[Frontiers in Bioscience, Scholar, 12, 70-91, Jan 1, 2020]

Beneficial effects of green tea on age related diseases

Juan Chen[1], Zhi Zhang[1], Ping Yu[1], Wen-Tao Gan[1], Kai-Han Ren[1], Fang Zhang[1], Feng Chen[2], Ming-Wei Wanga[1], Jun-Zhe Bao[3], Tengfei Wang[4]

[1]Department of Cardiology, the Affiliated Hospital of Hangzhou Normal University, Hangzhou, China, [2]Department of pharmacy, Nanjing Children's Hospital of Nanjing Medical University, Nanjing, China, [3]Department of Health Policy and Management, School of Public Health, Sun Yat-sen University, Guangzhou, China, [4]Department of Pharmacology, University of Tennessee Health Science Center, Memphis, TN, USA

TABLE OF CONTENTS

1. ABSTRACT

Green tea (*Camellia sinensis, Theaceace*), has been extensively studied for its putative effects in prevention of age related diseases. Here, we discuss the increasing evidence that consumption of green tea has preventative effects in obesity, hypertension, insulin resistance, type II diabetes, atherosclerosis, coronary heart disease and Metabolic Syndrome (MetS). The catechins in green tea has been found to be beneficial in obesity induced by a high-fat diet. These effects are mainly attributable to the gallate esters of catechins, (-)-epicatechin gallate (ECG) and (-)-epigallocatechin-3-gallate (EGCG).

2. INTRODUCTION

Green tea and tea planting originated in China and have spread throughout the world since the middle of the Tang Dynasty. At present, tea ranks as the second most frequently consumed beverage worldwide, surpassed only by water. As early as 4000 to 5000 years ago, the Chinese were aware that tea could promote health and prevent some human diseases, which was recorded in ancient medical books, such as Shen Nong's Herbal Classics. In recent years, the health benefits (1) of tea have been under investigation, including prevention of cardiovascular diseases (2) and cancer (3), as well as its antiarthritic (4), anti-inflammatory (5), antioxidative (6), antiangiogenic (7), antibacterial (8), cholesterol-lowering (9), neuroprotective (10), and antiviral (11) effects. Actually, antioxidative, antiinflammatory, antiproliferative, and antithrombotic effects on the vasculature, as well as beneficial effects on endothelial function, at least in part, account for the anti-atherogenic effects of green tea (4-7).

The definition of metabolic syndrome (MetS) was first put forward by the World Health

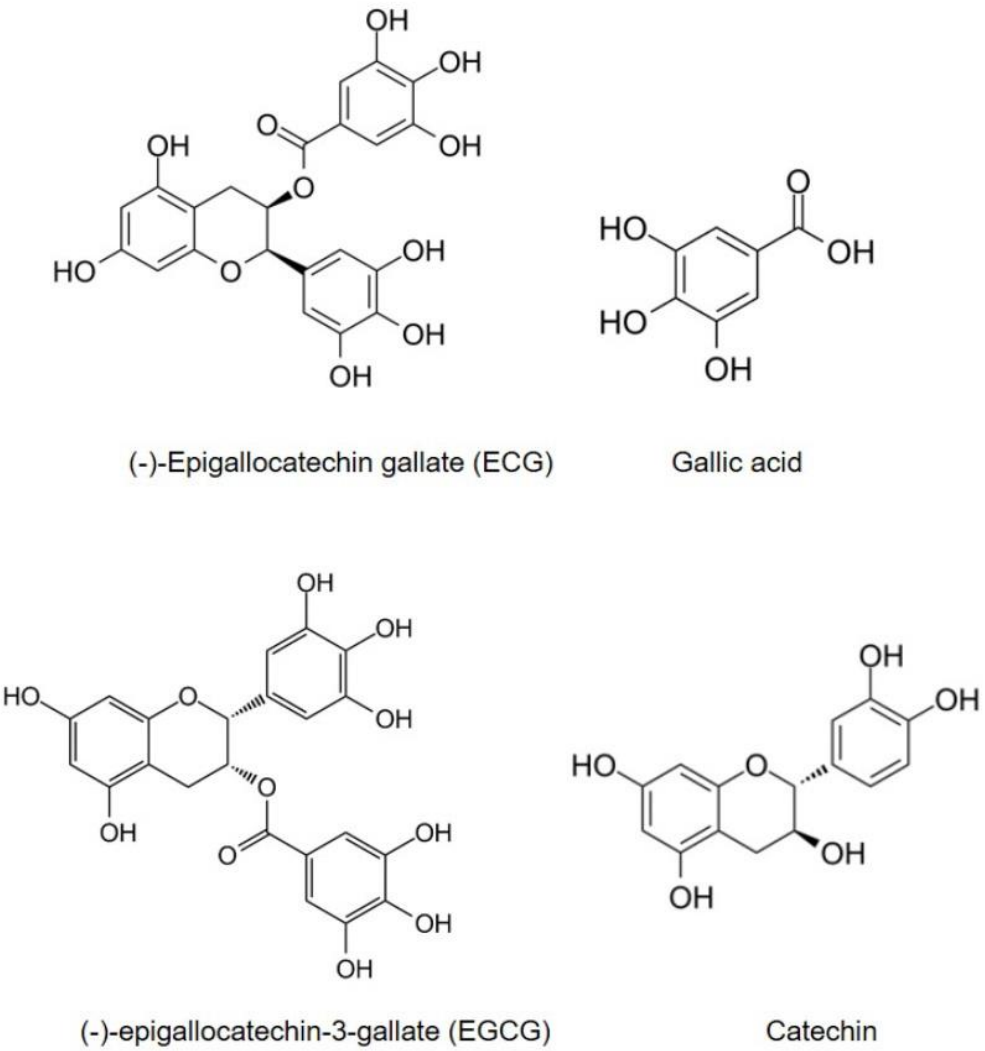

Figure 1. Chemical structures of epigallocatechin gallate (EGCG) and related compounds.

Organization (WHO) in 1999. MetS is defined by a multitude of pathophysiological disorders composed of abdominal obesity, insulin resistance, high blood pressure, and dyslipidemia. MetS has become a significant public health problem, affecting millions of people all over the world (12). The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines highlight the key features of this syndrome and propose a clinical definition to facilitate diagnosis and preventive interventions (13). Major challenges still remain for the integration of the key MetS features into clinical practice in identifying high-risk populations (14). Diagnosing MetS early and taking appropriate treatment can lower the risk of diabetes, atherosclerosis, and cardiovascular disease (Figure 1).

Over the last decades, several epidemiological studies have been carried out to investigate the beneficial effects of green tea ingredients and derivatives in MetS and atherosclerosis. However, the results have not always been consistent. For example, some studies

found that EGCG may ameliorate MetS by regulating the rhythmic expression of circadian clock genes (15,16), whereas another study found that green tea extract did not improve MetS significantly (17). Therefore, this review is aimed to provide an overview of the effect of green tea ingredients and derivatives on atherosclerosis and MetS.

3. EFFECT OF GREEN TEA ON HUMAN DISEASES

3.1. Obesity

Obesity is defined as a body mass index (BMI) equal to or greater than 30, which approximates at least 30 pounds of excess weight (18). It is associated with increased health-care costs, premature death, and reduced quality of life. The data from 195 countries reveal that the prevalence of obesity has doubled in more than 70 countries since 1980, and over 600 million adults were obese in 2015, with a high BMI related to 4 million deaths globally (19).

During the past decade, the effects of green tea and green tea polyphenols have been examined in some animal models of obesity. Fat-rich diets not only induce obesity in humans but also in animals. Therefore, animals that accumulate body fat in response to a high-fat diet (especially rodents) are commonly used in obesity research. To explain the beneficial properties of GTE in obesity, adult zebrafish in one study were allocated to four diet groups, and the results showed that a high-fat diet supplemented with GTE significantly suppressed increases in body weight, body fat volume, and body fat volume ratio in male and female zebrafish as compared with those fed the same diet lacking in GTE (20). In addition, studies of male and female rodents have shown that body weight and body fat accumulation induced by a fat-rich diet were suppressed by dietary GTE supplement (21-24). Meanwhile, studies in mice have shown that tea polyphenol extracts induced weight loss and had anti-inflammatory and angiogenic effects (25).

To investigate the anti-obesity effects of green tea extracts, including polyphenols, polysaccharides, caffeine, and a complex of polysaccharide and polyphenol, a dosage of 400 or 800 mg/kg was given to rats on a 6-week high-fat diet. The results indicated that polyphenols and polysaccharides could reduce rat serum leptin levels, inhibit the absorption of fatty acids, and then suppress body weight increase and fat accumulation (26). Many studies in humans confirm that GTE can cause weight loss. An open study (27) demonstrated the activity of green tea extract AR25 (Exolise) in treating obesity. AR25 exerted a direct inhibition of gastric and pancreatic lipases and stimulated thermogenesis *in vitro*. Body weight was reduced by 4.6% and waist circumference decreased by 4.48% after using AR25 for 3 months. Catechins (the major component of GTE) reduce body fat through inhibiting the malondialdehyde modified LDL (MDA-LDL).

Functional foods and nutraceuticals have gained extensive acceptability from consumers. Interestingly, one study (28) tested functional drinks containing catechins and EGCG in experimental rat models (Sprague Dawley). Catechins contributed to the prevention of various lifestyle-related diseases, particularly obesity. Functional drinks T2 and T3 were prepared by adding EGCG 550 mg/500 mL and compared with control T1, without an active ingredient. Results showed that the functional drinks with added EGCG can help treat obesity, hypercholesterolemia, and hyperglycemia effectively.

By assessing the impact of GTE on starch digestion and absorption, we found that the use of GTE was a viable alternative to pharmaceutical inhibitors of glycoside hydrolase enzymes (29). GTE is widely available, inexpensive, and well tolerated. It is promising for weight control and diabetes treatment.

In one investigation (30) to see if GTE activates the lipolytic pathway, attenuates obesity, and reduces low-grade inflammation in mice fed a high-fat diet, animals were randomized into four groups: CW (chow diet and water); CG (chow diet and water + green tea extract); HW (high-fat diet and water); HG (high-fat diet and water + green tea

extract).The mice were fed ad libitum with chow or a high-fat diet and concomitantly supplemented (oral gavage) with 400 mg/kg bodyweight/day of green tea extract (CG and HG, respectively). GTE promoted weight loss and reduction in adipose tissue pads, increased expression of lipases, decreased adipose mass, and reduced inflammatory molecules and cytokines.

In spontaneously hypertensive rats (SHR , model of metabolic syndrome with hypertension, insulin resistance, and overweight) treated with EGCG, after oral EGCG daily for 3 weeks, there was a modest reduction in body weight compared with a control group (45). EGCG might have direct or indirect pleiotropic effects to lower body weight that might be beneficial in the context of overweight.

A novel processed green tea, FGT (fermented green tea) extracts, exhibits anti-obesity effects (31). Moreover, FGT reduces body weight and fat mass in the absence of decreased food intake. Notably, FGT restores the changes in gut microbiota composition (e.g., the Firmicutes/Bacteroidetes and Bacteroides/Prevotella ratios), which are reported to be closely related to the development of obesity and insulin resistance induced by high-fat diets. In short, FGT reduced body weight and its associated symptoms and modulated composition of gut microbiota; thus, it could be used as a novel dietary component to control obesity and related symptoms.

As previously described, green tea catechins have been shown to suppress body weight in animals and humans. They activated adenosine monophosphate-activated protein kinase (AMPK) and thereby increased fatty acid oxidation in liver and skeletal muscles (32). This study also demonstrated that green tea catechins enhanced lipolysis in the presence of norepinephrine via a PKA-dependent pathway in 3T3-L1 adipocytes, providing a potential mechanism by which green tea catechins could reduce body fat.

Interestingly, post-fermented tea exhibited potential anti-obesity effects in mice fed a high-fat diet, and these effects may be mediated by first, inhibiting the absorption of lipids, second, by strengthening the feedback regulation of the expression of de novo lipogenic genes, and third, down-regulating carnitine palmitoyl transferase-1 (CPT1) expression in the liver (33). In addition, GT helps to control and prevent obesity by stimulating hepatic lipid metabolism. Lee *et al* (34) postulated a high-fat diet (HFD)-induced obesity pathway and validated it by investigating the key regulatory enzymes of mitochondrial β-oxidation: carnitine palmitoyltransferase-1 and -2, acyl-coenzyme A dehydrogenase, and acetyl-coenzyme A acyltransferase. The evidence showed that HFD-induced abnormal mitochondrial β-oxidation was moderated by the consumption of caffeine- and theanine-enriched GT. Results of metabolomic analysis of obese mice showed changes associated with abnormal lipid and energy metabolism, which were alleviated by GT intake, indicating the mechanism underlying the anti-obesity effects of GT.

Furthermore, obesity is currently regarded as an inflammatory condition partly because of the inflammatory cytokines and higher Th1 cell differentiation detected in obese animal models and human cohort studies. To explain therapeutic effects of EGCG in autoinflammatory diseases and obesity, the effects of EGCG on diet-induced obesity (DIO) mice and obese collagen-induced arthritis (CIA) mice were investigated. EGCG reduced the body weight and fat infiltration in liver tissue while improving serum lipid profiles in DIO mice. EGCG also induced a higher T-reg/Th17 cell ratio in CD4 (+) T-cell differentiation by decreasing the ratio of STAT3/STAT5 expression in DIO mice. EGCG was also effective in obese CIA mice (35).

A randomized clinical trial (36) investigated the possible effects of different daily doses of green tea (GT) intake on certain anthropometric, metabolic, and oxidative stress biomarkers of diabetic patients in 63 patients with type 2 diabetes (30 males and 33 females). After a 2-week period without green tea, they were randomly assigned into one of three groups, with a different daily intake of green tea: four cups of green tea per day (n = 24), two cups of green tea per day (n = 25), and the control group (n = 14) with no green tea intake for 2 months. Interestingly,

consumption of four cups of GT per day caused a significant decrease in body weight (73.2 to 71.9Kg) ($P < 0.001$), body mass index (27.4 to 26.9) ($P < 0.001$), waist circumference (95.8 to 91.5Cm) ($P < 0.001$), and systolic blood pressure (126.2 to 118.6 mmHg) ($P < 0.05$).

Consumption of green tea has been linked to a reduction in body fat and body weight. This review assesses the studies of green tea and its epigallocatechin gallato (EGCG) content, evaluating their effect on body fat and body weight in humans. Research results have varied; however, daily consumption of green tea with doses of EGCG between 100 and 460 mg/day has shown greater effectiveness in reducing body fat and weight in intervention periods of 12 weeks or more (37). A Narrative Review focuses on the effect of epigallocatechin-gallate (EGCG) on oxidative stress and inflammation, linked to the metabolic dysfunction of skeletal muscle in obesity and underlying mechanisms. EGCG works by increasing the expression of antioxidant enzymes, reversing the increase of reactive oxygen species (ROS) production in skeletal muscle, and regulating mitochondria-involved autophagy. Moreover, EGCG increases muscle lipid oxidation and stimulates glucose uptake in insulin-resistant skeletal muscle (38). EGCG can decrease obesity only partially via activation of AMPK and epididymal white adipose tissue weight in mice (39). These results suggest the possible therapeutic potential of dietary epigallocatechin gallate-rich GTE supplementation for preventing the development and progression of hepatic steatosis and obesity (40). Human peroxisome proliferator-activated receptors (PPAR) gamma protein was selected as the potential target as it is a key transcription factor for differentiation of adipose cells. Docking analysis of PPAR gamma and epigallocatechin gallate demonstrated that epigallocatechin gallate binds with PPAR gamma at its active site and blocks its activity. This study helps in understanding the mode of action of epigallocatechin gallate that would help in anti-obesity drug development (41).

Collectively, these results indicated that EGCG upregulated autophagic lipolysis in adipocytes, supporting the therapeutic potential of EGCG as a caloric restriction mimetic to prevent obesity and obesity-related metabolic diseases (42). Conversely, another study showed that (43) green tea or GTE intake or its extracts exerted no statistically significant effect on the weight of overweight or obese adults. Although there was a small decrease in the percentage of fat mass, it was not clinically significant. Mechanisms need to be further studied. Moreover, green tea preparations appear to induce a small, statistically nonsignificant weight loss in overweight or obese adults. Because the amount of weight loss was small, it was not likely to be clinically important. Green tea had no significant effect on the maintenance of weight loss (44).

3.2. Hypertension

Hypertension is another condition linked to metabolic syndrome. Epidemiological and intervention studies provide evidence that consumption of tea and other polyphenol-containing foods lower blood pressure. EGCG, a green tea polyphenol, improves insulin sensitivity and endothelial function, reduces blood pressure, and protects against myocardial ischemia/reperfusion injury in spontaneously hypertensive rats (SHR). The acute actions of EGCG to stimulate production of nitric oxide from endothelium using phosphatidylinositol 3-kinase-dependent pathways may explain, in part, the beneficial effects of EGCG therapy in simultaneously improving metabolic and cardiovascular pathophysiology in SHR. These findings may be relevant to understanding potential benefits of green tea consumption in patients with the MetS (45).

Another study examined the effects of EGCG on blood pressure and other metabolic risk factors in overweight or obese men (46). Results showed that dietary supplementation with EGCG had no significant effect on insulin resistance or other associated metabolic risk factors in a sample of overweight and obese men but did reduce diastolic blood pressure. This antihypertensive effect may contribute to some of the cardiovascular benefits associated with habitual green tea consumption. More recently, Nantz *et al* (47) conducted a

randomized, double-blind, placebo-controlled, parallel study in 111 healthy volunteers, comparing the effects of a standardized capsule containing 200 mg of decaffeinated catechin green tea extract with the effects of placebo. They observed a 5 mmHg decrease in systolic blood pressure that was significantly different from the effect of placebo. Furthermore, another study (48) revealed that mildly hypertensive type-2 diabetic individuals who drank three glasses of green or sour tea daily for 4 weeks showed significant decreased systolic and diastolic blood pressures.

During the past decade, the studies investigating the effects of green tea on blood pressure (BP) have generated inconsistent results. The overall outcome (49) suggested that green tea consumption significantly decreased systolic blood pressure (SBP) level by 21.98 mmHg (95% CI: 22.94, 21.01 mmHg; $P < 0.001$). Compared with the control group, green tea also showed a significant effect on lowering diastolic blood pressure (DBP) in the treatment group (21.92 mmHg; 95% CI: 23.17, 20.68 mmHg; $P < 0.002$). Interestingly, subgroup analysis further suggested that the positive effect of green tea polyphenols on BP was documented only in studies using a low-dose green tea polyphenol, with the long-term intervention duration or ruling out the confounding effects of caffeine. Furthermore, green tea or GTE supplementation was found to cause a small but significant reduction in BP among overweight and obese adults. Thus, more high-quality randomized controlled trials with large sample sizes are needed to further confirm the effect on BP in order to make recommendations for green tea or GTE supplementation among overweight and obese adults (50).

As previously described, the effect of tea intake on blood pressure is controversial; findings suggest that long-term (≥12 weeks) ingestion of tea could result in a significant reduction in systolic and diastolic BP (51). Furthermore, meta-analysis suggests that green tea and its catechins may improve blood pressure, and the effect may be greater in those with systolic blood pressure ≥130 mm Hg (52). Data from China (53) show that the consumption of green tea is inversely associated with 5-year blood pressure values, an effect abrogated by smoking. Also, many different dietary supplements are currently marketed for the management of hypertension, but the evidence for their effectiveness is mixed. Although green tea intake results in significant reductions in systolic blood pressure, total cholesterol, and LDL cholesterol, the effect on systolic blood pressure is small, whereas the effects on total and LDL cholesterol appear moderate. It is necessary to conduct longer term independent clinical trials to evaluate the effects of green tea on blood pressure (54).

Recently, it was reported that consumption of tea, especially green tea and British tea, was associated with lowering the risk of hypertension in Singaporean Chinese residents (55). On the other hand, resistance exercise (RE) may lead to a post-exercise hypotension (PEH) response. Other research results showed that three weeks of GTE ingestion did not influence systolic BP, diastolic BP, and heart rate but may have a favorable effect on mean arterial BP and rate pressure product in response to acute resistance exercise during a 1-h recovery period after the exercise (56)(Table 1).

3.3. Insulin resistance and diabetes

Insulin resistance is an early marker of type 2 diabetes (T2D), and development of insulin resistance is associated with obesity (57). Insulin resistance results in the interruption of insulin signaling in responsive tissues, thus leading to hyperinsulinemia and ultimately T2D. Over a long period, the body is unable to produce enough insulin to overcome insulin resistance and the pancreas may reduce or stop insulin production (58). The increasing prevalence of type 2 diabetes mellitus (T2DM) is associated with the rapid spread of obesity. Obesity induces insulin resistance, results in pancreatic β-cell dysfunction, and thus T2DM. Epidemiologically, it has been suggested that green tea consumption prevented type 2 diabetes, but this effect is still in dispute. Green tea catechins (GTCs) significantly decreased glucose level and increased glucose tolerance in animals. GTCs reduced ROS content in both animal and adipocyte models (59). EGCG attenuated the generation of ROS promoted by

Table 1. *In vivo* effects of green tea on metabolic syndrome and atherosclerosis

Compound(s)/Extract(s)	Model System	Dosage Given	Results	References
GTE	Zebrafish	5%	Suppress body weight increasing	20
EGCG	mice	0.32%,3.2 g/kg,20 mg/kg,50 mg/kg and 100 mg/kg	Decrease lipid absorption, body weight and epididymis white adipose tissue weight	21,22,35,39
GTPs	rats	0.5%	Enhance antioxidant capacity and suppressing inflammation	23
GTP	rats	0.5% wt./vol	Regulate obesity-related genes, anti-inflammation, anti-oxidant capacity	24
GTPs	mice	0.25%	Induce weight loss and anti-inflammatory and angiogenic effects	25
GT	rats	400 or 800 mg kg^{-1}	Reduce serum leptin levels and anti-inflammatory activity	26
EGCG	rats	550 mg/500mL	Decrease body weight	28
GTP	mice	400 mg/kg	Increase the lipolytic pathway and reduce adipose tissue	30
FGT	mice	500 mg/kg	Control obesity and related symptoms	31
GTCs	mice	0.2-0.5% (wt/wt)	Reduce body fat	32
JWFT	mice	0.5, 1.0 and 2.0 g/kg	Inhibit the increase in the body weight	33
GT	mice	1% GT	Anti-obesity	34
GTE	mice	30 mg/kg ,60 mg/kg , and 120 mg/kg	Reduce body weight gain	40
EGCG	rats	200 mg.kg(-1).day(-1)	Lower systolic blood pressure	45
EGCG	mice	150mg/kg/day;300mg/kg/day;	Improve adipose insulin resistance	59
GTE	mice	10 g GTE/kg	Preventing both obesity and obesity-induced T2DM	60
EGCG	rats	20.14+0.61 g per rat per day and 19.58+0.48 g per rat per day	Against hypercholesterolemia and hyperglycemia	62
fGT	mice	400 mg/kg fGT extracts	Anti-diabetic effects	69
EGCG	mice	300mg/kg b.w., i.g.	Therapeutic intervention in diabetes	74
GT	rabbits	3 g/l,2.5%	Reduce aortic lesion formation	78,98,99
GT	rats	0.5 and 1.0% (wt/wt)	Lower the lipid	79
GTAE	rats	1.1 and 2.0% GTAE	Prevent on the accumulation of visceral fat	80
GT	mice	4%	Reduce the body fat content, hepatic triacylglycerol and cholesterol accumulation	83
EGCG	mice	40 mg/kg/d, i.g,0.02%,10 mg/kg	Anti-atherosclerotic effects	86,90,96
Catechins	mice	0.3%	Inhibit the development of atherosclerosis	87
GTP	mice	3.2 or 6.4 g/L	Inhibit atherogenesis	88
EGCG	rabbit	EGCG was loaded in the nanoparticles 27 to yield EGCG-CS-PAA nanoparticles	Against rabbit atherosclerosis	89
GTE	mice	50 mg/kg,100mg/kg,300mg/kg	Decrease atherosclerosis	91
EGCG	rats	100mg/kg BW	Decrease the risk of cardiovascular disease	92
GT	rats	150 ml	Prevent atherosclerosis	93
GTC	mice	0.2 or 4%,0.8 g/L	Inhibit atherosclerosis	94,97

dexamethasone and TNF-α and increased glucose uptake ability. EGCG also decreased JNK phosphorylation and promoted GLUT-4 translocation. EGCG and GTCs could improve adipocyte insulin resistance and exert this effect on their ROS scavenging functions.

To compare the effect of GTE with that of GTE coadministered with poly-γ-glutamic acid (γ-PGA), db/db mice and age-matched nondiabetic mice were provided with a normal diet containing GTE (1%) and γ-PGA (0.1%) or GTE+γ-PGA (1%:0.1%) for 4 weeks (60). Results suggested that GTE+γ-PGA treatment may be a more useful method for preventing both obesity and obesity-induced T2DM than GTE or γ-PGA alone. Kim (61) examined the effects and mechanisms of GTP on glycogen synthesis and lipogenesis in HepG2 cells. The findings showed that GTP was capable of enhancing insulin-mediated glucose and lipid metabolism by regulating enzymes involved in glycogen synthesis and lipogenesis.

Green tea has many biologically active ingredients such as flavanols and polyphenols. GTE has a role in mitigating metabolic syndrome, especially in hyperglycemia and hypercholesterolemia (62). Rats with hyperglycemia and hypercholesterolemia were given ethanol extracts of green tea for 8 weeks. The serum glucose level was reduced the most in hyperglycemic rats. Meanwhile, green tea did not adversely affect the red blood cell, white blood cell, and platelet quantities in the rats.

A study was conducted in elderly men and women living in Mediterranean islands during 2005-2007 (63). This was one of the few studies that evaluated this hypothesis in elderly individuals whose disease burden was high. The association between tea intake and blood glucose level was investigated and the study revealed that moderate (i.e., 1-2 cups per day) and long-term tea consumption were related to a significant reduction in fasting blood glucose level and consequently lower likelihood of diabetes mellitus, irrespective of various other clinical and lifestyle characteristics.

Studies (64) using stratified analysis revealed that tea consumption ≥ 4cups per day might play a role in the prevention of type 2 diabetes. However, no statistically significant association was observed for sex and the follow-up durations stratified between tea consumption and type 2 diabetes. The EPIC-Inter Act case-cohort study was conducted in eight European countries, and investigators observed a linear inverse association between tea consumption and incidence of type 2 diabetes (65). People who drank at least 4 cups of tea per day may have a 16% lower risk of developing type 2 diabetes than non-tea drinkers do. Furthermore, whether consumption of all types of tea was associated similarly with lower risk of type 2 diabetes and whether this association was causal should be further investigated. In another study, representative samples were selected by a multistage, stratified, cluster, random-sampling method from Fujian Province in China, and investigators found inverse associations in Chinese women and men between green tea consumption and IFG (Impaired Fasting Glucose） and also between rock tea consumption and IGT(Impaired Glucose Tolerance (66). These inverse associations were more pronounced in subjects who drank 16 to 30 cups of tea each week.

In one study, green tea consumption lowered fasting glucose and Hb A1c concentration significantly (67). Meanwhile, subgroup analysis with the data from high-quality trials showed that green tea consumption significantly reduced fasting insulin concentration. The results of a study investigating the phytophenolic profile of Mauritian green tea and its antioxidant propensity showed that the green tea regimen could be part of a healthy lifestyle that might ameliorate features of metabolic syndrome and subsequently lower risks for individuals with the propensity to develop type 2 diabetes (68).

To evaluate the anti-obesity effect of FGT(green tea fermented with Aquilariae Lignum), Kang (69) examined the anti-diabetic effect of FGT compared to unfermented green tea (GT) on mice with type 2 diabetes and found FGT had stronger anti-diabetic effects than GT did. These results suggested that fermentation with appropriate amount

of Aquilariae Lignum (9:1) synergistically increased the anti-diabetic effects of GT in db/db mice. Thus, FGT could be as a new potent therapeutic agent for type 2 diabetes because it showed anti-obesity, anti-hypoglycemic, anti-hyperlipidemic, and antioxidant effects. GTE (green tea extract) significantly improved insulin resistance and increased glucagon-like peptide 1 only in within-group comparisons (70). Taking decaffeinated GTE daily with a dose of 856 mg EGCG for 16 weeks produced no severe adverse effects. In another study, tea consumption was linearly inversely associated with T2D risk (71). At the same time, a systematic review suggested that daily tea consumption (≥3 cups/day) was associated with a lower T2DM risk (72), which implies that the daily consumption level might be an important factor in determining the protective effect of tea against T2DM.

Furthermore, one trial (73) found green tea and sour tea could decrease oxidative stress and attenuate insulin resistance and might also decrease complications of diabetes mellitus (DM). In this study, 100 patients with type 2 diabetes were randomly assigned into a sour tea group (ST) and green tea group (GT). The patients were instructed to drink 150 ml sour tea or green tea infusion, respectively, three times a day for 4 weeks. Results revealed that green tea users had a significant decrease in fasting blood insulin. This study showed that daily use of 150 ml infusion of green tea or sour tea, three times a day for 4 weeks, had a positive effect on insulin resistance and certain lipoprotein metabolism in patients with type 2 DM. Thus, using these kinds of tea, particularly green tea, is recommended in patients with type 2 DM. EGCG improved glucose homeostasis and inhibited the process of gluconeogenesis (PEPCK and G-6-Pase) and lipogenesis (SREBP-1C, FAS, and ACC1) in the liver. Meanwhile, EGCG treatment activated PXR/CAR, accompanied by upregulated the expression of the PXR/CAR-mediated phase II drug metabolism enzyme in the small intestine and liver, involving SULT1A1, UGT1A1, and SULT2B1b. This study concluded that dietary polyphenol EGCG could serve as a promising PXR/CAR activator and therapeutic intervention in diabetes (74).

Conversely, GT did not lower plasma glucose, glycemic index, or insulin level in another study (75). This was a crossover design with 14 healthy volunteers, and the results suggested that green tea may increase satiety, but more clinical trials are needed to further evaluate the effects of green tea on satiety. Another study provided no evidence supporting that consumption of GT/GTE could reduce the levels of HbA1c, HOMA-IR, fasting insulin, or fasting glucose in people with pre-diabetes/T2DM (76).

3.4. Plasma cholesterol

Green tea and green tea polyphenols have been shown to modulate the levels of both HDL- and LDL-cholesterol in plasma and tissues. Improvement in serum lipid profiles is another possible mechanism that would account for the beneficial effect of tea on cardiovascular disease, and several observational studies suggest that tea might have such an effect. Earlier studies have shown no relationship between green or black tea consumption and total or LDL cholesterol levels (77). A recent study on cholesterol-fed New Zealand rabbits showed that green tea had potential anti-atherosclerotic effects (78). Previous studies (25) showed that a physiologically relevant dose of dietary EGCG reduced the development of obesity, hyperglycemia, insulin resistance, hypercholesterolemia, and hepatic steatosis in mice fed a high-fat diet. Histological analysis of liver samples showed decreased lipid accumulation in hepatocytes in mice treated with EGCG compared with mice on a high-fat diet without EGCG treatment. These effects may be related to decreased fat absorption and anti-inflammatory effects mediated by EGCG.

To understand whether GT inhibits the expression of genes regulating hepatic lipogenesis and intestinal lipid transport in fructose-fed ovariectomized (OX) rats, they fed OX rats with fructose to set up an animal model of diet-induced hypertriglyceridemia and found new evidence that GT significantly downregulated the expression of the sterol regulatory element-binding protein-1c (SREBP-1c) and its target genes such as fatty acid synthase (FAS) and stearoyl-CoA desaturase 1 (SCD1) in liver and the genes that regulate hepatic

cholesterol synthesis (HMGR) and efflux (ABCA1). Thus, the TG-lowering effect of GT in plasma and liver may be mediated partly via the suppression of lipogenesis and inhibition of luminal hydrolysis and micellar transfer of lipids to the enterocyte (79). In addition, in one study 2.0% green tea aqueous extract significantly decreased body weight gain, prevented visceral fat accumulation, and decreased protein availability in rats fed a high-fat diet (80). Further evidence (81,82)showed that the consumption of green tea catechins was associated with a significant reduction in total and LDL cholesterol levels; however, there was no significant effect on HDL cholesterol or triglyceride levels. Meanwhile, subgroup and sensitivity analysis showed that these changes were not influenced by the type of intervention, treatment dose of green tea catechins, individual health status, study duration, or quality of the study. Conversely, in C57BL/6J mice fed a high-fat diet, GT strongly reduced the body fat content and hepatic triglycerol and cholesterol accumulation (83).

Considering that the liver is an important organ in glucose and lipid metabolism, the effects and mechanisms of GTP on glycogen synthesis and lipogenesis in HepG2 cells were examined (61). AMPK and ACC are key enzymes that regulate lipogenesis in the liver. GTP-EGCG treatment significantly increased phospho-AMPKα (Thr172) and phospho-ACC (Ser79) expression in HepG2 cells. The findings showed that the beneficial effects of GTP in metabolic syndrome and diabetes resulted from direct enhancement of glycogen synthesis in the liver and decreased hepatic lipogenesis.

To understand the influence of GTE on lipid digestion and absorption, 32 healthy volunteers aged 23 to 30 years with normal exocrine pancreatic function were studied (84). Breath tests of 13C-labelled mixed triglycerides were performed twice in all subjects with and without GTE ingestion. Interestingly, the findings showed a single dose of GTE decreased lipid digestion and absorption from a test meal in humans. Similarly, a pilot study showed that a long-term diet containing green tea decreased lipid assimilation without involvement of luminal effects (85) (Table 2).

3.5. Atherosclerosis and metabolic syndrome

Atherosclerosis is one of the metabolic syndrome-related diseases caused by obesity. The anti-obesity effects of green tea and its ingredients have been reported previously (18-44). To explore the effect and mechanism of EGCG on atherosclerosis, male mice 7 weeks old with apolipoprotein E-knockout (ApoE$^{-/-}$) were fed with a high-fat diet (HFD) and meanwhile treated with normal saline or EGCG (40 mg/kg/d) for 18 weeks, and results showed EGCG significantly modulated the expression of high-fat-induced hepatic tetratricopeptide repeat domain protein 39B (TTC39B) in liver (86). Liu *et al* (87) investigated whether catechins and caffeine alone or in combination could prevent atherosclerosis, and the results indicated that the combination of catechin and caffeine had an inhibitory effect on the development of atherosclerosis in mice. In another study (88), green tea polyphenol supplements showed marked suppression effects on atherogenesis through improving lipid metabolism as well as through a direct impact on LDL and autophagy flux in the vessel wall. Moreover, the effectiveness of EGCG against atherosclerosis in rabbits was significantly improved by incorporating EGCG into the nanoformulation (89). EGCG inhibited porphyromonas gingivalis-induced atherosclerosis through anti-inflammatory and antioxidative (90).

Green tea not only reversed endothelial dysfunction but also reduced progression of atherosclerosis (91). It was also possible to decrease the risk of cardiovascular disease by reducing the inflammatory markers in rats with an atherogenic diet (92). Fermented tea has the effect of preventing hypercholesterolemia and atherosclerosis (93). Tea caused some improvement in a hamster model of atherosclerosis in plasma low-density lipoprotein (LDL), LDL/high density lipoprotein ratio, triglycerides, lipid peroxides, lower density lipoprotein lipid peroxides, and fibrinogen (94,95). In addition, EGCG differentially reduced evolving atherosclerotic lesions without influencing established atherosclerosis in apolipoprotein E-null mice (96), probably through the potent antioxidative activity of

Table 2. Clinical effects of green tea on metabolic syndrome and atherosclerosis

Compound(s) /Extract(s)	Subjects Used	Treatment Method	Duration	Results	References
GTE AR25	70 patients	Consume capsules of green tea polyphenols	12 weeks	Inhibit lipases and stimulate thermogenesis	27
GTE	28 healthy volunteers aged 19 to 28 years	Oral the test meal with GTE (GTE 4 g)	1 week	Decrease starch digestion and absorption	29
GT	63 patients with type 2 diabetes	Consumption of four cups of GT	2 months	Reduce weight	36
EGCG	100 overweight or obese male subjects aged 40-65 years	0.5% wt./vol	8 weeks	Regulate obesity-related genes, anti-inflammation, anti-oxidant capacity	46
Camellia sinensis compounds	Healthy men (n=52) and women (n=72) 21 to 50 y of age	100 mg of L-theanine	3 months	Decrease systolic blood pressure	47
GT	100 mildly hypertensive patients with diabetes	Drink green tea infusion	4 weeks	Decrease systolic and diastolic blood pressures	48
GT	1109 Chinese men	Drink green tea	5 years	Green tea is inversely associated with 5-year BP change	53
GT	The prevalence of hypertension (N=1184)	Drink green tea	12 months	Lower the risk of hypertension	55
GTE	300 men and women	GTE consumption	4 weeks	Did not influenced SBP and DBP	56
GT	aged 65 to 100 years	Drink green tea	2 years	Lower prevalence of diabetes	63
GT	9995 people were registered	Drink green tea	<1, 1–15, 16–30, and >30 cups per week	Protect against the development of type 2 diabetes mellitus	66
GT	Three hundred prediabetic Mauritians age ranged from 35 to 65 years	Drink green tea	14 weeks	Ameliorate features of metabolic syndrome	68
GTE	92 subjects with type 2 diabetes mellitus and lipid abnormalities	Take green tea extract	16 weeks	Decrease triglyceride	70
GT	100 type 2 diabetes patients	Take green tea	4 weeks	Positive effect on insulin resistance and certain lipoproteins	73
GT	14 healthy volunteers	Take green tea	2 hours	Did not lower plasma glucose, glycemic index or insulin level	75
GT	207 of the men and 164 of the wives	Daily green tea intake (< 1 cup, 1-4 cups, and > 4 cups)	3 days	Do not support the beneficial effects of green tea on serum lipid levels	77
GTE	32 healthy volunteers aged 23 to 30 years	EGCG content-257.6 mg	360 minutes	Decrease lipid digestion and absorption	84
GTE	Eight obese subjects aged 56-65 years	188.3 mg and 242.1 mg EGCG	3 months	Decrease lipid assimilation	85
GT	512 patients aged 30 years or older	0-1, 2–3, 4–6 cup/day	1 year	Inhibit coronary arteries	100

the tea (97). In female New Zealand white rabbits, green tea consumption reduced aortic lesion formation (78), as well as decreased the expression of vascular endothelial growth factor significantly in the atherosclerotic plaque of rabbit aorta (98). The relation between green tea consumption and coronary atherosclerosis was examined in Japan and the results showed green tea may be protective against coronary atherosclerosis in men (99).

4. CONCLUSIONS

In the last 30 years, research has identified tea as a potential promoter for human health. Given the high consumption, wide distribution, and the potential health effects of tea, further studies are reasonable and necessary. In this article, we have reviewed a representative part of the widely published literature about tea and its role in metabolic syndrome and atherosclerosis. In experimental models and human subjects, a few reasonable beneficial mechanisms have been identified, including anti-inflammatory, anti-platelet, and other favorable effects on the vascular endothelium. Future research needs to confirm the safety of tea consumption associated with its benefits and to clarify the potential mechanisms of action. Clinical intervention studies in the future could provide more convincing evidence of the effects of green tea.

5. ACKNOWLEDGMENTS

The presented study was supported by Hangzhou science and Technology Bureau fund (20171334M01;20191203B96;20191203B105); Zhejiang Kang Enbei Hospital Management Soft Science Project (2017ZHA-KEB318); Hangzhou science and Technology Association ((2017)28); Excellent Youth Project of the Affiliated Hospital of Hangzhou Normal University (2019). The authors declare that they have no conflicts of interest.

6. REFERENCES

1. N Khan, H Mukhtar: Tea Polyphenols in Promotion of Human Health. *Nutrients.* 25,11. pii: E39 (2018)
DOI: 10.3390/nu11010039.

2. J Pang, Z Zhang, TZ Zheng, BA Bassig, C Mao, X Liu, Y Zhu, K Shi, J Ge, YJ Yang, DJ Huang, M Bai, Y Peng: Green tea consumption and risk of cardiovascular and ischemic related diseases: A meta-analysis.*Int. J. Cardiol.* 1,967-974 (2016)
DOI: 10.1016/j.ijcard.2014.12.176.

3. Y Miyata, Y Shida, T Hakariya, H Sakai: Anti-Cancer Effects of Green Tea Polyphenols Against Prostate Cancer.*Molecules.* 7,24. pii: E193 (2019)
DOI: 10.3390/molecules24010193.

4. G Ramadan, NM El-Beih, RM Talaat, EA Abd El-Ghffar: Anti-inflammatory activity of green versus black tea aqueous extract in a rat model of human rheumatoid arthritis. *Int. J. Rheum.* Dis.20,203-213 (2017)
DOI: 10.1111/1756-185X.12666.

5. WC Reygaert: Green Tea Catechins: Their Use in Treating and Preventing Infectious Diseases. *Biomed. Res. Int.* 17,2018:9105261 (2018)
DOI: 10.1155/2018/9105261.

6. I Peluso, M Serafini: Antioxidants from black and green tea: from dietary modulation of oxidative stress to pharmacological mechanisms. *Br. J. Pharmacol.* 174,1195-1208 (2017)
DOI: 10.1111/bph.13649.

7. B Rashidi, M Malekzadeh, M Goodarzi, A Masoudifar, H Mirzaei: Green tea and its anti-angiogenesis effects. *Biomed. Pharmacother.* 89,949-956 (2017)
DOI: 10.1016/j.biopha.2017.01.161.

8. SD Falcinelli, MC Shi, AM Friedlander, J Chua: Green tea and epigallocatechin-3-gallate are bactericidal against Bacillus

anthracis. *FEMS. Microbiol. Lett.* 3,364 (2017)
DOI: 10.1093/femsle/fnx127.

9. S Huang, J Li, Y Wu, S Ranjbar, A Xing, HZhao, YWang, GC Shearer, L Bao, AH Lichtenstein, S Wu, X Gao: Tea Consumption and Longitudinal Change in High-Density Lipoprotein Cholesterol Concentration in Chinese Adults. *J. Am. Heart. Assoc.* 25,7. pii: e008814 (2018)
DOI: 10.1161/JAHA.118.008814.

10. K Sárközi, A Papp, E Horváth,Z Máté, E Hermesz, G Kozma, ZP Zomborszki, I Kálomista, G Galbács, A Szabó: Protective effect of green tea against neuro-functional alterations in rats treated with MnO2 nanoparticles. *J. Sci. Food. Agric.*97,1717-1724 (2017)
DOI: 10.1002/jsfa.7919.

11. D Furushima, K Ide, H Yamada: Effect of Tea Catechins on Influenza Infection and the Common Cold with a Focus on Epidemiological/Clinical Studies. *Molecules.* 20,23. pii: E1795 (2018)
DOI: 10.3390/molecules23071795.

12. DH Sherling, P Perumareddi, CH Hennekens: Metabolic Syndrome. *J Cardiovasc Pharmacol. Ther.* 22,365-367 (2017)
DOI: 10.1177/1074248416686187.

13. MP Reilly, DJ Rader: The metabolic syndrome: more than the sum of its parts? *Circulation.*108,1546-1551 (2003)
DOI: 10.1161/01.CIR.0000088846.-10655.E0

14. KA Grove, JD Lambert: Laboratory, epidemiological,and human intervention studies show that tea (camellia sinensis) may be useful in the prevention of obesity. *J. Nutr.*140,446-453 (2010)
DOI: 10.3945/jn.109.115972

15. Y Mi, G Qi, R Fan, X Ji, Z Liu, X Liu: EGCG ameliorates diet-induced metabolic syndrome associating with the circadian clock.Biochim. *Biophys. Acta. Mol. Basis. Dis.* 1863,1575-1589 (2017)
DOI: 10.1016/j.bbadis.2017.04.009.

16. S Legeay, M Rodier, L Fillon, S Faure, N Clere: Epigallocatechin Gallate: A Review of Its Beneficial Properties to Prevent Metabolic Syndrome. *Nutrients.*7,5443-5468 (2015)
DOI: 10.3390/nu7075230.

17. J Bajerska, S Mildner-Szkudlarz, J Walkowiak: Effects of rye bread enriched with green tea extract on weight maintenance and the characteristics of metabolic syndrome following weight loss: a pilot study. *J Med Food.* 18,698-705 (2014)
DOI: 10.1089/jmf.2014.0032.

18. CJ Lavie, D Laddu, R Arena, FB Ortega, MA Alpert,RF Kushner: Healthy Weight and Obesity Prevention: JACC Health Promotion Series. *J. Am. Coll. Cardiol.* 72,1506-1531 (2018)
DOI: 10.1016/j.jacc.2018.08.1037.

19. GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, Marczak L, Mokdad AH, Moradi-Lakeh M, Naghavi M, Salama JS, Vos T, Abate KH, Abbafati C, Ahmed MB, Al-Aly Z, Alkerwi A, Al-Raddadi R, Amare AT, Amberbir A, Amegah AK, Amini E, Amrock SM, Anjana RM, Ärnlöv J, Asayesh H, Banerjee A, Barac A, Baye E, Bennett DA, Beyene AS, Biadgilign S, Biryukov S, Bjertness E, Boneya DJ,

Campos-Nonato I, Carrero JJ, Cecilio P, Cercy K, Ciobanu LG, Cornaby L, Damtew SA, Dandona L, Dandona R, Dharmaratne SD, Duncan BB, Eshrati B, Esteghamati A, Feigin VL, Fernandes JC, Fürst T, Gebrehiwot TT, Gold A, Gona PN, Goto A, Habtewold TD, Hadush KT, Hafezi-Nejad N, Hay SI, Horino M, Islami F, Kamal R, Kasaeian A, Katikireddi SV, Kengne AP, Kesavachandran CN, Khader YS, Khang YH, Khubchandani J, Kim D, Kim YJ, Kinfu Y, Kosen S, Ku T, Defo BK, Kumar GA, Larson HJ, Leinsalu M, Liang X, Lim SS, Liu P, Lopez AD, Lozano R, Majeed A, Malekzadeh R, Malta DC, Mazidi M, McAlinden C, McGarvey ST, Mengistu DT, Mensah GA, Mensink GBM, Mezgebe HB, Mirrakhimov EM, Mueller UO, Noubiap JJ, Obermeyer CM, Ogbo FA, Owolabi MO, Patton GC, Pourmalek F, Qorbani M, Rafay A, Rai RK, Ranabhat CL, Reinig N, Safiri S, Salomon JA, Sanabria JR, Santos IS, Sartorius B, Sawhney M, Schmidhuber J, Schutte AE, Schmidt MI, Sepanlou SG, Shamsizadeh M, Sheikhbahaei S, Shin MJ, Shiri R, Shiue I, Roba HS, Silva DAS, Silverberg JI, Singh JA, Stranges S, Swaminathan S, Tabarés-Seisdedos R, Tadese F, Tedla BA, Tegegne BS, Terkawi AS, Thakur JS, Tonelli M, Topor-Madry R, Tyrovolas S, Ukwaja KN, Uthman OA, Vaezghasemi M, Vasankari T, Vlassov VV, Vollset SE, Weiderpass E, Werdecker A, Wesana J, Westerman R, Yano Y, Yonemoto N, Yonga G, Zaidi Z, Zenebe ZM, Zipkin B, Murray CJL: Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med* .377,13-27 (2017) DOI: 10.1056/NEJMoa1614362

20. S Meguro, T Hasumura, T Hase: Body Fat Accumulation in Zebrafish Isinduced by a diet rich in Fat and reduced by supplementation with green tea extract. *PLoS One.*18,10 (2015) DOI: 10.1371/journal.pone.0120142

21. YK Chen, C Cheung, KR Reuhl, AB Liu, MJ Lee, YP Lu, CS Yang: Effects of green tea polyphenol (-)-epigallocatechin-3-gallate on newly developed high-fat/Western-style diet-induced obesity and metabolic syndrome in mice. *J. Agric. Food. Chem.*59,11862-11871 (2011) DOI: 10.1021/jf2029016.

22. M Bose, JD Lambert,J Ju: The major green tea polyphenol, (-)-epigallocatechin-3-gallate, inhibits obesity, metabolic syndrome, and fatty liver disease in high-fat-fed mice. *J. Nutr.* 138,1677-1683 (2008) DOI: 10.1093/jn/138.9.1.677

23. CL Shen, JJ Cao, RY Dagda: Green tea polyphenols benefits body composition and improves bone quality in long-term high-fat diet-induced obese rats. *Nutr. Res.* 32,448-457 (2012) DOI: 0.1016/j.nutres.2012.05.001

24. C Lu, W Zhu, CL Shen: Green tea polyphenols reduce body weight in rats by modulating obesity-related genes. *PLoS. One.* 7,e38332 (2012) DOI: 10.1371/journal.pone.0038332

25. D Heber, Y Zhang, J Yang, JE Ma, SM Henning, Z Li: Green tea, black tea, and oolong tea polyphenols reduce visceral fat and inflammation in mice fed high-fat,high-sucrose obesogenic diets. *J.Nutr.*144,1385-1893 (2014) DOI: 10.3945/jn.114.191007

26. Y Xu, M Zhang, T Wu, S Dai, J Xu, Zhou Z: The anti-obesity effect of green tea polysaccharides, polyphenols and caffeine in rats fed with a high-fat diet. *Food. Funct.* 6,297-304 (2015)
DOI: 10.1039/c4fo00970c

27. P Chantre, D Lairon: Recent findings of green tea extract AR25 (Exolise) and its activity for thetreatment of obesity. *Phytomedicine.*9,3-8 (2002)
DOI: 10.1078/0944-7113-00078

28. RS Ahmad, MS Butt, MT Sultan, Z Mushtaq, S Ahmad, S Dewanjee, V De Feo, M Zia-Ul-Haq: Preventive role of green tea catechins from obesity and related disorders especially hypercholes-terolemia and hyperglycemia.J.*Transl-ational. Medicine.*1,79 (2015)
DOI: 10.1186/s12967-015-0436-x

29. K Lochocka, J Bajerska,A Glapa, E Fidler-Witon, JK Nowak, T Szczapa, P Grebowiec, A Lisowska, J Walkowiak: Green tea extract decreases starch digestion and absorption from a test meal in humans: a randomized, placebo-controlled crossover study. *Sci. Rep.*12015 (2015)
DOI: 10.1038/srep12015

30. CA Cunha, FS Lira, JC Rosa Neto, GD Pimentel, GI Souza, CM da Silva, CT de Souza, EB Ribeiro, AC Sawaya, CM Oller do Nascimento, B Rodrigues, P de Oliveira Carvalho, LM Oyama: Green tea extract supplementation induces the lipolytic pathway, attenuates obesity, andreduces low-grade inflammation in mice fed a high-fat diet. *Mediators. Inflamm.* 2013,635470 (2013)
DOI: 10.1155/2013/635470

31. DB Seo, HW Jeong, D Cho, BJ Lee, JH Lee, JY Choi, IH Bae, SJ Lee: Fermented Green Tea Extract Alleviates Obesity and Related Complications and Alters Gut Microbiota Composition in Diet-Induced Obese Mice. *J. Med. Food.* 18,549-556 (2015)
DOI: 10.1089/jmf.2014.3265

32. S Chen, N Osaki, A Shimotoyodome: Green tea catechins enhance norepinephrine-induced lipolysis via a protein kinase A-dependent pathway in adipocytes.Biochem. *Biophys. Res. Commun.* 461,1-7 (2015)
DOI: 10.1016/j.bbrc.2015.03.158

33. J Zhou, L Zhang, J Zhang, X Wan: Aqueous extract of post-fermented tea reverts the hepatic steatosis of hyperlipidemia rat by regulating the lipogenic genesexpression and hepatic fatty acid composition. *BMC. Complement. Altern. Med.*14,263 (2014)
DOI: 10.1186/1472-6882-14-263

34. LS Lee, JH Choi, MJ Sung, JY Hur, HJ Hur, JD Park, YC Kim, EJ Gu, B Min, HJ Kim: Green tea changes serum and liver metabolomic profiles in mice with high-fat diet-induced obesity. *Mol. Nutr. Food. Res.*59,784-794 (2015)
DOI: 10.1002/mnfr.201400470

35. JK Byun, BY Yoon, JY Jhun, HJ Oh, EK Kim, JK Min, ML Cho: Epigallocatechin-3-gallate ameliorates both obesity and autoinflammatory arthritis aggravated by obesity by altering the balance among CD4+ T-cell subsets. *Immunol. Lett.*157,51-59 (2014)
DOI: 10.1016/j.imlet.2013.11.006

36. A Mousavi, M Vafa, T Neyestani, M Khamseh, F Hoseini: The effects of green

tea consumption on metabolic and anthropometric indices in patients with Type 2 diabetes. *J. Res. Med. Sci.*18,1080-1086 (2013)

37. LC Vázquez Cisneros, P López-Uriarte, A López-Espinoza, M Navarro Meza, AC Espinoza-Gallardo, MB Guzmán Aburto: Effects of green tea and its epigallocatechin (EGCG) content on body weight and fat mass in humans: a systematic review. *Nutr. Hosp.*34,731-737 (2017)
DOI: 10.20960/nh.753

38. E Casanova, J Salvadó, A Crescenti, A Gibert-Ramos: Epigallocatechin Gallate Modulates Muscle Homeostasis in Type 2 Diabetes and Obesity by Targeting Energetic and Redox Pathways: A Narrative Review. *Int. J. Mol. Sci.*20. pii: E532 (2019)
DOI: 10.3390/ijms20030532.

39. F Li, C Gao, P Yan, M Zhang, Y Wang, Y Hu, X Wu, X Wang, J Sheng: EGCG Reduces Obesity and White Adipose Tissue Gain Partly Through AMPK Activation in Mice. *Front. Pharmacol.* 1366 (2018)
DOI: 10.3389/fphar.2018.01366.

40. UJ Bae, J Park, IW Park, BM Chae, MR Oh, SJ Jung, GS Ryu, SW Chae, BH Park: Epigallocatechin-3-Gallate-Rich Green Tea Extract Ameliorates Fatty Liver and Weight Gain in Mice Fed a High Fat Diet by Activating the Sirtuin 1 and AMP Activating Protein Kinase Pathway. *Am. J. Chin. Med.* 46,617-632 (2018)
DOI: 10.1142/S0192415X18500325.

41. MS Javaid, N Latief, B Ijaz, UA Ashfaq: Epigallocatechin Gallate as an anti-obesity therapeutic compound: an in silico approach for structure-based drug designing. *Nat. Prod. Res.* 32,2121-2125 (2018)
DOI: 10.1080/14786419.2017.1365074.

42. SN Kim, HJ Kwon, S Akindehin, HW Jeong, YH Lee: Effects of Epigallocatechin-3-Gallate on Autophagic Lipolysis in Adipocytes. *Nutrients.* 30,9. pii: E680 (2017)
DOI: 10.3390/nu9070680.

43. E Baladia, J Basulto, M Manera, R Martínez, D Calbet: Effect of green tea or green tea extract consumption on body weight and body composition; systematic review and meta-analysis. *Nutr. Hosp.*29,479-490 (2014)
DOI: 10.3305/nh.2014.29.3.7.118

44. TM Jurgens, AM Whelan, L Killian,S Doucette, S Kirk, E Foy: Green tea for weight loss and weight maintenance in overweight or obese adults. *Cochrane. Database. Syst. Rev.*12,12:CD008650 (2012)
DOI: 10.1002/14651858.

45. MA Potenza, FL Marasciulo, M Tarquinio, E Tiravanti, G Colantuono, A Federici, JA Kim, MJ Quon, M Montagnani: EGCG, a green tea polyphenol, improves endothelial function and insulin sensitivity, reduces blood pressure, and protects against myocardial I/R injury in SHR. Am. J. Physiol. *Endocrinol. Metab.* 292,E1378-87 (2017)
DOI: 10.1152/ajpendo.00698.2006

46. AL Brown, J Lane, J Coverly, J Stocks, S Jackson, A Stephen, L Bluck, A Coward, H Hendrickx: Effects of dietary supplementation with the green tea polyphenol epigallocatechin-3-gallate on insulin resistance and associated

metabolic risk factors: randomized controlled trial. *Br. J. Nutr.* 101,886-894 (2009)
DOI: 10.1017/S0007114508047727

47. MP Nantz, CA Rowe, JF Bukowski, SS Percival: Standardized capsule of Camellia sinensis lowers cardiovascular risk factors in a randomized, double-blind, placebo-controlled study. *Nutrition.*25,147-154 (2009)
DOI: 10.1016/j.nut.2008.07.018

48. H Mozaffari-Khosravi, Z Ahadi, K Barzegar: The effect of green tea and sour tea on blood pressure of patients with type 2 diabetes: a randomized clinical trial. *J. Diet. Suppl.* 10,105-15 (2013)
DOI: 10.3109/19390211.2013.790333

49. X Peng, R Zhou, B Wang, X Yu, X Yang, K Liu, M Mi: Effect of green tea consumption on blood pressure: a meta-analysis of 13 randomized controlled trials. *Sci. Rep.* 4,6251 (2014)
DOI: 10.1038/srep06251

50. G Li, Y Zhang, L Mbuagbaw, A Liu, MA Levine, A Holbrook: Effect of green tea supplementation on blood pressure among overweight and obese adults: a systematic review and meta-analysis. *J. Hypertens.* 33,243-254 (2015)
DOI: 10.1097/HJH.0000000000000426

51. G Liu, XN Mi, XX Zheng, YL Xu, J Lu, Huang XH: Effects of tea intake on blood pressure: a meta-analysis of randomised controlled trials. *Br. J. Nutr.* 112,1043-1054 (2014)
DOI: 10.1017/S0007114514001731

52. S Khalesi, J Sun, N Buys, A Jamshidi, E Nikbakht-Nasrabadi, H Khosravi-Boroujeni: Green tea catechins and blood pressure: a systematic review and meta-analysis of randomised controlled trials. *Eur. J. Nutr.* 53,1299-311 (2014)
DOI: 10.1007/s00394-014-0720-1

53. X Tong, AW Taylor, L Giles, GAWittert, Shi Z: Tea consumption is inversely related to 5-year blood pressure change among adults in Jiangsu, China: a cross-sectional study. *Nutr. J.* 13,98 ((2014)
DOI: 10.1186/1475-2891-13-98

54. I Onakpoya, E Spencer, C Heneghan, M Thompson: The effect of green tea on blood pressure and lipid profile: a systematic review and meta-analysis of randomized clinical trials. *Nutr. Metab. Cardiovasc. Dis.* 24,823-836 (2014)
DOI: 10.1016/j.numecd.2014.01.016

55. W Li, J Yang, XS Zhu, SC Li, PC Ho: Correlation between tea consumption and prevalence of hypertension among Singaporean Chinese residents aged 40 years. *J. Hum. Hypertens.* 30,11-7 (2016)
DOI: 10.1038/jhh.2015.45.

56. H Arazi, N Samami, J Kheirkhah, B Taati: The effect of three weeks green tea extract consumption on blood pressure, heart rate responses to a single bout resistance exercise in hypertensive women. *High. Blood. Press. Cardiovasc. Prev.* 21,213-219 (2014)
DOI: 10.1007/s40292-014-0048-1

57. V Fonseca, SE Inzucchi, E Ferrannini: Redefining the diagnosis of diabetes using glycated hemoglobin. *Diabetes. Care.* 32,1344-1345 (2009)
DOI: 10.2337/dc09-9034

58. AD Deshpande, M Harris-Hayes, M Schootman: Epidemiology of diabetes

and diabetes-related complications. *Phys. Ther.* 88,1254-1264 (2008)
DOI: 10.2522/ptj.20080020

59. J Yan, Y Zhao, S Suo, Y Liu, B Zhao: Green tea catechins ameliorate adipose insulin resistance by improving oxidative stress. *Free. Radic. Biol. Med.* 52,1648-1657 (2012)
DOI: 10.1016/j.freeradbiomed.201-2.01.033

60. KC Bae, JH Park, AY Na, SJ Kim, S Ahn, SP Kim, BC Oh, HC Cho, YW Kim, DK Song: Effect of Green Tea Extract/Poly-γ-Glutamic Acid Complex in Obese Type 2 Diabetic Mice. *Diabetes. Metab. J.* 2013 Jun;37 (3):196-206 (2012)
DOI: 10.4093/dmj.2013.37.3.1.96

61. Kim JJ, Tan Y, Xiao L, YL Sun, X Qu: Green tea polyphenol epigallocatechin-3-gallate enhance glycogen synthesis and inhibit lipogenesis in hepatocytes. *Biomed. Res. Int.* 2013,920128 (2013)
DOI: 10.1155/2013/920128

62. S Yousaf, MS Butt, HA Suleria, MJ Iqbal: The role of green tea extract and powder in mitigating metabolic syndromes with special reference to hyperglycemia and hypercholesterolemia. *Food. Funct.* 5,545-556 (2014)
DOI: 10.1039/c3fo60203f

63.DB Panagiotakos, C Lionis, A Zeimbekis, K Gelastopoulou, N Papairakleous, UN Das, E Polychronopoulos: Long-term tea intake is associated with reduced prevalence of (type 2) diabetes mellitus amongelderly people from Mediterranean islands: MEDIS epidemiological study. *Yonsei. Med. J.* 50,31-38 (2009)
DOI: 10.3349/ymj.2009.50.1.3.1

64. Y Jing, G Han, Y Hu, Y Bi, L Li, D Zhu: Tea consumption and risk of type 2 diabetes: a meta-analysis of cohort studies. *J. Gen. Intern. Med.* 24,557-562 (2009)
DOI: 10.1007/s11606-009-0929-5

65. Consortium InterAct, GJ van Woudenbergh, A Kuijsten, D Drogan, DL van der A, D Romaguera, E Ardanaz, P Amiano, A Barricarte, JW Beulens, H Boeing, HB Bueno-de-Mesquita, CC Dahm, MD Chirlaque, F Clavel, FL Crowe, PP Eomois, G Fagherazzi, PW Franks, J Halkjaer, KT Khaw, G Masala, A Mattiello, P Nilsson, K Overvad, J Ramón Quirós, O Rolandsson, I Romieu, C Sacerdote, MJ Sánchez, MB Schulze, N Slimani, I Sluijs, AM Spijkerman, G Tagliabue, A Tjønneland, R Tumino, NG Forouhi, S Sharp, C Langenberg, EJ Feskens, E Riboli, NJ Wareham: Tea consumption and incidence of type 2 diabetes in Europe: the EPIC-Inter Act case-cohort study. *PLoS. One.* 7,e36910 (2012)
DOI: 10.1371/journal.pone.0036910

66. H Huang, Q Guo, C Qiu, B Huang, X Fu, J Yao, J Liang, L Li, L Chen, K Tang, L Lin, J Lu, Y Bi, G Ning, J Wen, C Lin, G Chen: Associations of green tea and rock tea consumption with risk of impaired fasting glucose and impaired glucose tolerance in Chinese men and women. *PLoS. One.* 8,e79214 (2013)
DOI: 10.1371/journal.pone.0079214

67. K Liu, R Zhou, B Wang, K Chen, LY Shi, JD Zhu, MT Mi: Effect of green tea on glucose control and insulin sensitivity: a meta-analysis of 17 randomized controlled trials. *Am. J. Clin. Nutr.* 98,340-348 (2013)

DOI: 10.3945/ajcn.112.052746

68. NA Toolsee, OI Aruoma, TK Gunness, S Kowlessur, V Dambala, F Murad, K Googoolye, D Daus, J Indelicato, P Rondeau, E Bourdon, T Bahorun: Effectiveness of green tea in a randomized human cohort: relevance to diabetes and its complications. *Biomed. Res. Int.* 2013,412379 (2013)
DOI: 10.1155/2013/412379

69. SJ Kang, JE Lee, EK Lee, DH Jung, CH Song, SJ Park, SH Choi, CH Han, SK Ku, YJ Lee: Fermentation with Aquilariae Lignum enhances the anti-diabetic activity of green tea in type II diabetic db/db mouse. *Nutrients.* 6,3536-3571 (2014)
DOI: 10.3390/nu6093536

70. CY Liu, CJ Huang, LH Huang, IJ Chen, JP Chiu, CH Hsu: Effects of green tea extract on insulin resistance and glucagon-like peptide 1 in patients withtype 2 diabetes and lipid abnormalities: a randomized, double-blinded, and placebo-controlled trial. *PLoS. One.* 2014 Mar 10;9 (3):e91163.
DOI: 10.1371/journal.pone.0091163

71. WS Yang, WY Wang, WY Fan, Q Deng, X Wang: Tea consumption and risk of type 2 diabetes: a dose-response meta-analysis of cohort studies. *Br. J. Nutr.* 111,1329-1339 (2014)
DOI: 10.1017/S0007114513003887

72. J Yang, QX Mao, HX Xu, X Ma, CY Zeng: Tea consumption and risk of type 2 diabetes mellitus: a systematic review and meta-analysis update. *BMJ Open.*4,e005632 (2014)
DOI: 10.1136/bmjopen-2014-005632

73. H Mozaffari-Khosravi, Z Ahadi, M Fallah Tafti: The Effect of Green Tea versus Sour Tea on Insulin Resistance, Lipids Profiles and Oxidative Stress in Patients with Type 2 Diabetes Mellitus: A Randomized Clinical Trial. *Iran. Med. Sci.*39,424-432 (2014)

74. X Li, S Li, M Chen, J Wang, B Xie, Z Sun: (-)-Epigallocatechin-3-gallate (EGCG) inhibits starch digestion and improves glucose homeostasis through direct or indirect activation of PXR/CAR-mediated phase II metabolism in diabetic mice. *Food. Funct.* 9,4651-4663 (2018)
DOI: 10.1039/c8fo01293h

75. J Josic, AT Olsson, J Wickeberg, S Lindstedt, J Hlebowicz: Does green tea affect postprandial glucose, insulin and satiety in healthy subjects: a randomized controlled trial. *Nutr. J.* 9,63 (2010)
DOI: 10.1186/1475-2891-9-63

76. J Yu, P Song, R Perry, C Penfold, AR Cooper: The Effectiveness of Green Tea or Green Tea Extract on Insulin Resistance and Glycemic Control in Type 2 Diabetes Mellitus: A Meta-Analysis. *Diabetes. Metab. J.* 41,251-262 (2017)
DOI: 10.4093/dmj.2017.41.4.2.51.

77. Y Tsubono, S Tsugane: Green tea intake in relation to serum lipid levels in Middle-aged apanese men and women. *Ann. Epidemiol.*7,280-284 (1997)

78. LB Tijburg, SA Wiseman, GW Meijer, JA Weststrate: Effects of green tea, black tea and dietary lipophilic antioxidants on ldl oxidizability and atherosclerosis in hypercholesterolaemic rabbits. *Atherosclerosis.* 135,37-47 (1997)
DOI: 10.1016/s0021-9150(97)00139-1

79. S Shrestha, SJ Ehlers, JY Lee, ML Fernandez, SI Koo: Dietary Green Tea Extract Lowers Plasma and Hepatic Triglycerides and Decreases the Expression of Sterol Regulatory Element-Binding Protein-1c mRNA and Its Responsive Genes in Fructose-Fed,Ovariectomized Rats. *J. Nutr.*139,640-645 (2009)
DOI: 10.3945/jn.108.103341

80. J Bajerska, M Wozniewicz, J Jeszka, S Drzymala-Czyz, J Walkowiak: Green tea aqueous extract reduces visceral fat and decreases protein availability in rats fed with a high-fat diet. *Nutr. Res.*31,157-64 (2011)
DOI: 10.1016/j.nutres.2011.01.005

81. A Kim, A Chiu, MK Barone, D Avino, F Wang, CI Coleman, OJ Phung: Green tea catechins decrease total and low-density lipoprotein cholesterol: a systematic review and meta-analysis. *J. Am. Diet. Assoc.*111,1720-1729 (2011)
DOI: 10.1016/j.jada.2011.08.009

82. XX Zheng, YL Xu, SH Li, XX Liu, R Hui, XH Huang: Green tea intake lowers fasting serum total and LDL cholesterol in adults:a meta-analysis of 14 andomized controlled trials. *Am. J. Clin. Nutr.* 94,601-610 (2011)
DOI: 10.3945/ajcn.110.010926

83. U Axling, C Olsson, J Xu, C Fernandez, S Larsson, K Ström, S Ahrné, C Holm, G Molin, K Berger: Green tea powder and Lactobacillus plantarum affect gut microbiota, lipid metabolism and inflammation in high-fat fed C57BL/6J mice. *Nutr. Metab (Lond).* 9,105 (2012)
DOI: 10.1186/1743-7075-9-105

84. J Walkowiak, J Bajerska, A Kargulewicz, A Lisowska, G Siedlerski, T Szczapa, N Kobelska-Dubiel, M Grzymisławski: Single dose of green tea extract decreases lipid digestion and absorption from a test meal in humans. *Acta. Biochim. Pol.* 2013; 60,481-483 (2013)

85. A Lisowska, B Stawińska-Witoszyńska, J Bajerska, P Krzyżanowska, J Walkowiak: Green tea influences intestinal assimilation of lipids in humans: a pilot study. *Eur. Rev. Med. Pharmacol. Sci.*19,209-14 (2015)

86. LL Pan, Y Wu, RQ Wang, JW Chen, J Chen, Y Zhang, YJ Chen, M Geng, ZD Xu, M Dai, JH Li, W Wang, ZZ Zhang: (-)-Epigallocatechin-3-Gallate Ameliorates Atherosclerosis and Modulates Hepatic Lipid Metabolic Gene Expression in Apolipoprotein E Knockout Mice: Involvement of TTC39B. *Front. Pharmacol.*9,195 (2018)
DOI: 10.3389/fphar.2018.00195

87. L Liu, I Nagai, Y Gao, Y Matsushima, Y Kawai, K Sayama: Effects of catechinsand caffeine on the development of atherosclerosis in mice. *Biosci. Biotechnol.Biochem.* 81,1948-1955 (2017)
DOI: 10.1080/09168451.2017.1364618.

88. S Ding, J Jiang, P Yu, G Zhang, G Zhang, X Liu: Green tea polyphenol treatment attenuates atherosclerosis in high-fat diet-fed apolipoprotein E-knockout mice via alleviating dyslipidemia and up-regulating autophagy. *PLoS. One.* 12,:e0181666 (2017)
DOI: 10.1371/journal.pone.0181666.

89. Z Hong, Y Xu, JF Yin, J Jin, Y Jiang, Q Du: Improving the effectiveness of (-)-epigallocatechin gallate (EGCG) against rabbit atherosclerosis by EGCG-loaded

nanoparticles prepared from chitosan and polyaspartic acid. *J. Agric. Food. Chem.* 62,12603-12069 (2014)
DOI: 10.1021/jf504603n.

90. Y Cai, T Kurita-Ochiai, T Hashizume, M Yamamoto: Green tea epigallocatechin-3-gallate attenuates Porphyromonas gingivalis-induced atherosclerosis. *Pathog. Dis.* 67,76-83 (2013)
DOI: 10.1111/2049-632X.12001.

91. J Minatti, E Wazlawik, MA Hort, FL Zaleski, RM Ribeiro-do-Valle, M Maraschin, EL da Silva: Green tea extract reverses endothelial dysfunction and reduces atherosclerosis progression in homozygous knockout low-density lipoprotein receptor mice. *Nutr. Res.*32,684-693 (2012)
DOI: 10.1016/j.nutres.2012.08.003.

92. E Ramesh, P Geraldine, PA Thomas: Regulatory effect of epigallocatechin gallate on the expression of C-reactive protein and other inflammatory markers in an experimental model of atherosclerosis. *Chem. Biol. Interact.* 183,125-132 (2010)
DOI: 10.1016/j.cbi.2009.09.013.

93. M Miyamura, H Moriyama, S Murata, J Yokota, S Yoshioka, D Takuma, A Hamada, Y Nishioka: Inhibitory effects of "Goishi-tea" as a post-fermented-tea on dietary-induced hypercholesteremia and atherosclerosis in rabbits. *Yakugaku. Zasshi.*128,1037-1044 (2008)

94. J Suzuki, M Ogawa, A Izawa, YM Sagesaka, M Isobe: Dietary consumption of green tea catechins attenuate hyperlipidaemia-induced atherosclerosis and systemic organ damage in mice. *Acta. Cardiol.* 60,271-276 (2005)
DOI: 10.2143/AC.60.3.2.005003

95. JA Vinson, K Teufel, N Wu: Green and black teas inhibit atherosclerosis by lipid, antioxidant, and fibrinolytic mechanisms. *J. Agric. Food. Chem.* 52,3661-3665 (2004)
DOI: 10.1021/jf035255l

96. KY Chyu, SM Babbidge, X Zhao, R Dandillaya, AG Rietveld, J Yano,P Dimayuga, B Cercek, PK Shah: Differential effects of green tea-derived catechin on developing versus established atherosclerosis in apolipoprotein E-null mice. *Circulation.* 109,2448-2453 (2004)
DOI: 10.1161/01.CIR.0000128034.-70732.C2

97. Y Miura, T Chiba, I Tomita, H Koizumi, S Miura, K Umegaki, Y Hara, M Ikeda, T Tomita: Tea catechins prevent the development of atherosclerosis in apoprotein deficient mice. *J Nutr.* 131,27-32 (2001)
DOI: 10.1093/jn/131.1.2.7

98. N Kavantzas, A Chatziioannou, AE Yanni, D Tsakayannis, D Balafoutas, G Agrogiannis, D Perrea: Effect of green tea on angiogenesis and severity of atherosclerosis in cholesterol-fed rabbit. *Vascul. Pharmacol.*44,461-463 (2006)
DOI: 10.1016/j.vph.2006.03.008

99. S Sasazuki, H Kodama, K Yoshimasu, Y Liu, M Washio, K Tanaka, S Tokunaga, S Kono, H Arai, Y Doi, T Kawano, O Nakagaki, K Takada, S Koyanagi, K Hiyamuta, T Nii, K Shirai, M Ideishi, K Arakawa, M Mohri, A Takeshita: Relation between green tea consumption and the severity of coronary atherosclerosis among Japanese men and women. *Ann.*

Epidemiol. 10,401-408 (2000)

Key Words: Green tea; Obesity; Hypertension; Insulin resistance and diabetes; Plasma cholesterol; Atherosclerosis; Metabolic syndrome

Send correspondence to: Mingwei Wang, Department of Cardiology, the Affiliated Hospital of Hangzhou Normal University, Hangzhou, China, Tel: 8657188303590, E-mail: wmw990556@163.com