysfunction, Widlansky and colleagues investigated the effects of supplementation with 300 mg EGCG daily for 2 weeks on brachial artery flow-mediated dilation [77]. They observed that EGCG supplementation acutely improved brachial artery flow-mediated dilation and that changes in vascular function paralleled changes in EGCG plasma concentration. This was the first intervention study reporting a cardiovascular benefit for a single green tea catechin.

Oxidative Damage

The anti-oxidative effects of decaffeinated black or green tea consumption (4 cups per day) for 4 months were investigated in 133 smokers in a randomized, controlled study in a parallel, open-label design [78]. Compared to water green tea consumption (~144 mg EGCG in ~294 mg total catechins per day) decreased urinary 8-hydroxydeoxydeoxyguanosin, a marker of oxidative DNA damage. Black tea consumption did not alter this parameter. Similar results were obtained in a recent randomized, double-blinded, placebo-controlled trial with subjects at high risk for hepatocellular carcinoma [79]. Consumption of 500 or 1000 mg green tea catechins per day for 3 months resulted in significantly decreased urinary 8-hydroxydeoxyguanosin levels compared to placebo. The effects of moderate green tea consumption for 42 days (2 cups per day, ~214 mg EGCG in 320 mg green tea extract per day) on antioxidative status were investigated in 24 healthy volunteers in a randomized controlled trial (parallel, open-label design) [80]. Green tea consumption increased antioxidant capacity and decreased plasma peroxides in plasma and reduced oxidative damage and glutathione peroxidase activity in lymphocytes.

Hyperlipidemia

The acute effects of green tea catechin consumption on postprandial lipid responses were investigated in 9 subjects with mild hypertriglyceridemia in a randomized, controlled, double-blinded, cross-over study [81]. Beverages containing low (1 mg EGCG in 10 mg total catechins), moderate (68 mg EGCG in 224 mg total catechins) and high (243 mg EGCG in 674 mg total catechins) amounts of green tea catechins were consumed together with fat-enriched bread. Moderate and high amounts of catechins reduced the postprandial triglyceride response by 15.1% and 28.7%, respectively. There was also a trend towards a reduced postprandial response of remnant-like particle cholesterol in the high catechin group, which reached statistical significance 2 h after the meal.

Overweight and Obesity

In a multi-center, open and uncontrolled study, Chantré et al. [82] investigated the effects of encapsulated green tea extract (279 mg EGCG in 375 mg total catechins per day for 12 weeks) in 70 moderately overweight subjects. The authors observed a 4.6% decrease in body weight, compared to baseline, and a 4.5% reduction in waist-to-hip ratio. Hase et al. [83] and Tsuchida et al. [84] performed studies testing the effects of green tea extracts (300 mg EGCG in 483 mg total catechins and 115 mg EGCG in 588 mg total catechins, respectively, per day for 12 weeks) applying sophisticated techniques to measure body composition, in particular visceral fat, in 23 and 80 moderately-overweight subjects, respectively. Slight reductions in body weight and more pronounced decreases in body fat, especially visceral fat, were reported in both studies. Although these studies were not controlled for dietary intake and physical activity, the energy intake was recorded and no differences between the control and treatment groups over the study period of three months were reported. A different concept was used in the study by Nagao et al. [85]. They demonstrated that after a 12-week supplementation with green tea catechin-enriched oolong tea (~136 mg EGCG in ~700 mg total catechins per day) in 35 overweight, but otherwise healthy subjects, the reduction in body weight and body fat was significant compared to the control group. In contrast to the studies mentioned above, subjects received only 90% of their individual daily energy requirement.

Kovacs and colleagues [86] investigated the effects of green tea extract on the regain of body weight following consumption of a very low-energy diet for 4 weeks. In this randomized, placebo-controlled, parallel study in 104 overweight subjects, a green tea extract (323 mg EGCG in 573 mg total catechins, 104 mg caffeine per day) was consumed for a 12-week period. No beneficial effects of the green tea extract were found. The authors speculated that the magnitude of habitual caffeine intake may have adversely affected the effectiveness of green tea administration. This hypothesis was recently confirmed by the same group of investigators [87]. Subjects with low habitual caffeine intake, supplemented with green tea extract (270 mg EGCG, 150 mg caffeine), continued to lose body weight and fat mass during the 12-week weight maintenance period while all other groups regained weight. Furthermore, subjects with low habitual caffeine intake, supplemented with green tea extract, displayed significantly increased energy expenditure and a decreased respiratory quotient compared to all other groups, indicating a higher fat oxidation during the weight maintenance period. In another randomized, placebo-controlled, double-blind, parallel study, this group investigated the effects of encapsulated green tea extract (~596 mg EGCG in ~1207 mg total catechins, ~237 mg caffeine per day for 87 days) in 46 overweight females on a concomitant low-calorie diet weight-loss program [88]. Green tea extract did not induce additional weight loss over and above the effect of the low-calorie diet and did not influence resting energy expenditure in this experimental setting.

Energy Expenditure

In two randomized, controlled cross-over studies [89,90], a metabolic chamber was used for measuring 24-hour energy expenditure and substrate oxidation in the test subjects. Increases in energy expenditure of 2.9% and 4%, respectively, and fat oxidation of 12% and 35%, respectively, were observed in the two studies. Although the aims of both studies were comparable, different types of administration were employed, i.e. capsules (270 mg EGCG in 375 mg total catechins, 150 mg caffeine) or beverages (244 mg EGCG), respectively. A study performed by Komatsu et al. [91] appears to be hampered by methodological deficiencies, including the duration of the test,

which may have been too short, as well as the use of Douglas bags for gas analyses, which is less accurate than more modern methods. A recent randomized, double-blind, placebo-controlled, cross-over study investigated the thermogenic effect of a beverage containing green tea extract (282 mg EGCG in 540 mg total catechins, 300 mg caffeine) and calcium (633 mg) [92]. It was observed that, compared to placebo, the EGCG-containing beverage increased 24-hour energy expenditure by 106 kcal. The effects of different dosages of EGCG with a fixed dosage of caffeine were investigated by Berube-Parent et al. [93]. In this randomized, double blind, placebo-controlled, cross-over study, 14 healthy subjects received daily dosages of 600 mg caffeine together with 270, 600, 900 or 1200 mg EGCG or placebo capsules. The combinations of caffeine and EGCG increased 24-hour energy expenditure by 660, 713, 788 and 828 kJ, respectively, compared to placebo.

Type 2 Diabetes Mellitus

In 2004, the acute effects of green tea on glucose tolerance were investigated in healthy young Japanese volunteers [94]. It was observed that consumption of 1.5 g green tea extract, 20 min prior to an oral glucose load significantly reduced plasma glucose levels during the glucose tolerance test.

In a recent randomized cross-over study, the anti-diabetic effects of oolong tea consumption for 30 days were determined in 20 subjects with T2DM taking oral hyperglycemic drugs [95]. The consumption of 1.5 L of oolong tea (390 mg EGCG in 950 mg total catechins) resulted in markedly decreased plasma levels of glucose and fructosamine. Another randomized cross-over study in 22 subjects with coronary artery disease, revealed that consumption of 1.0 L oolong tea (45 mg EGCG in 245 mg total catechins) for 30 days increased serum adiponectin and LDL particle size, and decreased hemoglobin A1c [96]. Increased adiponectin is desirable in subjects with T2DM, due to its beneficial effects on insulin sensitivity, while decreased hemoglobin A1c indicates a long-term glucose-lowering efficacy of oolong tea.

Hase et al. [83] observed that the consumption of green tea catechins (300 mg EGCG in 480 mg total catechins) for 12 weeks reduced glucose and insulin levels in healthy, slightly overweight, Japanese subjects. This suggested that chronic consumption of green tea catechins improves insulin sensitivity. However, the consumption of green tea catechins also caused weight loss, which as a consequence could have decreased the levels of glucose and insulin.

In a randomized, controlled study in 69 Japanese subjects with pre-diabetes or diabetes, the effects of consumption of green tea extract (456 mg catechins per day) for 2 months was investigated [97]. Although body weight, BMI, systolic and diastolic blood pressure, blood glucose and insulin levels, HOMA index, and hemoglobin A1c were reduced in subjects receiving green tea extract, no significant differences between the test- and control-groups were observed. In subjects consuming green tea extract, changes in fasting glucose and insulin were significantly correlated with changes in BMI. However, the results of the study have to be interpreted with caution for several reasons, principally related to the lack of control of dietary catechin intake. At baseline, subjects in both groups consumed a significant amount of catechins, with subjects in the intervention group consuming significantly more catechins than the control group. Throughout the study, subjects in the control group increased their catechin consumption, reaching up to 469 mg per day. Moreover, subjects in the intervention group consumed, on average, 747 mg per day which was less than twice the amount of catechins consumed by the control group and were profoundly varying in the change in catechin intake from baseline to the end of the study (e.g. some subjects decreased catechin consumption by 100 mg per day while some subjects increased catechin consumption by 700 mg).

In a randomized cross-over study (no wash-out period) in 55 Korean subjects with T2DM, the effects of daily consumption of 900 mL water containing 9 g of green tea over a 1 month period were investigated [98]. A trend towards reduced fasting glucose was observed ($P=0.09$) but no other parameter changed. Unfortunately, no information about catechin composition of the green tea, plasma or intake levels were provided, which makes it very difficult to interpret the findings.

ANIMAL MODEL STUDIES

Atherosclerosis

In rabbits administered a hypercholesterolemic diet, consumption of green tea (2.5% [w/v] in drinking water for 17 weeks) reduced the development of atherosclerotic lesions by ~30% and reduced VEGF expression in the atherosclerotic lesions [99]. In another study, the effects of EGCG on atherosclerotic plaque development were investigated in apolipoprotein E-null mice [100]. Intraperitoneal administration of EGCG (10 mg/kg for 42 days) reduced atherosclerotic lesions induced by cuff-injury of the carotid artery by 73%. Furthermore, EGCG enhanced the anti-oxidative potential of the plasma and reduced the superoxide production in the media of the injured artery. EGCG inhibited the proliferation of vascular smooth muscle cells *in vitro,* possibly via modulation of redox sensitive genes; these findings which were later confirmed by another study [101]. However, there was no effect of EGCG on established atherosclerotic lesions, suggesting that consumption of green tea catechins during, rather than after, lesion development is crucial. Plasma EGCG 1 hour after i.p. administration was ~138 ng/mL, a concentration that can be achieved in human subjects by consumption of a few cups of green tea or the ingestion of low to moderate dosages of EGCG [102].

Myocardial Benefits

The effect of EGCG on myocardial ischemia-reperfusion injury was investigated in rats [103]. EGCG was administered i.v. as a bolus (10 mg/kg) at the end of the 30-min ischemia period, followed by continuous infusion during the reperfusion period (10 mg/kg/h). EGCG treatment significantly diminished myocardial injury (myocardial damage score and plasma creatine phosphokinase), plasma interleukin-6 and neutrophil infiltration. Furthermore, nuclear factor-κB and activator protein-1 DNA binding were reduced by EGCG treatment.

In a comprehensive study by Li and colleagues [104], the effects of EGCG on cardiac hypertrophy were investigated *in vitro* and *in vivo*. Cardiac hypertrophy was induced in rats by pressure overload due to constriction of the abdominal aorta. The rats then received EGCG (50 mg/kg) orally for 21 days. EGCG treatment prevented the overload-induced cardiac hypertrophy (measured by myocyte diameter and heart weight:body weight), the increase in systolic blood pressure, and the decrease in fractional shortening. Furthermore, the generation of reactive oxygen species and the expression of NADPH oxidase due to angiotensin II and pressure overload were reduced by EGCG. EGCG inhibited the angiotensin II induced activation of nuclear factor-κB and activator protein-1.

Another cardiovascular benefit of EGCG was observed in isolated guinea pig hearts [105]. EGCG added to the perfusion medium (10 and 100 μM) increased left ventricular pressure, as well as nitric oxide and calcium content of the heart, without increasing the heart rate. Thus, EGCG exerted positive inotrophic effects without accompanying positive chronotrophic effects in an NO-dependent manner.

Models of Hypertension

The fact that EGCG prolongs the life span of stroke-prone spontaneously hypertensive rats (SHRSP) was first suggested in 1995 [106]. In this small study, EGCG (0.5% in drinking water, equal to 500 mg/kg) consumption from 5 to 51 weeks of age reduced the incidence of stroke (2 of 5 control animals, 0 of 5 EGCG-treated animals) and reduced mortality (3 of 5 control animals, 1 of 5 EGCG-treated animals). These effects were later reproduced and extended following administration of a mixture of green tea catechins (56.1% EGCG) [107]. Malignant-SHRSP consumed green tea catechins (0.5% in drinking water equal to 116.5 mg/rat) from 5 weeks of age. In rats treated with green tea catechins, systolic and diastolic blood pressure increased more slowly than in control rats. As a consequence, green tea catechins delayed stroke onset by 10.4 days ($\sim$13%). The plasma concentration of EGCG was within the physiological range ($\sim$173 ng/mL).

Recently, Potenza and colleagues [108] investigated the cardiovascular and metabolic effects of EGCG in spontaneously hypertensive rats (SHR). EGCG (200 mg/kg for 3 weeks) significantly reduced systolic blood pressure and enhanced both endothelial function and insulin sensitivity. Moreover, perfused hearts of rats treated with EGCG displayed lower infarct volume and improved ventricular function after ischemia-reperfusion. The NOS inhibitor, L-NAME, effectively blocked most of the above-mentioned effects. These findings led the authors to conclude that EGCG exerts beneficial effects via increased NO production in PI 3-kinase dependent pathways, which might explain both the cardiovascular and the metabolic efficacy.

Nutrient Absorption

In rats receiving an oral lipid emulsion, co-administration of EGCG (100 mg/kg) resulted in significantly reduced plasma triglyceride concentrations [109]. The effect of EGC was weaker compared to that of EGCG, suggesting that the galloyl-moiety increases the activity of catechins. A green tea extract, with a high content of catechins with a galloyl-moiety, dose-dependently (50–200 mg/kg) decreased postprandial triglyceride levels. In 1993, Matsumoto et al. [110] reported that green tea catechins suppressed glucose absorption in rats after starch and sucrose administration. It was observed that intestinal α-amylase and sucrase activities were significantly reduced following catechin dosing (5, 10 and 80 mg/kg orally per gavage). As a result, blood glucose and insulin levels after starch and sucrose consumption were significantly and dose-dependently reduced by green tea catechins.

Yang et al. [111] studied the effects of green tea consumption in a rat model of hyperlipidemia, induced by feeding with a high-sucrose dict. Green tea did not modify protein absorption, bile acid concentration or daily bile acid excretion but did reduce fat absorption. Unfortunately, blood glucose levels were not determined in this study. In Sprague Dawley rats fed a high-fat diet, consumption of a water extract of green tea for 2 weeks resulted in a slight, but statistically significant, reduction in food digestibility whereas food intake was not changed [112]. Blood glucose levels were not determined.

In New Zealand Black (NZB) mice, EGCG supplementation resulted in a dose-dependent reduction in diet-induced obesity [113]. The animals were only slightly hyperglycemic and EGCG reversed this trend. Total food intake and food digestibility were not changed by EGCG supplementation. However, the energy content of the feces was slightly, but significantly, increased at the highest dosage of EGCG. This finding is in agreement with a recent investigation in which EGCG caused a small, but statistically significant, reduction in fat and cholesterol absorption [114]. It remains to be investigated to what extent the slightly increased energy excretion contributes to the observed anti-diabetic effects of EGCG.

Effects in Streptozotocin- or Alloxan-Induced Diabetes Models

Babu and colleagues [115] conducted a number of studies investigating the effects of green tea in rats with streptozotocin-induced (STZ, 60 mg/kg) diabetes. They observed oral administration of green tea extract (300 mg/kg for 4 weeks) reduced lipid peroxides and activity of antioxidant enzymes, whereas it increased glutathione content in the heart and aorta of diabetic rats. In another study, they found reduced blood glucose concentrations, as well as decreased lipid peroxides, triglycerides, and protein glycation in the heart of diabetic rats [116]. Furthermore, green tea extract blunted the rise in cardiac calcium and sodium concentrations due to increased calcium-ATPase and sodium/potassium-ATPase activities in diabetic rats. It was also reported that green tea extract caused recovery of body weight and heart weight/body weight ratio and also reduced blood glucose as well as serum cholesterol, triglyceride, free fatty acid, and LDL cholesterol, while increasing HDL cholesterol [117]. In myocardium, green tea extract decreased cholesterol, triglyceride and free fatty acids as well as lipoprotein lipase activity. In another study with the same experimental design, green tea extract reduced systolic blood pressure, blood glucose, and serum lipid peroxides and elevated serum glutathione and vitamin C [118]. The accumulation of aortic collagen, extent of glycation, formation of advanced glycation end products and cross-linking of collagen were reduced by green tea extract. Similar results were reported in another study [119]. Green tea extract reduced the increase in blood glucose, glycated hemoglobin, and systolic blood pressure in diabetic rats. It was also found that green tea extract prevented the diabetes-induced increase in aspartate transaminase, lactate dehydrogenase, and creatine kinase activities in serum as well as Maillard-type fluorescence and collagen cross-linking in myocardium.

Yamabe et al. [120] investigated the effects of EGCG (25, 50, 100 mg/kg for 50 days) in rats with streptozotocin-induced diabetes and subtotal nephrectomy. EGCG reduced hyperglycemia, proteinuria, and lipid peroxidation and also reduced renal advanced glycation end-product accumulation in the kidney cortex.

In the early 1980s, the anti-diabetic effects of epicatechin were investigated in alloxan-induced diabetic rats. Epicatechin treatment (30 mg/kg i.p. twice daily) for 2 days prior to alloxan injection was shown to prevent the subsequent rise in blood glucose levels and the decrease in beta cells in pancreatic islets [121]. The authors suggested that the reaction of epicatechin with the hydroxyl radicals generated by alloxan was responsible for the observed anti-diabetic effects, however, this was not substantiated by experimental proof. In 2 other studies, epicatechin (30 mg/kg i.p. twice daily for 4 days) was administered starting 24 hours after alloxan injection [122, 123]. Surprisingly, even though epicatechin was administered after alloxan administration, there was still normalization of glucose and insulin levels as well as of β-cell content of pancreatic islets, while control animals, without epicatechin treatment, displayed marked deleterious changes in these parameters. However, the preventive and therapeutic effects of epicatechin treatment on alloxan-induced diabetes was not reproduced by other groups [124–127]. The effects of epicatechin on STZ-induced diabetes (high- and multiple low-dose treatments) were investigated in another study [127]. Only a non-significant trend towards lowered glucose levels was observed. These differing results could be caused by various factors [128]. Retrospectively, the use of different strains of animals, as well as different dosing schedules employed by the various research groups, appear to be the most likely explanations. Since more research groups reported no effect of epicatechin on alloxan- and STZ-induced diabetes, the relevance of the early positive reports can be questioned. Several years later, the preventative effects of epicatechin on STZ-induced diabetes were assessed by another research group [129]. In this study, the first epicatechin treatment was started 6 hours prior to STZ injection, then continued for 6 days (30 mg/kg i.p. twice daily). Epicatechin treatment prevented the decrease in body weight and pancreas weight, as well as the increase in water consumption and blood glucose levels, caused by STZ. Additionally, it was observed that epicatechin treatment preserved pancreas histology, which was severely altered by STZ. In 2003, the pancreas-protective effects of EGCG were investigated in a similar model [130]. Multiple low dosages of STZ were injected into C57BL/KsJ mice for 5 consecutive days, while EGCG treatment (100 mg/kg i.p.) was started on the first day of STZ injection and lasted 10 days. Apparently, during the first 5 days STZ and EGCG were co-injected. EGCG treatment resulted in significantly reduced blood glucose levels, compared with the STZ-treated control group. Furthermore, EGCG partially prevented the STZ-induced deleterious changes in the pancreas. The expression of iNOS mRNA in pancreatic islets was increased in the STZ group and this increase was markedly suppressed in EGCG treated mice.

Using a different experimental design (male Sprague-Dawley rats, STZ 60 mg/kg, 5 mg/kg EGCG i.p. for 4 days), no beneficial effects of EGCG on pancreas function were observed [131]. These results suggest that either the high dosage of STZ or the lower dosage and shorter treatment duration of EGCG may be responsible for the lack of efficacy.

The anti-diabetic effects of green and black tea extract were investigated in STZ-induced diabetic rats [132]. In contrast to the above-mentioned studies, single catechins were not injected i.p. but green tea and black tea were administered orally and their preventative and curative effects on diabetes development were assessed. Green tea exerted pronounced preventative and curative effects and, interestingly, black tea displayed similar effects. However, no information on the dosage of catechins was provided and the only efficacy parameter measured was blood glucose.

Recently, the anti-diabetic effects of green tea extract were investigated in ddY mice, previously injected with STZ, and in db/db mice [94]. In diabetic ddY mice, acute oral administration of

green tea extract (300 mg/kg) resulted in a pronounced decrease in blood glucose levels between 2 and 6 hours after administration. In db/db mice, acute oral administration of green tea extract (300 mg/kg) also significantly decreased blood glucose, which was determined 2 hours after administration. When green tea extract was administered to rats aged 12 months, increased levels of the red blood cell superoxide dismutase and decreased levels of liver malondialdehyde were observed [133]. Furthermore, decreased glucose and triglyceride were detected in the blood of green tea consuming rats. Interestingly, black tea, containing a different polyphenol pattern, exerted very similar effects.

In alloxan-induced diabetic rats, oral application of green tea extract (100 mg/kg for 15 days), starting 3 days after alloxan injection, resulted in increased levels of GSH and superoxide dismutase together with decreased levels of lipid peroxidation [134]. The blood glucose levels were decreased after green tea consumption and liver and kidney function improved. In another study, the effects of consuming green tea catechin-containing diets for 4 weeks on oxidative stress were investigated in STZ-induced diabetic rats [135]. It was observed that green tea catechins inhibited the production of superoxide, lipid peroxide, and oxidized protein in the kidney. Furthermore, it was found that green tea catechins reduced leukotriene B4 production in leukocytes, suggesting a decreased inflammatory response to the STZ-induced diabetes. Recently, the effects of green tea consumption for 12 months on intra- and extracellular oxidative stress and glucotoxicity were studied in STZ-induced diabetic rats [136]. Green tea consumption ameliorated the diabetes-induced oxidative stress determined by increased erythrocyte glutathione content, as well as by decreased retinal superoxide formation, plasma hydroperoxides, and renal mitochondrial respiratory chain defects. Surprisingly, tendon collagen glycoxidation and cross-linking were worsened by green tea consumption, suggesting that green tea may exert different effects in the intra- and extracellular compartments. Blood glucose and glycated hemoglobin were not altered by green tea consumption. No information on the dosage and the composition of the individual green tea catechins was provided. In a similar study design, the development of diabetic cataracts was monitored [137]. Rats were rendered diabetic by STZ injection and, after one week, green tea extract was provided via drinking water for 3 months. Green tea resulted in lower plasma and lens glucose and normalized plasma and lens glycated protein, compared with the diabetic control group. Cataract development and lipid peroxidation in plasma and lens were inhibited by green tea consumption. Black tea was also investigated in this study and exerted similar effects as the green tea. Unfortunately, the catechin composition of both teas was not assessed. A recent study investigated the anti-oxidative potential of epicatechin in liver, kidney, and heart of STZ-induced diabetic rats [138]. Epicatechin was administered i.p. for 35 days (15 and 30 mg/kg), starting 2 days after STZ injection. Decreased levels of lipid peroxidation and increased activities of catalase, superoxide dismutase, and glutathione peroxidase were observed in epicatechin-treated diabetic rats, compared with diabetic controls. Epicatechin appeared to exert dose-dependent effects in all tissues investigated. Additionally, epicatechin significantly reduced blood glucose levels.

Insulin Sensitivity

Wu and colleagues [139] investigated the effects of green tea consumption on insulin sensitivity in rats. Rats on a regular diet receiving green tea extract via drinking water (~370 mg/kg for 12 weeks) displayed significantly decreased fasting plasma levels of glucose, insulin, free fatty acids and triglycerides. During an oral glucose tolerance test, plasma insulin was observed to be lower in green tea consuming rats. Interestingly, adipocytes isolated from these rats displayed an enhanced capacity for glucose uptake and increased specific insulin binding compared to adipocytes from the control group. The same group of investigators assessed the effects of green tea consumption in a rat model of insulin resistance [140]. Rats were fed a high-fructose diet and subsequently developed insulin resistance and hypertension. Rats consuming green tea extract via drinking water (~370 mg/kg for 12 weeks) showed attenuated development of hypertension due to the high fructose diet. Oral glucose tolerance was significantly improved and plasma insulin levels after glucose challenge were lower, suggesting enhanced insulin sensitivity. Isolated adipocytes from green tea-consuming rats were characterized by increased glucose uptake, especially at higher insulin levels, and by increased specific insulin binding, compared with adipocytes of rats on the high fructose diet alone. Furthermore, green tea reversed the high fructose diet-induced decrease in GLUT4 content in adipocytes.

Young Wistar rats drinking green tea for 3 weeks displayed significantly reduced adipose tissue weight compared to controls drinking water [141]. Body weight and food and fluid intake were not changed by green tea consumption. Plasma free fatty acids and total cholesterol were reduced and the LDL/HDL ratio decreased, indicating the green tea beneficially modified the lipid profile. Furthermore, glucose uptake in skeletal muscle was increased, while glucose uptake in adipose tissue was decreased. These effects were likely mediated via increased GLUT4 translocation in skeletal muscle and decreased GLUT4 translocation in adipose tissue. Interestingly, the protein expression of PPARγ, a key regulator of adipocyte differentiation, was decreased in adipose tissue.

Recently, Li and colleagues [142] investigated the effects of green tea extract on glucose and lipid metabolism in a fructose-induced, insulin-resistant hamster model. Supplementation with green tea extract for 4 weeks at a dosage of 300 mg/kg improved oral glucose tolerance and reduced serum insulin levels. Furthermore, increased protein expression of PPARα

and PPARγ was detected, suggesting the green tea extract modified glucose and lipid metabolism partly via PPARs.

Effects in Obesity Models

Yang et al. [111] studied the effects of drinking green, oolong and black tea in a rat model of hyperlipidemia induced by feeding a high-sucrose diet. Even though this model is not suitable for the study of obesity, it provides valuable insights into lipid metabolism. Green tea consumption decreased total plasma triglycerides and cholesterol with the shortest onset and greatest magnitude compared to oolong and black tea. HDL cholesterol was not changed by any of the treatments. In liver and heart, green tea prevented the lipotrophic effects of the high-sucrose diet. Green tea did not modify protein absorption, bile acid concentration or daily bile acid excretion slightly but significantly reduced fat absorption. The authors concluded that the effects of green tea on lipid metabolism were stronger than the effects of oolong tea and black tea. This study provided information on the pronounced effects of green tea on lipid metabolism and, thereby, the rationale for investigating green tea in obesity models.

In Sprague Dawley rats fed a high-fat diet, consumption of a water extract of green tea for 2 weeks resulted in decreased body fat accumulation [112]. This effect appeared to be mediated by increased energy expenditure and a slight, but statistically significant, reduction in food digestibility whereas food intake was not changed. Furthermore, the protein content of interscapular brown adipose tissue was increased by consumption of green tea, indicating an increased thermogenic capacity. Beta-adrenoreceptor blockade by propranolol partially abolished the decrease in body fat and the increases in energy expenditure and brown fat protein content caused by green tea, while the reduction in digestibility was not affected. Therefore, it can be concluded that green tea reduces body fat and increases energy expenditure, which is partially mediated via β-adrenoreceptor activation.

In ICR mice, the effects of different green tea components were investigated [143]. Caffeine and theanine suppressed body weight and body fat, while catechins did not change these parameters but instead reduced serum triglycerides and free fatty acids. However, these findings are in contrast to the results of other studies investigating the anti-obesity effects of green tea catechins. The authors speculated that the relatively low dosage of catechins (0.3% w/w of diet) and possibly the study duration of 16 weeks, which was shorter compared to another study [144], influenced the results. Moreover, ICR mice are outbred and genetically heterogeneous mice that are not commonly used for studies in obesity research. Additionally, it appears that the mice were fed a regular, low-fat diet that in most mouse models does not lead to the development of obesity, especially when given at a young age as in the described study [143]. Therefore, the animal model chosen in this study might not be appropriate for the investigation of anti-obesity effects. However, the study highlighted the fact that green tea is likely to contain more than one weight-suppressing ingredient and that a combination of those ingredients, especially of caffeine and catechins, might synergistically decrease body weight and body fat.

In Zucker rats, a ten-day administration of powdered green tea dissolved in water resulted in significantly attenuated body weight gain and decreased adipose tissue weight, while food intake was not affected [145]. Liver weight and plasma cholesterol levels were significantly reduced by consumption of green tea.

Murase et al. [144] investigated the effects of green tea extract, with relatively low caffeine and high catechin contents, in C57BL/6J mice fed a high fat diet for 11 months. They found that supplementation with green tea catechins reduced body weight, adipose tissue mass, and liver fat content in a dose-dependent manner. Plasma levels of cholesterol, glucose, insulin and leptin were also decreased in a dose-dependent fashion by intake of green tea catechins. In the liver, β-oxidation as determined by [^{14}C]-palmitic acid oxidation activity, was increased by green tea extract, whereas in intestine, brown adipose tissue, and skeletal muscle no changes were detected. Furthermore, acyl-CoA oxidase and medium chain acyl-CoA dehydrogenase mRNA expression increased in the liver, indicative of increased lipid oxidation.

Recently, it was demonstrated by indirect calorimetry that consumption of green tea catechins over a period of 10 weeks, in addition to endurance training, stimulates fat oxidation in BALB/c mice [146]. Beta-oxidation in the gastrocnemius muscle of mice fed green tea catechins was elevated, and exercise capacity was increased. Furthermore, the effects of the most abundant green tea catechin, EGCG, were also assessed in this study. Consumption of increasing doses of EGCG, in addition to endurance training, increased exercise capacity, as well as β-oxidation and the expression of fatty acid translocase/CD36 mRNA, in skeletal muscle. This study provides evidence that endurance exercise in addition to long-term consumption of green tea catechins, or of EGCG alone, improves exercise capacity and stimulates lipid metabolism in mice. If the same effects are demonstrated in clinical studies, the habitual consumption of green tea catechins or EGCG holds potential for endurance athletes to improve their exercise capacity.

In a study by Kao et al. [147], in which EGCG (85 mg/kg) was injected i.p. into lean and obese Zucker rats, the anti-obesity effects of EGCG were investigated. Marked decreases in food intake, body weight, blood glucose and insulin levels were observed.

In 3 recent studies, the anti-obesity and anti-diabetic effects of a defined green tea extract containing $>$94% EGCG and $<$0.1% caffeine was investigated [113, 148, 149]. Dietary supplementation with EGCG prevented the increase in body weight and adipose tissue mass induced by feeding a high-fat diet to C57B1/6J mice [148] and NZB mice [113]. In obese

Sprague Dawley rats, dietary supplementation with EGCG resulted in a significant weight loss within 4 weeks. In both models, energy intake was not affected by EGCG supplementation. In genetically obese and diabetic ZDF rats and db/db mice, EGCG supplementation improved oral glucose tolerance and insulin secretion and decreased fasting blood glucose, plasma triglycerides and free fatty acids.

CONCLUSIONS

Studies in models of cardiovascular and metabolic diseases suggest that green tea and EGCG may contribute to the maintenance of health and the treatment of disease. Several intervention studies have demonstrated green tea catechins containing 200–300 mg EGCG exert beneficial effects on cardiovascular and metabolic health. These studies are consistent with the epidemiological evidence that the consumption of 5–6 or more cups of green tea per day protects cardiovascular and metabolic health. However, the results of the intervention studies are equivocal, which is not surprising considering the variety of study designs, subject populations, and green tea products tested. Therefore, consistent results from well-designed, long-term intervention studies with standardized green tea products would greatly facilitate our understanding of the benefits of green tea catechins. This could potentially transform a beverage traditionally associated with a number of health benefits into an evidence-based functional food.

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