

## Review

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

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**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. It is rich in phytochemicals including, flavonoids, tannins, caffeine, polyphenols, boheic acid, theophylline, theobromine, anthocyanins, gallic acid, and finally epigallocatechin-3-gallate, which is considered to be 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- $\beta$  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

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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- $\beta$  ( $A\beta$ ) 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  $A\beta$  plaques is occurring up to two decades prior to the onset of any clinical symptoms [4]. The  $A\beta$  peptide is a core component of amyloid plaques and is generated from the processing of its parent protein, the amyloid- $\beta$  protein precursor ( $A\beta$ PP) [5]. Enzymatic cleavage of  $A\beta$ PP via beta secretase enzyme-1 (BACE1) followed by  $\gamma$ -secretase generates multiple  $A\beta$  species including the common soluble monomeric peptides of 40 amino acids and the more insoluble  $A\beta$  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, have 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 contain theanine which appears to be associated with improved cognitive function [32].

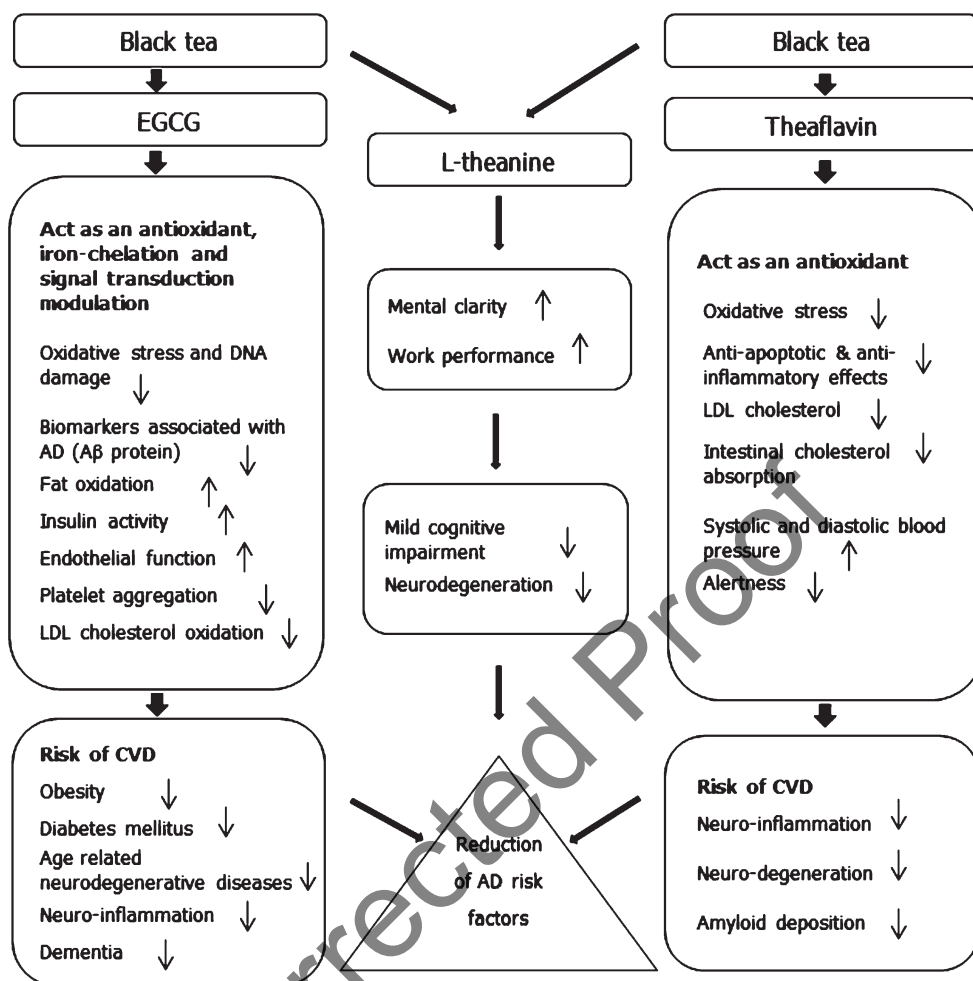


Fig. 1. Schematic diagram of importance of green and black tea phytochemicals on the reduction of AD progression. EGCG, (–) epigallocatechin gallate; AD, Alzheimer's disease, LDL, low-density lipoprotein; CVD, cardiovascular disease.

## TEA MANUFACTURING

Depending on the variety of *Camellia sinensis* (tea) used, the length of the fermentation/oxidation of tea leaves/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 thearubigins, 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  $\alpha$ -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, myricetin, 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* <sup>a</sup>
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 (%) <sup>b</sup>	30	5	4.5
Oxidized phenolic compounds (%) <sup>c</sup>	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. <sup>a</sup>Infusion time: 3 minutes. <sup>b</sup>Especially flavonoids. <sup>c</sup>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 teas 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 include 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 <sup>2</sup> [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- $\alpha$  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  $890 \pm 13$  mg polyphenols and  $366 \pm 5$  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 A $\beta$ , and mitochondrial dysfunction in AD brains [60, 142]. A $\beta$ -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 A $\beta$  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 A $\beta$  and  $\alpha$ -synuclein fibrillogenesis [146]. Long-term administration of green tea catechins lessened A $\beta$ -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 A $\beta$  toxicity [18]. These effects were mainly observed with gallic acid (1–20  $\mu$ M), ECG (1–20  $\mu$ M), and EGCG (1–10  $\mu$ M), while effects of EC and EGC against A $\beta$  toxicity was not evident [18]. Inhibition of A $\beta$  aggregation by EGCG and gallic acid [18] was also observed using black and green tea. A $\beta$ PP undergo proteolytic processing either by amyloidogenic pathway or non-amyloidogenic pathway, while most is managed through the non-amyloidogenic pathway, which impedes A $\beta$  formation. The first enzymatic cleavage is arbitrated by alpha-secretase, appearing within the A $\beta$  domain. This prevents the formation and release of the A $\beta$  peptide. In cell culture and transgenic mice, EGCG influenced the generation of the non-amyloidogenic soluble form of A $\beta$ PP [143, 144, 148]. This enhances the  $\alpha$ -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 A $\beta$ PP via a protein kinase C-dependent activation of  $\alpha$ -secretase resulting in decreased quantities of holoprotein A $\beta$ PP levels [144]. This effect was further observed in an AD transgenic mouse model (“Swedish” mutant APP overexpressing, APP<sup>swTg</sup>) [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  $\beta$ - and  $\gamma$ -secretases [151], which enhanced cell survival.

L-Theanine ( $\gamma$ -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 [246]	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 <sub>3</sub> , 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. MND A 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-theanine 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 comorbidity 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. administered 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  $\beta$ -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  $\alpha$ -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  $\alpha$ -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  $\alpha$ -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  $\beta$ -cell damage [192, 193] and protect the infiltrated immune cell-mediated  $\beta$ -cell destruction, and thereby increase  $\beta$ -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 A $\beta$  formation [48, 143], promotion of A $\beta$  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 catechins 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- $\beta$ -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.

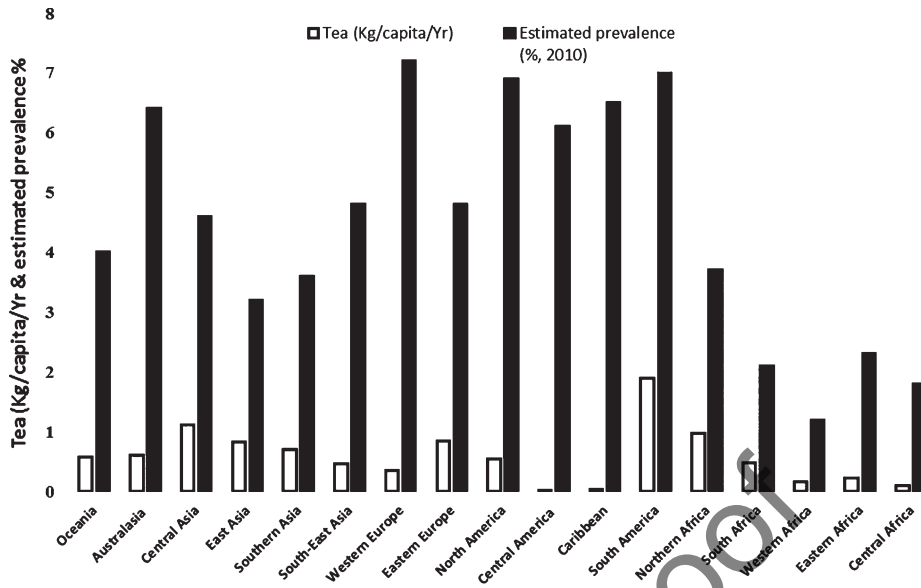


Fig. 2. The relationship between tea consumption and crude AD prevalence in different geographical regions in the world [1].

## 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.

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