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Review

The potential role of green tea catechins in the prevention of the metabolic syndrome – A review

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ABSTRACT

The metabolic syndrome (MetS) represents an emerging health burden for governments and health care providers. Particularly relevant for prevention and early management of MetS are lifestyle conditions including physical activity and the diet. It has been shown that green tea, when consumed on a daily basis, supports health. Many of the beneficial effects of green tea are related to its catechin, particularly (−)-epigallocatechin-3-gallate (EGCG), content. There is conclusive evidence from *in vitro* and animal studies which provide the concepts for underlying functional mechanisms of green tea catechins and their biological actions. An increasing number of human studies have explored the effects of green tea catechins on the major MetS conditions such as obesity, type-2 diabetes and cardiovascular risk factors. This article provides a comprehensive overview of the human studies addressing the potential benefits of green tea catechins on the MetS.

The number of human studies in this field is still limited. However, the majority of human epidemiological and intervention studies demonstrate beneficial effects of green tea or green tea extracts, rich in EGCG on weight management, glucose control and cardiovascular risk factors. The optimal dose has not yet been established.

The current body of evidence in humans warrants further attention. In particular, well-controlled long-term human studies would help to fully understand the protective effects of green tea catechins on parameters related to the MetS.

Contents

Abbreviations: BMI, body mass index; COMT, catechol-*O*-methyl-transferase; EC, (−)-epicatechin; ECG, (−)-epicatechin-3-gallate; EGC, (−)-epigallocatechin; EGCG, (−)-epigallocatechin-3-gallate; HDL, high density lipoprotein; IDF, International Diabetes Federation; GTE, green tea extract; LDL, low density lipoprotein; MetS, metabolic syndrome; NCEP, National Cholesterol Education Program; WHO, World Health Organization; VLDL, very low density lipoprotein; IGF, insulin-like growth factor; CCK, cholecystokinin; GLUT4, glucose transporter 4; ACC, acetyl-CoA carboxylase; FAS, fatty acid synthase; GPDH, α-glycerophosphate dehydrogenase; SCD1, stearoyl-CoA desaturase 1; HSL, hormone sensitive lipase.

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1. Introduction

1.1. The metabolic syndrome

Metabolic syndrome (MetS) refers to a clustering of several cardiometabolic risk factors, including hyperglycaemia, dyslipidaemia and elevated blood pressure, wherein abdominal obesity and insulin resistance represent core parameters of this cluster (Eckel et al., 2005). Several definitions of MetS exist: the first operational definition of MetS was provided by the WHO in 1999, placing hyperglycaemia and/or insulin resistance at the centre of MetS with additional related metabolic conditions (WHO, 1999). More recently, the National Cholesterol Education Program (NCEP) suggests that at least three of the following conditions must be met for a diagnosis of MetS: abdominal obesity, elevated triglyceride levels, reduced HDL-cholesterol level, elevated blood pressure or elevated fasting glucose level (Grundy et al., 2005). In addition to the NCEP recommendations, the International Diabetes Federation (IDF) emphasizes the importance of abdominal obesity by introducing increased waist circumference as a required condition (Alberti et al., 2005). Overall, the various definitions commonly require particular core criteria to be met, such as central obesity, hyperglycaemia, dyslipedaemia, and high blood pressure. Nevertheless, they differ in threshold levels or other, additional criteria.

Governments and health care providers have to face the emerging health burden of MetS. Depending upon the viewpoint, this burden can be evaluated according to its economical or epidemiological impact (Yach et al., 2006). In general, the prevalence of MetS is increasing (Ford et al., 2004), this in turn is accompanied with the increasing prevalence of both obese and ageing populations. For example, the age-adjusted prevalence of MetS in US adults ranges between 34.6% and 39.1% (depending on the definition used), whereas it is more common with increasing age (Ford, 2005).

It is widely accepted that particularly physical inactivity and imbalanced diets contribute to the global emergence of obesity and diabetes. Thus, these factors represent the tools by which individuals can tackle the underlying reasons for the development of MetS. Therefore, the clinical relevance of MetS is that it identifies people who have an increased long-term risk of cardiovascular disease and type-2 diabetes. At the same time, the need to implement lifestyle changes becomes crucial, i.e. providing an opportunity for preventive interventions such as weight reduction, increased physical activity and dietary modifications (Eckel et al., 2005; Grundy et al., 2005).

1.2. The link between green tea catechins and metabolic syndrome

The increasing emergence of MetS will place a growing burden on healthcare resources and healthcare providers are faced with the challenge of managing this worldwide epidemic. Drugs will certainly continue to play a role in treatment and the pharmaceutical industry has recognized the huge commercial potential. However, the key management issue lies in evoking changes in lifestyle, which is particularly relevant for prevention and early management of MetS.

How is this concept linked to green tea catechins? Firstly, green tea obviously possesses significant health-promoting effects (Balentine et al., 1997). A number of epidemiological studies show that green tea, when consumed on a daily basis, is part of a lifestyle which supports healthiness and long life (Nakachi et al., 2000; Sato et al., 1989; Setiawan et al., 2001; Sueoka et al., 2001; Zhang et al., 2004). Traditionally, green tea was used to improve blood flow, eliminate alcohol and toxins, improve resistance to disease, relieve joint pain and to clear urine and improve its flow (Balentine et al., 1997). More recently, research has focused a great deal on effects of green tea related to the prevention of cancer (Kavanagh et al., 2001) and cardiovascular diseases (Sueoka et al., 2001). Other beneficial effects of green tea catechins on inflammation (Dona et al., 2003), angiogenesis (Oak et al., 2005; Rodriguez et al., 2006; Sartippour et al., 2002), and oxidation (Osada et al., 2001) are emerging areas of interest. The biological mechanisms of green tea catechins in the area of MetS have been reviewed elsewhere and will only be mentioned briefly here. An increasing body of evidence suggests that several pathways in the development of MetS can be positively affected by green tea catechins, especially (−)-epigallocatechin-3-gallate (EGCG) (Fig. 1). The inclined reader is referred to Kao et al. (2006) and Wolfram et al. (2006) for more detailed information about these mechanisms.

The health-promoting effects of regular green tea consumption are mainly attributed to its polyphenol content, which represents 35% of the dry weight (Scholz and Bertram, 1995; Yang and Landau, 2000). These polyphenols in turn consist of several fractions such as flavanols and flavonols (Balentine et al., 1997).

It is particularly the catechins from the flavanols fraction which have received a lot of attention. Green tea is derived from drying and steaming the fresh tea leaves and thus no oxidation occurs, resulting in high levels of catechins. In contrast, black tea undergoes a full fermentation stage before drying and steaming. During fermentation tea catechins become oxidized or condensed into other large polyphenolic molecules such as theaflavins and thearubigins. The processing of tea and its influence on final polyphenol content is reviewed by Cabrera et al. (2006). Green tea catechins are mainly comprised of: (−)-epigallocatechin-3-gallate: EGCG; (−)-epigallocatechin: EGC; (−)-epicatechin-3-gallate: ECG; and (−)-epicatechin: EC. EGCG is the most abundant catechin in green tea representing approximately 43% (Scholz and Bertram, 1995; Yang and Landau, 2000). Many of the aforementioned beneficial effects of green tea on obesity, type-2 diabetes and cardiovascular risk factors are related to its EGCG content (Lambert et al., 2003; Mandel et al., 2004; Moyers and Kumar, 2004; Park and Surh, 2004).

In this review, recent human studies on the effects of short- or long-term consumption of green tea catechins are examined and summarized, with the aim to determine the role(s) of catechins in alleviating the symptoms associated with MetS. The potential role of green tea catechins in supporting lifestyle changes, which in turn is a strong weapon in fighting MetS, will be demonstrated.

2. Green tea catechins and their potential to reduce body fat

2.1. Epidemiological (observational) and interventional clinical studies

Obesity is recognized as an increasing health burden worldwide. In 2003/2004, the age-adjusted prevalence of overweight and obesity in the US was 66.3% and 32.2%, respectively (Ogden et al., 2006). While conventional weight management programs show only limited success, particularly in the long-term, there is

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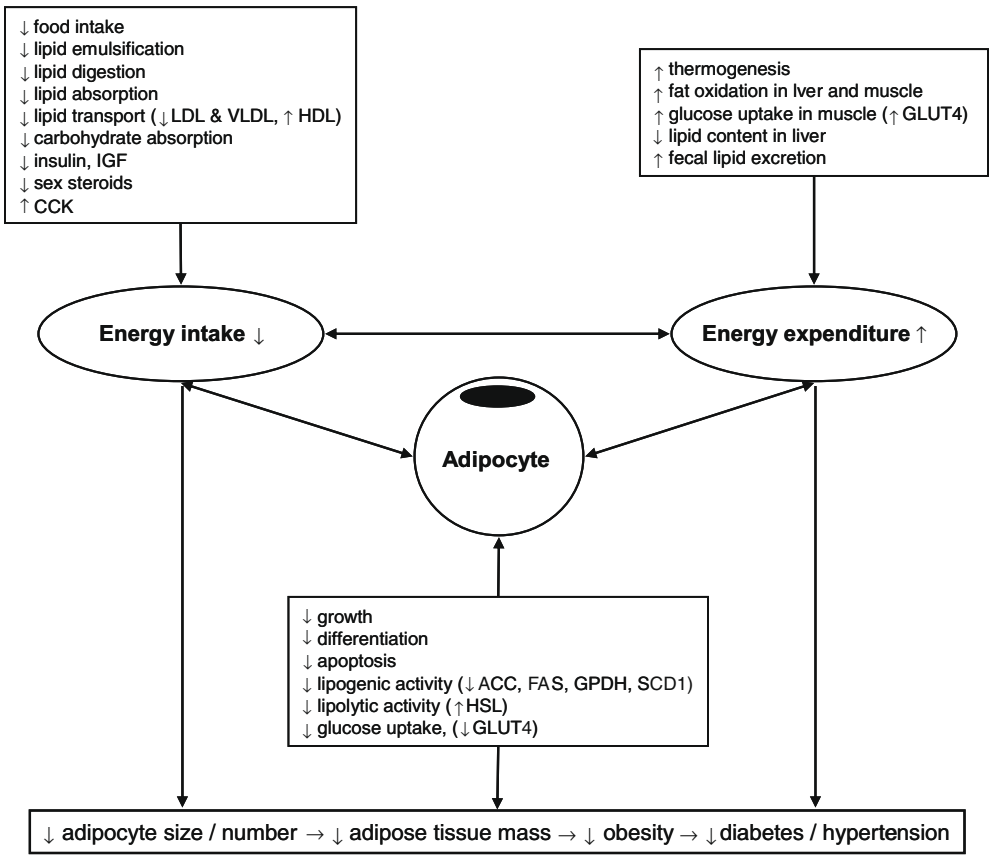

Fig. 1. Mechanisms by which EGCG may decrease energy intake, increase energy expenditure, and reduce adipose tissue mass and prevent or treat obesity and its associated diseases, diabetes and hypertension.

growing interest in alternative strategies for weight management. One natural ingredient in focus is green tea.

An early indication for the benefits of green tea for weight management is seen in Chinese traditions, where green tea is said to wash out fat. This ancient knowledge was more recently supported by an epidemiological study conducted in Taiwan (Wu et al., 2003). Subjects with an average habitual tea consumption of 434 ml/day for more than ten years showed a lower percentage of total body fat, smaller waist circumference and decreased waist-to-hip ratio. The catechin or EGCG intake was not reported per se, however, extrapolating data provided by Higdon and Frei (2003), who estimated the EGCG content of a single cup of green tea (237 ml) to range between 30 and 130 mg, would result in a daily EGCG intake in the range of 55–238 mg.

In humans, the effects on body weight and body fat in response to supplementation with green tea catechins rich in EGCG were explored in several intervention studies, in which the investigators approached the topic from slightly different angles, as outlined below. Please refer to Table 1 for a summary of the studies which will be reviewed.

In obese female patients (median BMI of 30.5 kg/m^2) with polycystic ovary syndrome (PCOS), a body weight reduction of 2.4% was reported following a 12-week supplementation with encapsulated green tea, while the control group gained body weight and body fat (Chan et al., 2006). Unfortunately, this promising finding lacks statistical significance for the between-group difference, possibly due to the fact that the female patients might have responded differently to the green tea catechins because of the high degree of obesity as well as various metabolic changes due to PCOS when compared to studies of overweight but otherwise healthy subjects. For example, (Chantre and Lairon, 2002) investigated the effects of encapsulated green tea extract in moderately overweight subjects (average BMI of 28.9) and observed a 4.6% decrease in body weight and a 4.5% reduction in waist-to-hip ratio vs. baseline. Interestingly, these changes are almost comparable to drug therapies. These results have, nevertheless, to be viewed with caution since this study was an open, uncontrolled study (e.g. not blinded and lacking a control group). Nevertheless, more tightly controlled studies also support the concept that green tea catechins are effective in weight and fat loss. Two studies on overweight males and females reported slight reductions in body weight and more pronounced decreases in body fat, especially visceral fat (Hase et al., 2001; Tsuchida et al., 2002). Although dietary intake and physical activity were not strictly followed, no differences in energy intake were observed between control and treatment groups over the three months study period, suggesting that the observed changes were not caused by suppressive effects on satiety. In a study where green tea catechins were imbedded into a dietary regime, Nagao et al. (2005) demonstrated that after a 12-week supplementation of overweight, but otherwise healthy subjects with green tea catechin-enriched oolong tea, body weight and body fat was reduced significantly when compared to the control group (diet alone). In contrast to the studies mentioned above, these subjects had received just 90% of their individual energy requirement. This approach provides direct evidence that green tea catechins can contribute to lifestyle changes related to weight management. Furthermore, the same authors showed significant decreases in body weight and body fat in subjects who had been following their usual lifestyle while taking green tea catechins (Nagao et al., 2007). This study is of special value because it correlates anti-obesity effects of green tea catechins with improvements in cardiovascular risk factors like systolic blood pressure and LDL cholesterol in a relatively

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Table 1
Human studies assessing the effect of green tea, green tea extract, rich in EGCG on weight management.

Citations	Type of study	Population	Test components (daily dosage)	Duration of intake	Main outcomes		
					Weight (kg)	Fat mass (kg)	BMI
Chantre and Lairon (2002)	Multi-center, open, uncontrolled	7 M, 63 F BMI: 28.9	GTE (375 mg catechins, of which 270 mg was EGCG)	12 weeks	−3.5	Not reported	Not reported
Hase et al. (2001)	Case–control	23 M, BMI: 24–25	Control (118.5 mg catechins, of which 32 mg was EGCG and 75 mg caffeine) GTE (483.0 mg catechins, of which 300 mg was EGCG and 75.5 mg caffeine)	12 weeks	−0.5	−1.7	−0.6
Kajimoto et al. (2006)	Double blind, three parallel arm, controlled	98 M, 97 F BMI: 25.7	Control beverage (41 mg catechins, of which 9 mg was EGCG and 52 mg caffeine)	12 weeks			
			Green tea beverage, low (444 mg catechins, of which 152 mg was EGCG and 50 mg caffeine)		−1.1*	−3.9%*	−0.4*
			Green tea beverage, high (646 mg catechins, of which 224 mg was EGCG and 49 mg caffeine)		−1.2*	−3.9%*	−0.4*
Kovacs et al. (2004)	Randomized parallel, placebo-controlled	26 M, 78 F BMI: 25–35	Control (placebo) GTE (573 mg catechins, of which 323 mg was EGCG, and 104 mg caffeine)	13 weeks	0.6	0.5	0.2
Nagao et al. (2007)	Multi-center, Randomized, double-blind, controlled	140 M, 100 F, BMI: 26.8	Control beverage (96 mg catechins, of which 16 mg was EGCG and 75 mg caffeine) Green tea beverage (583 mg catechins, of which 100 mg was EGCG and 72 mg caffeine)	12 weeks	−1.6*	−1.8*	−0.6*
Nagao et al. (2005)	Double blind, controlled	35 M, BMI: 24.9–25.0	Control (oolong tea containing 19 mg catechins, of which 3 mg was EGCG and 78 mg caffeine) GTE (690 mg catechins, of which 136 mg was EGCG, and 75 mg caffeine)	12 weeks at low calorie diet	−1.1*	−0.7*	−0.4*
Tsuchida et al. (2002)	Randomized, double-blind, controlled	43 M, 37 F BMI: 25.9–26.5	Control (126.5 mg catechins, of which 25.2 mg was EGCG and 81 mg caffeine) GTE (588 mg catechins, of which 115 mg was EGCG and 83 mg caffeine)	12 weeks	−1.3*	−1.4*	−0.5*
Diepvens et al. (2006)	Double-blind, placebo-controlled, parallel design	46 F, BMI: 27.7	Control + low energy diet (2790 mg maltodextrin) GTE + low energy diet (1206.9 mg catechins, of which 595.8 mg was EGCG and 236.7 mg caffeine)	12 weeks	0	0	0.1
Chan et al. (2006)	Randomized, parallel, placebo-controlled	34 obese f, BMI: 30.9	Capsulated green tea powder (659 mg catechins, of which was 538 mg EGCG and 150 mg caffeine)	12 weeks	−1.8	−0.2%	−0.3
Westerterp-Plantenga et al. (2005)	Randomized, parallel, placebo-controlled	23 M, 53 F BMI: 25–35	Low habitual caffeine control (<300 mg caffeine) (placebo)	13 weeks	Low habitual caffeine		
			High habitual caffeine control (>300 mg caffeine) (placebo)		−2.8	−2.1*	−0.9*
			Low habitual caffeine GTE (<300 mg caffeine) (375 mg catechins, of which 270 mg was EGCG and 150 mg caffeine)		High habitual caffeine		
			High habitual caffeine GTE (>300 mg caffeine) (375 mg catechins, of which 270 mg was EGCG and 150 mg caffeine)		0.3	0.1	0.2
Auvichayapat et al. (2008)	Randomized, controlled	18 M, 42 F BMI: 27–28	Control (cellulose) GTE (140.8 mg catechins, of which 100 mg was EGCG and 87 mg caffeine)	12 weeks	−0.7*	−0.86	−1.09
Hsu et al. (2008)	Randomized, parallel, double-blind, placebo-controlled	78 obese F BMI: 30.8	Control (cellulose) GTE (491 mg catechins, of which 302 mg was EGCG and 27 mg caffeine)	12 weeks	−0.12	−0.05	Not reported

Main outcomes = net effects of GTE (change corrected for change in control group), unless stated otherwise, *$p < 0.05$. M, male; F, female; BMI, body mass index. # Hase et al. (2001) reported percentages of change. For the mean of this article the absolute figures were calculated by relating the changes to the absolute baseline values reported by Hase et al. (2001).

large ($n = 240$) population. After 12 weeks of supplementation of 78 obese females (BMI 30.8) with only 27 mg caffeine but 491 mg catechins, slight reductions of 0.12 kg body weight and 0.05 kg body fat were observed (Hsu et al., 2008). An explanation for this "neutral" result is not possible however it is striking that most of the studies reporting significant results were conducted with moderately overweight subjects and not obese. Therefore, the extent and duration of obesity should be more tightly controlled in future studies. Another recent study reported a moderate but statistically significant reduction in body weight of 0.7 kg after supplementation of small amounts of catechins (140.8 mg of total catechins containing 100 mg EGCG and 27 mg caffeine) over 12 weeks (Auvichayapat et al., 2008). It is important to mention that the study population consisted of sedentary overweight (BMI 27-28) subjects whose diet was provided by a hospital-based nutrition unit. Thus, the level of control of one of the main confounders (diet) typical in this type of study was high. In another study with a different approach, a daily consumption of a control beverage with a low dose of green tea catechins (41 mg) was compared with two higher dose levels (444 and 665 mg) of green tea catechins beverages (Kajimoto et al., 2006). In the two higher dose level groups, body weight and BMI were significantly reduced, however, no clear dose–response relationship could be observed. This finding is unexpected because several epidemiological studies in the context of cancer or heart health suggest that increasing consumption of green tea intake is correlated with greater protective effects. This contradiction between epidemiological and intervention studies has to be addressed in specifically designed human intervention studies in order to gain insight into the dose-response relationship of catechins under certain conditions.

It should be mentioned that caffeine dosage in some of the above discussed studies was relatively small (<100 mg). It has been argued that some of the anti-obesity effects of green tea are due to caffeine. However, in the majority of reports showing that caffeine increases fat oxidation and thermogenesis, more than 100 mg caffeine was used. Thus, it could be deduced that the observed effects on body weight and body fat in the studies by Nagao et al. (2005, 2007), Tsuchida et al. (2002), Kajimoto et al. (2006), Auvichayapat et al. (2008) and Hsu et al. (2008), are likely to be caused by the green tea catechins.

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A different angle was taken by Kovacs et al. (2004) who examined how green tea catechins might influence the body weight regain after a weight loss program. During the first 4 weeks, subjects consumed a very low calorie diet. Subsequently, the subjects consumed their habitual diet plus green tea supplements for 13 weeks and the effects of green tea catechins on body weight regain and body fat were studied. Neither the expected body weight and body fat loss nor a difference in body weight regain in response to the green tea catechins could be demonstrated. It is not necessarily surprising that a natural ingredient like green tea catechins did not further increase the already substantial weight loss resulting from a very low calorie diet. However, this argument does not account for the weight maintenance period. The authors speculated that the magnitude of habitual caffeine intake might have masked the effects of the green tea catechins. This hypothesis was recently confirmed by Westerterp-Plantenga et al. (2005) who showed in a similar set-up that in low-level caffeine consumers green tea extract supplementation further reduces significantly body weight and body fat during weight maintenance, whereas in high level caffeine consumers this effect of green tea catechins could not be observed. In contrast to this hypothesis, Diepvens et al. (2006) found no effect of 1206 mg catechins and 236 mg caffeine on body weight and body fat in overweight females being on a low calorie diet with supplementation over 12 weeks. While Kovacs et al. (2004) as well as Westerterp-Plantega et al. (2005) studied subjects in a weight maintenance period, Diepvens et al. (2006) assessed the effects of catechins during a weight loss period. Possibly, the effects of the catechins are not additional to the weight reducing effect of the low calorie diet, as the latter already represents a strong stimulus to lose body weight and body fat.

In general, most of the above-mentioned studies showed that supplementation with green tea catechins led to significant decreases in body weight and body fat when compared to baseline. The reduction in body weight ranged from 0.7 kg (Auvichayapat et al., 2008) to 3.5 kg (Chantre and Lairon, 2002), and the loss in body fat ranged from 0.7 kg (Nagao et al., 2005) to 1.8 kg (Nagao et al., 2007). These reductions were somewhat diminished when comparisons to the control groups were made. Compared to the control group, a significant effect of green tea catechins on body weight and body fat was reported for both subjects on a moderate energy-restricted diet (Nagao et al., 2005), as well as for subjects with a typical lifestyle diet (Kajimoto et al., 2006; Nagao et al., 2007). In a body weight regain study, decreases in body weight and body fat of 5.8 kg and 3.1 kg, respectively, were reported after 4 weeks of energy restriction (Kovacs et al., 2004). Although still remaining below the baseline value, there were net increases in body weight and body fat of 1.7 kg and 0.2 kg, respectively, after 13 weeks when compared to the 4 weeks values (Kovacs et al., 2004). In another study, basically no effect of high dose catechins on body weight and body fat were observed during a weight loss period supplemented with catechins (Diepvens et al., 2006). Altogether, the weight regain study results vary and are difficult to compare because of different study regimes, populations and confounders such as caffeine intake. Nonetheless, the overall trend is in favour of a beneficial effect of green tea catechins in a weight management program. Further confirmation may be achieved by more tightly controlled human studies.

In addition to studies assessing the overall anti-obesity effect of green tea catechins, several mechanistic studies have been carried out. In particular, the effect of green tea extract and/or EGCG on energy expenditure and fat oxidation in humans has received a lot of attention (Table 2). While some have found increases in energy expenditure and fat oxidation by 4% and 35%, respectively, after supplementation with a green tea extract containing 270 mg EGCG and 150 mg caffeine (Dulloo et al., 1999), others reported increases of 2.9% and 12%, respectively, for the same parameters after drinking oolong tea containing 244 mg EGCG and 270 mg caffeine (Rumpler et al., 2001). The difference in the magnitude for fat oxidation is noticeable, particularly if considering that caffeine intake in the latter study was almost twice as high as in the first study. Caffeine is known to promote thermogenesis and fat oxidation. The interaction and also individual roles of caffeine and EGCG on thermogenesis and fat oxidation remain to be explored. In general, caffeine content is higher in black tea, with values between 41.5 and 67.4 mg/g tea, whereas green tea shows mean caffeine content of 32.5 mg/g tea (Cabrera et al., 2003). Higher caffeine levels are found in coffee beverages ranging from 500 to 600 mg/l beverage (James, 1989).

The overall trend of increased fat oxidation (3.3%) and thermogenesis (4.6%) in response to a beverage containing green tea extract (282 mg EGCG), calcium (633 mg) and caffeine (300 mg) is supported by another recent study (Rudelle et al., 2007). In addition, Berube-Parent et al. (2005) also found an increase in energy expenditure by 8% after 270 mg EGCG together with 600 mg caffeine (Berube-Parent et al., 2005). However, in contrast to Dulloo et al. (1999) and Rumpler et al. (2001) these authors did not find a clear increase in fat oxidation. Based on a high standard caffeine dose, increasing the amount of EGCG did not further increase fat oxidation. As speculated above, the high dose of caffeine (600 mg) might have interfered with the efficacy of EGCG (Westerterp-Plantenga et al., 2005). A cumulative increase in energy expenditure without affecting fat oxidation was also shown after a single administration of oolong tea with 156 mg EGCG and 161 mg caffeine (Komatsu, 2003). However, direct comparison of this study with the other studies is difficult since a different methodology was applied, i.e., some used Douglas bags for assessing gas exchange (Komatsu, 2003), whereas in the majority of studies respiratory chambers were used for assessing thermogenic responses and fat oxidation.

A recent cross-over, placebo controlled study reported an increase in fat oxidation of 17% after a supplement containing various green tea polyphenols and 366 mg EGCG (but no caffeine) compared to the control (Venables et al., 2008). This study was performed in normal weight men during exercise and clearly supports findings in animals that green tea catechins change the metabolism in favour of increased fat utilization. The assumption that this effect is largely caused by EGCG is supported by a study in overweight men (Boschmann and Thielecke, 2007). In this small study the authors reported a significant reduction in the postprandial respiratory quotient after three days supplementation of 300 mg EGCG (Teavigo®) per day, suggesting an increased fat oxidation. It is worth mentioning that this study provides the first evidence that a single catechin, namely EGCG has the potential to moderately affect fat oxidation.

So far, the most remarkable findings have been reported from a long-term investigation where increases in fat oxidation of 37% and 32% at rest and during exercise, respectively, were observed in 14 healthy subjects who consumed a beverage containing 570 mg green tea catechins (218 mg EGCG) for eight weeks (Ota et al., 2005). Interestingly, the beverage contained <40 mg caffeine, suggesting that EGCG and/or other catechins are mainly responsible for this observation. The authors did not report the habitual caffeine consumption. In a different study, the effects of an encapsulated green tea extract (250 mg, with low doses of catechins and caffeine) on resting energy expenditure and respiratory quotient were tested vs. placebo (Auvichayapat et al., 2008). The total daily dose was 140 mg catechins (with 100 mg EGCG) and 87 mg caffeine. The test subjects were overweight (BMI 27–28) and had a sedentary lifestyle. Interestingly, the effects of EGCG were significant for the above parameters after 8 weeks. After 12 weeks significance was found only for resting energy expenditure. Nonetheless, the reduced respiratory quotient in this investigation may suggest

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Table 2
Effects of caffeine, oolong tea, green tea or green tea extract (GTE), rich in EGCG, on fat oxidation and energy expenditure in humans.

Citation	Type of study	Population	Test components	Duration of intake	Main outcomes
Berube-Parent et al. (2005)	Randomized, double-blind, placebo-controlled, cross-over	14 M, BMI: 20–27	Placebo 600 mg caffeine + 270 mg EGCG 600 mg caffeine + 600 mg EGCG 600 mg caffeine + 900 mg EGCG 600 mg caffeine + 1200 mg EGCG	1 day	24 h EE sig. increased by 8% vs placebo and remained rather stable with increasing EGCG conc. decrease in RQ by 0.02 ($p < 0.001$) and increase in fat oxidation by 20 g/day, CHO oxidation remained rather stable
Dulloo et al. (1999)	Randomized, double-blind, placebo-controlled, cross-over	10 M, BMI: 25.1	Control (placebo) GTE (375 mg catechins, of which 270 mg was EGCG, and 150 mg caffeine) Caffeine (150 mg)	1 day	GTE: 24 h energy expenditure increased by 4% ($p < 0,01$), 24 h RQ decreased by 3.4% ($p < 0.001$) due to increased fat oxidation (35%, $p < 0.001$), urinary norephinephrine increased by 40% ($p < 0.05$)
Komatsu (2003)	Randomized, controlled, cross-over	11 F, BMI: 21.1	Control (water) Oolong tea (206 mg catechins, of which 81 mg was EGCG and 77 mg caffeine) Green tea (293 mg catechins, of which 156 mg was EGCG and 161 mg caffeine)	Single administration	Control: cumulative increase in EE of 11.2 ± 1.1 kJ/2 h Oolong tea: Cumulative increase in EE of 110.7 ± 17.7 kJ/2 h ($p < 0.05$) and no significant difference in RQ Green tea: Cumulative increase in EE of 49.5 ± 0.4 kJ/2 h ($p < 0.05$) and no significant difference in RQ
Ota et al. (2005)	Controlled, parallel	14 M, BMI: 23–24.5	Control (exercise) Green tea beverage (570 mg catechins, of which 218 mg was EGCG, <40 mg caffeine) + exercise	8 weeks	EE was non-significantly increased sedentary fat oxidation at rest and during exercise in conjunction with green tea beverage increased significantly compared to exercising alone by 36% or 31%, respectively ($p = 0.02$)
Rudelle et al. (2007)	Randomized, double-blind, placebo-controlled, cross-over	31 M, F BMI: 21.8	Control Treatment (Caffeine 300 mg, EGCG 282 mg, calcium 633 mg)	3 days	24 h EE sig. increased by 4.6% vs placebo ($p = 0.002$) Fat oxidation increased by 3.2 g/24 h n.s. (3.3%) CHO oxidation increased by 20 g/24 h n.s. (6.5%)
Rumpler et al. (2001)	Randomized, cross-over	12 M, BMI: 25.9	Control (water) Caffeine (270 mg) Half-strength tea (331 mg catechins, of which 122 mg was EGCG) Full-strength tea (662 mg catechins, of which 244 mg was EGCG)	3 days	Caffeine: 24 h EE increased by 3.4% and fat oxidation by 8% above control ($p < 0.01$) Half-strength tea: 24 h EE increased by 0.5% and fat oxidation by 2% above control Full-strength tea: 24 h EE increased by 2.9% and fat oxidation by 12% above control ($p < 0.01$)
Venables et al. (2008)	Cross-over, placebo-controlled	12 M, BMI: 23.9	Control (1517 mg gluten-free corn flower) Treatment (890 mg polyphenols, of which was EGCG 366 mg, caffeine-free)	Acute	Average fat oxidation rates were 17% higher after ingestion of GTE, than after ingestion of placebo (0.41 ± 0.03 and 0.35 ± 0.03 g/min, respectively; $p < 0.05$). The contribution of fat oxidation to EE was also significantly higher, by a similar percentage, after GTE supplementation.
Boschmann and Thielecke (2007)	Randomized double blind, placebo-controlled, cross-over pilot study	6 M, BMI: 29.1	Control (300 mg lactose) Treatment (EGCG 300 mg)	3 days	Postprandial RQ values were significantly lower with EGCG compared to the placebo (0.84 ± 0.03 and 0.91 ± 0.07; $p < 0.05$) REE was unchanged
Auvichayapat et al. (2008)	Randomized, controlled	18 M, 42 F BMI: 27–28	Control (cellulose) GTE (140.8 mg catechins, of which 100 mg was EGCG and 87 mg caffeine)	12 weeks	Significant increase in REE compared to placebo after 8 weeks, by 372.21 kJ/day and 173.46 kJ/day for GTE and placebo, respectively ($p < 0.001$). RQ decreased by 0.03 and 0.01 for GTE and placebo, respectively ($p < 0.05$)
Unpublished*	Randomized, double-blind, placebo-controlled	38 F, BMI: 31.2	Control (exercise + placebo) Treatment (exercise + 300 mg EGCG)	12 weeks	EGCG increased fat oxidation during exercise by 36% compared to exercising alone (statistically not significant)

M, male; F, female; BMI, body mass index; EE, energy expenditure; REE, resting energy expenditure; RQ, respiratory quotient.
* Personal communication (Prof. P. Howe, University of South Australia, Adelaide).

an increased fat oxidation which complements the long-term study by Ota et al. (2005) in exercising subjects. Similar trends were found with a highly purified green tea extract (Teavigo®) containing 300 mg EGCG. In a double-blind, parallel placebo controlled study 38 untrained female volunteers with an average BMI of 31.2 kg/m^2 underwent a physical exercise program for 12 weeks. Half of the volunteers took 300 mg EGCG in addition to the training program. In this group, fat oxidation was increased by about 36% at relative workload when compared to the control group (Prof. P.R.C. Howe, personal communication). The habitual caffeine consumption was <300 mg per day. Although this difference was not statistically significant, it is consistent with other evidence for effects of green tea catechins, specifically EGCG, on fat oxidation. In contrast to caffeine, these long-term studies indicate that there is no increased metabolic resistance to the effects of EGCG.

The optimal EGCG dose to increase fat oxidation and support a weight management has not yet been established. The dosage of EGCG used in the various studies described above ranged from 100 mg/day (Nagao et al., 2007) to 540 mg/day (Chan et al., 2006), while the duration of the studies varied from one day (Berube-Parent et al., 2005; Dulloo et al., 1999; Komatsu, 2003) to 13 weeks (Kovacs et al., 2004). The test items were administered either in the form of capsules containing green tea extract, at up to six capsules/day (Dulloo et al., 1999), or beverages at up to 1500 ml/day (Rumpler et al., 2001). The overall positive results suggest that the optimal dose and duration time for green tea catechins or EGCG administration lies within a reasonable range that can be easily integrated into a weight management program.

2.2. Animal studies and in vitro mechanistic plausibility

The mechanistic actions of EGGC have been revealed in *in vitro* and animal studies. Molecular mechanisms potentially contribut-

ing to the anti-obesity effects of green tea have been extensively reviewed elsewhere (Wolfram et al., 2006). In brief, *in vitro* data suggest that green tea catechins, in particularly EGCG, exert their anti-obesity effects via several mechanisms including (1) inhibition of adipocyte differentiation and proliferation (Hung et al., 2005; Wolfram et al., 2005), (2) reduction of fat absorption (Juhel et al., 2000; Raederstorff et al., 2003; Yang et al., 2001), and (3) inhibition of COMT (catechol-*O*-methyl-transferase) in brown adipose tissue (Dulloo et al., 2000).

In vivo animal studies reporting anti-obesity effects of green tea catechins, in particular EGCG, are numerous. The findings comprise: (1) reduction of fat mass (Ashida et al., 2004; Choo, 2003; Hasegawa et al., 2003; Klaus et al., 2005; Wolfram et al., 2005); (2) reduction in triacylglycerides in hyperlipidemia models (Yang et al., 2001) as well as reduction of free fatty acids and total cholesterol (Ashida et al., 2004) and; (3) in combination with endurance exercise promoted beta-oxidation and enhanced exercise capacity in mice (Murase et al., 2006; Shimotoyodome et al., 2005). Listing all individual references is beyond the scope of this review; the inclined reader is therefore referred to 3 recent review articles, which summarize the current concepts (Crespy and Williamson, 2004; Kao et al., 2006; Wolfram et al., 2006).

3. Green tea catechins and improved glucose tolerance

3.1. Epidemiological (observational) and interventional clinical studies

The chance of developing diabetes increases with the grade of obesity. Just like it is for obesity, the link between nutrition and diabetes is clearly established (Riccardi et al., 2004). Therefore there is currently an intensive search for natural ingredients for prevention and treatment of diabetes. Among others green tea catechins have received a great deal of attention in recent research.

A large epidemiological study conducted in Japan showed that subjects with an average habitual consumption of >6 cups of green tea per day had a decreased risk for diabetes (Iso et al., 2006). A total of 17,413 subjects with no history of type-2 diabetes were followed up for 5 years. The consumption of >6 cups of green tea was inversely associated with the risk for diabetes, odds ratio 0.67 (CI: 0.47–0.94), compared to those who drank less than 1 cup per week. Support comes from a cross-sectional study of 3224 Japanese men where impaired fasting glucose was less frequent in those who consumed more green tea (Yamaji et al., 2004). However, the same study did not find a clear association between green tea consumption and glucose tolerance. This discrepancy is somewhat surprising; however, it might be explainable by the hypothesis that green tea catechins could affect various pathways in the aetiology of diabetes to a different degree.

Human intervention studies were designed to explore this issue further. An overview of human studies addressing the effects of green tea catechins on glucose control is provided in Table 3. The anti-hyperglycaemic effects of oolong tea have been assessed in a randomized cross-over study. Twenty type-2 diabetics consumed, in addition to their normal medication, either 1.5 l oolong tea or water (Hosoda et al., 2003). The consumption of oolong tea, which contained 386 mg EGCG, resulted in a significant reduction in plasma levels of glucose and fructosamine, suggesting that diabetic patients may benefit from ingestion of oolong tea, high in EGCG. In a similar study in healthy volunteers, (Hase et al., 2001) found that after 12 weeks intake of green tea extract containing 300 mg EGCG, not only plasma glucose but also insulin was reduced. However, the subjects also experienced slight weight loss. Thus it is not clear whether the improved insulin sensitivity is a direct effect of EGCG or the consequence of the weight loss. Taken together, these studies suggest that green tea catechins help to maintain healthy glucose levels. Further support is provided by a placebo-controlled study with 22 healthy volunteers, where the verum group consumed 1.5 g green tea powder containing 84 mg EGCG (Tsuneki et al., 2004). The authors found that consumption of this powder prior to an oral glucose challenge resulted in smaller increases in plasma glucose levels during the oral glucose tolerance test. A recent study in 20 healthy volunteers showed that green tea containing 300 mg EGCG reduced carbohydrate absorption after a carbohydrate rich meal (Zhong et al., 2006). Furthermore, Fukino et al. (2005) showed in a study of general polyphenol intake, that, although not statistically significant, levels of glucose, insulin, HOMA and HbA1C were reduced in borderline diabetics and diabetic patients taking polyphenols for two months. It might be speculated that between group differences were not significant due to the relatively high polyphenol intake of the control group compared to the intervention group (469 vs. 747 mg). In addition, the lack of restriction on drinking green tea in the control group might have masked potential differences. This hypothesis is supported by the finding that cardiovascular parameters were also reduced in the control group, suggesting the control group became more sensitive about improving their health. The same authors found, in subjects with borderline diabetes, that the intake of 456 mg catechins for two months moderately but significantly reduced HbA1C (Fukino et al., 2008). This is a remarkable finding because the intervention resulted in nearly normal values of this marker for long-term glucose control. The small differences in catechin intake between control and treatment group may have prevented statistical significant differences for fasting glucose and insulin levels. Due to the design of the study, a carry over effect cannot be excluded further diminishing potential differences between the treatment group and control group.

EGCG may protect against the development of long-term complications of diabetes, as reported by Rizvi et al. (2005). The oxidative stress in erythrocytes induced by tert-butyl hydroxyperoxide was measured in response to EGCG, EGC, ECG, and EC in 31 type-2 diabetics and compared to 31 healthy control subjects. EGCG (1–10 μmol/l) was the most potent catechin in reducing oxidative stress thereby reducing an important factor in the development of glucose metabolism disorders. This *ex vivo* finding is of interest because plasma EGCG levels in the micromolar range are also achievable by natural intake; the concentration of EGCG after an intake of a large dose of green tea varies 0.63–1.8 μmol/l (Leenen et al., 2000; van Hethof et al., 1998). In contrast, Ryu et al. (2006) did not find improvement of plasma glucose levels or insulin resistance in type-2 diabetes patients after consumption of 900 ml water containing 9 g green tea over 4 weeks. However, this study assessed fasting glucose and insulin values, different outcome parameters compared to oxidative stress. Additionally, in this context a period of 4 weeks might not be sufficient to find changes in fasting glucose and insulin values. It has been shown in a long-term study that 12-weeks consumption of green tea rich in EGCG tends to decrease fasting glucose and insulin (Hase et al., 2001).

The optimal dose of EGCG for glucose control has not yet been established. Based on the available literature a dose range of 84–386 mg EGCG/day may be adequate to support glucose homeostasis (Hosoda et al., 2003; Tsuneki et al., 2004).

3.2. Animal studies and in vitro mechanistic plausibility

The underlying mechanisms and pathways by which green tea catechins could potentially improve glucose haemostasis have been explored in *in vitro* and animal based studies. The reduction of carbohydrate absorption by inhibition of various digestive enzymes is of considerable interest in the prevention of diabetes

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Table 3
Human studies assessing the effect of green tea, green tea extract, rich in EGCG on glucose control.

Citation	Type of study	Population	Test components	Duration of intake	Main outcomes
Hosoda et al. (2003)	Randomized, controlled, crossover	20 subjects with type-2 diabetes	Control (water) 1.5 l oolong tea (containing 386 mg EGCG)	30 day	Plasma glucose and fructosamine were reduced from 229 to 162 μmol/l ($p < 0.001$) or 409.9 to 323.3 μmol/l ($p < 0.01$)
Tsuneki et al. (2004)	Controlled	22 healthy subjects	Control (water) 1.5 g Green tea powder (84 mg EGCG) after an oral glucose challenge	Single administration	Plasma glucose was significantly reduced after an OGTT
Hase et al. (2001)	Case–control	23 healthy males	Control (118.5 mg catechins, of which 32 mg was EGCG) GTE (483.0 mg catechins, of which 300 mg was EGCG)	12 weeks	Significant reductions in plasma glucose and insulin
Zhong et al. (2006)	Randomized, placebo-controlled, cross-over	20 healthy subjects	Green tea extract (containing 300 mg EGCG), black tea extract, mulberry tea extract, 0.1 g each placebo	Single administration	The tea extract decreased carbohydrate absorption after a carbohydrate meal by 25%
Rizvi et al. (2005)		31 type-2 diabetics, 31 healthy subjects	EGCG, EGC, ECG, EC, each 10^{-5}–10^{-8} mol/l	*Ex vivo*	Oxidative stress in erythrocytes measured as MDA reduced gluthation
Fukino et al. (2005)	Randomized, controlled	53 males and 13 females with borderline or established diabetes	Green tea extract/powder dissolved in hot water, resulting in 747 mg and 445 mg polyphenol intake in the intervention and control group	2 months	Body weight, BMI, systolic and diastolic blood pressures, blood glucose level, Hb A1c level, insulin level and HOMA index after taking the supplementation for 2 mo, were lower than the respective value before intervention: however, these parameters in the intervention group at 2 mo did not significantly differ from those in the control group. Within the intervention group, changes in insulin level tended to be associated with changes in polyphenol intake. In addition, changes in BMI were associated with changes in blood glucose level and insulin level
Ryu et al. (2006)	Randomized cross-over	31 male, 24 female type-2 diabetics	900 ml green tea containing 9 g green tea	4 weeks	Blood glucose and insulin resistance in type-2 diabetes patients were unchanged
Fukino et al. (2008)	Randomized, controlled	49 male, 11 female borderline diabetics	Green tea extract/powder dissolved in hot water, resulting in 456 mg catechins intake in the intervention group	2 months	Significant reduction of Hb A1c compared to control group, no significant changes in fasting insulin glucose, and HOMA index

thereby addressing the core condition of the MetS. It has been shown that green tea catechins reduced α-amylase and sucrase activities in rat intestine (Matsumoto et al., 1993). A more detailed investigation of this phenomenon revealed the importance of the esterified moiety in EGCG for the inhibitory effect on α-glucosidase (Matsui et al., 2007). In another study EGCG reduced the glucose uptake from rat intestine and inhibited the sodium-dependent glucose transporter significantly (Kobayashi et al., 2000). In this experiment ECG was even more potent than EGCG. Presently available *in vitro* data thus suggest that green tea catechins could reduce glucose absorption by inhibiting gastro-intestinal enzymes involved in nutrient digestion. Furthermore, animal investigations showed glucose uptake in skeletal muscle significantly increased, while glucose uptake in adipose tissue was significantly decreased following the ingestion of green tea catechins. These effects could be a result of the effects of green tea catechins on GLUT4 translocation in skeletal muscle, which was found to be increased and on GLUT4 translocation in adipose tissue, which in turn was decreased (Ashida et al., 2004).

Overall, the harmonizing effects of green tea catechins on disorders of glucose metabolism implicated in type-2 diabetes seem to be mediated by various mechanisms, including decreased carbohydrate absorption, decreased hepatic glucose production, increased insulin secretion and insulin sensitivity, as well as increased uptake of glucose into skeletal muscle. The mechanistic basis for the overall beneficial effects of green tea rich in EGCG on glucose homoeostasis are thoroughly discussed elsewhere (Crespy and Williamson, 2004; Kao et al., 2006).

4. Green tea catechins and maintaining a healthy cardiovascular system

4.1. Epidemiological (observational) and interventional clinical studies

Another field in which green tea catechins received a lot of attention is cardiovascular health. The relationship between green tea consumption and the maintenance of cardiovascular health has been well investigated (Imai and Nakachi, 1995; Nakachi et al., 2000; Sano et al., 2004; Sato et al., 1989; Yusuf et al., 2005). The majority of epidemiological studies demonstrate that tea consumption benefits the cardiovascular system (Vita, 2003) and more recently an inverse correlation between green tea consumption and mortality due to cardiovascular disease was found (Kuriyama et al., 2006). Please refer to Table 4 for a summary of the evaluated studies.

Imai and Nakachi (1995) found an inverse association between green tea consumption and markers of cardiovascular disease in 1371 men. The prevalence of heart disease was 26.0, 29.4, and 39.8 per 1000 in populations with a daily consumption of >10, 4–9, and <3 cups of green tea per day, respectively. These observations were supported by the fact that the population showed significantly reduced levels of cholesterol ($p < 0.001$) and triacylglycerides ($p < 0.02$). Further support for this observed effect is provided by a similar study comprising 8552 subjects (Nakachi et al., 2000) in which the investigators clustered green tea consumption in the same way as Imai and Nakachi (1995). These authors calculated a relative risk of death from cardiovascular dis-

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Table 4
Human studies assessing the effect of green tea, green tea extract, rich in EGCG on cardiovascular health.

Citations	Type of study	Population	Test components (daily dosage)	Duration of intake	Main outcomes	Authors conclusion
Blood flow						
Kim et al. (2006)	Open design	20 young smokers	8 g powdered green tea per day, containing 3.2% EGCG	2 weeks	Flow mediated dilatation improved by ca. 2%	A short-term administration of green tea consumption induces a rapid improvement of EPC levels and FMD. Green tea consumption may be effective to prevent future cardiovascular events in chronic smokers
Murakami and Ohsato (2003)	Open design	150 Japanese visiting the ambulatory, age >60	>800 ml green tea ($n = 77$), <800 ml green tea ($n = 73$)	4 months	Pulse wave velocity was significantly smaller in the group with high green tea intake ($p < 0.01$), while flow mediated dilatation was increased ($p < 0.01$). serum total cholesterol was decreased ($p = 0.03$)	The dietary intake of green tea pleitropically protects Japanese from athero-thrombogenic processes reducing several risk factors, preserving arterial compliance and endothelial function, and may contribute to low incidence of cardiovascular events in Japan
Nagaya et al. (2004)	Randomized cross-over	20 healthy smokers	400 ml green tea, containing 247 mg EGCG	Single dose	Green tea had no influence on blood parameters, including glucose and lipids or blood pressure and heart rate, forearm blood flow to reactive hyperaemia was significantly increased ($p < 0.001$) while forearm blood flow after sublingual administration of glyceril trinitrate was unaffected	The results suggest that green tea consumption reverses endothelial dysfunction in healthy smokers, possibly through its antioxidant effect
Vlachopoulos et al. (2006)	Randomized cross-over	13 healthy volunteers	6 g green tea	Single dose	Green tea increased augmentation index by 6.6% ($p < 0.01$) throughout the study. These changes were less than the respective changes produced by caffeine. Green tea had a significant pressor effect	Green tea increases acutely wave reflections. Tea flavonoids may play a role in the attenuation of the Effects of caffeine contained in tea
Ryu et al. (2006)	Randomized cross-over	31 male, 24 female type-2 diabetics	900 ml green tea containing 9 g green tea	4 weeks	Inflammatory markers and pulse wave velocity in type-2 diabetes patients were unchanged	The tested mechanisms are unlikely to explain the cardiovascular risk reduction by tea consumption observed in epidemiological studies
Blood pressure						
Yang et al. (2004)	Cohort study	711 men and 796 women, >20 years without a hypertensive history during 1996 in Taiwan	<120 ml tea/day 120–599 ml tea/day >600 ml tea/day	Habitual tea intake	Six hundred subjects (39.8%) were habitual tea drinkers, defined by tea consumption of 120 ml/day or more for at least 1 year. Compared with no habitual tea drinkers, the risk of developing hypertension decreased by 46% for those who drank 120–599 ml/day and was further reduced by 65% for those who drank 600 ml/day or more after carefully adjusting for age, sex, socioeconomic status, family history of hypertension, body mass index, waist-hip ratio, lifestyle factors (total physical activity, high sodium intake, cigarette smoking, alcohol consumption, and coffee drinking), and dietary factors (vegetable, fruit, unrefined grain, fish, milk, visible-fat food, and deep fried food intake). However, tea consumption for more than 1 year was not associated with a further reduction of hypertension risk	Habitual moderate strength green or oolong tea consumption, 120 ml/day or more for 1 year, significantly reduces the risk of developing hypertension in the Chinese population
Cardiovascular health in general/antioxidative properties						
Imai and Nakachi (1995)	Cross-sectional study	1371 men	Daily green tea consumption <3 cups, 4–9 cups, and >10 cups	Habitual intake	Cholesterol and triacylglycerides, were significantly decreased ($p < 0.001$, and 0.02). The prevalence of heart disease was 26.0, 29.4, and 39.8 per 1000 in populations with a daily consumption of >10, 4–9, and <3 cups per day	The inverse association between consumption of green tea and various serum markers shows that green tea may act protectively against cardiovascular disease and disorders of the liver
Sano et al. (2004)	Case–control	109 patients with coronary artery disease, 94 patients without coronary artery disease, all underwent elective coronary angiography	Average intake of green tea in patients with CAD 4 ± 4 cups green tea per day, in patients without CAD 6 ± 4 cups green tea per day	Habitual intake	Green tea consumption was significantly higher in patients without CAD than in those with CAD (5.9 ± 0.5 vs 3.5 ± 0.3 cups/day; $p < 0.001$). An inverse relationship between the intake of green tea and the incidence of CAD was observed ($p < 0.001$). The green tea intake per day was an independent predictor for CAD based on a multivariate logistic regression analysis (odds ratio: 0.84 and 95% confidence interval: 0.76–0.91)	Green tea consumption was associated with a lower incidence of CAD in the present study population in Japan. Therefore, the more green tea patients consume, the less likely they are to have CAD

(*continued on next page*)

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Table 4 (*continued*)

Citations	Type of study	Population	Test components (daily dosage)	Duration of intake	Main outcomes	Authors conclusion
Pearson et al. (1998)	*Ex vivo*	Human LDL, human aortic endothelial cells	Nikken tea extract powder, containing 23.5% EGCG, and green tea catechin powder containing 29.7% EGCG	12 h	LDL oxidation was inhibited 3.9–98% at concentrations ranging from 0.08 to 5 ppm of the green tea extracts	The polyphenolic compounds of green tea may have nutritional benefits as inhibitors of LDL oxidation
Princen et al. (1998)	Randomized, single blind, placebo-controlled, parallel	32 male, 32 female subjects	Six cups of green tea (150 ml) equivalent to 3 g green tea solids, containing 309 mg EGCG and 6 × 4 capsules per day equivalent to 9 g green tea solids containing 864 mg EGCG	4 weeks	No effect on plasma cholesterol and triglycerides, HDL and LDL cholesterol, plasma vitamins C and E, beta-carotene, and uric acid. No differences were found in parameters of LDL oxidation	Although tea polyphenols had a potent antioxidant activity on LDL oxidation *in vitro*, no effect was found on LDL oxidation *ex vivo* after consumption of green tea or intake of a green tea polyphenol isolate
Serafini et al. (2000)	Clinical trial	5 healthy non-smokers	300 ml water (control) or green tea (300 ml, containing 6 g green tea)	Single dose	Plasma total antioxidant capacity values of subjects who drank green tea rose at 30 min ($p < 0.05$). Green tea was efficient in protecting low density lipoprotein from oxidation driven by peroxyl and ferril radicals, respectively	Phenol-rich beverages are a natural source of antioxidants; however, the phenolic content alone cannot be considered an index of their *in vivo* antioxidant activity
Nakachi et al. (2000)	Prospective cohort study	8552 residents over 40 years	Daily green tea consumption <3 cups, 4–9 cups, and >10 cups	Habitual intake follow up over 11 years	The relative risk of death from cardiovascular disease was decreased to 0.58 (0.34–0.99) for men, 0.82 (0.49–1.38) for women, and 0.72 (0.60–1.04) for members of both sexes consuming over 10 cups a day	Green tea can be used as a multiple targeting preventive without toxicity both in the general population where target diseases of prevention are various and sometimes uncertain, ans also in high-risk populations with green tea alone or in combination with other disease-specific preventives
Sasazuki et al. (2000)	Cross-sectional study	512 patients who underwent cardioangiography	Daily green tea consumption 0–1 cups, 2–3 cups, and >4 cups	Habitual intake	Increased consumption of green tea was associated with decreased serum concentrations of total cholesterol (p for trend < 0.001) and triglyceride (p for trend = 0.02) and an increased proportion of high density lipoprotein cholesterol together with a decreased proportion of low and very low lipoprotein cholesterols (p for trend = 0.02), which resulted in a decreased atherogenic index (p for trend = 0.02). Moreover, increased consumption of green tea, especially more than 10 cups a day, was related to decreased concentrations of hepatological markers in serum, aspartate aminotransferase (p for trend = 0.06), alanine transferase (p for trend = 0.07), and ferritin (p for trend = 0.02)	The results indicate that green tea may be protective against coronary atherosclerosis at least in men
Sung et al. (2005)	Clinical Trial	12 healthy male volunteers	600 ml green tea per day (5.2 g green tea)	4 weeks	The levels of ox-LDL and soluble vascular cell adhesion molecule-1 (sVCAM-1) were significantly decreased. No change in lipid profile	The results of this study suggest an *in vivo* anti-oxidative effect for green tea and an influence of green tea on atherosclerotic biological markers. The effect of green tea seen on ox-LDL and sVCAM-1 provides a potential mechanism for the cardiovascular benefits of regular ingestion of green tea

ease at 0.58 (CI: 0.34–0.99) for men and 0.82 (CI: 0.49–1.38) for women who consume >10 cups of green tea. Why the effect is smaller in men can not be explained by the current data. However, it might be speculated that other lifestyle factors such as smoking and physical activity or sex hormones contribute to this discrepancy.

A number of potential mechanisms related to the observed effects have been addressed in various studies. Murakami and Ohsato (2003) reported endothelial function significantly improved in a population of Japanese patients who consumed >800 ml green tea over 4 months. They reported that other cardiovascular risk factors were also improved and concluded that green tea may contribute to the low incidence of cardiovascular disease in Japan. These results are strengthened by a randomized cross-over study in smokers, where a single dose of 400 ml green tea was shown to acutely reverse endothelial dysfunction (Nagaya et al., 2004). A recent study by Kim et al. (2006) also examined the effect of green tea consumption on endothelial function in smokers. Twenty young smokers consumed 8 g green tea per day (3.2% EGCG) over a period of two weeks, which resulted in a significant improvement of flow mediated dilatation, a measure for endothelial function. Taken together, green tea catechins seem to improve endothelial function. A high risk population like smokers may in particular benefit from consumption of green tea catechins and thereby prevent cardiovascular events.

Oxidized LDL is recognized as a risk factor for atherosclerosis. The potential of green tea extract rich in EGCG to affect LDL oxidation was assessed by Pearson et al. (1998). Human LDL and human

aortic endothelial cells were used for this *ex vivo* study. LDL oxidation was inhibited by 3.9% after 12 h incubation with 0.08 ppm green tea extract. This was drastically increased to 98% inhibition after incubation with 5 ppm green tea extract. Interestingly, these concentrations, particularly the first, represent a dose which would potentially be achievable by natural intake. Two clinical trials substantiate this finding. A single consumption of 300 ml green tea containing 6 g green tea solids by healthy subjects, increased total plasma antioxidant capacity and efficiently protected LDL from oxidation compared to the control beverage (Serafini et al., 2000). Similarly, in a 4 week study the daily consumption of 600 ml green tea, containing 5.2 g tea solids significantly decreased the levels of oxidized LDL (Sung et al., 2005). In contrast, in another study, no effect was found on *ex vivo* LDL oxidation after 4 weeks consumption of either 900 ml green tea, containing 309 mg EGCG or 24 green tea extract capsules per day, containing 864 mg EGCG (Princen et al., 1998). The lack of efficacy in this study might be related to the method used to assess LDL oxidizability. LDL isolated from serum was used. However, since the oxidation of lipoproteins occurs in the aqueous phase of the serum, LDL should not be isolated from serum measurement.

Another cardiovascular risk factor within the context of MetS is hypertension. The effect of drinking green tea on developing hypertension was evaluated in a cohort study with 1507 subjects (Yang et al., 2004). Compared with no habitual tea drinkers, the risk of developing hypertension decreased by 46% for those people who drank 120–599 ml/day and this was further reduced by 65% for those who drank 600 ml/day or more. This finding might be explained by the beneficial effect of green tea on aortic stiffness and wave reflection, since aortic stiffness and wave reflection lead to increased systolic blood pressure and pulse rate. A study exploring this relationship showed that a single administration of 6 g green tea solids resulted in acute increases of wave reflection, thereby eliciting a significant pressor effect (Vlachopoulos et al., 2006). However, when green tea containing 9 g solids were administered to type-2 diabetics over 4 weeks pulse wave velocity was unchanged (Ryu et al., 2006). Unfortunately, the provided data do not allow conclusions for one or the other finding. Nonetheless, one can speculate that the different metabolic status of diabetes patients compared to healthy individuals explains these discrepancies.

The effect of habitual green tea consumption on coronary artery disease was investigated (Sano et al., 2004; Sasazuki et al., 2000). In both studies, patients underwent coronary angiography. Green tea consumption was associated with a lower incidence of coronary artery disease. In addition, green tea intake was an independent predictor for cardiovascular disease (odds ratio: 0.84; CI: 0.76–0.91) (Sano et al., 2004). Furthermore, it was shown that a daily consumption of >4 cups significantly reduced risk factors for coronary artery disease including total cholesterol, LDL-cholesterol, and triacylglyerides, while it increased the protective HDL-cholesterol.

The optimal daily dose for cardiovascular health is difficult to derive from the above discussed human studies because the exact amount of EGCG is rarely provided. The test items were administered either as encapsulated green tea extract with up to 24 capsules/day (Princen et al., 1998) or as green tea beverages with up to 1500 ml/day (Nakachi et al., 2000). An approximation might be made by applying the range of EGCG found in different green tea samples. The EGCG content of a single cup of tea prepared with 1.5 g of green tea can range between 34.5 and 109.5 mg. This figure is derived from 23 to 73 mg water extractable EGCG/g of green tea (Bronner and Beecher, 1998; Lee et al., 1995; Scholz and Bertram, 1995). Based on this assumption a daily dosage of EGCG ranging from 69 to 657 mg appears beneficial. For specific recommendations more well-designed intervention studies relating the dose to a specified outcome measure are needed.

4.2. Animal studies and in vitro mechanistic plausibility

The body of *in vitro* evidence, as well as *in vivo* animal studies for the efficacy of green tea catechins or pure EGCG on biological mechanisms connected to cardiovascular health is numerous. The interested reader is referred to comprehensive review articles summarizing the underlying concepts (Cheng, 2006; Stangl et al., 2006). In brief, the suggested mechanisms in the support of cardiovascular health by green tea involve potent antioxidant activity (Higdon and Frei, 2003), anti-inflammatory properties (Yang et al., 1998), inhibition of vascular smooth muscle growth (Locher et al., 2002), counteraction of vasoconstriction (Chen et al., 2000; Tijburg et al., 1997), prevention of stroke (Ikeda et al., 2007; Sato et al., 1989) as well as reduction of hypertension (Potenza et al., 2007; Yang et al., 2004).

5. Summary

Epidemiological evidence indicates that populations with high intake of green tea catechins benefit in terms of body weight and body fat, glucose homeostasis, and cardiovascular health. Almost all studies exploring anthropometric parameters showed a reduction in body weight and body fat in response to green tea catechins, when compared to baseline. These differences tended to be smaller when changes in the control groups were taken into account. Several studies, including three long-term studies, suggest that green tea catechins increased fat oxidation. In order to get a better understanding of the anti-obesity properties of green tea catechins, it might be necessary to extend the duration of the supplementation of green tea catechins to more than 12 weeks and to increase the level of control for energy intake and physical activity, as well as habitual caffeine consumption, thereby minimizing the variations introduced by these confounders. Data from *in vitro* and *in vivo* studies suggest that green tea catechins, in particularly EGCG, exert their anti-obesity effects via several mechanisms including inhibition of adipocyte differentiation and proliferation, reduction of fat absorption, and inhibition of COMT (catechol-*O*-methyl-transferase) in brown adipose tissue leading finally to reduction in (1) fat mass, (2) triacylglycerides in hyperlipidemia models, and (3) free fatty acids and total cholesterol. Furthermore, combined with endurance exercise, beta-oxidation is promoted and exercise capacity was enhanced in mice.

The majority of human intervention studies investigating glucose homeostasis demonstrate improved glucose levels in response to green tea catechins. Potentially conflicting results might be due to the limited number of human studies, and assessing different endpoints in varying populations with rather different study designs. Nonetheless, the emerging evidence warrants further studies to explore the benefits of green tea catechins on glucose homeostasis. This is particularly true considering the strong data from *in vitro* and *in vivo* animal studies, which suggest several mechanisms contribute to the overall benefits of green tea catechins, including decreased carbohydrate absorption, decreased hepatic glucose production and increased insulin sensitivity.

When assessing the literature with respect to the effects of green tea catechins for promoting cardiovascular health, it becomes apparent that the majority of human studies demonstrate benefits of green tea rich in EGCG on several parameters related to cardiovascular health. This conclusion is substantiated by both *in vitro* and *in vivo* animal data, which indicates several mechanisms by which green tea catechins contribute to supporting a healthy cardiovascular system. Effects include, for example, improved endothelial function, increased antioxidant activities and an improved pressure control. All of these effects have meanwhile

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also been shown in human studies. However, the results of human studies exploring the effects of green tea catechins on cardiovascular health are not utterly consistent. Scrutinizing the discrepancies amongst those studies, reveals that it is crucial to consider potential confounders and differences in methodology, population, and design of the studies.

Although the number of intervention studies exploring the effects of green tea catechins on body weight and body fat, glucose homeostasis, as well as cardiovascular health is increasing, more well-designed human studies are necessary to substantiate the current evidence.

In summary, green tea catechins have the potential to alleviate symptoms of the MetS.

6. Conclusions

Green tea catechins, in particular EGCG, are ingested in considerable amounts through consumption of green tea beverages, especially in Asia. Human studies show anti-obesity, anti-diabetic and cardio-protective effects of green tea catechins. This efficacy is supported by conclusive evidence from animal studies which have also provided the concepts for underlying functional mechanisms. Overall, the scientific evidence supports the rewards of ingesting green tea catechins, with special attention to EGCG. The positive trends and effects of this natural ingredient warrant further attention. In particular, well-controlled long-term human studies would help to fully understand the protective effects of green tea catechins on parameters related to the MetS and to determine the optimal doses relevant for use in prevention, early management and treatment of the rising health burden of MetS.

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