Nutrition Today
Volume 53, Issue 5, 2018, pages 213-228

Potential Health Benefits of Tea

Nutrition Today (accepted manuscript)
DOI: http://doi.org/10.1097/NT.0000000000000294

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Funding was provided by The Coca-Cola Company.

The authors have no conflicts of interest to disclose.

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Volume 53, Issue 5, 2018, pages 213-228

Abstract

Brewed tea (from the *Camellia sinensis* plant) is the second most commonly consumed beverage in the world, and its consumption has been associated with several human health benefits. Tea polyphenols are absorbed in the intestine following consumption and metabolized by both human and microbial systems to yield a mixture of complex metabolites that can be found in circulation and throughout the body. Identification of tea phenolic constituents and their metabolites has served to strengthen the association between tea consumption and specific health benefits, as well as to measure potential differences between tea product forms. The current state of research suggests that long-term consumption of tea and tea polyphenols may provide distinct health benefits, with the strongest associations being the promotion of cardiovascular health, as well as antidiabetic and antiobesity effects. However, much regarding tea and health remains to be discovered. This includes development of a better understanding of the role of abundant oxidized polyphenol forms in oolong and black tea, whose bioavailability and specific role in health benefits remain unknown. This technical summary focuses on tea polyphenol bioaccessibility/bioavailability, discusses potential bioactivity, and highlights studies that link tea consumption and health.

Introduction

Over the years, tea has been investigated (via observational, preclinical, and clinical studies) for its potential to reduce the risk and or progression of various chronic diseases[1-5]. However, differences in tea profiles (i.e., concentrations of different bioactive compounds) and variable doses used across studies have made it challenging to compare results and to build on epidemiological associations and to translate findings to clinical health outcomes. This technical summary will describe tea polyphenols in relation to health and discuss factors that affect bioactivity (*for a brief introduction to the chemistry of tea polyphenols, please refer to Production and Polyphenolic Composition of Tea*). The latter part of this review will highlight the potential effects of tea on health and will discuss select clinical trials, interventions, and epidemiological studies with a focus on cardiovascular disease, metabolic disorders, and cancer. In order to consider biological effects of brewed tea and tea beverages, research that employed tea extracts (often green tea extract) or isolated polyphenols (such as epigallocatechin gallate) will not be discussed in this review. Readers should be aware that since this review includes only tea in food/beverage applications, points made in this review must not be extrapolated to pure compounds/tea extracts. Exposures encountered from the use of pure compounds/tea extracts, which tend to be much higher in dose and may have different effects (e.g., due to the presence of other compounds in the supplement or a lack of interactions from food components) are not addressed.

As this is meant to be a summarized, narrative review, interested readers can refer to additional resources that have reviewed polyphenol bioavailability[6] and the effect of tea polyphenols on disease in human studies[7-13] more extensively. Accordingly, this narrative review aims to provide a conceptual, fundamental overview of tea polyphenols and potential health

effects. To gain a more complete understanding of this topic, readers are urged to consult systematic, evidence-based reviews, which consider all (rather than select representative) clinical studies and methodically analyze potential benefits and risks associated with clinical tea studies.

Polyphenols in our diet

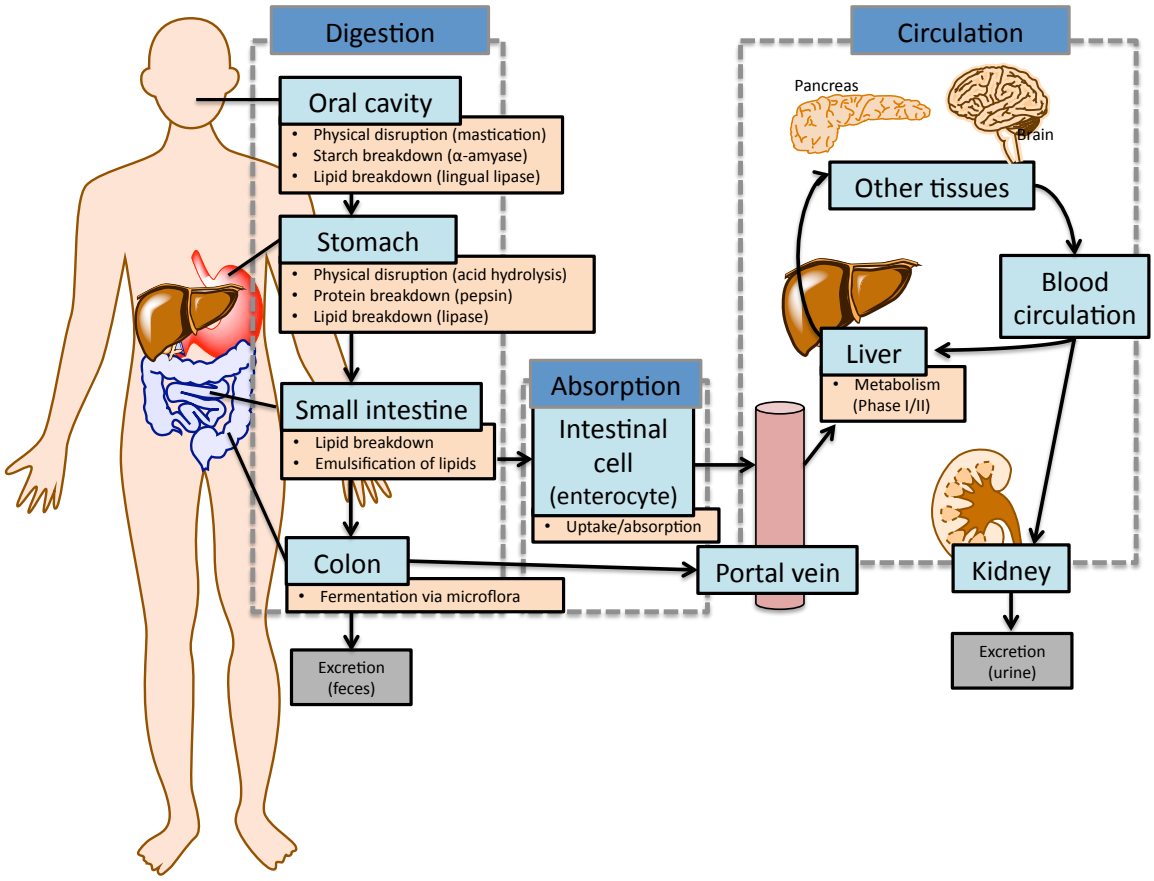
Flavonoids and other polyphenols are present in many common foods and beverages, including wine, whole grains, fruits/vegetables, and cocoa. Of the many dietary sources, tea is one of the major flavonoid sources in the American diet: American tea drinkers consume a daily flavonoid intake that is ~20 times higher compared to those who do not consume tea[14]. Epidemiological data have shown lower relative risks of multiple chronic diseases in populations with higher levels of tea consumption, including cancer, cardiovascular disease, and other conditions[1,2]. These epidemiological associations have served as the basis for hypothesis generation and in the design of clinical trials assessing the impact of tea in humans.

Bioavailability of tea polyphenols

To better understand tea and its potential health effects, it is important to consider the bioaccessibility and bioavailability of the primary phenolic components of tea. Following tea consumption, there are a series of complex biochemical and biological steps that occur in the human body, which for simplicity, can be broadly grouped as digestion, absorption, and distribution to target tissues (**Figure 1A**). Bioaccessibility refers to the portion of a compound that is transferred from the ingested food or beverage into the aqueous phase in the intestinal lumen, i.e., the portion that is available for uptake by the intestinal cells (enterocytes), the main site of absorption. Bioavailability corresponds to the proportion of polyphenols that are actually absorbed, and present in circulation as native compounds or metabolites of human/microbial origin. Despite having received much attention for their potential health benefits, tea polyphenols

are not required for basic human survival, growth or reproduction and are thus non-essential (non-nutrient) bioactives. The human body also recognizes them as xenobiotics and metabolizes these compounds to facilitate excretion by urinary, bile or other pathways. However, it is important to note that because of this level of metabolism by both human and microbial systems, metabolites, not native forms in tea, are the main forms that are subsequently in circulation and available for tissue uptake, further metabolism and biological activity[15].

Figure 1. Graphical summary of digestion, absorption, and circulation of tea polyphenols. Figure adapted from previous authors[5,15].



Bioavailability of tea polyphenols is reported to vary widely between different compounds and different preparations. The phenolic acids (mainly gallic acid) and catechin

monomers, abundant in green tea, are more bioavailable than procyanidins, theaflavins, or thearubigins, present in oxidized oolong and black teas, due to their smaller molecular weight[16].

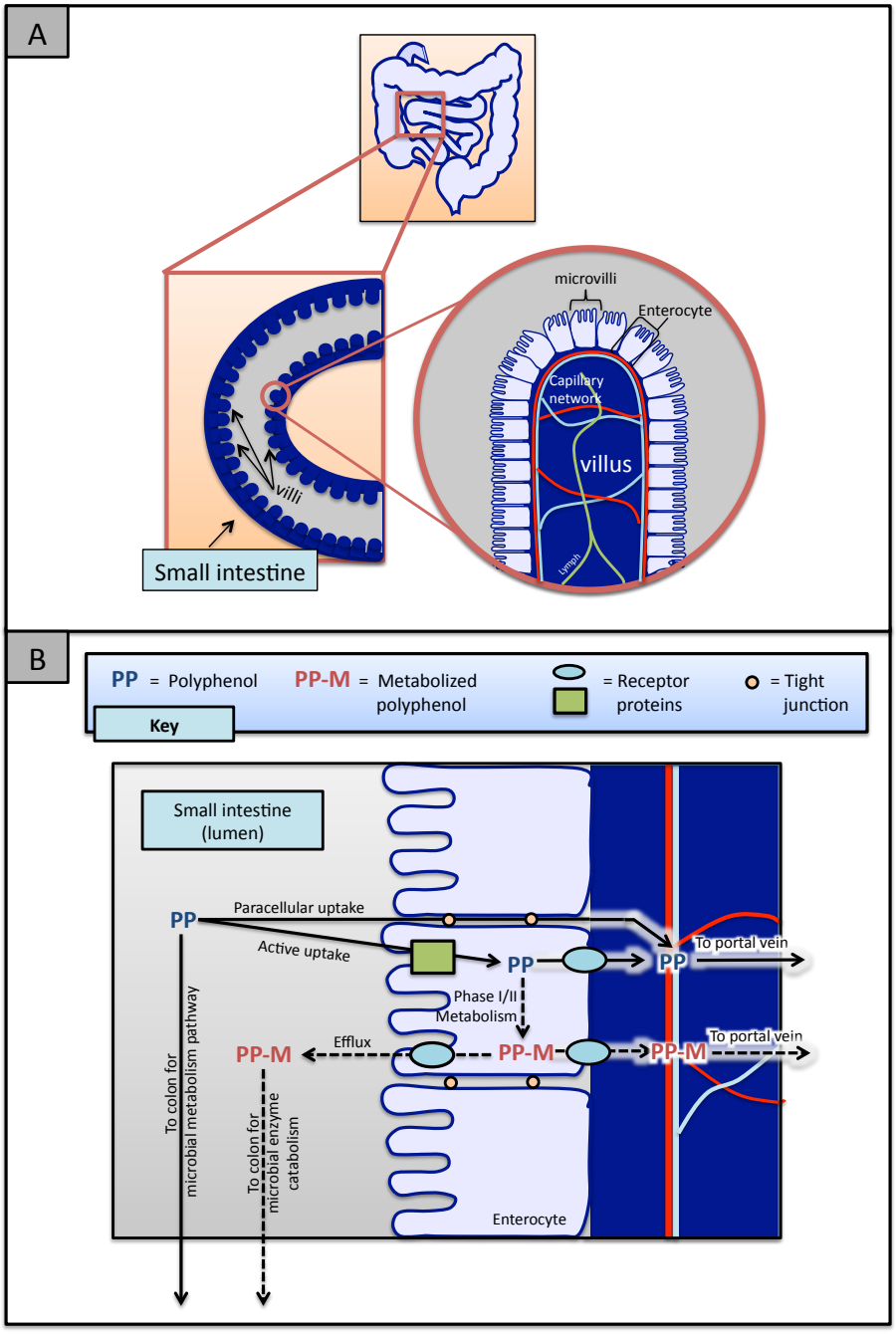
Polyphenol digestion, absorption and metabolism

Tea beverages, as a delivery system for bioactives, have inherent advantages compared to solid food matrices, as the bioactives are introduced already in a soluble aqueous solution. This precludes the need for efficient digestive release from a solid material, although sensitivity to digestive conditions has been reported to be a problem[15]. During absorption in the small intestine, polyphenols in tea (mostly catechin monomers) are subjected to Phase II metabolic activities (chemical reactions) in the enterocyte[16] (**Figure 2A, 2B**). After intestinal absorption of native tea polyphenols (mostly unconjugated monomeric catechins molecules), these compounds are transported to the liver where they are metabolized by the hepatic Phase II conjugation system with methyl, sulfate and glucuronide conjugation, altering circulating profiles and polarity[17] (making it more water soluble, in the case of sulfate and glucuronide forms, or more lipid soluble, in the case of methyl forms). Phase II phenolic metabolites can be recycled into the small intestine by biliary excretion where they pass into the colon and are catabolized by microbial communities (and potentially reabsorbed)[18] (**Figure 2B**).

Another main pathway impacting the overall level of tea polyphenol absorption is microbial metabolism in the lower intestine. The colon is home to a diverse collection of microorganisms, also known collectively as *microbiota* or *microbiome,* which can ferment unabsorbed materials and consequently break down compounds (e.g., polyphenols) into simpler ones (metabolites). These microbial metabolites can then be absorbed from the colon, transported in the blood, and circulate to other tissues. It is well established that the human microbiota is

capable of metabolizing tea polyphenols efficiently and generation of several prominent small molecular weight metabolites that are efficiently absorbed[15,19-21].

Figure 2. Close up view of an intestinal villus and the epithelia (A) and schematic diagram of absorption and metabolism of polyphenols in the enterocyte (B). Figure adapted from previous authors[5,15].



Both native tea polyphenols as well as conjugated metabolites excreted from the intestine to the lumen are subjected to microbial digestion. These compounds can be deconjugated (e.g. glycosides removed from catechins) and/or degraded (e.g. phenolic acids cleavage products) by microbial communities in the lower intestine, after which they may be absorbed and subjected to further hepatic metabolism[18] or undergo microbial metabolism (ring cleavage and epimerization reactions) in the colon[16]. Examples of common microbial metabolites of tea catechins include valerolactones [20,21], hydroxy benzoic acids[19], and phenyl acetic acids[15] . Colonic microbes appear to convert polyphenols to smaller compounds with ultimate conversion to hippuric acid, a major compound detected in human urine after consumption of both black and green tea[22]. In this regard, polyphenol absorption from tea, while primarily thought of from the perspective of uptake of native polyphenols in the small intestinal, is perhaps more dependent on colonic microbial catabolism of tea polyphenols and absorption in the lower intestine/colon. It has been reported that microbial metabolites are more absorbable in humans compared to their native parent compounds and these small molecular weight phenolics may have similar or increased bioefficacy as compared to the native compounds[16]. As such, consideration of the interactions between tea and microbiota in relation to health endpoints has increased substantially.

Tea polyphenol forms in circulation

A variety of tea catechin metabolites and native forms have been detected in human plasma after tea ingestion (**Tables 1-5**), which may be freely circulating or bound to proteins in the bloodstream[16]. Tables 1-3 highlight reported bioavailability of (−)-epigallocatechin gallate (EGCG), (−)-epigallocatechin (EGC), and (−)-epicatechin (EC), respectively, in human clinical studies. EGCG, EGC, and EC are major catechins found in green tea. EGCG and EGC are gallocatechins, which have a third B-ring hydroxyl group at C5', while EC is considered to be a

catechin gallate as it has an esterified gallic acid residue at the C3 hydroyl[15]. General differences in catechin bioavailability can be observed (across Tables 1-3) as EGCG is less bioavailable compared to other catechins[23,24]. During black tea processing, catechins are oxidized and form polymerized compounds (e.g., thearubigins and theabrownins), which are characteristic of black tea. In humans, peak plasma levels of tea catechins are usually in the 0.2-0.3 μM range after ingestion of relevant amounts of green tea (i.e., 400-750 mL)[25]. A pilot study analyzed bioavailability of black tea theaflavins after consumption of 700 mg of mixed theaflavins (which the authors specify as equivalent to ~30 cups of black tea) and found peak plasma concentrations of only about 2-7 nM[26], indicating that normal black tea consumption likely will not lead to appreciable absorption of native theaflavins. Considering the poor bioavailability of many polyphenols, toxicity from typical tea beverage consumption is likely only achievable through extreme misuse of beverage and food products. Although native tea polyphenols may be limited in circulation, a variety of metabolites can be detected as a result of microbial fermentation. In a study conducted on green tea metabolites, only two metabolites (4-hydroxyphenyl acetic acid and hippuric acid) were detected in urine from subjects with an ileostomy while a more diverse metabolite profile (also containing pyrocatechol, pyroallol, valerolactone, benzoic and hydroxyphenyl acids) was found in urine samples from subjects with an intact colon[19]. Thus the circulation, subsequent delivery to tissue, and eventual excretion of tea polyphenols (and derivative compounds) can be substantially affected by the colonic microflora. Further work is needed to fully elucidate the link between tea polyphenol metabolites and actual bioactivity.

Translating experimental dose to a serving of tea

Translating experimental results on tea polyphenols from *in vitro* or animal studies to humans requires careful interpretation. Polyphenol doses used in (animal or cell) model studies

are often not translatable to human doses as these are often 10-1000X greater than what would be expected from consumption of most tea products[25]. These doses are often employed to obtain significant results in an abbreviated timeframe of animal research and are not necessarily a good representation of normal dietary consumption patterns in humans. Relating such findings directly to human nutrition (low doses, chronically over decades) is often questionable and likely has contributed to the failure of many human trials. The difficulty of translating cell and animal results to human clinical situations and, perhaps more critically, clinical trials to recommendations for the broad population is well documented.

It is also important to consider that the exact conditions in the human body are difficult to replicate in the lab and may not perfectly correspond to animal models. The human body inherently adapts to exposure of compounds, including polyphenols. Large acute doses may induce upregulation of the xenobiotic detoxification system, resulting in lower bioavailability of the desired compounds (and potentially attenuated effects) over time.

Some clinical studies that have investigated the effects of tea on cardiovascular disease, metabolic disease, and cancer are summarized in **Table 6**. Tea dose for many of these studies is expressed in terms of volume (mL) or servings (tea cups). Although the exact polyphenol concentrations differ depending on various factors (*discussed in more detail in Production and Polyphenolic Composition of Tea),* a reasonable target composition for a standard 6 oz (237mL) US brewed cup of green tea would be 250 mg total catechins (or greater than 300 mg total polyphenols) and 50 mg caffeine while a reasonable composition for a cup of brewed black tea (237mL) would be 150 mg catechins, 200 mg of theaflavins and thearubigens (or >350 mg total polyphenols) and 50 mg caffeine. When comparing studies, it is important to consider the volume of tea in a dose as well as the concentrations and polyphenolic profile. Studies that

utilize purified phenolics (e.g., EGCG) have doses that are more concentrated and have less complex profiles (one type of polyphenol as opposed to a mix) compared to those that use actual brewed tea. Similarly, using tea extract (e.g., green tea extract) may not completely model brewed tea perfectly as these are more concentrated. Another consideration is that other compounds (e.g., minerals) that are co-consumed with the tea can alter absorption. Thus studies may account for this by using a control diet[27], having subjects consume the tea post fasting and without a meal, and/or by calculation of consumed micronutrients[28] . The following sections focus primarily on human clinical studies using brewed tea and summarize the potential effects of tea consumption on health.

Tea and cardiovascular disease

Epidemiological studies have indicated that habitual tea consumption lowers risk factors of cardiovascular disease[2]. In the Rotterdam study, participants (>54 years, no history of myocardial infraction) were observed in a longitudinal analysis over a period of 4-7 years; after adjustment for lifestyle and nutritional factors, it was observed that individuals with daily tea intake of >375 mL had a lower relative risk of myocardial infraction than non-tea consumers (RR=0.57, 95% CI= 0.33, 0.98)[2]. Tea has been shown to improve flow-mediated dilation (FMD)[29] and blood pressure[28], which are associated with reduced risk of cardiovascular disease. A cross-sectional study was performed in 218 women (>70 years) using 24-hour dietary recall and urine 4-O-methylgallic acid as measurements of tea intake; systolic and diastolic blood pressures were significantly lower in women with high levels of tea consumption as compared to women with low levels of tea consumption[30]. Aside from FMD and blood pressure-related studies, clinical trials have also been performed to determine if green and/or black tea consumption can reduce blood lipid peroxidation levels in adults[31,32]; results of these trials have

been mixed where no effect is observed in some studies while a small preventative effect is observed in other studies. Despite this, the overall association between tea consumption and cardiovascular health appears to be strong (**Table 6**).

Metabolic effects of tea consumption: metabolic syndrome, obesity, and type 2 diabetes

Obesity and Type 2 Diabetes Mellitus (T2DM) continue to be significant public health challenges in the United States and globally; about 30 million people in the United States[33]. An additional ~80 million Americans are afflicted with prediabetes (impaired fasting glucose or impaired glucose tolerance), which is a high-risk state for developing T2DM[34]. Nutritional-based strategies for controlling and preventing T2DM represent a potential treatment option for patients to supplement pharmaceutical regimes. Heavy tea consumption (about 4 cups per day) has been shown to be a significant factor in weight reduction and prevention of metabolic syndrome[35]. One meta-analysis based on 7 epidemiological studies found a lower risk of T2DM in those who consumed 3-4 cups of tea per day in comparison to those who consumed no tea; another retrospective cohort in Japan (17,413 people aged 40-65) indicated that consumption of 6 or more cups of green tea was associated with a 33% reduced risk of developing T2DM[25]. However, another prospective analysis of 39,908 Singaporean Chinese subjects found a decreased relative risk of T2DM in those consuming ≥4 cups of coffee or ≥1 cup of black tea daily with relative risks of 0.70 (95% CI: 0.53, 0.93) and 0.84 (95% CI: 0.74, 1.00), respectively, but no reduced relative risk in consumers of green tea[36]. Yet, a meta-analysis of 17 clinical trials (comprising of 1133 subjects) concluded that green tea favorably reduced fasting glucose and Hb A_{1c}[8].

Tea consumption may alleviate metabolic syndrome by increasing AMP-activated protein kinase activity in the liver, which downregulates enzymes involved in gluconeogenesis (thus

decreasing gluconeogenesis)[35]. Another suggested mechanism of action includes the inhibition of α-amylase by green tea polyphenols, which would lower carbohydrate digestion and blood glucose response to starch rich meals[37]. However, only a limited number of large scale studies relating tea bioactives derived from brewed tea to metabolic syndrome have been performed in this area and are marked by inconsistency in results among different studies. This may be attributable to differences across studies (e.g., study durations, dosage, health status of subjects, genetic and environmental differences). Metabolic effects of tea are not as well established as cardiovascular health benefits. However, this continues to be an evolving area of research that initially started in relation to weight management and has evolved to energy management and cognitive function.

Tea and cancer

A 2016 cohort study in Japan followed 89,555 people from 1995-1999 to observe potential effects of green tea consumption on biliary tract cancer and related cancers. Daily consumption of high levels of green tea (>720 mL per day) resulted in a significantly reduced risk (hazard ratio=0.67, 95% CI=0.46, 0.97) when compared to those consuming <120 mL of green tea per day[38]. Regular consumption of green tea appeared to decrease the risk of colorectal cancer in an observational study[39], but further evidence from clinical trials with tea infusions (rather than green tea catechins) are needed to better investigate this association [40]. Intervention studies have been performed in men with prostate cancer to observe the effect of black and green tea consumption prior to prostatectomy[41]. Bioaccumulation of green tea catechins in the prostate tissue was observed; significant decrease of an inflammation factor (nuclear factor kappa B) was observed after green tea consumption in one clinical trial[41]. A 2006 meta-analysis of 13 epidemiological studies analyzing the association between tea consumption and breast cancer

established a slightly reduced odds ratio (OR) comparing highest consumers of green tea to lowest consumers of green tea (OR= 0.78, 95% CI= 0.61, 0.98)[1].

A 1999 clinical research trial tested a mixed tea product (green tea supplemented with tea catechins and theaflavins/thearubigins) in 59 patients with oral mucosa leukoplakia; 37.9% of green tea-treated patients experienced a decrease in oral mucosa leukoplakia size compared to 6.7% of placebo patients[42]. Variations in individual patients also have an effect as several studies indicate that genetics significantly affects cancer-related biomarkers in tea drinkers (i.e. beneficial effects were seen in high expressors of certain enzymes)[43]. Further work in this area could help identify individuals that may be more receptive to amelioration/prevention of cancer by chronic green tea consumption.

Tea and brain health

EGCG and EGCG metabolites have been shown to be permeable across *in vitro* blood brain barrier models[44,45], which suggests that some tea polyphenols and metabolites may have the potential to reach the brain and affect cognitive health. In previous studies, tea consumption was correlated with a reduced risk of neurocognitive disorders[46] and Parkinson disease in Finnish[47] and in Chinese-Singaporean subjects[48] who habitually drank three or more cups of tea per day. Previous studies have hypothesized that caffeine is the bioactive compound responsible for the reduced risk[49,50]**,** another study[**51**] found that black tea consumption, which was not confounded by caffeine content, decreased Parkinson's disease risk while green tea intake did not show an association. This suggests that characteristic oxidized polyphenols (e.g., thearubigins and theaflavins) in black tea may have a distinct effect. However, regular consumption of black or green tea have both been shown to reduce the risk of neurocognitive disorders[46] in elderly Chinese subjects. Consumption of black tea was also found to enhance improve memory, reduce

errors, and speed up performance of subjects in a variety of cognitive tasks compared to consumption of a water control[52], although the study did not differentiate if the effects were due to caffeine or tea polyphenol content.

Contraindications of tea consumption

While often only focused on for health benefits, contraindications of heavy tea consumption have been reported. One concern is that consuming beverages (e.g., tea) at a high temperatures has repeatedly been associated with an increased risk of esophageal cancer. However, some observational studies suggest that green tea decreases the risk of esophageal cancers but only in non-smoking, non-alcohol drinking women (smoking and drinking have been shown to be major risk factors in development of esophageal cancer)[3,4].

Renal stone formation is also strongly linked to dietary habits, which can be problematic for some tea drinkers, especially for gallstone formers (individuals prone to gallstone formation)[53]. Black tea contains high levels of oxalate which can be a major risk factor of gallstone formation for gallstone formers, who are consequently often instructed to limit black tea consumption[53].

Effects on tea consumption on mineral absorption

Tea polyphenols can bind to minerals, consequently limiting their bioavailability. This effect could be beneficial by preventing toxicity of certain minerals or deleterious by contributing to dietary mineral deficiencies. For example, aluminum, a major mineral in tea that could have toxicological concerns at high intake levels, is poorly bioavailable from tea due to limited absorption in the gastrointestinal tract and efficient renal excretion[54]. Similarly, co-

consumption of mercury-rich fish with green tea extract reduced mercury bioaccessibility by 82-92%[55].

Iron deficiency is the most prevalent and common nutrient deficiency in the world[56] (and is a greater concern for individuals on plant-based diets—diets that are limited in red meat (a bioavailable heme iron source) and high in phytates (iron absorption limiters)—and women, who have higher iron requirements than men[57]. Co-consuming tea with non-heme iron has been shown to limit absorption as iron-polyphenol complexes are formed in the intestinal lumen[58]. Human trials have indicated that consuming tea with a meal significantly limits iron absorption in both iron deficient and non-deficient individuals[57,59]. Although coffee, cocoa, herbal and black teas all have significant inhibitory effects on iron absorption, black tea has been reported as the most potent inhibitor, potentially due to the higher galloyl ester content[59].

Linking bioavailability to bioactivity

The rationale for performing pharmacokinetic and bioavailability studies is that a specific bioactive must be available at the site of action to impart its desired activity. Caution must be used when interpreting postprandial blood levels as predictors of activity as this will not perfectly predict the quantity of bioactive compound that is absorbed and utilized[60]. The situation *in vivo* is complex, and much work remains to be done to definitively establish blood predictors of activity. Several issues arise with using blood bioavailability of specific compounds as predictors or markers of activity. First, as stated above, tea has hundreds of potentially bioactive compounds. While bioactivity studies have focused on the predominant constituents on a mass or molar basis, it is unknown whether these are in fact the compounds whose bioavailability is critical for activity. Second, using blood bioavailability to predict activity assumes that reaching circulation implies access to the site of activity. However, most tea (and indeed, polyphenol)

research has been done in cells (no barrier to activity) or whole animals (no site specificity). Furthermore, compounds may have much greater (e.g., in the intestinal lumen) or much lower (e.g., in the brain) concentrations at the site of activity compared to blood levels. Some compounds with essentially zero bioavailability (large catechin oxidation products) may have potent bioactive actions in the gut lumen (inhibition of digestive enzymes, modulation of microbial communities) or mucosa (modulation of gut junctions and villi/crypt architecture, immune modulation, etc.). Finally, if gut luminal/mucosal activities or production of microbial metabolites are crucial for observed activity, bioavailability may in fact be inversely proportional to activity (i.e. less absorption of native compounds could actually be desirable).

Future outlook: targeting health with tea products

Based on currently available knowledge, efforts should focus on obtaining maximum benefit from a reasonable dose of tea obtainable in common food and beverages for the target population (likely to differ significantly amongst countries). As such, formulation of products should target levels of key bioactives (polyphenols, caffeine and theanine) achievable in brewed tea and should be consumed at a high enough quantity to allow for a substantial bioavailable fraction (Tables 1-5). Physiological responses observed in clinical studies (**Table 6**) occurred in humans consuming ~3-10 cups of tea per day. These findings suggest that consumption of polyphenols from ~3-10 cups of brewed tea per day may provide beneficial health effects, however, development of more concentrated tea or strategically formulated tea products could provide beneficial health effects without the need to consume multiple cups of tea everyday.

Efforts to better leverage tea include strategies to moderately increase tea “strength”, improve tea stability, or increase consumption via a broader product spectrum (new types of teas, tea-containing products). Future tea products could shift the need to rely on tea strength and

focus on leveraging processing or ingredient interactions to maximize polyphenol bioactivity. However, the potential impact of minor constituents, poorly- or non-bioavailable bioactives (theaflavins, thearubigins, theabrownins), or microbial metabolites must be better understood in order to more fully leverage the inherent profile of tea for health endpoints.

Table 1. Bioavailability of epigallocatechin gallate (EGCG) observed in human clinical trials after ingestion of brewed green and black tea infusions

EGCG Source	Amount	Dosage Delivered	AUC value (μmol h/L)	Plasma C_{max} (raw, nmol/L)	Plasma C_{max} (dose normalized nmol/L/mg EGCG)	T_{max} (h)	# of subjects	Reference
Green tea	3 g of leaves in 400 mL water (consumed with a "polyphpenol-free" breakfast)	68 mg EGCG		70	1.03		12	[61]
Green tea	5 g of leaves in 400 mL water (consumed with a "polyphpenol-free" breakfast)	114 mg EGCG		90	0.79		12	[61]

Green tea	7 g of leaves in 400 mL water (consumed with a "polyphpenol-free" breakfast)	158 mg EGCG		96	0.61		12	[61]
Green tea	500 mL	53 mg EGCG	0.17	55	1.04	1.9	10	[62]
Green tea	3 bags of tea in 426 mL water (consumed with or without sugar and milk)	213 mg EGCG	0.270	80	0.38	1.3	30	[24]
Green tea (decaffeinated)	1.5 g in 500 mL water (w/45 g sucrose, 7.5 g coffee whitener)	110 mg EGCG		259	2.35	1.6	6	[23]
Green tea (decaffeinated)	3 g in 500 mL water (w/ 45 g sucrose, 7.5 g coffee whitener)	219 mg EGCG		711	3.25	2.4	6	[23]

Green tea (decaffeinated)	4.5 g in 500 mL water (w/ 45 g sucrose, 7.5 g coffee whitener)	329 mg EGCG	700	2.13	2.7	6	[23]
Black tea	250 mL consumed 4x over 6 h (1000 mL total) (consumed with sugar cookies)	36.54 mg EGCG (consumed at 0, 2, 4 and 6 hr)	20	0.55		15	[63]

Note: Unless specified, study did not indicate that subjects were instructed to consume the tea with a meal.

Table 2. Bioavailability of epigallocatechin (EGC) observed in human clinical trials after ingestion of brewed green and black tea infusions

EGC Source	Amount	Dosage Delivered	AUC value (μmol h/L)	Plasma C_{max} (raw, nmol/L)	Plasma C_{max} (dose normalized nmol/L/mg EGC)	T_{max} (h)	# subjects	Reference
Green tea	3 g of leaves in 400 mL water (consumed with a "polyphpenol-free" breakfast)	59 mg EGC		185	3.14		12	[61]
Green tea	5 g of leaves in	99 mg EGC		298	3.01		12	[61]

	400 mL water (consumed with a "polyphpenol-free" breakfast)						
Green tea	7 g of leaves in 400 mL water (consumed with a "polyphpenol-free" breakfast)	137 mg EGC	278	2.03		12	[61]

Green tea	3 bags of tea in 426 mL water (consumed with or without sugar and milk)	270 mg EGC	2.59	740	2.74	1.3	30	[24]
Green tea (decaffeinated)	1.5 g in 500 mL water (w/ 45 g sucrose, 7.5 g coffee whitener)	102 mg EGC		483	4.74	1.4	6	[23]
Green tea (decaffeinated)	3 g in 500 mL water	204 mg EGC		1650	8.09	1.8	6	[23]

	(w/ 45 g sucrose, 7.5 g coffee whitener)						
Green tea (decaffeinated)	4.5 g in 500 mL water (w/ 45 g sucrose, 7.5 g coffee whitener)	306 mg EGC	1790	5.85	1.3	6	[23]
Black tea	250 mL tea consumed 4x over 6 h (1000 mL total) (consumed	15.48 mg EGC (consumed at 0, 2, 4 and 6 hr)	145	9.37		15	[63]

	with sugar cookies

Note: Unless specified, study did not indicate that subjects were instructed to consume the tea with a meal.

Table 3. Bioavailability of epicatechin (EC) as observed in human clinical trials after ingestion of brewed green and black tea infusions

EC Source	Amount	Dosage Delivered	AUC value (μmol h/L)	Plasma C_{max} (raw, nmol/L)	Plasma C_{max} (dose normalized nmol/L/mg EC)	T_{max} (h)	# subjects	Study
Green tea	3 g of leaves in 400 mL water (consumed with a "polyphpenol-free" breakfast)	29 mg EC		127	4.38		12	[61]
Green tea	5 g of leaves in 400 mL water	48 mg EC		189	3.94		12	[61]

Green tea	7 g of leaves in 400 mL water (consumed with a "polyphpenol-free" breakfast)	66 mg EC		220	3.33		12	[61]
Green tea	3 bags in 426 mL water (consumed with or without sugar and milk)	77 mg EC	1.01	330	4.29	1.2	30	[24]

Green tea (decaffeinated)	1.5 g in 500 mL water (w/ 45 g sucrose, 7.5 g coffee whitener)	37.5 mg EC	189	5.04	1.4	6	[23]
Green tea (decaffeinated)	3 g decaffeinated in 500 mL water (w/ 45 g sucrose, 7.5 g coffee whitener)	75 mg EC	651	8.68	1.8	6	[23]
Green tea (decaffeinated)	4.5 g decaffeinated in 500 mL	112.5 mg EC	654	5.81	1.8	6	[23]

	water (w/ 45 g sucrose, 7.5 g coffee whitener)					
Black tea	250 mL consumed 4x over 6 h (1000 mL total) (consumed with sugar cookies)	16.74 mg EC (consumed at 0, 2, 4 and 6 hr)	174	10.39	15	[63]

Note: Unless specified, study did not indicate that subjects were instructed to consume the tea with a meal.

Table 4. Bioavailability of selected catechins and their metabolites as observed in human clinical trials after ingestion of brewed green and black tea infusions

Compound	Source	Amount	Dosage Delivered	AUC value (μmol h/L)	Plasma C_{max} (raw, nmol/L)	Plasma C_{max} (dose normalized nmol/L/mg delivered)	T_{max} (h)	# subjects	Reference
4'-O-Methyl-EGC	Green tea	3 g of leaves in 400 mL water (consumed with a "polyphpenol-free" breakfast)	N/A		76	N/A*	12	[61]	

Green tea	5 g of leaves in 400 mL water (consumed with a "polyphpenol-free" breakfast)	N/A	79	N/A*	12	[61]
Green tea	7 g of leaves in 400 mL water (consumed with a "polyphpenol-free" breakfast)	N/A	87	N/A*	12	[61]

ECG	Green tea	500 mL (no meal)	11 mg ECG	0.12	25	2.27	1.6	10	[62]
	Green tea	3 bags in 426 mL water (consumed with or without sugar and milk)	119 mg ECG	0.32	82	0.69	1.4	30	[24]
	Black tea	250 mL consumed 4x over 6 h (1000 mL total) (consumed with sugar cookies)	31.14 mg ECG (consumed at 0, 2, 4 and 6 hr)		51	1.64		15	[63]

*These values cannot be calculated as 4'-O-methyl-epigallocatechin is a metabolite (i.e. there was no "dosage delivered")
Note: Unless specified, study did not indicate that subjects were instructed to consume the tea with a meal.

Table 5. Bioavailability of catechins when quantified as "total catechins" after consumption of green and black tea infusions in human clinical trials

Compound	Source	Amount	Dosage Delivered	AUC value (μmol h/L)	Plasma C_{max} (raw, nmol/L)	Plasma C_{max} (dose normalized, nmol/L/mg)	T_{max} (h)	# subjects	Reference
Total catechins	Green tea	0.5 g of tea solids in 150 mL water (consumed every 2 h, with milk or water, with or	130 mg total catechins per cup		1,000	7.69	9		[64]

	without a meal)							
Green tea	3 g of tea solids in 600 mL water	930 mg total catechins	2.22	550	0.59	2.3	12	[65]
Green tea	2 g of tea solids in 300 mL water	640 mg total catechins		1,800	2.81	1.5	21	[66]
Black tea	0.5 g of tea solids in 150 mL water (consumed every 2 h,	50 mg total catechins per cup		300	6.00		9	[64]

	with milk or water, with or without a meal)					
Black tea	0.5 g of tea solids in 150 mL water (consumed every 2 h, with milk or water, with or without a meal)	50 mg total catechins per cup	260	5.20	9	[64]

Black tea	3 g of tea solids in 600 mL water	300 mg total catechins	0.53	170	0.52	2.2	12	[65]
Black tea	3 g tea solids in 500 mL water plus 100 mL milk	300 mg total catechins	0.60	180	0.60	2	12	[65]
Black tea	2 g of tea solids in 300 mL water	140 mg total catechins		340	2.43	1.5	21	[66]

Note: Unless specified, study did not indicate that subjects were instructed to consume the tea with a meal.

Table 6. Overview of select human clinical trials involving consumption of tea infusions

Study Subjects	Experimental Design	Dose/Duration	Outcome	Study
19 healthy men with sitting systolic-diastolic blood pressure less than 140/90 mm Hg	Randomized, double-blind, crossover trial	Acute dosing of reconstituted spray dried Lipton black tea formulated with 100, 200, 400, or 800 mg flavonoids/day for 1-week periods (5 separate week periods separated by 1-week washout). Consumed (post fasting) with breakfast and then after	All doses of black tea significantly increased FMD compared to the control but the effect was dose dependent (highest dose showed the most pronounced effect). Black tea intake also decreased office systolic and diastolic blood pressure.	[29]

	8 hours (co-consumption with meal is not specified). Sugar was allowed, except on day 7.	
111 subjects (men and women) with systolic blood pressure between 115-150 mm Hg	3 cups daily of black tea for 6 months. Subjects were instructed to consume tea when they would typically consume it (with or without a meal).	Black tea treatment = lower nighttime rates of systolic and diastolic blood pressure variation [28] by 10% at beginning, month 3 and month 6 of study

15 adults with moderate hypercholesterolemia	Randomized double blind crossover study	3 week intervention per treatment, subjects completed all treatments (5 servings of black tea, caffeinated placebo, or placebo per day, consumed with breakfast and dinner)	Compared to caffeinated water treatment, black tea treatment reduced: total cholesterol 6.5%, LDL cholesterol 11.1%, apolipoprotein B 5%, lipoprotein (a) 16.4%	[27]
20 healthy men	Randomized crossover (Latin square design)	Acute dosing of black tea, green tea, water w/ caffeine matched and water, >1 week between treatments	Significant increases in urinary 4-O-methylgallic acid observed in green and black tea treatments, *ex vivo* lipoprotein oxidation time trending towards greater lag time	[31]

		(consumed without added sugar and milk).		
13 healthy subjects	Randomized crossover trial	7 days of each treatment (1000 mL/day of black tea, green tea, or caffeinated water)	No effect on *in vivo* lipid peroxidation as measured by urinary F_2-isoprostane levels	***Add ref***
22 healthy subjects with slightly raised cholesterol (≥ 5 mmol/L) and/or triacylglycerols (≥ 1.8 mmol/L)	Randomized-controlled crossover trial	4 week intervention period of either 1250 mL black tea or water per day	No effect on *in vivo* lipid peroxidation as measured by urinary F_2-isoprostane levels	[32]
35 obese subjects with metabolic syndrome	Randomized controlled trial	4 cups daily of green tea for 8 weeks (no sugar or milk added, but artificial	No significant effects on biomarkers of MetS or inflammation, significantly reduced plasma serum amyloid	65

		sweetener allowed)	alpha (risk factor of CVD)
35 obese subjects with metabolic syndrome	Randomized, controlled prospective trial	4 cups daily of green tea for 8 weeks (no sugar or milk added, but artificial sweetener allowed)	Significant reduction in body weight and body mass index, decreasing trend in LDL and HDL, decreased biomarkers of oxidative stress (malondialdehyde and hydroxynonenals) [67]
12 healthy men	Randomized crossover (Latin square design)	3 days of each treatment (1500 mL per day of full strength oolong tea, half strength oolong tea, water w/ caffeine matched, or water), on 3rd day energy	Energy expenditure was increased by 2.9% after the full strength oolong tea treatment and fat oxidation was 12% higher after the full strength treatment [68]

		expenditure was measured		
20 subjects with T2DM taking antihyperglycemic medicine	Randomized crossover trial	4 week intervention period, 1500 mL oolong tea or water per day (consumption with or without a meal was not controlled)	Oolong tea intervention resulted in significantly reduced fasting blood glucose (229 to 162 mg/dL) and fructosamine (409 to 323 μmol/L) levels compared to baseline	[69]
14 healthy subjects	Randomized crossover trial	Acute administration of 300 mL green tea or water concurrently with a meal	No significant difference in blood glucose or insulin areas under the curve associated with green tea meal, self-reported satiety levels were significantly higher after green tea meal compared with control meal	[70]

133 heavy smokers	Randomized controlled intervention	4 cups per day of black or decaffeinated green tea or water for 4 months	Decaffeinated green tea treatment resulted in significant reduction (-31%) in urinary 8-hydroxydeoxyguanosine levels (biomarker of oxidative DNA damage)	[71]
113 men diagnosed with prostate cancer		6 cups daily of green tea black tea for 3-8 weeks prior to study	Green tea treatment = Significantly reduced nuclear NFκB in prostate tissue	[41]

Note: Unless specified, study did not indicate that subjects were instructed to consume the tea with a meal.

References

1. Sun C-L, Yuan J-M, Koh W-P, Mimi CY. Green tea, black tea and breast cancer risk: a meta-analysis of epidemiological studies. *Carcinogenesis.* 2006;27(7):1310-1315.

2. Geleijnse JM, Launer LJ, van der Kuip DA, Hofman A, Witteman JC. Inverse association of tea and flavonoid intakes with incident myocardial infarction: the Rotterdam Study. *The American journal of clinical nutrition.* 2002;75(5):880-886.

3. Kinjo Y, Cui Y, Akiba S, et al. Mortality risks of oesophageal cancer associated with hot tea, alcohol, tobacco and diet in Japan. *Journal of Epidemiology.* 1998;8(4):235-243.

4. Yuan J-M. Cancer prevention by green tea: evidence from epidemiologic studies. *The American journal of clinical nutrition.* 2013;98(6):1676S-1681S.

5. Redan BW, Buhman KK, Novotny JA, Ferruzzi MG. Altered transport and metabolism of phenolic compounds in obesity and diabetes: implications for functional food development and assessment. *Advances in Nutrition.* 2016;7(6):1090-1104.

6. Manach C, Williamson G, Morand C, Scalbert A, Rémésy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies–. *The American journal of clinical nutrition.* 2005;81(1):230S-242S.

7. González-Sarrías A, Combet E, Pinto P, et al. A systematic review and meta-analysis of the effects of flavanol-containing tea, cocoa and apple products on selected cardiometabolic risk biomarkers: exploring the factors responsible for variability in their efficacy. *Nutrients, 2017, vol. 9, num. 7, p. 746.* 2017.

8. Liu K, Zhou R, Wang B, et al. Effect of green tea on glucose control and insulin sensitivity: a meta-analysis of 17 randomized controlled trials–. *The American journal of clinical nutrition.* 2013;98(2):340-348.

9. Williamson G, Manach C. Bioavailability and bioefficacy of polyphenols in humans. II. Review of 93 intervention studies–. *The American journal of clinical nutrition.* 2005;81(1):243S-255S.

10. Yarmolinsky J, Gon G, Edwards P. Effect of tea on blood pressure for secondary prevention of cardiovascular disease: a systematic review and meta-analysis of randomized controlled trials. *Nutrition reviews.* 2015;73(4):236-246.

11. Jurgens TM, Whelan AM, Killian L, Doucette S, Kirk S, Foy E. Green tea for weight loss and weight maintenance in overweight or obese adults. *The Cochrane database of systematic reviews.* 2012;12.

12. Hartley L, Flowers N, Holmes J, et al. Green and Black Tea for the Primary Prevention of Cardiovascular Disease (CVD): A Cochrane Systematic Review. *J Epidemiol Community Health.* 2013;67(Suppl 1):A52-A53.

13. Boehm K, Borrelli F, Ernst E, et al. Green tea (Camellia sinensis) for the prevention of cancer. *The Cochrane Library.* 2009.

14. Song WO, Chun OK. Tea is the major source of flavan-3-ol and flavonol in the US diet. *The Journal of nutrition.* 2008;138(8):1543S-1547S.

15. Neilson AP, Ferruzzi MG. Influence of formulation and processing on absorption and metabolism of flavan-3-ols from tea and cocoa. *Annual review of food science and technology.* 2011;2:125-151.

16. Bohn T. Dietary factors affecting polyphenol bioavailability. *Nutrition Reviews.* 2014;72(7):429-452.

17. Rein MJ, Renouf M, Cruz-Hernandez C, Actis-Goretta L, Thakkar SK, da Silva Pinto M. Bioavailability of bioactive food compounds: a challenging journey to bioefficacy. *British Journal of Clinical Pharmacology.* 2013;75(3):588-602.

18. Bohn T, McDougall GJ, Alegría A, et al. Mind the gap—deficits in our knowledge of aspects impacting the bioavailability of phytochemicals and their metabolites—a position paper focusing on carotenoids and polyphenols. *Molecular Nutrition & Food Research.* 2015;59(7):1307-1323.

19. Roowi S, Stalmach A, Mullen W, Lean ME, Edwards CA, Crozier A. Green tea flavan-3-ols: colonic degradation and urinary excretion of catabolites by humans. *Journal of agricultural and food chemistry.* 2009;58(2):1296-1304.

20. Appeldoorn MM, Vincken J-P, Aura A-M, Hollman PC, Gruppen H. Procyanidin dimers are metabolized by human microbiota with 2-(3, 4-dihydroxyphenyl) acetic acid and 5-(3, 4-dihydroxyphenyl)-γ-valerolactone as the major metabolites. *Journal of agricultural and food chemistry.* 2009;57(3):1084-1092.

21. Sánchez-Patán F, Chioua M, Garrido I, et al. Synthesis, analytical features, and biological relevance of 5-(3′, 4′-dihydroxyphenyl)-γ-valerolactone, a microbial metabolite derived from the catabolism of dietary flavan-3-ols. *Journal of agricultural and food chemistry.* 2011;59(13):7083-7091.

22. Mulder TP, Rietveld AG, van Amelsvoort JM. Consumption of both black tea and green tea results in an increase in the excretion of hippuric acid into urine. *The American journal of clinical nutrition.* 2005;81(1):256S-260S.

23. Yang CS, Chen L, Lee MJ, Balentine D, Kuo MC, Schantz SP. Blood and urine levels of tea catechins after ingestion of different amounts of green tea by human volunteers. *Cancer Epidemiology Biomarkers & Prevention.* 1998;7(4):351.

24. Henning SM, Niu Y, Lee NH, et al. Bioavailability and antioxidant activity of tea flavanols after consumption of green tea, black tea, or a green tea extract supplement. *The American journal of clinical nutrition.* 2004;80(6):1558-1564.

25. Yang CS, Hong J. Prevention of chronic diseases by tea: possible mechanisms and human relevance. *Annual review of nutrition.* 2013;33:161.

26. Mulder TP, van Platerink CJ, Schuyl PW, van Amelsvoort JM. Analysis of theaflavins in biological fluids using liquid chromatography–electrospray mass spectrometry. *Journal of Chromatography B: Biomedical Sciences and Applications.* 2001;760(2):271-279.

27. Davies MJ, Judd JT, Baer DJ, et al. Black tea consumption reduces total and LDL cholesterol in mildly hypercholesterolemic adults. *The Journal of nutrition.* 2003;133(10):3298S-3302S.

28. Hodgson JM, Croft KD, Woodman RJ, et al. Black tea lowers the rate of blood pressure variation: a randomized controlled trial. *The American journal of clinical nutrition.* 2013;97(5):943.

29. Grassi D, Mulder TP, Draijer R, Desideri G, Molhuizen HO, Ferri C. Black tea consumption dose-dependently improves flow-mediated dilation in healthy males. *Journal of hypertension.* 2009;27(4):774-781.

30. Hodgson JM, Devine A, Puddey IB, Chan SY, Beilin LJ, Prince RL. Tea intake is inversely related to blood pressure in older women. *The Journal of nutrition.* 2003;133(9):2883-2886.

31. Hodgson JM, Puddey IB, Croft KD, et al. Acute effects of ingestion of black and green tea on lipoprotein oxidation. *The American journal of clinical nutrition.* 2000;71(5):1103-1107.

32. Hodgson JM, Croft KD, Mori TA, Burke V, Beilin LJ, Puddey IB. Regular ingestion of tea does not inhibit in vivo lipid peroxidation in humans. *The Journal of nutrition.* 2002;132(1):55-58.

33. CDC. National Diabetes Statistics Report. 2017; https://http://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. Accessed May 14, 2018.

34. Perreault L, Pan Q, Mather KJ, et al. Effect of regression from prediabetes to normal glucose regulation on long-term reduction in diabetes risk: results from the Diabetes Prevention Program Outcomes Study. *Lancet.* Jun 2012;379(9833):2243-2251.

35. Yang CS, Zhang J, Zhang L, Huang J, Wang Y. Mechanisms of body weight reduction and metabolic syndrome alleviation by tea. *Molecular Nutrition & Food Research.* 2016;60(1):160-174.

36. Odegaard AO, Pereira MA, Koh W-P, Arakawa K, Lee H-P, Mimi CY. Coffee, tea, and incident type 2 diabetes: the Singapore Chinese Health Study. *The American journal of clinical nutrition.* 2008;88(4):979-985.

37. Miao M, Jiang B, Jiang H, Zhang T, Li X. Interaction mechanism between green tea extract and human alpha-amylase for reducing starch digestion. *Food Chem.* Nov 1 2015;186:20-25.

38. Makiuchi T, Sobue T, Kitamura T, et al. Association between green tea/coffee consumption and biliary tract cancer: A population-based cohort study in Japan. *Cancer Sci.* Jan 2016;107(1):76-83.

39. Yang G, Zheng W, Xiang Y-B, et al. Green tea consumption and colorectal cancer risk: a report from the Shanghai Men's Health Study. *Carcinogenesis.* 2011;32(11):1684-1688.

40. Núñez-Sánchez MA, González-Sarrías A, Romo-Vaquero M, et al. Dietary phenolics against colorectal cancer—From promising preclinical results to poor translation into clinical trials: Pitfalls and future needs. *Molecular nutrition & food research.* 2015;59(7):1274-1291.

41. Henning SM, Wang P, Said JW, et al. Randomized clinical trial of brewed green and black tea in men with prostate cancer prior to prostatectomy: Green and Black Tea in Prostate Cancer. *The Prostate.* 2015;75(5):550-559.

42. Li N, Sun Z, Han C, Chen J. The chemopreventive effects of tea on human oral precancerous mucosa lesions. *Experimental Biology and Medicine.* 1999;220(4):218-224.

43. Chow HHS, Hakim IA. Pharmacokinetic and chemoprevention studies on tea in humans. *Pharmacol. Res.* 2011;64(2):105-112.

44. Pervin M, Unno K, Nakagawa A, et al. Blood brain barrier permeability of (−)-epigallocatechin gallate, its proliferation-enhancing activity of human neuroblastoma SH-SY5Y cells, and its preventive effect on age-related cognitive dysfunction in mice. *Biochemistry and biophysics reports.* 2017;9:180-186.

45. Unno K, Pervin M, Nakagawa A, et al. Blood–Brain Barrier Permeability of Green Tea Catechin Metabolites and their Neuritogenic Activity in Human Neuroblastoma SH-SY5Y Cells. *Molecular nutrition & food research.* 2017;61(12).

46. Feng L, Chong M-S, Lim W-S, et al. Tea consumption reduces the incidence of neurocognitive disorders: Findings from the Singapore Longitudinal Aging Study. *The journal of nutrition, health & aging.* 2016;20(10):1002-1009.

47. Hu G, Bidel S, Jousilahti P, Antikainen R, Tuomilehto J. Coffee and tea consumption and the risk of Parkinson's disease. *Movement disorders.* 2007;22(15):2242-2248.

48. Tan E-K, Tan C, Fook-Chong S, et al. Dose-dependent protective effect of coffee, tea, and smoking in Parkinson's disease: a study in ethnic Chinese. *Journal of the neurological sciences.* 2003;216(1):163-167.

49. Ascherio A, Zhang SM, Hernán MA, et al. Prospective study of caffeine consumption and risk of Parkinson's disease in men and women. *Annals of neurology.* 2001;50(1):56-63.

50. Ross GW, Abbott RD, Petrovitch H, et al. Association of coffee and caffeine intake with the risk of Parkinson disease. *Jama.* 2000;283(20):2674-2679.

51. Tan LC, Koh W-P, Yuan J-M, et al. Differential effects of black versus green tea on risk of Parkinson's disease in the Singapore Chinese Health Study. *American journal of epidemiology.* 2007;167(5):553-560.

52. Rizwan A, Zinchenko A, Özdem C, Rana MS, Al-Amin MM. The effect of black tea on human cognitive performance in a cognitive test battery. *Clinical Phytoscience.* 2017;3(1):13.

53. Gasińska A, Gajewska D. Tea and coffee as the main sources of oxalate in diets of patients with kidney oxalate stones. *Rocz. PZH.* 2007;58(1):61-67.

54. Mehra A, Baker C. Leaching and bioavailability of aluminium, copper and manganese from tea (Camellia sinensis). *Food Chemistry.* 2007;100(4):1456-1463.

55. Shim S-M, Ferruzzi MG, Kim Y-C, Janle EM, Santerre CR. Impact of phytochemical-rich foods on bioaccessibility of mercury from fish. *Food Chemistry.* 2009;112(1):46-50.

56. World Health Organization. Micronutrient deficiencies. 2015; http://www.who.int/nutrition/topics/ida/en/. Accessed February 15, 2018.

57. Thankachan P, Walczyk T, Muthayya S, Kurpad AV, Hurrell RF. Iron absorption in young Indian women: the interaction of iron status with the influence of tea and ascorbic acid–. *The American journal of clinical nutrition.* 2008;87(4):881-886.

58. South PK, House WA, Miller DD. Tea consumption does not affect iron absorption in rats unless tea and iron are consumed together. *Nutrition Research.* 1997;17(8):1303-1310.

59. Hurrell RF, Reddy M, Cook JD. Inhibition of non-haem iron absorption in man by polyphenolic-containing beverages. *British Journal of Nutrition.* 1999;81(4):289-295.

60. Carbonell-Capella JM, Buniowska M, Barba FJ, Esteve MJ, Frígola A. Analytical methods for determining bioavailability and bioaccessibility of bioactive compounds from fruits and vegetables: A review. *Comprehensive Reviews in Food Science and Food Safety.* 2014;13(2):155-171.

61. Renouf M, Marmet C, Guy PA, et al. Dose-response plasma appearance of green tea catechins in adults. *Mol Nutr Food Res.* May 2013;57(5):833-839.

62. Stalmach A, Troufflard S, Serafini M, Crozier A. Absorption, metabolism and excretion of Choladi green tea flavan-3-ols by humans. *Molecular Nutrition & Food Research.* 2009;53(S1):S44-S53.

63. Warden BA, Smith LS, Beecher GR, Balentine DA, Clevidence BA. Catechins are bioavailable in men and women drinking black tea throughout the day. *The Journal of nutrition.* 2001;131(6):1731-1737.

64. van het Hof KH, Wiseman SA, Yang CS, Tijburg LB. Plasma and lipoprotein levels of tea catechins following repeated tea consumption. *Proceedings of the Society for Experimental Biology and Medicine. Society for Experimental Biology and Medicine (New York, N.Y.).* 1999;220(4):203-209.

65. van het Hof KH, Kivits GA, Weststrate JA, Tijburg LB. Bioavailability of catechins from tea: the effect of milk. *European journal of clinical nutrition.* 1998;52(5):356-359.

66. Leenen R, Roodenburg AJ, Tijburg LB, Wiseman SA. A single dose of tea with or without milk increases plasma antioxidant activity in humans. *European journal of clinical nutrition.* 2000;54(1):87-92.

67. Basu A, Sanchez K, Leyva MJ, et al. Green Tea Supplementation Affects Body Weight, Lipids, and Lipid Peroxidation in Obese Subjects with Metabolic Syndrome. *Journal of the American College of Nutrition.* February 1, 2010 2010;29(1):31-40.

68. Rumpler W, Seale J, Clevidence B, et al. Oolong tea increases metabolic rate and fat oxidation in men. *The Journal of nutrition.* 2001;131(11):2848-2852.

69. Hosoda K, Wang M-F, Liao M-L, et al. Antihyperglycemic Effect of Oolong Tea in Type 2 Diabetes. *Diabetes Care.* June 1, 2003 2003;26(6):1714-1718.

70. Josic J, Olsson AT, Wickeberg J, et al. Does green tea affect postprandial glucose, insulin and satiety in healthy subjects: a randomized controlled trial. *Nutrition journal.* 2010;9(1):63-63.

71. Hakim IA, Harris RB, Brown S, et al. Effect of increased tea consumption on oxidative DNA damage among smokers: A randomized controlled study. *JOURNAL OF NUTRITION.* 2003;133(10):3303S-3309S.