Journal of Alzheimer's Disease xx (20xx) x–xx
DOI 10.3233/JAD-161200
IOS Press

Review

Diabetes and Alzheimer's Disease: Can Tea Phytochemicals Play a Role in Prevention?

Fernando W.M.A.D. Binosha[a,b,1], Geeshani Somaratne[c,d,1], Shehan Williams[e], Kathryn G. Goozee[a,f,g,h,i], Harjinder Singh[c,d] and Ralph N. Martins[a,b,f,g,h,i,*]

[a]*Centre of Excellence in Alzheimer's Disease Research and Care, School of Medical Sciences, Edith Cowan University, Joondalup, Australia*
[b]*School of Biomedical Science, Macquarie University, Sydney, NSW, Australia*
[c]*Massey Institute of Food Science and Technology, Massey University, Palmerston North, New Zealand*
[d]*Riddet Institute, Massey University, Palmerston North, New Zealand*
[e]*Faculty of Medicine, University of Kelaniya, Colombo, Sri Lanka*
[f]*KARVIAH Research Centre, Anglicare, Castle Hill, NSW, Australia*
[g]*School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Nedlands, WA, Australia*
[h]*Department of Biomedical Sciences, Macquarie University, Sydney, NSW, Australia*
[i]*KaRa Institute of Neurological Diseases, Sydney, NSW, Australia*

Accepted 12 March 2017

Abstract. Dementia and diabetes mellitus are prevalent disorders in the elderly population. While recognized as two distinct diseases, diabetes has more recently recognized as a significant contributor to risk for developing dementia, and some studies make reference to type 3 diabetes, a condition resulting from insulin resistance in the brain. Alzheimer's disease, the most common form of dementia, and diabetes, interestingly, share underlying pathological processes, commonality in risk factors, and, importantly, pathways for intervention. Tea has been suggested to possess potent antioxidant properties rich in phytochemicals including, flavonoids, tannins, caffeine, polyphenols, boheic acid, theophylline, theobromine, anthocyanins, gallic acid, and finally epigallocatechin-3-gallate, considered the most potent active ingredient. Flavonoid phytochemicals, known as catechins, within tea offer potential benefits for reducing the risk of diabetes and Alzheimer's disease by targeting common risk factors, including obesity, hyperlipidemia, hypertension, cardiovascular disease, and stroke. Studies also show that catechins may prevent the formation of amyloid-β plaques and enhance cognitive functions, and thus may be useful in treating patients who have Alzheimer's disease or dementia. Furthermore, other phytochemicals found within tea offer important antioxidant properties along with innate properties capable of modulating intracellular neuronal signal transduction pathways and mitochondrial function.

Keywords: Alzheimer's disease, cognitive impairment, diabetes, phytochemicals, tea

INTRODUCTION

Currently there are more than 46.8 million people with dementia worldwide, with Alzheimer's disease (AD) accounting for approximately 50–70%. Based on current health projections, epidemic proportions are anticipated with numbers expected to double

[1]These authors contributed equally to this work.

*Correspondence to: Professor R.N. Martins, Centre of Excellence in Alzheimer's Disease Research and Care, School of Medical Sciences, Edith Cowan University, Joondalup, Australia. Tel.: +61 8 6304 5456; Fax: +61 8 93474299; E-mail: r.martins@ecu.edu.au.

every 20 years, increasing to 65 million people by 2030 and a staggering 131.5 million by 2050 [1].

In 2010, the cost of dementia was calculated to be 604 billion USD; however, by 2015, the figure had grown to 818 billion USD, an increase of 35.4%. Based on these projections, unless a significant breakthrough is found, by 2018 the cost will rise to 1 trillion dollars, and by 2030, the figure will reach over 2 trillion USD.

The neurodegenerative process in AD is characterized by the presence of cerebral extracellular deposition of amyloid-β (Aβ) plaques, intraneuronal neurofibrillary tangles, and cerebral atrophy [2]. However, while not considered a characteristic hallmark, the presence of accumulating cerebrovascular amyloid is reported in up to 90% of the cases [3]. Recent advances in imaging technology has clearly demonstrated that the buildup of cerebral Aβ plaques is occurring up to two decades prior to the onset of any clinical symptoms [4]. The Aβ peptide is a core component of amyloid plaques and is generated from the processing of its parent protein, the amyloid-β protein precursor (AβPP) [5]. Enzymatic cleavage of AβPP via beta secretase enzyme-1 (BACE1) followed by γ-secretase generates multiple Aβ species including the common soluble monomeric peptides of 40 amino acids and the more insoluble Aβ peptide of 42 amino acids. While the exact etiology of AD remains to be elucidated, increasing age, lifestyle choices including being sedentary, and poor sleep patterns, combined with particular dietary patterns are thought to contribute to the risk of AD.

Diabetes is a highly prominent chronic health condition in the older person, with worldwide figures reporting 5.1 million deaths in 2013. Type 2 diabetes (T2D) represents up to 90% of all cases of diabetes and is strongly associated with poor lifestyle choices including sedentary lifestyle, high sugar/dietary fat intake, and poor sleep, each which can independently contribute to increased inflammation, altered metabolism, disruption to mitochondrial function, and alteration in DNA expression. In diabetes, islet amyloid polypeptide (IAPP, or amylin), is referred to as a regulatory peptide of insulin and glucagon secretion; however in T2D, IAPP has been shown to aggregate as pancreatic islet amyloid deposits [6]. Several clinical longitudinal studies report a pathophysiological link between AD and T2D, with almost a twofold greater risk of developing AD in the presence of diabetes [7–10]. AD and T2D are multifactorial in their etiology, and interestingly, both share many underlying pathological processes of aggregation and accumulation of amyloid in their pathogenesis.

While the etiology remains to be fully elucidated, strategies that target common pathways particularly using lifestyle approaches, such as exercise and nutrition [11–14], suggest an important synergistic approach toward preventing T2D and AD, by enhancing glucose control, lowering insulin resistance, and reducing inflammation.

Tea, derived from the dried tea powder/leaves produced from the fresh buds of the flowering plant *Camellia sinensis* [15, 16], is proposed as one such approach. Literature suggests that tea, especially black, white, and green tea, may positively influence pathology and reduce risk factors associated with AD [17–19] and diabetes [20, 21] (Fig. 1). The beneficial properties of tea are largely attributed to the high polyphenol content, particularly the catechins which are powerful antioxidants [22–24]. Among the different types of tea available, the most common are green, black, purple, and white tea, with regional, cultural, and socioeconomic variance influencing [16] choice. Black tea represents 78% of global tea production, green tea 20%, and Oolong tea is less than 2% [15, 16, 25]. Black tea is regularly consumed in both Western and some Asian countries, whereas green tea is more frequently consumed in China, Japan, and a few countries in Europe, North Africa, and the Middle East [16, 26], and Oolong tea is more frequently consumed in southeastern China and Taiwan [25]. While better known in Western countries, white tea is less prevalent [27], while purple tea developed in Kenya is a variant of green tea which in addition to the green tea properties, also contains anthocyanins [28].

Tea and its extracts, irrespective of type, has been associated with a variety of health benefits [29], including anti-microbial [29], anti-inflammatory [29], anti-tumor [12], anti-viral [29], antioxidant [30], and anti-diabetic [31] properties. Many of the corresponding bioactivities are possibly attributed to epicatechins, a major phytochemical responsible for the flavor and aroma of the green tea brew [16–18]. In addition, a number of oxidized polymeric polyphenol molecules known as theaflavins and thearubigins, are present in the aqueous extract of fully or partially fermented tea; these are likely to be responsible for the health benefits of black and Oolong tea [15, 19]. In addition to tea polyphenols, tea leaves also contains theanine which appear to be associated with improved cognitive function [32].

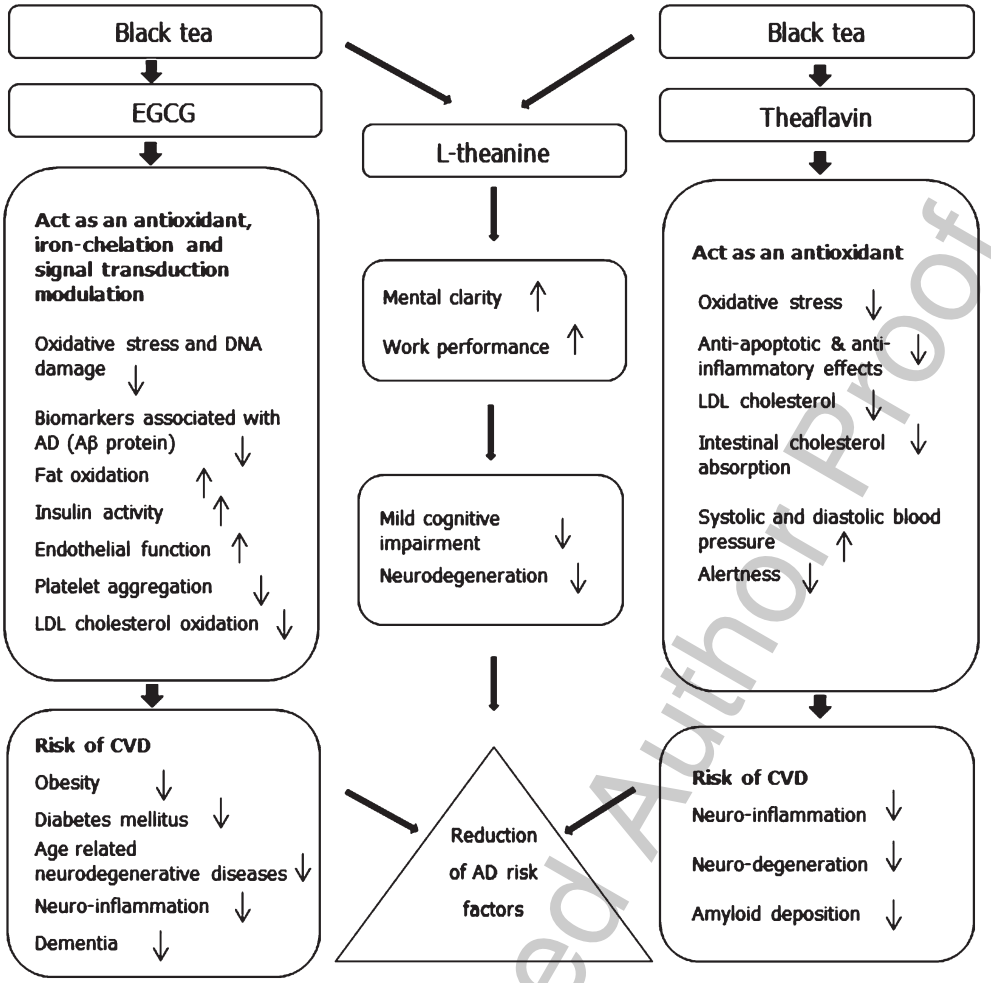

Fig. 1. Schematic diagram of importance of green and black tea phytochemicals on the reduction of AD progression. EGCG, (–)-epigallocatechin gallate; AD, Alzheimer's disease, LDL, low-density lipoprotein; CVD, cardiovascular disease.

TEA MANUFACTURING

Depending on the variety of camellia sinensis (tea) used, the length of the fermentation/oxidation of tea leafs/buds, tea is divided into four key categories; white (nonoxidized/non fermented buds), green (nonoxidized/non fermented leaves), oolong (partially oxidized/fermented leaves), and black (oxidized/fermented leaves) [16, 33]. Green tea and white tea are the least processed tea which is manufactured by heating the leaves/buds immediately after harvesting through a process of steaming in order to prevent oxidation followed by rolling and drying of the leaves. White tea is manufactured only from the buds and immature tender tea leaves whereas green tea is prepared using matured tea leaves and buds. Among the white and green tea, white tea undergoes the least amount of processing and, hence, believed to have highest level of polyphenols. However, white tea is quite expensive and mainly produced in China, and limited data is available. The production of black tea involves the withering, rolling, and fermentation of the tea leaves, followed by a firing processes [30, 33]. The manufacturing process of Oolong tea is similar to black tea except that the length of the fermentation differs, being only partially fermented. The fermentation process leads to the generation of complex oxidation products, such as theaflavins and therubigins, that directly contribute to the unique sensory attributes including aroma, color and taste of the tea [16, 26, 34]. Higher bioavailability and antioxidant phytochemicals are reported in green and white tea

achieved through reduced levels of processing and differences in production and methods of fermentation, through to finally brewing [15, 16].

CHEMICAL COMPOSITION OF TEA

The chemical composition of fresh tea leaves (Table 1) depends on the environmental conditions during growth, fermentation, and the manufacturing process [35]. Black tea and green tea are comprised of approximately 15–20% protein and approximately 1–4% amino acids, including theanine (or 5-N-ethylglutamine), glutamic acid, glycine, serine, aspartic acid, tyrosine, valine, leucine, theonine, arginine, and lysine [31, 34–37] (Table 1). Theanine is a unique amino acid exclusively present in tea, accounting for 50% of the total amino acids. The unique aroma of the tea is also derived from its amino acids [34], while the carbohydrate content of tea is approximately 5–7% dry weight and it contains pectins, glucose, fructose, cellulose, and sucrose [29, 34]. Tea also contains approximately 5% minerals and trace elements [29, 34, 38, 39] notably potassium, manganese, and fluoride ions [34, 38, 39]. Tea also contributes trace levels of lipids, including essential fatty acids (linoleic and α-linolenic acids), stigmasterol, and vitamins, including vitamin B, C, and E [29, 34, 38, 39].

The composition of green tea and white is similar except the level of antioxidants differs. Further, xanthic bases, (e.g., caffeine, theophylline) pigments (e.g., chlorophyll and carotenoids) and volatile compounds, including aldehydes, alcohols, esters, lactones, and hydrocarbons are also found in tea leaves [29, 34, 38, 39]. Although chlorophyll, carotenoids, fat soluble compounds, and other volatile constituents are not the main components in a tea brew, they again contribute to the characteristic flavor, aroma, and color of tea brew [34]. Tea contain 3 to 4% of methylxanthines such as caffeine which are not destroyed by the different processing methods [16, 39]; however, the caffeine content of white tea is often much higher [40].

The phytochemicals of tea leaves mainly belong to the polyphenol group [41, 42] and fresh tea leaves comprise approximately 25 to 35% polyphenolic compounds [39, 43]. These polyphenols in tea are primarily categorized into six groups of compounds, being flavanols, hydroxyl-4-flavanols, anthocyanins, flavones, flavonols, and phenolic acids [16, 34]. Tea flavonols contains primarily quercetin, kaempferol, myrecetin, and their glycosides [34, 44]. A major tea phenolic acid is gallic acid [34], however, most of the tea polyphenols are flavanols, generally identified as catechins. The major tea catechins in tea are flavan-3-ols [45], (–)-epicatechin (EC), (–)-epicatechin gallate (ECG), (–)- epigallocatechin (EGC), and (–)-epigallocatechin gallate (EGCG) [36, 37, 46]; trace amounts of (+)-catechin and (+)-gallocatechin are also present [47, 48]. Both, catechins and epicatechins are stereoisomers [48] and most of the therapeutic properties of tea are linked with the 'epi' catechins compared to the catechins [48]. Generally, fermentation results in catechins and gallic acid polymeric compounds, such as dimeric catechins (e.g., theaflavins), oligomers (e.g., thearubigins), theaflavinic acids, theasinensis, and proanthocyanidin polymers [36, 37]. Catechins and other phenolic compounds leave a bitter, astringent, and mixed sweet taste in the mouth after drinking tea [16]. Theogallin is a trihydroxybenzoic acid glycoside, a type of another polyphenolic in tea reported to be higher in white tea compared with green [40].

Tea composition is affected by the oxidation process [49], thus, the concentration of catechins is different for each type of tea. Catechins are present in higher quantities in green tea (20–80 mg/g) than in black tea (5–30 mg/g), due to the differences in the processing conditions of tea leaves [50, 51]. Some work indicates [52] that the total catechin content for white teas ranged widely from 14.40 to 369.60 mg/g of dry plant material for water extracts and 47.16 to 163.94 mg/g for methanol extracts. Total catechin content for green teas also ranged more than

Table 1
Chemical composition (%) of green tea, black tea and black tea infusion

Compound	Green Tea*	Black Tea*	Infusion*[a]
Protein (%)	15–27	15–27	trace
Amino Acids (%)	1–4	1–4	3.5
Fiber (%)	26	26	0
Others Carbohydrates (%)	7	7	4
Lipids (%)	7	7	trace
Pigments (%)	2	2	trace
Minerals (%)	5	5	4.5
Phenolic Compounds (%)[b]	30	5	4.5
Oxidized phenolic compounds (%)[c]	0	25	4.5
Total Catechins (mg/g)	150–200	40–60	ND
Caffeine (mg/g)	20–60	20–50	ND
Theanine (mg/g)	8–20	5–10	ND
Theaflavins (mg/g)	0	5–20	ND
Thearubigins (mg/g)	0	60–180	ND

Data obtained from Chacko et al. [29] and Zuo et al. [236]. ND, not determined. [a]Infusion time: 3 minutes. [b]Especially flavonoids. [c]Especially thearubigins and theaflavins. *Data refers to dry weight of tea leaves.

10-fold, from 21.38 to 228.20 mg/g of dry plant material for water extracts and 32.23 to 141.24 mg/g for methanol extracts. These findings show that catechin content between tea vary dependent on the extraction method. Certain white teas have similar quantities of total catechins to some green teas, but less antioxidant capacity, signifying that white teas have fewer non-catechin antioxidants [52].

The health benefits of green tea and white tea are mainly attributed to the epicatechins as described below, which make up 30% of the dry weight of green tea leaves [29]. The quantity of EGCG is approximately 75–80 mg/g [51] and is the most abundant epicatechin found in green tea (65%) representing more than two thirds of the total epicatechin [47] content. Furthermore, 100–200 mg of EGCG can be incorporated into the diet through a cup of green tea [53]. Studies have also reported 5.23–9.49 g/100 g of EGCG in white tea and 4.4–9.6 g/100 g of EGCG in green tea [40]. However, due to the limited availability and less popularity of white tea, less research has been done on its composition. Furthermore other confounding influences on the qualitative value and quantity of epicatechins consumed from tea [29] likely includes the climate and growing conditions of the tea and brewing methods prior to consumption [16, 29].

ROLE OF TEA AS A SOURCE OF ANTIOXIDANTS AND REDUCTION OF OXIDATIVE STRESS

Accumulating evidence indicates that oxidative stress, and overproduction of reactive oxygen species, plays an important role in AD, vascular damage, and progression of various vascular conditions including atherosclerosis, ischemic heart disease, and hypertension, all risk factors of AD. Evidence also indicates oxidative stress plays a pivotal role in the development of diabetes complications, both microvascular and cardiovascular [54]. Antioxidants have a high potential to scavenge free radicals and/or to prevent progression of free radical initiated chain reactions thereby delaying or inhibiting oxidative stress [55–58]. The focus on dietary approaches to enhance antioxidant intake to reduce the risk of diabetes and dementia targeting oxidative stress thus seems plausible.

Tea flavonoids such as catechins, theaovins, and thearubigins have been largely studied to identify its antioxidant functions and are considered important antioxidants. Tea leaves have high levels of antioxidants, and studies suggest that tea could be considered a neuro-protective agent [29, 51, 59, 60]. Studies have reported that tea can decrease the biomarkers of oxidative stress [61], lipid peroxidation, and increase the plasma antioxidant capacity [62–64].

In vitro work using different techniques such as cell culture and enhanced chemiluminescence demonstrated that green, white, and black tea extracts indeed have considerable antioxidant activities due to the presence of catechins, theaovins, and thearubigins [65]. These polyphenols prevent oxidation of low-density lipoprotein (LDL), thus reduce the risk of cardiovascular disease (CVD) [65–67].

The antioxidant functions of green and black tea derived polyphenols have extensively been demonstrated in different models of neurotoxicity; however, scarce data have been reported on the antioxidant activity of white tea extracts. Recent work reported that white tea extracts protect striatal cell lines against oxidative stress-mediated cell death by the production of reactive oxygen and nitrogen species. Therefore, regular consumption of white tea may be clinically useful for treating age-related and neurodegenerative disorders [68].

However, research on the effect of tea antioxidants in humans is limited and inconsistent. The effects of tea on the antioxidant activity of plasma in humans have been assessed under different conditions, such as the effect of tea on the quantity of plasma antioxidants after consumption of tea, either long or short term using a single dose. A small increase of plasma antioxidant levels after consumption of a single daily dose of green tea for four weeks has been reported, a result not seen with black tea [69]. However, rapid ingestion of a high quantity of tea flavonoids did not result in an increase of plasma antioxidants [70]. Serafini et al. [71] demonstrated a significant increase in plasma antioxidant levels after having a single dose of either black or green tea, although green tea was six fold more potent than black tea. Interestingly, this work reported a decrease in the plasma antioxidants with milk, suggesting that the addition of milk may reduce the absorption of flavonoids in the small intestine. However, in contrast, *in vivo* work led by Van het Hof et al. [72] reported that the bioavailability of phytochemicals such as green and black tea was not impaired by addition of milk. In support of this evidence, another study [62] revealed that a single dose of black or green tea could induce plasma antioxidant activity *in vivo* with or without the addition of milk. It has also been reported tea polyphenols could lower

the oxidative stress in liver [73] and brain [74, 75]. A study in animal models showed that catechins and vitamin C regulated the impaired oxidant/antioxidant system and delayed complications related to oxidative stress [29, 76]. Nevertheless, the consumption of green tea catechins did not help to alter the plasma status of vitamin E and vitamin C *in vivo* [77, 78].

ROLE OF TEA ON DYSLIPIDEMIA, ELEVATED LDL CHOLESTEROL, STROKE, AND HYPERTENSION

Hypertension, peripheral artery disease, stroke, atherosclerosis, and cerebrovascular disease are some of the risk factors of AD [79–81] and diabetes. Tea has been shown to decrease LDL levels, oxidative damage, blood pressure, and inflammatory markers which are associated with hypertension, peripheral artery disease, stroke, atherosclerosis, and cerebrovascular disease (Table 2) in a number of cross sectional and longitudinal studies. These studies, however, have not been able to establish the quantity of daily intake of tea required to achieve these positive results.

The study which investigated the association of caffeinated coffee, decaffeinated coffee, and tea in 340 cases of myocardial infarction [82] reported a lower risk of myocardial infarction only with tea [82]. Moderate strength green tea or Oolong tea consumption (120 mL/d or more for 1 year) reported lower risk of developing hypertension in a Chinese population of 1,507 subjects (711 men and 796 women) [83]. Further studies, revealed that the daily consumption of four or more cups of black tea or moderate consumption of coffee and tea were inversely associated with risk of stroke [84, 85].

A meta-analysis suggested that daily consumption of either green or black tea equaling 3 cups per day could lower the risk of stroke by 21% compared to those consuming <1 cup per day [86]. A large study with 82,369 Japanese (aged 45–74 years; without CVD or cancer) who had a mean follow-up of 13 years till the end of 2007 showed that green tea and coffee consumption could reduce the risk of CVD and stroke [87, 88]. The Tokamachi–Nakasato cohort (with 2087 men and 4271 women, aged 40–89 without a history of stroke or heart disease) revealed that green tea consumption was associated with a reduced risk of total stroke incidence, cerebral infarction, and cerebral hemorrhage, after five years of follow-up. The same group indicated that the consumption of roasted green tea leaves was not associated with reduced stroke risk [89]. Green tea and roasted tea are the most commonly consumed teas in Japan. Another study comprised of 203 Japanese patients who underwent coronary angiography (109 patients with significant coronary stenosis taking 3.5 green tea cups and 94 patients without coronary stenosis taking 6 cups of green tea) resulted in lower incidence of coronary artery disease in both groups [90]. The Ohsaki National Health Insurance Cohort Study of 40,530 Japanese participants aged 40–79 years also demonstrated reduced risk of coronary heart disease,

Table 2
Summary of randomized double-blind, placebo-controlled human clinical trials examining tea and cardiovascular function

	Participants	Prevention of AD risk factors
1.	19 healthy men [237]	Consumption of black tea not only increases flow mediated dilation but also decreases both systolic and diastolic blood pressure and peripheral arterial stiffness.
2.	10 healthy male [238]	Black tea intake improves coronary flow velocity which is vital for maintaining a healthy cardiovascular system.
3.	240 subjects with visceral fat-type obesity [131]	Green tea catechins reduce body fat, blood pressure, and LDL cholesterol.
4.	Healthy Japanese men [239]	Green tea catechins can lower body weight, BMI, waist circumference, body fat mass, and subcutaneous fat, and reduce LDL cholesterol oxidation.
5.	143 heavy smokers, aged 18–79 years [240]	Antioxidative activity of tea polyphenols decrease oxidative DNA damage.
6.	111 subjects (systolic blood pressure between 115 and 150 mm Hg) [241]	Daily intake of black tea can lower blood pressure and can affect the rate of blood pressure alteration in night hours.
7.	Healthy men and women [242]	Black tea decreases in plasma uric acid and C-reactive protein content which may beneficial for people with high risk of CVD.
8.	Study subjects were sedentary males, aged 40–69 years, with BMI $\geq$ 28 and $\leq$ 38 kg/m^2 [243]	Daily green tea consumption may be cardio-protective and a protective outcome of green tea catechins on weight gain/obesity.
9.	75 healthy non-smoking men [244]	Black tea intake contributes stress recovery and leads to lower stress which is a risk factor of CVD.

EGCG, (–)-epigallocatechin gallate; AD, Alzheimer's disease; LDL, low-density lipoprotein; CVD, cardiovascular disease; BMI, body mass index.

in those consuming less than a half-cup of green tea per day [91], which was a significantly lower quantities compared to earlier reports. However, the Zutphen Elderly study reported a weak inverse correlation to coronary heart disease mortality with intake of tea, onions, and apples [92]. Overall there was more evidence in support of the benefits of tea in reducing the risk of CVD [93–95] under *in vitro* and *in vivo* conditions, but the known daily intake of tea necessary to achieve these positive results remains to be elucidated.

The cholesterol mediating effect of tea on CVD is an additional mechanism of interest and is linked to lowering risk of CVD. The high quantities of phytochemicals in tea, especially theaflavins, could interfere with the formation of dietary mixed micelles, and lower intestinal cholesterol absorption [96–101]. The main theaflavins that are important for these effects are theaflavin-3-gallate [102–104]. Tea has also been reported to optimize blood vessel function and platelet function, reduce oxidative damage [105–109], and enhance endothelium-dependent vasodilatation [108–111]. Tea has also been recognized for its anti-inflammatory action; for instance, English breakfast tea leaves suppressed tumor necrosis factor-α production, exhibiting IC50 values below 0.5 mg/ml in RAW 264.7 macrophages [112]. Other work indicated that tea reduced the C-reactive protein, an important inflammatory marker [113, 114], increased levels of high density lipoprotein and lowered the levels of triglycerides [114].

ROLE OF TEA IN OBESITY

Obesity is a chronic inflammatory disorder that leads to insulin resistance and diabetes which is a risk factor of AD [115]. Numerous *in vitro*, animal, and human studies have supported the notion that tea has anti-obesity and anti-hypolipidemic effects [116, 117].

A study with mice reported a lower body weight gain and lower deposition of white adipose tissues with a high-fat diet containing 29% lard and green or black tea *ad libitum* for 14 weeks [118]. Rats also showed a reduction of body fat and increase in lean mass after consumption of a 15% fat diet for 6 months combined with green tea, black tea, or EGCG [119]. A study which investigated the effect of a four-week treatment of male KK-AY/TaJcl mice with African black tea extract demonstrated a significant reduction in body weight ($p < 0.05$) [120].

The development of obesity is dependent on the adipocyte hypertrophy (increased fat cell size), adipocyte hyperplasia (increased fat cell number), and angiogenesis. In periods of food overabundance, evidence suggests that additional fat mass stores in the body and leads to obesity [121]. In 2011, a meta-analysis of 11 clinical studies suggested that a mixture of tea catechin-caffeine rich in black tea could have an effect on fat oxidation and also on energy expenditure by 4.7% over 24 h [122]. *In vitro* studies with cultured human preadipocytes using white tea extract solution that contained polyphenols and methylxanthines significantly impeded adipogenesis and stimulated the activity of lipolysis [123]. Green tea extract, comprising high levels of caffeine and catechin polyphenols, also significantly enhanced energy expenditure and fat oxidation in healthy men due to activation of thermogenesis, fat oxidation, or both [124]. Another study demonstrated the reduction of body weight and waist circumference by 4.60% and 4.48%, respectively, after consumption of green tea in moderately obese patients [125]. This effect was also observed with EGCG in mice and in humans [126, 127]. A randomized double-blind placebo-controlled cross-over pilot study with six overweight men demonstrated high thermogenesis and fat oxidation after consuming 300 mg EGCG per day for two days [128]. In addition, drinking green tea extract combined with regular exercise may increase fat metabolism, while decreasing obesity caused by a fat-rich diet, more efficiently than exercise or green tea extract alone [129]. Another study [130] reported a 17% increase in high mean fat oxidation rate in healthy men after intake of green tea extract (comprised of 890 ± 13 mg polyphenols and 366 ± 5 mg EGCG) with moderate exercise, compared to a placebo ($p < 0.05$). A 12-week, double-blind placebo-controlled study using green tea catechins in Japan was shown to decrease excess body fat, hypertension, and LDL cholesterol levels compared to the control group [131], suggesting that green tea catechins may be important in preventing obesity related metabolic syndromes such as CVD [131]. Research had also indicated that the anti-obesity effect of tea catechin may be due to stimulation of hepatic lipid metabolism [132] by polyphenols.

Apart from animal human work, *in vitro* research using black tea polyphenol extracts also reported inhibition of intestinal lipid absorption [133]. Theaflavins under *in vitro* conditions using HepG2 also reduced total lipid, triglyceride, cholesterol levels in fatty acid-overloaded liver cell lines and activated

AMP-activated protein kinase signaling pathway, which is important to regulate glucose and lipid metabolisms [134] in the human body.

Studies have identified that purple tea also regulated weight gain by inhibiting fat absorption and enhancing hepatic fat metabolism [28]. Several randomized controlled trials in humans demonstrated that Oolong tea may increase energy metabolism, metabolic rate, and fat oxidation [135–137], as shown for black and green tea.

Studies further acknowledged that fully fermented black tea leaves and partially fermented oolong tea leaves were more effective on growth suppressive and hypolipidemic properties compared to the non-fermented green tea leaves [138], indicating the importance of fermentation.

These findings suggest that EGCG and or tea has the potential to increase fat oxidation and therefore mediates the anti-obesity effects of green tea. However, the optimal dose of EGCG for weight reduction has yet to be established [128, 139], though, some findings have suggested that 665 mg of catechins per day may be important in counteracting obesity [139].

The anti-obesity effects of white, green, and black are being increasingly investigated in cell culture, animal models, and humans as discussed in this review. Taken together, data indicate that the consumption of tea and tea extracts may help reduce body weight, mainly body fat, by increasing postprandial thermogenesis. Therefore, tea has the potential to reduce the prevalence of diabetes as well as AD.

ROLE OF PHYTOCHEMICALS IN TEA IN ALZHEIMER'S DISEASE

In recent decades, experimental and epidemiologic studies have reported that tea consumption may influence the onset and progression of AD. Phytochemicals in tea including flavanols, hydroxyl-4-flavanols, anthocyanins, flavones, and phenolic acids can pass the blood-brain barrier (BBB) and exert neuroprotective effects. While there are some inconsistencies in the findings, most of the literature were supportive of a neuroprotective role [22, 140, 141].

Several studies have revealed that EGCG and other flavonoids, such as luteolin in tea could reduce toxic levels of brain Aβ, and mitochondrial dysfunction in AD brains [60, 142]. Aβ-induced mitochondrial dysfunction has been shown to be occurring during the onset and progression of AD and T2D and the field of mitochondrial-targeted therapeutics is gaining prominence in both AD and diabetes.

EGCG also prevented Aβ peptides-induced neurotoxicity [143, 144], elongation of the fibrils [145], and stabilization of the formed fibrils [145] in cell cultures. Theaflavins (TF1, TF2a, TF2b, and TF3), the main polyphenolic components found in fermented black tea, demonstrated potential as an inhibitor of Aβ and α-synuclein fibrillogenesis [146]. Long-term administration of green tea catechins lessened Aβ -induced cognitive impairment in animal models by increasing antioxidative defenses [147]. In addition, catechin gallates found in both green and black teas (5–25 micro g/mL) were shown to be neuroprotective against Aβ toxicity [18]. These effects were mainly observed with gallic acid (1–20 μM), ECG (1–20 μM), and EGCG (1–10 μM), while effects of EC and EGC against Aβ toxicity was not evident [18]. Inhibition of Aβ aggregation by EGCG and gallic acid [18] was also observed using black and green tea. AβPP undergo proteolytic processing either by amyloidogenic pathway or non-amyloidogenic pathway, while most is managed through the non-amyloidogenic pathway, which impedes Aβ formation. The first enzymatic cleavage is arbitrated by alpha-secretase, appearing within the Aβ domain. This prevents the formation and release of the Aβ peptide. In cell culture and transgenic mice, EGCG influenced the generation of the non-amyloidogenic soluble form of AβPP [143, 144, 148]. This enhances the α-secretase activity while reducing cerebral amyloidosis. Administration of EGCG (2 mg/kg) in mice for 7 or 14 days significantly promoted the non-amyloidogenic pathway of AβPP via a protein kinase C-dependent activation of α-secretase resulting in decreased quantities of holoprotein AβPP levels [144]. This effect was further observed in an AD transgenic mouse model ("Swedish" mutant APP overexpressing, APPswTg) [149] using intraperitoneal (i.p.) injection (20 mg/kg) [150] and oral administration in the drinking water (50 mg/kg) [149]. EGCG was also reported to prevent lipopolysaccharide-mediated apoptotic cell death through the inhibition of β- and γ-secretases [151], which enhanced cell survival.

L-Theanine (γ-glutamylethylamide), a unique amino acid present predominantly in tea, has recently received attention due to its neuroprotective properties. The chemical structure of L-theanine resembles that of glutamate, a chemical essential to protein biosynthesis and a excitatory neurotransmitter. The levels of glutamate are critical, as too much glutamate

Table 3
Summary of randomized double-blind, placebo-controlled human clinical trials examining the influence of tea on cognition, mood, and glucose control

	Participants	Prevention of AD risk factors or neuroprotective effects
1.	Healthy volunteers [156]	L-theanine provides relaxation effect under resting condition.
2.	Human subjects with mild cognitive impairment [24]	A combination of green tea extract and L-theanine has potential as a management strategy for cognitive improvement.
3.	Overweight adults [245]	Combination of 120 mg of N-oleyl-phosphatidyl-ethanolamine and 105 mg of EGCG supplementation improves mood.
4.	Diabetes [168]	Green tea-extract powder lowered the hemoglobin A1c (glycated hemoglobin) level in individuals with borderline diabetes.
5.	cognitively intact adults aged 65–85 years [246]	Nutraceuticals that contained an exclusive formulation of blueberry, carnosine, green tea, vitamin D_3, and biovin can improve the cognitive health of older adults.
6.	12 nursing home elders with cognitive dysfunction [24]	Green tea (2 g/day) intake significantly improved the subjects' Mini-Mental State Examination scores. Regular intake of green tea may be beneficial in decreasing the progression of cognitive dysfunction or enhancing cognitive function.

EGCG, (–)-epigallocatechin gallate; AD, Alzheimer's disease.

results in neuronal toxicity. MNDA receptor antagonists are an approved pharmacological approach to mediating glutamate receptor activity, as chronic mild glutamate excitotoxicity is associated with calcium influx, neuronal cell death [152], and cognitive dysfunction. Theanine is a natural glutamate antagonist which may protect and prevent neuronal death [153] as seen when cells were exposure to theanine [154]. The death of hippocampal CA1 (cornus ammonis) pyramidal neurons by transient forebrain ischemia and the death of the hippocampal CA3 region by kainate was prevented by the administration of theanine [155]. Theaflavin also attenuated 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine/probenecid (MPTP/p1) induced apoptosis and neurodegeneration by increasing nigral tyrosine hydroxylase and dopamine transporter and reducing apoptotic markers [97] such as caspase-3, 8, and 9.

A number of human clinical studies also demonstrated that L-theanine in tea may increase memory, attention, control responsiveness, and capacity to solve complex problems (Table 3). These findings suggested that L-theanine may have some relaxing effects [156] under resting conditions [157] and anti-stress effects [158] via the inhibition of cortical neuron excitation. However, L-theanine was not effective under conditions of increased anxiety [157]. In response to earlier positive reports of the effects of L-theanine on attention-related task performance [159], further literature emerged. Caffeine and L-theanine in tea demonstrated improvements in cognition, enhanced speed and accuracy of attention related performances, increased mental clarity and alertness, and improved mood as well as work performance [160, 161]. When comparing the effect of 50 mg caffeine, with and without 100 mg L-theanine, on word recognition, rapid visual information processing, critical flicker fusion threshold, attention switching, and mood, the combinations of coffee and L-theanin were more effective [160] than caffeine alone. Effects of tea, coffee, and other beverage consumption on fatigue/exhaustion, mindfulness, and work engagement indicated that tea could enhance work performance and reduce tiredness [161], but observed negative effects on evening recovery and morning moods. Two double-blind, randomized, placebo-controlled human clinical trials which studied the effect of black tea on attention using tasks measuring ability to switch and the intersensory-attention test reported that black tea significantly enhance accuracy on switching (study 1, $p < 0.002$; study 2, $p = 0.007$) and self-reported alertness [96]. In support of this, a small randomized, double-blind, placebo-controlled study also reported beneficial effects on cognition in mild cognitive impairment [162]. Although these mechanisms are still unclear, polyphenols within tea may have a therapeutic potential for AD [145].

ROLE OF TEA IN INSULIN RESISTANCE AND PREVENTION OF DIABETES

Diabetes mellitus is a life threatening metabolic syndrome that leads to major complications, such as retinopathy, nephropathy, and neuropathy [163]. The presence of diabetes confers a 60% greater risk of dementia such as AD and even more for vascular-related dementia [164–166]. Furthermore, women are reported to have an even higher risk than men. Given the continued under-diagnosing of dementia and mild cognitive impairment, and the established long latent

phase before symptoms of AD become apparent, the estimation of diabetes and AD comobidity is highly conservative.

Epidemiological and human clinical studies have shown the association between tea consumption and a reduced risk for T2D [167–169]. In 2002, Anderson and Polansky [169] identified the insulin-potentiating activity of tea and its effects on insulin sensitivity and noted the beneficial effects of tea on the reduction of symptoms in diabetes mellitus, such as a 15-fold increase of insulin activity. However, the addition of 5 g of 2% milk per cup and 50 g of milk per cup reduced the insulin-potentiating activity by one-third and ∼90%, respectively [169]. This reduction was also observed with non-dairy creamers and soy milk [169]. A randomized crossover clinical study of 60 humans, aged 32–73 years with a 2-month supplementation of 544 mg polyphenol (456 mg catechin) per day, showed reverse action on the glucose irregularity in those with borderline diabetes. The study also noted a significant effect on the glycated hemoglobin (HbA1c) level ($p = 0.03$) [168] when an additional polyphenol was introduced at baseline. A study using Sprague-Dawley rats and a 12-week intervention of green tea infusion also demonstrated increased insulin sensitivity by increasing the glucose uptake and insulin binding of adipocytes [170]. The same group did further research to identify the active component under *in vitro* conditions and confirmed that green tea polyphenols were the most important components to increase glucose uptake by adipocytes. Another group used the same mouse model to evaluate the effects of green tea supplementation on insulin resistance, hypertension, and the glucose transporters I and IV contents in adipose tissue using a high fructose diet with water or green tea (0.5 g of lyophilized green tea powder dissolved in 100 mL of deionized distilled water) for 12 weeks. This study concluded that the group without the green tea developed fasting hyperglycemia, hyperinsulinemia, and elevated blood pressure along with low quantity of insulin binding adipocytes and low glucose transporter IV (GLUT IV) content of adipocytes compared to the test group. This work also revealed that underlying mechanism to enhance insulin resistance by green tea is due to its association with the increased expression of GLUT IV [171]. A meta-analysis of 22 randomized controlled trials with 1,584 subjects indicated that green tea catechins with or without caffeine could result in a significant reduction in fasting blood glucose level and the effect of green tea catechins was not dependent on the caffeine percentage [172].

It is also noted that the protein level of the insulin signaling pathway and insulin sensitivity of insulin resistant rats can be enhanced through a daily consumption of 200 mg green tea polyphenols per kg of body weight [173]. Sabu et al. administrated a daily dose of green tea polyphenol (100 mg/kg body weight) in an alloxan-induced diabetic model of rats, and reported increased glucose tolerance and decreased serum glucose level [174]. Further to this, again in an alloxan-induced diabetic model, the administration of the aqueous extracts of green and black tea (50 or 100 mg/kg body weight daily for 28 days) significantly attenuated liver function enzymes produced, [175] demonstrating a protective quality. Investigations with the hot water extract of black tea on streptozotocin (STZ)-induced diabetes in rats exhibited significantly reduced blood glucose level suggesting both preventive and curative effects of black tea [176]. After 4 weeks feeding of 0.5% aqueous extracts of white tea to STZ-induced diabetic rats, significantly reduced blood glucose concentrations and significantly increased glucose tolerance ability was seen. This study further reported increased liver weight and liver glycogen along with lower levels of cholesterol and LDL-cholesterol [177], suggesting that white tea could increase the glucose tolerance not only by increasing the insulin sensitivity but also by increasing the hepatic glycogen synthesis [177]. However, the anti-diabetic effect of white tea has not been fully elucidated either in humans or cell culture models. It is also suggested that white tea may exhibit anti-diabetic effect by reducing oxidative stress and hyperlipidemia followed by reducing insulin resistance [177]. Daily consumption of green tea [178] EGCG (25 mg/kg body weight) also significantly reduced the serum glucose, total cholesterol, triglyceride, and LDL-cholesterol in a STZ-induced diabetic rats. Administering green and black tea over a 3-month period in a STZ-induced diabetic rat model showed that hyperglycemic effects were reduced, while inhibitory processes that interfered with the pathological biochemical pathway associated with diabetic cataracts were enhanced [179]. In contrast, studies also identified that green tea could not reverse the serum protein levels relevant to diabetes [180].

TEA DOSAGES AND ADMINISTRATION

Establishing the efficacious dose of tea remains to be elucidated; however, a lower intake appears

more beneficial for the prevention of diabetes and higher doses could pose detrimental effects [181]. This study indicated that a 0.5% or 2.0% dose of green tea were not effective in reducing diabetes-associated parameters such as blood glucose levels or enhancing glucose tolerance in a high-fat diet-fed STZ-induced diabetes model of rats [181]. Administration of barley β-glucan, tea polyphenols, and their combination has demonstrated beneficial effects to improve glucose tolerance, lipid metabolism, and serum antioxidant status in STZ-induced diabetic rats [182]. Though the studies indicated that black tea, green tea, and white tea can be used as an adjunct remedy by diabetic patients to alleviate diabetes associated abnormalities, a prospective large scale dose response clinical trial for tea is required to determine the most effective dose.

Few studies have identified the underlying mechanism of polyphenols on the effect of diabetes [183, 184]. The rapid absorption of glucose changes the mechanisms of glucose homeostasis, and consumption of high-glycemic diets may therefore increase the risk for obesity, T2D, CVD, and AD. The presence of soluble-phenolic-linked antioxidants and α-glucosidase inhibitors (the mechanistic target of prescribed anti-diabetic medication), within the tea polyphenols retard carbohydrate digestion and absorption and thereby prevent hyperglycemia in the postprandial state [184]. Furthermore the water extract from black tea, as opposed to white or Oolong tea, had significantly higher α-glucosidase inhibitory activity [184]. The antidiabetic effect of theaflavins and catechins has been compared [185–188] and theaflavins have demonstrated potent anti-hyperglycemic effect compared with catechins [189], thus indicating the importance of individual contributions of these structurally different compounds in the underlying mechanism. Research has identified that theaflavins have the potential to delay or inhibit glucose production by inhibition of AGH (maltase) activity more than catechins [189]. Catechins also have been proven to produce the effect through the promotion of hepatic glycogen synthesis [190] and inhibition of intestinal glucose transport [188], but has not identified whether this effect is more than the theaflavins. However, further investigation is recommended to understand anti-hyperglycemic mechanisms and the strong AGH (maltase) inhibitory action of theaflavins. Since most evidence is limited to *in vitro* and animal studies, the clinical significance of these compounds needs to be determined from human trials.

Insulin resistance pathways of EGCG is involved in the modulation of insulin-like growth factor (IGF) which stimulate glucose uptake in 3T3-L1 adipocytes. This suggested that EGCG may suppress IGF stimulation of 3T3-L1 adipocyte glucose uptake through inhibition of the GLUT4 translocation and suppress IGF-stimulated phosphorylation of IGF signaling molecules but without modifying the GLUT1 pathway [191]. In addition to the earlier discussed α-glucosidase inhibitor pathway, EGCG has the capacity to prevent or limit intestinal glucose absorption by the use of the sodium-dependent glucose transporter (SGLT1), and thus control blood sugar levels [188]. Further evidence suggested that EGCG may possibly inhibit cytokine mediated β-cell damage [192, 193] and protect the infiltrated immune cell-mediated β-cell destruction, and thereby increase β-cell mass and insulin secretion [194]. Recently, three black tea theaflavins (theaflavin 3′-O-gallate, theaflavin 3, and 3′di-O-gallate and thearubigins) were identified as novel mimics of insulin/IGF-1 action on the forkhead transcription factor family O and phosphoenolpyruvate carboxykinase [195]. Increased concentrations of plasminogen activator inhibitor-1 in the blood is a precedent of obesity as well as T2D. Studies also indicated that theaflavin-3'-gallate was more potent for the inhibition of plasminogen activator inhibitor-1 followed by theaflavin-3, 3′di-O-gallate, when compared to theaflavin and theaflavin-3-gallate [196].

BIOAVAILABILITY AND PHARMACOKINETICS IN TEA POLYPHENOLS

As discussed in this review, studies in cell lines, animal models, and human trials have clearly demonstrated that dietary polyphenols including tea polyphenols have the potential to significantly attenuate AD and T2D risk by inhibition of Aβ formation [48, 143], promotion of Aβ clearance [143, 144], inhibition of tau phosphorylation [149, 197] and tau aggregation [149], reduction of cholesterol [100], and promotion of anti-obesity [116] pathways. However, a critical aspect to achieving efficacy is understanding the metabolic pathway that directly impacts on bioavailability. While considerable research *in vitro* and in animals are promising, translating targeted delivery of bioactive tea polyphenols in humans have had limited success. The bioavailability of polyphenols is dependent on its chemical structure, molecular

weight, and the complex metabolic interplay exerted in human kinetics. In order for a single polyphenol compound to exert its effect, the inert form requires transformation to the bioactive metabolites, through synergistic processes not fully understood, involving other polyphenols.

Furthermore, the chemical structure of polyphenols including tea polyphenols varies widely from one compound to another [198], which determines the rate and extent of intestinal absorption, penetration via the BBB, the nature of the metabolites, and biological activities in the human tissues. Higher absorption of polyphenols is important to have high bioavailability. Absorption rate of the polyphenols that are present as aglycones are higher than the polyphenols in the form of esters, glycosides, or polymers [198]. Unfortunately, most polyphenols fall into the latter category. These polyphenols present as conjugates, and metabolism of these conjugates to aglycones is facilitated by acid hydrolysis and microflora in the gut, yielding the bioactive metabolites. However, probability of these aglycone polyphenolics reaching the target cells or their spectra of biological activities remains largely unclear.

Bioavailability of tea polyphenols have been measured in several studies either by measuring antioxidant capacity via plasma or by measuring metabolite concentrations in plasma and urine after consumption of polyphenols. Previous investigations have identified an increase of antioxidant activity after consumption of different quantities of tea as 40% with 300 ml green or black tea [71], 13% with 900 ml green tea/300 ml black tea [72], 16–19% with single dose of 400 mg EGCG [199], 4% with 20 g of dry green tea [200], 40% with 300 ml green tea [201], and 52% with 300 ml black tea [201]. Further work also identified bioavailability of cathechins in biological fluids such as plasma [202–208], serum [203, 209], saliva [210], urine [202, 211–215], and feces [216], and in tissues such as prostate cells [217, 218], brain [219], and cancer cells [220] of humans and animals. Collectively, research indicates that consumption of tea increases the antioxidant activity by 3.5–70% and quantity of EGCG, EC, and ECG in plasma between 5–150 ng/ml. Despite the increasing amount of data available, the quantity of bioavailable tea polyphenols delivered in target tissues remains unclear. Moreover, data obtained in these investigations are highly variable and non-conclusive.

Although analysis of plasma provides valuable information of the metabolites of tea polyphenols in the circulatory system, precise quantities of metabolites that are absorbed from the gastrointestinal tract is not provided. Urinary excretion provides more details of the quantities of unabsorbed and unavailable, but does not precisely measure the metabolites being absorbed or delivered. There is also a suggestion in the literature that green tea flavan-3-ols are less bioavailable due to its instability under digestive conditions. Furthermore, it is reported that up to 80% of green tea flavan-3-ols are removed with *in vitro* digestion models under gastric and small intestine conditions [221, 222]. Therefore, it is important to identify more accurate methods to evaluate their bioavailability in humans and additional human clinical trials are required to understand therapeutic efficacy of polyphenols.

The ability of polyphenols and their metabolites to cross the BBB and be confined in brain tissues for a substantial time to exert targeted benefits is essential. However, only few studies have established that polyphenols such as quercetin-3-O-glucoside [223], 3′-O-methyl-epicatechin-5-O-β-glucuronide, catechin, and epicatechinin can cross the BBB to exert their protective effects, such as promotion of cAMP response element-binding protein signal transduction and mammalian target of rapamycin signaling [224, 225]. In addition, limited information exists on the distribution of polyphenols in different brain region such as cerebellum which is important for learning, memory, and coordination of motor functions. Ferruzzi et al. [226] reported ∼290 and ∼576 pg/g of catechin, methyl-catechin (MeO-C) and EC, MeO-EC in whole rat brain, and Ishisaka et al. identified ∼40 pmol/g of Quer aglycon and ∼48 pmol/g of MeO-Quer [227] in rat brain tissues. Understanding the regional bioavailability of polyphenols in the brain is important to detect dose dependence in brain accumulation between brain regions and specific metabolites [228].

Since the preparation of tea is not standardized, the optimum dose of tea polyphenols for AD and T2D prevention approaches is still unknown. Therefore, plasma and brain bioavailability, metabolism in human gut, retention time in brain, efficacy in target places, dosage, tolerability, and interactions with other drugs have to be investigated via human clinical trial before tea polyphenols can be recommended in the treatment of AD and T2D. In addition, more longitudinal human studies with large number of participants who are well phenotyped will help researchers further understand the complex human interplay between tea and other polyphenols, genetic profiles, and digestive processes.

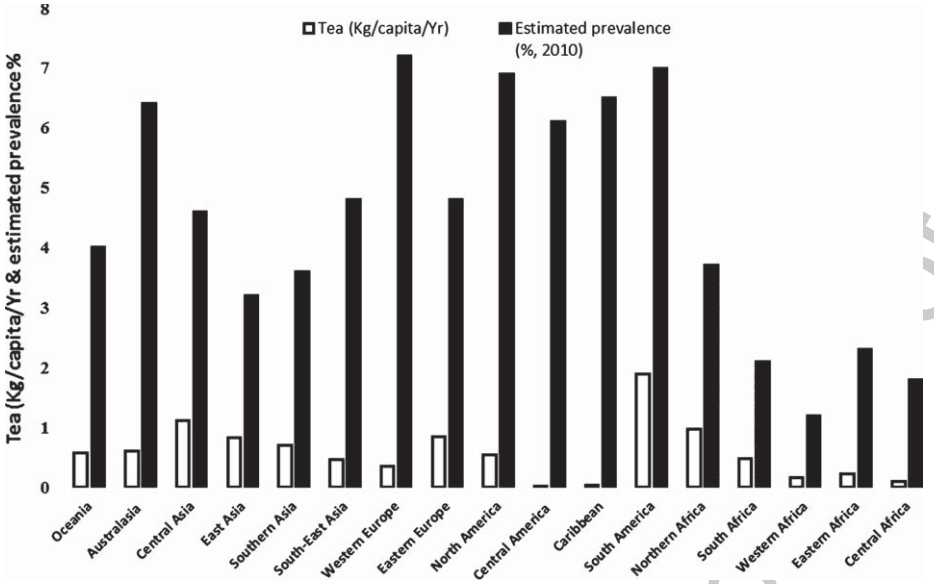

Fig. 2. The relationship between tea consumption and crude AD prevalence in different geographical regions in the world [1].

TEA CONSUMPTION AND AD PREVALENCE IN THE WORLD

Evaluation of the relationship between tea consumption and AD prevalence has yet to be undertaken. Data suggests incongruent distribution of dementia worldwide, which may reflect cultural, socioeconomic, and lifestyle differences among nations; however, interestingly, higher prevalence of AD is reported in the more developed countries [229–231]. More affluent lifestyles may increase the level of risk due to increased levels of lifestyle-associated comorbidities, including hypertension, smoking, obesity, and diabetes; however, greater rates of detection of AD may also contribute to the elevated distribution. Beresniak et al. [232], using data from 50 participating countries in the World Health Survey, investigated the potential statistical relationship between black tea consumption and the onset of diabetes. The study reported a linear statistical correlation between high black tea consumption and low diabetes occurrence in participating countries [232].

China and its developing western-Pacific neighbors for instance have the highest number of people with dementia (6 million), followed by Western Europe with 4.9 million, and North America with 3.4 million [229–231]. According to the available data, world tea consumption continues to increase continuously with the total tea consumption in 2013 at 4.84 million tonnes [233]. In particular, tea consumption in developed countries versus developing countries were 814.8 and 4027.3 tons, respectively, in 2013 [233]. In India, consumption expanded by 2.4 percent in 2009 and 6.6 percent in 2013 [233]. These figures are of limited value in the absence of per capita consumption of tea which cannot be determined due to limited data. The tea consumption and estimated AD prevalence (%) in major regions in the world are shown in Fig. 2 [1, 234]. However, any association between tea consumption and the prevalence of AD should be cautiously evaluated.

CONCLUSION

The daily consumption of green, black, and white tea varieties has been occurring for centuries across Japan, Indian, China, and almost all Asian countries, and the safety profile of tea has not been disputed. Tea consumption in underdeveloped nations is higher than in less developed countries, and while epidemiological data suggests a lower prevalence of dementia in less developed countries, this should be cautiously interpreted. Tea appears to offer a multimodel mechanism for the reduction of risk factors associated with CVD, high LDL cholesterol, and obesity, and thus by extension may have a role in diabetes mellitus and AD. Considerable evidence, largely from *in vitro* studies, supports the phytochemical capacity of tea to target AD and diabetic pathology. Therefore, consumption of compounds with polyphenols might lead to delay the onset of AD [235]. In addition, tea

consumption is associated with improved cognition. Collectively, findings from a number of studies indicate that catechins within tea may also be beneficial for both type 1 diabetes and T2D [169, 172, 191] and therefore by extension also potentially "type 3" diabetes (in AD). However, further *in vitro* analysis to elucidate the exact mechanisms of tea coupled with specific investigation of the neuron-protective effects of tea phytochemicals is warranted. In addition, randomized clinical trials which are placebo controlled using standardized dose and compounds are required before tea can be considered as a therapeutic agent useful for preventing diabetes or AD. The quantity and the dose of tea phytochemicals, particularly EGCG, required to modify cell signaling pathways and attenuate the progression of AD is yet to be established.

Overall, tea appears to offer a safe and acceptable therapeutic and/or complementary approach toward lowering the risk factors associated with diabetes and AD. However, to date, the manner, type, and amount required in order to achieve the potential benefits remains to be determined by prospective clinical trials.

ACKNOWLEDGMENTS

The present review did not receive any financial support. All authors contributed to the literature search, analysis of the data published, manuscript writing and revisions of the article.

Authors' disclosures available online (http://j-alz.com/manuscript-disclosures/16-1200r1).

REFERENCES

[1] World Alzheimer Report (2015) The Global Impact of Dementia: An analysis of prevalence, incidence, cost and trends updates. https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf

[2] Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT (2011) Neuropathological alterations in Alzheimer disease. *Cold Spring Harb Perspect Med* **1**, a006189.

[3] Vinters HV (1987) Cerebral amyloid angiopathy. A critical review. *Stroke* **18**, 311-324.

[4] Villemagne VL, Burnham S, Bourgeat P, Brown B, Ellis KA, Salvado O, Szoeke C, Macaulay SL, Martins R, Maruff P, Ames D, Rowe CC, Masters CL (2013) Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: A prospective cohort study. *Lancet Neurol* **12**, 357-367.

[5] Krishnaswamy S, Verdile G, Groth D, Kanyenda L, Martins RN (2009) The structure and function of Alzheimer's gamma secretase enzyme complex. *Crit Rev Clin Lab Sci* **46**, 282-301.

[6] Westermark P, Andersson A, Westermark GT (2011) Islet amyloid polypeptide, islet amyloid, and diabetes mellitus. *Physiol Rev* **91**, 795-826.

[7] Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM (1999) Diabetes mellitus and the risk of dementia: The Rotterdam Study. *Neurology* **53**, 1937-1942.

[8] Frisardi V, Solfrizzi V, Capurso C, Imbimbo BP, Vendemiale G, Seripa D, Pilotto A, Panza F (2010) Is insulin resistant brain state a central feature of the metabolic-cognitive syndrome? *J Alzheimers Dis* **21**, 57-63.

[9] Lester-Coll N, Rivera EJ, Soscia SJ, Doiron K, Wands JR, de la Monte SM (2006) Intracerebral streptozotocin model of type 3 diabetes: Relevance to sporadic Alzheimer's disease. *J Alzheimers Dis* **9**, 13-33.

[10] Kim B, Feldman EL (2015) Insulin resistance as a key link for the increased risk of cognitive impairment in the metabolic syndrome. *Exp Mol Med* **47**, e149.

[11] Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K (2001) Physical activity and risk of cognitive impairment and dementia in elderly persons. *Arch Neurol* **58**, 498-504.

[12] Gonzalez-Gross M, Marcos A, Pietrzik K (2001) Nutrition and cognitive impairment in the elderly. *Br J Nutr* **86**, 313-321.

[13] Gardener S, Gu Y, Rainey-Smith SR, Keogh JB, Clifton PM, Mathieson SL, Taddei K, Mondal A, Ward VK, Scarmeas N, Barnes M, Ellis KA, Head R, Masters CL, Ames D, Macaulay SL, Rowe CC, Szoeke C, Martins RN (2012) Adherence to a Mediterranean diet and Alzheimer/'s disease risk in an Australian population. *Transl Psychiatry* **2**, e164.

[14] Brown BM, Peiffer JJ, Sohrabi HR, Mondal A, Gupta VB, Rainey-Smith SR, Taddei K, Burnham S, Ellis KA, Szoeke C, Masters CL, Ames D, Rowe CC, Martins RN (2012) Intense physical activity is associated with cognitive performance in the elderly. *Transl Psychiatry* **2**, e191.

[15] Mukhtar H, Ahmad N (2000) Tea polyphenols: Prevention of cancer and optimizing health. *Am J Clin Nutr* **71**, 1698s-1702s.

[16] Chaturvedula VSP, Prakash I (2011) The aroma, taste, color and bioactive constituents of tea. *J Med Plants* **5**, 2110-2124.

[17] Jeon S-Y, Bae K, Seong Y-H, Song K-S (2003) Green tea catechins as a BACE1 (β-Secretase) inhibitor. *Bioorg Med Chem Lett* **13**, 3905-3908.

[18] Bastianetto S, Yao ZX, Papadopoulos V, Quirion R (2006) Neuroprotective effects of green and black teas and their catechin gallate esters against beta-amyloid-induced toxicity. *Eur J Neurosci* **23**, 55-64.

[19] Gargi S, Biswajit B (2013) Black tea as a part of daily diet: A boon for healthy living. *IJTS* **9**, 51-59.

[20] Ferreira MA, Silva DM, de Morais AC Jr, Mota JF, Botelho PB (2016) Therapeutic potential of green tea on risk factors for type 2 diabetes in obese adults - a review. *Obes Rev* **17**, 1316-1328.

[21] Nunes AR, Alves MG, Moreira PI, Oliveira PF, Silva BM (2014) Can tea consumption be a safe and effective therapy against diabetes mellitus-induced neurodegeneration? *Curr Neuropharmacol* **12**, 475-489.

[22] Schmidt A, Hammann F, Wölnerhanssen B, Meyer-Gerspach AC, Drewe J, Beglinger C, Borgwardt S (2014) Green tea extract enhances parieto-frontal connectivity during working memory processing. *Psychopharmacology* **231**, 3879-3888.

[23] Ide K, Yamada H (2015) Clinical benefits of green tea consumption for cognitive dysfunction. *Pharma Nutrition* **3**, 136-145.

[24] Ide K, Yamada H, Takuma N, Park M, Wakamiya N, Nakase J, Ukawa Y, Sagesaka YM (2014) Green tea consumption affects cognitive dysfunction in the elderly: A pilot study. *Nutrients* **6**, 4032-4042.

[25] Katiyar S, Mukhtar H (1996) Tea in chemoprevention of cancer. *Int J Oncol* **8**, 221-238.

[26] Tomata Y, Kakizaki M, Nakaya N, Tsuboya T, Sone T, Kuriyama S, Hozawa A, Tsuji I (2012) Green tea consumption and the risk of incident functional disability in elderly Japanese: The Ohsaki Cohort 2006 Study. *Am J Clin Nutr* **95**, 732-739.

[27] Gondoin A, Grussu D, Stewart D, McDougall GJ (2010) White and green tea polyphenols inhibit pancreatic lipase in vitro. *Food Res Int* **43**, 1537-1544.

[28] Shimoda H, Hitoe S, Nakamura S, Matsuda H (2015) Purple tea and its extract suppress diet-induced fat accumulation in mice and human subjects by inhibiting fat absorption and enhancing hepatic carnitine palmitoyltransferase expression. *Int J Biomed Sci* **11**, 67-75.

[29] Chacko SM, Thambi PT, Kuttan R, Nishigaki I (2010) Beneficial effects of green tea: A literature review. *Chin Med* **5**, 13-13.

[30] Langley-Evans SC (2000) Consumption of black tea elicits an increase in plasma antioxidant potential in humans. *Int J Food Sci Nutr* **51**, 309-315.

[31] Park J-H, Bae J-H, Im S-S, Song D-K (2014) Green tea and type 2 diabetes. *Integr Med Res* **3**, 4-10.

[32] Ng T-P, Feng L, Niti M, Kua E-H, Yap K-B (2008) Tea consumption and cognitive impairment and decline in older Chinese adults. *Am J Clin Nutr* **88**, 224-231.

[33] Sharma V, Rao LJM (2009) A thought on the biological activities of black tea. *Crit Rev Food Sci Nutr* **49**, 379-404.

[34] Harbowy ME, Balentine DA, Davies AP, Cai Y (1997) Tea chemistry. *CRC Crit Rev Plant Sci* **16**, 415-480.

[35] Alcázar A, Ballesteros O, Jurado JM, Pablos F, Martín MJ, Vilches JL, Navalón A (2007) Differentiation of green, white, black, oolong, and pu-erh teas according to their free amino acids content. *J Agric Food Chem* **55**, 5960-5965.

[36] Balentine DA, Wiseman SA, Bouwens LCM (1997) The chemistry of tea flavonoids. *Crit Rev Food Sci Nutr* **37**, 693-704.

[37] Graham HN (1992) Green tea composition, consumption, and polyphenol chemistry. *Prev Med* **21**, 334-350.

[38] Kim HM, Kim J (2013) The effects of green tea on obesity and type 2 diabetes. *Diabetes Metab* **37**, 173-175.

[39] Tounekti T, Joubert E, Hernández I, Munné-Bosch S (2013) Improving the polyphenol content of tea. *CRC Crit Rev Plant Sci* **32**, 192-215.

[40] Hilal Y, Engelhardt U (2007) Characterisation of white tea – Comparison to green and black tea. *J Verbrauch Lebensm* **2**, 414-421.

[41] Du G-J, Zhang Z, Wen X-D, Yu C, Calway T, Yuan C-S, Wang C-Z (2012) Epigallocatechin gallate (EGCG) is the most effective cancer chemopreventive polyphenol in green tea. *Nutrients* **4**, 1679-1691.

[42] Riemersma RA, Rice-Evans CA, Tyrrell RM, Clifford MN, Lean MEJ (2001) Tea flavonoids and cardiovascular health. *QJM* **94**, 277-282.

[43] Butt MS, Imran A, Sharif MK, Ahmad RS, Xiao H, Imran M, Rsool HA (2014) Black tea polyphenols: A mechanistic treatise. *Crit Rev Food Sci Nutr* **54**, 1002-1011.

[44] Thilakarathna SH, Rupasinghe HPV (2013) Flavonoid bioavailability and attempts for bioavailability enhancement. *Nutrients* **5**, 3367-3387.

[45] Aron PM, Kennedy JA (2008) Flavan-3-ols: Nature, occurrence and biological activity. *Mol Nutr Food Res* **52**, 79-104.

[46] Ramdani D, Chaudhry AS, Seal CJ (2013) Chemical composition, plant secondary metabolites, and minerals of green and black teas and the effect of different tea-to-water ratios during their extraction on the composition of their spent leaves as potential additives for ruminants. *J Agric Food Chem* **61**, 4961-4967.

[47] Zaveri NT (2006) Green tea and its polyphenolic catechins: Medicinal uses in cancer and noncancer applications. *Life Sci* **78**, 2073-2080.

[48] Ban JY, Jeon S-Y, Bae K, Song K-S, Seong YH (2006) Catechin and epicatechin from Smilacis chinae rhizome protect cultured rat cortical neurons against amyloid beta protein (25-35)-induced neurotoxicity through inhibition of cytosolic calcium elevation. *Life Sci* **79**, 2251-2259.

[49] McKay DL, Blumberg JB (2002) The role of tea in human health: An update. *J Am Coll Nutr* **21**, 1-13.

[50] Clifford MN, van der Hooft JJ, Crozier A (2013) Human studies on the absorption, distribution, metabolism, and excretion of tea polyphenols. *Am J Clin Nutr* **6 S**, 1619S-1630S.

[51] Cabrera C, Gimenez R, Lopez MC (2003) Determination of tea components with antioxidant activity. *J Agric Food Chem* **51**, 4427-4435.

[52] Unachukwu UJ, Ahmed S, Kavalier A, Lyles JT, Kennelly EJ (2010) White and green teas (Camellia sinensis-var.sinensis): Variation in phenolic, methylxanthine, and antioxidant profiles. *J Food Sci* **75**, C541-C548.

[53] Singh BN, Shankar S, Srivastava RK (2011) Green tea catechin, epigallocatechin-3-gallate (EGCG): Mechanisms, perspectives and clinical applications. *Biochem Pharmacol* **82**, 1807-1821.

[54] Giacco F, Brownlee M (2010) Oxidative stress and diabetic complications. *Circ Res* **107**, 1058-1070.

[55] Lobo V, Patil A, Phatak A, Chandra N (2010) Free radicals, antioxidants and functional foods: Impact on human health. *Pharmacogn Rev* **4**, 118-126.

[56] Uttara B, Singh AV, Zamboni P, Mahajan RT (2009) Oxidative stress and neurodegenerative diseases: A review of upstream and downstream antioxidant therapeutic options. *Curr Neuropharmacol* **7**, 65-74.

[57] Josefson D (2002) Foods rich in antioxidants may reduce risk of Alzheimer's disease. *BMJ* **325**, 7-7.

[58] Rahman K (2007) Studies on free radicals, antioxidants, and co-factors. *Clin Interv Aging* **2**, 219-236.

[59] Kumar GP, Khanum F (2012) Neuroprotective potential of phytochemicals. *Pharmacogn Rev* **6**, 81-90.

[60] Dragicevic N, Smith A, Lin X, Yuan F, Copes N, Delic V, Tan J, Cao C, Shytle RD, Bradshaw PC (2011) Green tea epigallocatechin-3-gallate (EGCG) and other flavonoids reduce Alzheimer's amyloid-induced mitochondrial dysfunction. *J Alzheimers Dis* **26**, 507-521.

[61] Khan N, Mukhtar H (2007) Tea polyphenols for health promotion. *Life Sci* **81**, 519-533.

[62] Leenen R, Roodenburg AJ, Tijburg LB, Wiseman SA (2000) A single dose of tea with or without milk increases plasma antioxidant activity in humans. *Eur J Clin Nutr* **54**, 87-92.

[63] Rietveld A, Wiseman S (2003) Antioxidant effects of tea: Evidence from human clinical trials. *J Nutr* **133**, 3285S-3292S.

[64] Erba D, Riso P, Bordoni A, Foti P, Biagi PL, Testolin G (2005) Effectiveness of moderate green tea consumption on antioxidative status and plasma lipid profile in humans. *J Nutr Biochem* **16**, 144-149.

[65] Yen G-C, Chen H-Y (1995) Antioxidant activity of various tea extracts in relation to their antimutagenicity. *J Agric Food Chem* **43**, 27-32.

[66] Robinson EE, Maxwell SR, Thorpe GH (1997) An investigation of the antioxidant activity of black tea using enhanced chemiluminescence. *Free Radic Res* **26**, 291-302.

[67] Gardner PT, McPhail DB, Duthie GG (1998) Electron spin resonance spectroscopic assessment of the antioxidant potential of teas in aqueous and organic media. *J Sci Food Agr* **76**, 257-262.

[68] Almajano MP, Vila I, Gines S (2011) Neuroprotective effects of white tea against oxidative stress-induced toxicity in striatal cells. *Neurotox Res* **20**, 372-378.

[69] van het Hof KH, de Boer HS, Wiseman SA, Lien N, Westrate JA, Tijburg LB (1997) Consumption of green or black tea does not increase resistance of low-density lipoprotein to oxidation in humans. *Am J Clin Nutr* **66**, 1125-1132.

[70] Maxwell S, Thorpe G (1996) Tea flavonoids have little short term impact on serum antioxidant activity. *BMJ* **313**, 229-229.

[71] Serafini M, Ghiselli A, Ferro-Luzzi A (1996) In vivo antioxidant effect of green and black tea in man. *Eur J Clin Nutr* **50**, 28-32.

[72] van het Hof KH, Kivits GA, Weststrate JA, Tijburg LB (1998) Bioavailability of catechins from tea: The effect of milk. *Eur J Clin Nutr* **52**, 356-359.

[73] Luczaj W, Waszkiewicz E, Skrzydlewska E, Roszkowska-Jakimiec W (2004) Green tea protection against age-dependent ethanol-induced oxidative stress. *J Toxicol Environ Health A* **67**, 595-606.

[74] Unno K, Takabayashi F, Kishido T, Oku N (2004) Suppressive effect of green tea catechins on morphologic and functional regression of the brain in aged mice with accelerated senescence (SAMP10). *Exp Gerontol* **39**, 1027-1034.

[75] Freese R, Basu S, Hietanen E, Nair J, Nakachi K, Bartsch H, Mutanen M (1999) Green tea extract decreases plasma malondialdehyde concentration but does not affect other indicators of oxidative stress, nitric oxide production, or hemostatic factors during a high-linoleic acid diet in healthy females. *Eur J Nutr* **38**, 149-157.

[76] Meki AR, Hamed EA, Ezam KA (2009) Effect of green tea extract and vitamin C on oxidant or antioxidant status of rheumatoid arthritis rat model. *Indian J Clin Biochem* **24**, 280-287.

[77] Tijburg LB, Wiseman SA, Meijer GW, Weststrate JA (1997) Effects of green tea, black tea and dietary lipophilic antioxidants on LDL oxidizability and atherosclerosis in hypercholesterolaemic rabbits. *Atherosclerosis* **135**, 37-47.

[78] Alessio HM, Hagerman AE, Romanello M, Carando S, Threlkeld MS, Rogers J, Dimitrova Y, Muhammed S, Wiley RL (2002) Consumption of green tea protects rats from exercise-induced oxidative stress in kidney and liver. *Nutr Res* **22**, 1177-1188.

[79] Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J, Nissinen A (2001) Midlife vascular risk factors and Alzheimer's disease in later life: Longitudinal, population based study. *BMJ* **322**, 1447-1451.

[80] Duron E, Hanon O (2008) Vascular risk factors, cognitve decline, and dementia. *Vasc Health Risk Manag* **4**, 363-381.

[81] de Bruijn RF, Ikram MA (2014) Cardiovascular risk factors and future risk of Alzheimer's disease. *BMC Med* **12**, 1-9.

[82] Sesso HD, Gaziano JM, Buring JE, Hennekens CH (1999) Coffee and tea intake and the risk of myocardial infarction. *Am J Epidemiol* **149**, 162-167.

[83] Yang YC, Lu FH, Wu JS, Wu CH, Chang CJ (2004) The protective effect of habitual tea consumption on hypertension. *Arch Intern Med* **164**, 1534-1540.

[84] Larsson SC, Virtamo J, Wolk A (2013) Black tea consumption and risk of stroke in women and men. *Ann Epidemiol* **23**, 157-160.

[85] Larsson SC, Mannisto S, Virtanen MJ, Kontto J, Albanes D, Virtamo J (2008) Coffee and tea consumption and risk of stroke subtypes in male smokers. *Stroke* **39**, 1681-1687.

[86] Arab L, Liu W, Elashoff D (2009) Green and black tea consumption and risk of stroke: A meta-analysis. *Stroke* **40**, 1786-1792.

[87] Kokubo Y, Iso H, Saito I, Yamagishi K, Yatsuya H, Ishihara J, Inoue M, Tsugane S (2013) The impact of green tea and coffee consumption on the reduced risk of stroke incidence in Japanese population: The Japan Public Health Center-Based Study Cohort. *Stroke* **44**, 1369-1374.

[88] Albrecht DS, Clubbs EA, Ferruzzi M, Bomser JA (2008) Epigallocatechin-3-gallate (EGCG) inhibits PC-3 prostate cancer cell proliferation via MEK-independent ERK1/2 activation. *Chem Biol Interact* **171**, 89-95.

[89] Tanabe N, Suzuki H, Aizawa Y, Seki N (2008) Consumption of green and roasted teas and the risk of stroke incidence: Results from the Tokamachi-Nakasato cohort study in Japan. *Int J Epidemiol* **37**, 1030-1040.

[90] Sano J, Inami S, Seimiya K, Ohba T, Sakai S, Takano T, Mizuno K (2004) Effects of green tea intake on the development of coronary artery disease. *Circ J* **68**, 665-670.

[91] Kuriyama S, Shimazu T, Ohmori K, Kikuchi N, Nakaya N, Nishino Y, Tsubono Y, Tsuji I (2006) Green tea consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan: The Ohsaki study. *JAMA* **296**, 1255-1265.

[92] Hertog MGL, Feskens EJM, Kromhout D, Hertog MGL, Hollman PCH, Hertog MGL, Katan MB (1993) Dietary antioxidant flavonoids and risk of coronary heart disease: The Zutphen Elderly Study. *Lancet* **342**, 1007-1011.

[93] Miura Y, Chiba T, Miura S, Tomita I, Umegaki K, Ikeda M, Tomita T (2000) Green tea polyphenols (flavan 3-ols) prevent oxidative modification of low density lipoproteins: An ex vivo study in humans. *J Nutr Biochem* **11**, 216-222.

[94] Negishi H, Xu JW, Ikeda K, Njelekela M, Nara Y, Yamori Y (2004) Black and green tea polyphenols attenuate blood pressure increases in stroke-prone spontaneously hypertensive rats. *J Nutr* **134**, 38-42.

[95] Maeda K, Kuzuya M, Cheng XW, Asai T, Kanda S, Tamaya-Mori N, Sasaki T, Shibata T, Iguchi A (2003) Green tea catechins inhibit the cultured smooth muscle cell invasion through the basement barrier. *Atherosclerosis* **166**, 23-30.

[96] De Bruin EA, Rowson MJ, Van Buren L, Rycroft JA, Owen GN (2011) Black tea improves attention and self-reported alertness. *Appetite* **56**, 235-240.

[97] Anandhan A, Tamilselvam K, Radhiga T, Rao S, Essa MM, Manivasagam T (2012) Theaflavin, a black tea polyphenol, protects nigral dopaminergic neurons against chronic MPTP/probenecid induced Parkinson's disease. *Brain Res* **1433**, 104-113.

[98] Ho C-T, Chen Q, Shi H, Zhang K-Q, Rosen RT (1992) Antioxidative effect of polyphenol extract prepared from various Chinese teas. *Prev Med* **21**, 520-525.

[99] Bohn SK, Ward NC, Hodgson JM, Croft KD (2012) Effects of tea and coffee on cardiovascular disease risk. *Food Funct* **3**, 575-591.

[100] Vermeer MA, Mulder TPJ, Molhuizen HOF (2008) Theaflavins from black tea, especially theaflavin-3-gallate, reduce the incorporation of cholesterol into mixed micelles. *J Agric Food Chem* **56**, 12031-12036.

[101] Fuchs D, de Graaf Y, van Kerckhoven R, Draijer R (2014) Effect of tea theaflavins and catechins on microvascular function. *Nutrients* **6**, 5772-5785.

[102] Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM (2003) Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med* **348**.

[103] Hodgson JM (2006) Effects of tea and tea flavonoids on endothelial function and blood pressure: A brief review. *Clin Exp Pharmacol Physiol* **33**, 838-841.

[104] Babu PV, Liu D (2008) Green tea catechins and cardiovascular health: An update. *Curr Med Chem* **15**, 1840-1850.

[105] Davies MJ, Judd JT, Baer DJ, Clevidence BA, Paul DR, Edwards AJ, Wiseman SA, Muesing RA, Chen SC (2003) Black tea consumption reduces total and LDL cholesterol in mildly hypercholesterolemic adults. *J Nutr* **133**, 3298S-3302S.

[106] Hakim IA, Alsaif MA, Alduwaihy M, Al-Rubeaan K, Al-Nuaim AR, Al-Attas OS (2003) Tea consumption and the prevalence of coronary heart disease in Saudi adults: Results from a Saudi national study. *Prev Med* **36**, 64-70.

[107] Geleijnse JM, Launer LJ, Van der Kuip DA, Hofman A, Witteman JC (2002) Inverse association of tea and flavonoid intakes with incident myocardial infarction: The Rotterdam Study. *Am J Clin Nutr* **75**, 880-886.

[108] Grassi D, Aggio A, Onori L, Croce G, Tiberti S, Ferri C, Ferri L, Desideri G (2008) Tea, flavonoids, and nitric oxide-mediated vascular reactivity. *J Nutr* **138**, 1554S-1560S.

[109] Ras RT, Zock PL, Draijer R (2011) Tea consumption enhances endothelial-dependent vasodilation; a meta-analysis. *PLoS One* **6**, e16974.

[110] Duffy SJ, Keaney JF Jr, Holbrook M, Gokce N, Swerdloff PL, Frei B, Vita JA (2001) Short- and long-term black tea consumption reverses endothelial dysfunction in patients with coronary artery disease. *Circulation* **104**, 151-156.

[111] Jochmann N, Lorenz M, Krosigk A, Martus P, Bohm V, Baumann G, Stangl K, Stangl V (2008) The efficacy of black tea in ameliorating endothelial function is equivalent to that of green tea. *Br J Nutr* **99**, 863-868.

[112] Gunawardena D, Shanmugam K, Low M, Bennett L, Govindaraghavan S, Head R, Ooi L, Munch G (2014) Determination of anti-inflammatory activities of standardised preparations of plant- and mushroom-based foods. *Eur J Nutr* **53**, 335-343.

[113] Deka A, Vita JA (2011) Tea and cardiovascular disease. *Pharmacol Res* **64**, 136-145.

[114] De Bacquer D, Clays E, Delanghe J, De Backer G (2006) Epidemiological evidence for an association between habitual tea consumption and markers of chronic inflammation. *Atherosclerosis* **189**, 428-435.

[115] de la Monte SM (2012) Brain insulin resistance and deficiency as therapeutic targets in Alzheimer's disease. *Curr Alzheimer Res* **9**, 35-66.

[116] Gupta J, Siddique YH, Beg T, Ara G, Afzal M (2008) A review on the beneficial effects of tea polyphenols on human health. *Int J Pharmacol* **4**, 314-338.

[117] Pan M-H, Lai C-S, Wang H, Lo C-Y, Ho C-T, Li S (2013) Black tea in chemo-prevention of cancer and other human diseases. *Food Sci Hum Wellness* **2**, 12-21.

[118] Nishiumi S, Bessyo H, Kubo M, Aoki Y, Tanaka A, Yoshida K-i, Ashida H (2010) Green and black tea suppress hyperglycemia and insulin resistance by retaining the expression of glucose transporter 4 in muscle of high-fat diet-fed C57BL/6J mice. *J Agric Food Chem* **58**, 12916-12923.

[119] Chen N, Bezzina R, Hinch E, Lewandowski PA, Cameron-Smith D, Mathai ML, Jois M, Sinclair AJ, Begg DP, Wark JD, Weisinger HS, Weisinger RS (2009) Green tea, black tea, and epigallocatechin modify body composition, improve glucose tolerance, and differentially alter metabolic gene expression in rats fed a high-fat diet. *Nutr Res* **29**, 784-793.

[120] Shoji Y, Nakashima H (2006) Glucose-lowering effect of powder formulation of African black tea extract in KK-A(y)/TaJcl diabetic mouse. *Arch Pharm Res* **29**, 786-794.

[121] Avram MM, Avram AS, James WD (2007) Subcutaneous fat in normal and diseased states 3. Adipogenesis: From stem cell to fat cell. *J Am Acad Dermatol* **56**, 472-492.

[122] Hursel R, Viechtbauer W, Dulloo AG, Tremblay A, Tappy L, Rumpler W, Westerterp-Plantenga MS (2011) The effects of catechin rich teas and caffeine on energy expenditure and fat oxidation: A meta-analysis. *Obes Rev* **12**, e573-e581.

[123] Sohle J, Knott A, Holtzmann U, Siegner R, Gronniger E, Schepky A, Gallinat S, Wenck H, Stab F, Winnefeld M (2009) White Tea extract induces lipolytic activity and inhibits adipogenesis in human subcutaneous (pre)-adipocytes. *Nutr Metab (Lond)* **6**, 20.

[124] Dulloo AG, Duret C, Rohrer D, Girardier L, Mensi N, Fathi M, Chantre P, Vandermander J (1999) Efficacy of a green tea extract rich in catechin polyphenols and caffeine in increasing 24-h energy expenditure and fat oxidation in humans. *Am J Clin Nutr* **70**, 1040-1045.

[125] Chantre P, Lairon D (2002) Recent findings of green tea extract AR25 (Exolise) and its activity for the treatment of obesity. *Phytomedicine* **9**, 3-8.

[126] Klaus S, Pultz S, Thone-Reineke C, Wolfram S (2005) Epigallocatechin gallate attenuates diet-induced obesity in mice by decreasing energy absorption and increasing fat oxidation. *Int J Obes (Lond)* **29**, 615-623.

[127] Dulloo AG, Seydoux J, Girardier L, Chantre P, Vandermander J (2000) Green tea and thermogenesis: Interactions between catechin-polyphenols, caffeine and sympathetic activity. *Int J Obes Relat Metab Disord* **24**, 252-258.

[128] Boschmann M, Thielecke F (2007) The effects of epigallocatechin-3-gallate on thermogenesis and fat oxidation in obese men: A pilot study. *J Am Coll Nutr* **26**, 389S-395S.

[129] Shimotoyodome A, Haramizu S, Inaba M, Murase T, Tokimitsu I (2005) Exercise and green tea extract

stimulate fat oxidation and prevent obesity in mice. *Med Sci Sports Exerc* **37**, 1884-1892.

[130] Venables MC, Hulston CJ, Cox HR, Jeukendrup AE (2008) Green tea extract ingestion, fat oxidation, and glucose tolerance in healthy humans. *Am J Clin Nutr* **87**, 778-784.

[131] Nagao T, Hase T, Tokimitsu I (2007) A green tea extract high in catechins reduces body fat and cardiovascular risks in humans. *Obesity (Silver Spring)* **15**, 1473-1483.

[132] Murase T, Nagasawa A, Suzuki J, Hase T, Tokimitsu I (2002) Beneficial effects of tea catechins on diet-induced obesity: Stimulation of lipid catabolism in the liver. *Int J Obes Relat Metab Disord* **26**, 1459-1464.

[133] Uchiyama S, Taniguchi Y, Saka A, Yoshida A, Yajima H (2011) Prevention of diet-induced obesity by dietary black tea polyphenols extract in vitro and in vivo. *Nutrition* **27**, 287-292.

[134] Lin CL, Huang HC, Lin JK (2007) Theaflavins attenuate hepatic lipid accumulation through activating AMPK in human HepG2 cells. *J Lipid Res* **48**, 2334-2343.

[135] Komatsu T, Nakamori M, Komatsu K, Hosoda K, Okamura M, Toyama K, Ishikura Y, Sakai T, Kunii D, Yamamoto S (2003) Oolong tea increases energy metabolism in Japanese females. *J Med Invest* **50**, 170-175.

[136] Rumpler W, Seale J, Clevidence B, Judd J, Wiley E, Yamamoto S, Komatsu T, Sawaki T, Ishikura Y, Hosoda K (2001) Oolong tea increases metabolic rate and fat oxidation in men. *J Nutr* **131**, 2848-2852.

[137] He RR, Chen L, Lin BH, Matsui Y, Yao XS, Kurihara H (2009) Beneficial effects of oolong tea consumption on diet-induced overweight and obese subjects. *Chin J Integr Med* **15**, 34-41.

[138] Kuo KL, Weng MS, Chiang CT, Tsai YJ, Lin-Shiau SY, Lin JK (2005) Comparative studies on the hypolipidemic and growth suppressive effects of oolong, black, pu-erh, and green tea leaves in rats. *J Agric Food Chem* **53**, 480-489.

[139] Kajimoto O, Kajimoto Y, Yabune M, Nakamura T, Kotani K, Suzuki Y, Nozawa A, Nagata K, Unno T, Sagesaka YM, Kakuda T, Yoshikawa T (2005) Tea catechins with a galloyl moiety reduce body weight and fat. *J Health Sci* **51**, 161-171.

[140] Weinreb O, Amit T, Mandel S, Youdim MB (2009) Neuroprotective molecular mechanisms of (-)-epigallocatechin-3-gallate: A reflective outcome of its antioxidant, iron chelating and neuritogenic properties. *Genes Nutr* **4**, 283-296.

[141] Mandel SA, Amit T, Kalfon L, Reznichenko L, Youdim MB (2008) Targeting multiple neurodegenerative diseases etiologies with multimodal-acting green tea catechins. *J Nutr* **138**, 1578S-1583S.

[142] Mao P, Reddy PH (2011) Aging and amyloid beta-induced oxidative DNA damage and mitochondrial dysfunction in Alzheimer's disease: Implications for early intervention and therapeutics. *Biochim Biophys Acta* **1812**, 1359-1370.

[143] Choi YT, Jung CH, Lee SR, Bae JH, Baek WK, Suh MH, Park J, Park CW, Suh SI (2001) The green tea polyphenol (-)-epigallocatechin gallate attenuates beta-amyloid-induced neurotoxicity in cultured hippocampal neurons. *Life Sci* **70**, 603-614.

[144] Levites Y, Amit T, Mandel S, Youdim MB (2003) Neuroprotection and neurorescue against Abeta toxicity and PKC-dependent release of nonamyloidogenic soluble precursor protein by green tea polyphenol (-)-epigallocatechin-3-gallate. *FASEB J* **17**, 952-954.

[145] Ono K, Yoshiike Y, Takashima A, Hasegawa K, Naiki H, Yamada M (2003) Potent anti-amyloidogenic and fibril-destabilizing effects of polyphenols in vitro: Implications for the prevention and therapeutics of Alzheimer's disease. *J Neurochem* **87**, 172-181.

[146] Grelle G, Otto A, Lorenz M, Frank RF, Wanker EE, Bieschke J (2011) Black tea theaflavins inhibit formation of toxic amyloid-beta and alpha-synuclein fibrils. *Biochemistry* **50**, 10624-10636.

[147] Haque AM, Hashimoto M, Katakura M, Hara Y, Shido O (2008) Green tea catechins prevent cognitive deficits caused by Abeta1-40 in rats. *J Nutr Biochem* **19**, 619-626.

[148] Walton NM, Shin R, Tajinda K, Heusner CL, Kogan JH, Miyake S, Chen Q, Tamura K, Matsumoto M (2012) Adult neurogenesis transiently generates oxidative stress. *PLoS One* **7**, e35264.

[149] Rezai-Zadeh K, Arendash GW, Hou H, Fernandez F, Jensen M, Runfeldt M, Shytle RD, Tan J (2008) Green tea epigallocatechin-3-gallate (EGCG) reduces beta-amyloid mediated cognitive impairment and modulates tau pathology in Alzheimer transgenic mice. *Brain Res* **1214**, 177-187.

[150] Rezai-Zadeh K, Shytle D, Sun N, Mori T, Hou H, Jeanniton D, Ehrhart J, Townsend K, Zeng J, Morgan D, Hardy J, Town T, Tan J (2005) Green tea epigallocatechin-3-gallate (EGCG) modulates amyloid precursor protein cleavage and reduces cerebral amyloidosis in Alzheimer transgenic mice. *J Neurosci* **25**, 8807-8814.

[151] Lee YK, Yuk DY, Lee JW, Lee SY, Ha TY, Oh KW, Yun YP, Hong JT (2009) (-)-Epigallocatechin-3-gallate prevents lipopolysaccharide-induced elevation of beta-amyloid generation and memory deficiency. *Brain Res* **1250**, 164-174.

[152] Danysz W, Parsons CG (2012) Alzheimer's disease, beta-amyloid, glutamate, NMDA receptors and memantine–searching for the connections. *Br J Pharmacol* **167**, 324-352.

[153] Kakuda T (2011) Neuroprotective effects of theanine and its preventive effects on cognitive dysfunction. *Pharmacol Res* **64**, 162-168.

[154] Egashira N, Ishigami N, Pu F, Mishima K, Iwasaki K, Orito K, Oishi R, Fujiwara M (2008) Theanine prevents memory impairment induced by repeated cerebral ischemia in rats. *Phytother Res* **22**, 65-68.

[155] Kakuda T (2002) Neuroprotective effects of the green tea components theanine and catechins. *Biol Pharm Bull* **25**, 1513-1518.

[156] Juneja LR, Chu D-C, Okubo T, Nagato Y, Yokogoshi H (1999) L-theanine—a unique amino acid of green tea and its relaxation effect in humans. *Trends Food Sci Tech* **10**, 199-204.

[157] Lu K, Gray MA, Oliver C, Liley DT, Harrison BJ, Bartholomeusz CF, Phan KL, Nathan PJ (2004) The acute effects of L-theanine in comparison with alprazolam on anticipatory anxiety in humans. *Hum Psychopharmacol* **19**, 457-465.

[158] Kimura K, Ozeki M, Juneja LR, Ohira H (2007) L-Theanine reduces psychological and physiological stress responses. *Biol Psychol* **74**, 39-45.

[159] Kelly SP, Gomez-Ramirez M, Montesi JL, Foxe JJ (2008) L-theanine and caffeine in combination affect human cognition as evidenced by oscillatory alpha-band activity and attention task performance. *J Nutr* **138**, 1572S-1577S.

[160] Owen GN, Parnell H, De Bruin EA, Rycroft JA (2008) The combined effects of L-theanine and caffeine on

cognitive performance and mood. *Nutr Neurosci* **11**, 193-198.

[161] Bryan J, Tuckey M, Einother SJ, Garczarek U, Garrick A, De Bruin EA (2012) Relationships between tea and other beverage consumption to work performance and mood. *Appetite* **58**, 339-346.

[162] Park SK, Jung IC, Lee WK, Lee YS, Park HK, Go HJ, Kim K, Lim NK, Hong JT, Ly SY, Rho SS (2011) A combination of green tea extract and l-theanine improves memory and attention in subjects with mild cognitive impairment: A double-blind placebo-controlled study. *J Med Food* **14**, 334-343.

[163] Cade WT (2008) Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. *Phys Ther* **88**, 1322-1335.

[164] Janson J, Laedtke T, Parisi JE, O'Brien P, Petersen RC, Butler PC (2004) Increased risk of type 2 diabetes in Alzheimer disease. *Diabetes* **53**, 474-481.

[165] Glenner GG, Eanes ED, Wiley CA (1988) Amyloid fibrils formed from a segment of the pancreatic islet amyloid protein. *Biochem Biophys Res Commun* **155**, 608-614.

[166] Chatterjee S, Peters SA, Woodward M, Mejia Arango S, Batty GD, Beckett N, Beiser A, Borenstein AR, Crane PK, Haan M, Hassing LB, Hayden KM, Kiyohara Y, Larson EB, Li CY, Ninomiya T, Ohara T, Peters R, Russ TC, Seshadri S, Strand BH, Walker R, Xu W, Huxley RR (2016) Type 2 diabetes as a risk factor for dementia in women compared with men: A pooled analysis of 2.3 million people comprising more than 100,000 cases of dementia. *Diabetes Care* **39**, 300-307.

[167] Toolsee NA, Aruoma OI, Gunness TK, Kowlessur S, Dambala V, Murad F, Googoolye K, Daus D, Indelicato J, Rondeau P, Bourdon E, Bahorun T (2013) Effectiveness of green tea in a randomized human cohort: Relevance to diabetes and its complications. *BioMed Res Int* **2013**, 12.

[168] Fukino Y, Ikeda A, Maruyama K, Aoki N, Okubo T, Iso H (2008) Randomized controlled trial for an effect of green tea-extract powder supplementation on glucose abnormalities. *Eur J Clin Nutr* **62**, 953-960.

[169] Anderson RA, Polansky MM (2002) Tea enhances insulin activity. *J Agric Food Chem* **50**, 7182-7186.

[170] Wu LY, Juan CC, Ho LT, Hsu YP, Hwang LS (2004) Effect of green tea supplementation on insulin sensitivity in Sprague-Dawley rats. *J Agric Food Chem* **52**, 643-648.

[171] Wu LY, Juan CC, Hwang LS, Hsu YP, Ho PH, Ho LT (2004) Green tea supplementation ameliorates insulin resistance and increases glucose transporter IV content in a fructose-fed rat model. *Eur J Nutr* **43**, 116-124.

[172] Zheng XX, Xu YL, Li SH, Hui R, Wu YJ, Huang XH (2013) Effects of green tea catechins with or without caffeine on glycemic control in adults: A meta-analysis of randomized controlled trials. *Am J Clin Nutr* **97**, 750-762.

[173] Qin B, Polansky MM, Harry D, Anderson RA (2010) Green tea polyphenols improve cardiac muscle mRNA and protein levels of signal pathways related to insulin and lipid metabolism and inflammation in insulin-resistant rats. *Mol Nutr Food Res* **54**(Suppl 1), S14-S23.

[174] Sabu MC, Smitha K, Ramadasan K (2002) Anti-diabetic activity of green tea polyphenols and their role in reducing oxidative stress in experimental diabetes. *J Ethnopharmacol* **83**, 109-116.

[175] Ramadan G, El-Beih NM, Abd El-Ghffar EA (2009) Modulatory effects of black v. green tea aqueous extract on hyperglycaemia, hyperlipidaemia and liver dysfunction in diabetic and obese rat models. *Br J Nutr* **102**, 1611-1619.

[176] Gomes A, Vedasiromoni JR, Das M, Sharma RM, Ganguly DK (1995) Anti-hyperglycemic effect of black tea (Camellia sinensis) in rat. *J Ethnopharmacol* **45**, 223-226.

[177] Islam MS (2011) Effects of the aqueous extract of white tea (Camellia sinensis) in a streptozotocin-induced diabetes model of rats. *Phytomedicine* **19**, 25-31.

[178] Roghani M, Baluchnejadmojarad T (2010) Hypoglycemic and hypolipidemic effect and antioxidant activity of chronic epigallocatechin-gallate in streptozotocin-diabetic rats. *Pathophysiology* **17**, 55-59.

[179] Vinson JA, Zhang J (2005) Black and green teas equally inhibit diabetic cataracts in a streptozotocin-induced rat model of diabetes. *J Agric Food Chem* **53**, 3710-3713.

[180] Tsuneki H, Ishizuka M, Terasawa M, Wu J-B, Sasaoka T, Kimura I (2004) Effect of green tea on blood glucose levels and serum proteomic patterns in diabetic (db/db) mice and on glucose metabolism in healthy humans. *BMC Pharmacol* **4**, 18-18.

[181] Islam MS, Choi H (2007) Green tea, anti-diabetic or diabetogenic: A dose response study. *Biofactors* **29**, 45-53.

[182] Gao R, Wang Y, Wu Z, Ming J, Zhao G (2012) Interaction of barley beta-glucan and tea polyphenols on glucose metabolism in streptozotocin-induced diabetic rats. *J Food Sci* **77**, H128-H134.

[183] Bhandari MR, Jong-Anurakkun N, Hong G, Kawabata J (2008) alpha-Glucosidase and alpha-amylase inhibitory activities of Nepalese medicinal herb Pakhanbhed (Bergenia ciliata, Haw.). *Food Chem* **106**, 247-252.

[184] Kwon YI, Apostolidis E, Shetty K (2008) Inhibitory potential of wine and tea against alpha-amylase and alpha-glucosidase for management of hyperglycemia linked to type 2 diabetes. *J Food Biochem* **32**, 15-31.

[185] Tanaka T, Inoue K, Betsumiya Y, Mine C, Kouno I (2001) Two types of oxidative dimerization of the black tea polyphenol theaflavin. *J Agric Food Chem* **49**, 5785-5789.

[186] Sang S, Lambert JD, Tian S, Hong J, Hou Z, Ryu JH, Stark RE, Rosen RT, Huang MT, Yang CS, Ho CT (2004) Enzymatic synthesis of tea theaflavin derivatives and their anti-inflammatory and cytotoxic activities. *Bioorg Med Chem* **12**, 459-467.

[187] Gupta S, Mahmood S, Khan Rizwan H, Mahmood A (2010) Inhibition of brush border sucrase by polyphenols in mouse intestine. *Biosci Rep* **30**, 111-117.

[188] Kobayashi Y, Suzuki M, Satsu H, Arai S, Hara Y, Suzuki K, Miyamoto Y, Shimizu M (2000) Green tea polyphenols inhibit the sodium-dependent glucose transporter of intestinal epithelial cells by a competitive mechanism. *J Agric Food Chem* **48**, 5618-5623.

[189] Matsui T, Tanaka T, Tamura S, Toshima A, Tamaya K, Miyata Y, Tanaka K, Matsumoto K (2007) α-glucosidase inhibitory profile of catechins and theaflavins. *J Agric Food Chem* **55**, 99-105.

[190] Collins QF, Liu H-Y, Pi J, Liu Z, Quon MJ, Cao W (2007) Epigallocatechin-3-gallate (EGCG), a green tea polyphenol, suppresses hepatic gluconeogenesis through 5′-Amp-activated protein kinase. *J Biol Chem* **282**, 30143-30149.

[191] Ku HC, Tsuei YW, Kao CC, Weng JT, Shih LJ, Chang HH, Liu CW, Tsai SW, Kuo YC, Kao YH (2014) Green tea (-)-epigallocatechin gallate suppresses IGF-I and IGF-II stimulation of 3T3-L1 adipocyte glucose uptake via the glucose transporter 4, but not glucose transporter 1 pathway. *Gen Comp Endocrinol* **199**, 46-55.

[192] Han MK (2003) Epigallocatechin gallate, a constituent of green tea, suppresses cytokine-induced pancreatic beta-cell damage. *Exp Mol Med* **35**, 136-139.
[193] Song E-K, Hur H, Han M-K (2003) Epigallocatechin gallate prevents autoimmune diabetes induced by multiple low doses of streptozotocin in mice. *Arch Pharm Res* **26**, 559-563.
[194] Fu Z, Zhen W, Yuskavage J, Liu D (2011) Epigallocatechin gallate delays the onset of type 1 diabetes in spontaneous non-obese diabetic mice. *BJN* **105**, 1218-1225.
[195] Cameron AR, Anton S, Melville L, Houston NP, Dayal S, McDougall GJ, Stewart D, Rena G (2008) Black tea polyphenols mimic insulin/insulin-like growth factor-1 signalling to the longevity factor FOXO1a. *Aging Cell* **7**, 69-77.
[196] Jankun J, Skotnicka M, Lysiak-Szydlowska W, Al-Senaidy A, Skrzypczak-Jankun E (2011) Diverse inhibition of plasminogen activator inhibitor type 1 by theaflavins of black tea. *Int J Mol Med* **27**, 525-529.
[197] Wang J, Santa-Maria I, Ho L, Ksiezak-Reding H, Ono K, Teplow DB, Pasinetti GM (2010) Grape derived polyphenols attenuate tau neuropathology in a mouse model of Alzheimer's disease. *J Alzheimers Dis* **22**, 653-661.
[198] Scalbert A, Williamson G (2000) Dietary intake and bioavailability of polyphenols. *J Nutr* **130**, 2073S-2085S.
[199] Pietta P, Simonetti P, Gardana C, Brusamolino A, Morazzoni P, Bombardelli E (1998) Relationship between rate and extent of catechin absorption and plasma antioxidant status. *Biochem Mol Biol Int* **46**, 895-903.
[200] Benzie IF, Szeto YT, Strain JJ, Tomlinson B (1999) Consumption of green tea causes rapid increase in plasma antioxidant power in humans. *Nutr Cancer* **34**, 83-87.
[201] Serafini M, Laranjinha JA, Almeida LM, Maiani G (2000) Inhibition of human LDL lipid peroxidation by phenol-rich beverages and their impact on plasma total antioxidant capacity in humans. *J Nutr Biochem* **11**, 585-590.
[202] Stalmach A, Mullen W, Steiling H, Williamson G, Lean ME, Crozier A (2010) Absorption, metabolism, and excretion of green tea flavan-3-ols in humans with an ileostomy. *Mol Nutr Food Res* **54**, 323-334.
[203] El-Hady DA, El-Maali NA (2008) Determination of catechin isomers in human plasma subsequent to green tea ingestion using chiral capillary electrophoresis with a high-sensitivity cell. *Talanta* **76**, 138-145.
[204] Masukawa Y, Matsui Y, Shimizu N, Kondou N, Endou H, Kuzukawa M, Hase T (2006) Determination of green tea catechins in human plasma using liquid chromatography-electrospray ionization mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci* **834**, 26-34.
[205] Unno T, Sagesaka YM, Kakuda T (2005) Analysis of tea catechins in human plasma by high-performance liquid chromatography with solid-phase extraction. *J Agric Food Chem* **53**, 9885-9889.
[206] Kotani A, Miyashita N, Kusu F (2003) Determination of catechins in human plasma after commercial canned green tea ingestion by high-performance liquid chromatography with electrochemical detection using a microbore column. *J Chromatogr B Analyt Technol Biomed Life Sci* **788**, 269-275.
[207] Takino M, Daishima S, Yamaguchi K, Nakahara T (2003) Quantitative liquid chromatography-mass spectrometry determination of catechins in human plasma by automated on-line extraction using turbulent flow chromatography. *Analyst* **128**, 46-50.
[208] Umegaki K, Sugisawa A, Yamada K, Higuchi M (2001) Analytical method of measuring tea catechins in human plasma by solid-phase extraction and HPLC with electrochemical detection. *J Nutr Sci Vitaminol (Tokyo)* **47**, 402-408.
[209] Kivits GAA, van der Sman FJP, Tijburg LBM (1997) Analysis of catechins from green and black tea in humans: A specific and sensitive colorimetric assay of total catechins in biological fluids. *Int J Food Sci Nutr* **48**, 387-392.
[210] Tsuchiya H, Sato M, Kato H, Okubo T, Juneja LR, Kim M (1997) Simultaneous determination of catechins in human saliva by high-performance liquid chromatography. *J Chromatogr B Biomed Sci Appl* **703**, 253-258.
[211] Auger C, Mullen W, Hara Y, Crozier A (2008) Bioavailability of polyphenon E flavan-3-ols in humans with an ileostomy. *J Nutr* **138**, 1535s-1542s.
[212] Mulder TPJ, van Platerink CJ, Wijnand Schuyl PJ, van Amelsvoort JMM (2001) Analysis of theaflavins in biological fluids using liquid chromatography–electrospray mass spectrometry. *J Chromatogr B Biomed Sci Appl* **760**, 271-279.
[213] Manach C, Williamson G, Morand C, Scalbert A, Remesy C (2005) Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *Am J Clin Nutr* **81**, 230s-242s.
[214] Clifford MN, Copeland EL, Bloxsidge JP, Mitchell LA (2000) Hippuric acid as a major excretion product associated with black tea consumption. *Xenobiotica* **30**, 317-326.
[215] Yang B, Arai K, Kusu F (2000) Determination of catechins in human urine subsequent to tea ingestion by high-performance liquid chromatography with electrochemical detection. *Anal Biochem* **283**, 77-82.
[216] Lee JE, Lee BJ, Hwang JA, Ko KS, Chung JO, Kim EH, Lee SJ, Hong YS (2011) Metabolic dependence of green tea on plucking positions revisited: A metabolomic study. *J Agric Food Chem* **59**, 10579-10585.
[217] Henning SM, Aronson W, Niu Y, Conde F, Lee NH, Seeram NP, Lee RP, Lu J, Harris DM, Moro A, Hong J, Pak-Shan L, Barnard RJ, Ziaee HG, Csathy G, Go VL, Wang H, Heber D (2006) Tea polyphenols and theaflavins are present in prostate tissue of humans and mice after green and black tea consumption. *J Nutr* **136**, 1839-1843.
[218] Wang P, Aronson WJ, Huang M, Zhang Y, Lee R-P, Heber D, Henning SM (2010) Green Tea Polyphenols and Metabolites in Prostatectomy Tissue: Implications for Cancer Prevention. *Cancer Prev Res (Phila)* **3**, 985-993.
[219] Rechner AR, Spencer JP, Kuhnle G, Hahn U, Rice-Evans CA (2001) Novel biomarkers of the metabolism of caffeic acid derivatives in vivo. *Free Radic Biol Med* **30**, 1213-1222.
[220] Kim S, Lee MJ, Hong J, Li C, Smith TJ, Yang GY, Seril DN, Yang CS (2000) Plasma and tissue levels of tea catechins in rats and mice during chronic consumption of green tea polyphenols. *Nutr Cancer* **37**, 41-48.
[221] Record IR, Lane JM (2001) Simulated intestinal digestion of green and black teas. *Food Chem* **73**, 481-486.
[222] Green RJ, Murphy AS, Schulz B, Watkins BA, Ferruzzi MG (2007) Common tea formulations modulate in vitro digestive recovery of green tea catechins. *Mol Nutr Food Res* **51**, 1152-1162.
[223] Ho L, Ferruzzi MG, Janle EM, Wang J, Gong B, Chen T-Y, Lobo J, Cooper B, Wu QL, Talcott ST, Percival SS, Simon JE, Pasinetti GM (2013) Identification of brain-targeted bioactive dietary quercetin-3-O-glucuronide as a

novel intervention for Alzheimer's disease. *FASEB J* **27**, 769-781.

[224] Zhao W, Wang J, Bi W, Ferruzzi M, Yemul S, Freire D, Mazzola P, Ho L, Dubner L, Pasinetti GM (2015) Novel application of brain-targeting polyphenol compounds in sleep deprivation-induced cognitive dysfunction. *Neurochem Int* **89**, 191-197.

[225] Faria A, Pestana D, Teixeira D, Couraud PO, Romero I, Weksler B, de Freitas V, Mateus N, Calhau C (2011) Insights into the putative catechin and epicatechin transport across blood-brain barrier. *Food Funct* **2**, 39-44.

[226] Ferruzzi MG, Lobo JK, Janle EM, Cooper B, Simon JE, Wu QL, Welch C, Ho L, Weaver C, Pasinetti GM (2009) Bioavailability of gallic acid and catechins from grape seed polyphenol extract is improved by repeated dosing in rats: Implications for treatment in Alzheimer's disease. *J Alzheimers Dis* **18**, 113-124.

[227] Ishisaka A, Ichikawa S, Sakakibara H, Piskula MK, Nakamura T, Kato Y, Ito M, Miyamoto K, Tsuji A, Kawai Y, Terao J (2011) Accumulation of orally administered quercetin in brain tissue and its antioxidative effects in rats. *Free Radic Biol Med* **51**, 1329-1336.

[228] Chen T-Y, Kritchevsky J, Hargett K, Feller K, Klobusnik R, Song BJ, Cooper B, Jouni Z, Ferruzzi MG, Janle EM (2015) Plasma bioavailability and regional brain distribution of polyphenols from apple/grape seed and bilberry extracts in a young swine model. *Mol Nutr Food Res* **59**, 2432-2447.

[229] Rizzi L, Rosset I, Roriz-Cruz M (2014) Global epidemiology of dementia: Alzheimer and vascular types. *Biomed Res Int* **2014**, 8.

[230] Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, Jorm A, Mathers C, Menezes PR, Rimmer E, Scazufca M (2005) Global prevalence of dementia: A Delphi consensus study. *Lancet* **366**, 2112-2117.

[231] Duthey B (2013) Alzheimer's Disease (AD) - World Health Organization. http://www.who.int/medicines/areas/priority.../BP6_11Alzheimer.pdf

[232] Beresniak A, Duru G, Berger G, Bremond-Gignac D (2012) Relationships between black tea consumption and key health indicators in the world: An ecological study. *BMJ Open* **2**, pii: e000648.

[233] Chang K (2015) World tea production and trade: Current and future development. Food and Agriculture Organization of the United Nations. Available from www.fao.org/3/a-i4480e.pdf

[234] FAOSTAT (2010) *Tea production*. Food and Agriculture Organization of the United Nations, Rome, Italy. http://faostat3.fao.org/download/Q/QC/E.

[235] Apetz N, Munch G, Govindaraghavan S, Gyengesi E (2014) Natural compounds and plant extracts as therapeutics against chronic inflammation in Alzheimer's disease–a translational perspective. *CNS Neurol Disord Drug Targets* **13**, 1175-1191.

[236] Zuo Y, Chen H, Deng Y (2002) Simultaneous determination of catechins, caffeine and gallic acids in green, Oolong, black and pu-erh teas using HPLC with a photodiode array detector. *Talanta* **57**, 307-316.

[237] Grassi D, Mulder TP, Draijer R, Desideri G, Molhuizen HO, Ferri C (2009) Black tea consumption dose-dependently improves flow-mediated dilation in healthy males. *J Hypertens* **27**, 774-781.

[238] Hirata K, Shimada K, Watanabe H, Otsuka R, Tokai K, Yoshiyama M, Homma S, Yoshikawa J (2004) Black tea increases coronary flow velocity reserve in healthy male subjects. *Am J Cardiol* **93**, 1384-1388, A1386.

[239] Nagao T, Komine Y, Soga S, Meguro S, Hase T, Tanaka Y, Tokimitsu I (2005) Ingestion of a tea rich in catechins leads to a reduction in body fat and malondialdehyde-modified LDL in men. *Am J Clin Nutr* **81**, 122-129.

[240] Hakim IA, Harris RB, Brown S, Chow HH, Wiseman S, Agarwal S, Talbot W (2003) Effect of increased tea consumption on oxidative DNA damage among smokers: A randomized controlled study. *J Nutr* **133**, 3303S-3309S.

[241] Hodgson JM, Croft KD, Woodman RJ, Puddey IB, Fuchs D, Draijer R, Lukoshkova E, Head GA (2013) Black tea lowers the rate of blood pressure variation: A randomized controlled trial. *Am J Clin Nutr* **97**, 943-950.

[242] Bahorun T, Luximon-Ramma A, Gunness TK, Sookar D, Bhoyroo S, Jugessur R, Reebye D, Googoolye K, Crozier A, Aruoma OI (2010) Black tea reduces uric acid and C-reactive protein levels in humans susceptible to cardiovascular diseases. *Toxicology* **278**, 68-74.

[243] Brown AL, Lane J, Holyoak C, Nicol B, Mayes AE, Dadd T (2011) Health effects of green tea catechins in overweight and obese men: A randomised controlled cross-over trial. *Br J Nutr* **106**, 1880-1889.

[244] Steptoe A, Gibson EL, Vuononvirta R, Williams ED, Hamer M, Rycroft JA, Erusalimsky JD, Wardle J (2007) The effects of tea on psychophysiological stress responsivity and post-stress recovery: A randomised double-blind trial. *Psychopharmacology (Berl)* **190**, 81-89.

[245] Mangine GT, Gonzalez AM, Wells AJ, McCormack WP, Fragala MS, Stout JR, Hoffman JR (2012) The effect of a dietary supplement (N-oleyl-phosphatidyl-ethanolamine and epigallocatechin gallate) on dietary compliance and body fat loss in adults who are overweight: A double-blind, randomized control trial. *Lipids Health Dis* **11**, 127-127.

[246] Small BJ, Rawson KS, Martin C, Eisel SL, Sanberg CD, McEvoy CL, Sanberg PR, Shytle RD, Tan J, Bickford PC (2014) Nutraceutical intervention improves older adults' cognitive functioning. *Rejuvenation Res* **17**, 27-32.