Fifth International Scientific Symposium on Tea & Human Health
Speaker Presentation Summaries

Tea and Human Health: An Overview of Current Findings

Ever since humans began brewing tea some 50 centuries ago, it was thought to provide health benefits. Now, modern research has strongly suggests that tea provides myriad health benefits to virtually every organ and system in the human body, from the heart, brain and bones to total body metabolic advantages that may promote a healthy weight.

Not only is tea one of the most ancient beverages, it's also one of the most researched. Over the past several decades, thousands of peer-reviewed studies have been published that have identified and quantified thousands of bioactive compounds in the leaves of the *Camellia sinensis* plant that are used to make green, black and oolong tea. Studies have been conducted that reveal the mechanisms of actions by which specific tea compounds may elicit health benefits and show how these diverse elements in tea work synergistically to promote health when consumed as a plant-based beverage.

The extensive tea research includes laboratory, animal studies, observational studies of large populations and randomized clinical trials. The benefits of tea are often attributed to the phenolic compounds (some of which act as antioxidants). Numerous studies with the major catechins in tea, namely epicatechins in green tea and the theaflavins and thearubinigins in black tea show that these compounds are at least partially digested, create many bioactive metabolites and sometimes pass through the body intact whereby they provide health benefits via the microbiota.

The most recent research suggests that consuming tea as it was intended—as a beverage—was the best way to help ensure tea would impart the most health benefits. Supplements of specific catechins may have a particular benefit but lack the total spectrum of advantages that the beverage contains. Hundreds of thousands of bioactive elements are found within tea's leaves and together, they work synergistically to impact virtually every cell in the human body—from the heart, bones, brain, skin, and gastrointestinal tract.

Research suggests tea can help reduce the risk of the most common chronic diseases associated with aging including heart disease, cancer, obesity, neurological decline, cognition and osteoporosis. New research is also evaluating the health benefits of the process of brewing and enjoying tea and whether that also improves health.

As tea research advances into the next millennia, here are some exciting recent findings presented at the Fifth International Tea & Human Health Symposium.

Weight Management:

An a meta-analyses including six published tea research studies, 24-hour energy expenditure increased with a catechin-caffeine mixture by 4.7% or 102 calories over 24 hours and fat oxidation increased during the same period, revealing that tea may aid weight loss.

Hursel R, Viechtbauer W, Dulloo AG et al. The effects of catechin rich teas and caffeine on energy expenditure and fat oxidation: a meta-analysis. *Obes Rev*. 2011 Jul;12(7):e573-81.

In a meta-analyses of 11 published clinical studies, catechins or epigallocatechin gallate (EGCG)-caffeine mixture have a modest positive effect on weight loss and weight maintenance.

Hursel R, Viechtbauer W, Westerterp-Plantenga MS.
The effects of green tea on weight loss and weight maintenance: a meta-analysis. Int J Obes (Lond). 2009 Sep;33(9):956-61. Epub 2009 Jul 14.

Cognitive Function and Neurological Decline:

A published randomized human clinical trial found that subjects given a daily supplement with green tea extract and theanine from tea experienced improvements in mild cognitive impairments (MCI).

Pack S, Jung IC, Lee WK, et al. A Combination of Green Tea Extract and l-Theanine Improves Memory and Attention in Subjects with Mild Cognitive Impairment: A Double-Blind Placebo-Controlled Study. *J Med Food.* 14 (4) 2011, 334–343.

Caffeine and L-theanine in tea may offer cognitive benefits and improve mental clarity and work performance. A cross-sectional study showed that participants who consumed more tea felt less tired and reported higher levels of subjective work performance.

Bryan, J, Tuckey, M., Einöther S.J.L. et al. The relationship between tea and other beverage consumption, work performance and mood. Appetite, 2012. 58 (1), 339–346.

In a test of attention and self-reported measure of alertness, subjects consumed two cups of tea (100 mg caffeine and 46 mg L-theanine) versus a placebo beverage. Results indicated that accuracy on the Attention Switching task was improved after tea as compared to the placebo, as well as performance on two of the four subtasks from the Intersensory Attention task.

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

Heart Health:

Tea consumption improves endothelial function by increasing nitric oxide bioavailability and enhancing vasorelaxation. Tea catechins, epigallocatechin-3-gallate and epicatechin, provided at concentrations achievable in human tissues,) relaxed blood vessel tone of

isolated arterial walls in an animal model.

Aggio A, Grassi D, Onori E, et al. Endothelium/nitric oxide mechanism mediates vasorelaxation and counteracts vasoconstriction induced by low concentration of flavanols. Eur J Nutr. 2012. DOI 10.1007/s00394-012-0320-x.

A meta-analysis of 10 cohort and 7 case control studies revealed that 3 cups per day of tea is associated with a 11 percent reduction in risk of myocardial infarction.

Peters U. Peters, C. Poole et al., "Does tea affect cardiovascular disease? A meta-analysis", *Am J Epidemiol.* 154, pp. 495-503 (2001).

In a randomized, double blind, placebo controlled study of 19 males, daily black tea increased flow mediated dilation (FMD) from an average of 7.8% to up to 10.3%, depending upon flavonoid dosages. The flavonoids in as little as one cup of tea (about 100 mg flavonoids) were found to improve FMD. Black tea decreased systolic blood pressure by -2.6 mm/Hg and diastolic by -2.2 mm/Hg.

Grassi D, Mulder TP, Draijer R, et al. Black tea consumption dose-dependently improves flow-mediated dilation in healthy males. *J Hypertens*. 2009, 27:774–781.

Bone Health:

Green tea polyphenols appear to provide specific bone-building benefits including improving bone formation, decreasing bone degradation.

Shen CL, Yeh JK, Cao J, Wang J-S. Green tea and bone metabolism. Nutr Res 2009; 29(7):437-456. Review.

In a human clinical trial, green tea polyphenols significantly increased serum bone-specific alkaline phosphatase (bone formation biomarker), elevated the change of bone-specific alkaline phosphatase/tartrate-resistant acid phosphatase (bone resorption biomarker) and improved muscle strength at 6 months in postmenopausal women with low bone mass.

Shen CL, Chyu MC, Yeh JK, Zhang Y, Pence BC, Felton CK, Brismee JM, Arjmandi BH, Doctolero S, Wang JS. Effect of green tea and Tai Chi on bone health in postmenopausal osteopenic women: a 6-month randomized placebo-controlled trial. Osteoporos Int 2012; 23(5):1541-52.

Cancer:

A review of published clinical studies suggests that the consumption of 5 cups of green tea per day can help prevent several types of cancer and may provide recurrence protection against colorectal cancer.

Fujiki H, Imai K, Nakachi K, Shimizu M et al. Challenging the effectiveness of green tea in primary and tertiary cancer prevention. *J Cancer Res Clin Oncol.* 2012 Aug;138(8):1259-70. Epub 2012 Jun 15.

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Flavonoids: Where We Are and Where We Need To Go - Foods, Databases and Labels
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Flavonoids are phenolic compounds in foods that are among the most ubiquitous of the non-nutrient bioactive compounds with potentially positive health effects. Although tea is the greatest contributor of flavonoids in the American diet, at present, no dietary reference intake exists for these compounds. Although our understanding is far from complete, their bioavailability, mechanisms of action, metabolism and their impact on the microbiome are now becoming clearer.

Scientific interest in flavonoids stems from the possibility that one or more flavonoid classes or compounds has beneficial effects in decreasing risks of chronic degenerative diseases such as cardiovascular disease, diabetes, certain cancers, as well for improving bone health, cognitive function and weight management.

New analytical techniques to characterize and quantify flavonoids in foods and beverages has recently become available, allowing researchers to further investigate total dietary intakes in large population-based cohort studies to assess the effects of flavonoid intakes and foods rich in flavonoids, like tea, on human health.

Tea Polyphenols: Absorption, Metabolism and Bioactivity
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Green tea contains high levels of a diversity of polyphenolic compounds including flavan-3-ols (–)-epicatechin, (–)-epigallocatechin and (–)-epigallocatechin-3-*O*-gallate being among the major constituents, along with smaller amounts of chlorogenic acids, kaempferol and myricetin-based sugar conjugates. During oxidation to produce black tea, changes occur in the flavan-3-ol content of the tea leaves with monomers being converted by polyphenol oxidase activity to dimer-like theaflavins and high molecular weight thearubigins. Little was known about the structure of thearubigins until a recent study revealed that black teas containing ~5000 thearubigin components, which are responsible for the red-brown color of tea and the astringent taste. Ongoing research is needed to further characterize these compounds.

Human feeding studies with green tea have established that (–)-epicatechin is efficiently absorbed in the small intestine and appears transiently in the circulatory system as sulfated and glucuronidate metabolites. (–)-Epigallocatechin is absorbed much less readily as is (–)-epigallocatechin-3-*O*-gallate. Recent *in vitro* studies indicate that colonic catabolites formed in this manner, at physiological doses, have antiglycative and neuroprotective effects. Residual levels of flavan-3-ol monomers in black tea appear to be absorbed in a similar manner while theaflavins have resulted in only 0.001% of intake being excreted in urine. Research is underway to determine if black tea theaflavins and thearubigins travel to the colon where they are further

degraded by the microbiota, which may provide new mechanisms whereby tea provides health benefits.

Interactions Between Tea and the Human Microbiome
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Black tea is one of the second most consumed beverage globally and accounts for a significant part of polyphenol intake in the world population. Black tea polyphenols mainly (60-70%) exist as high-molecular weight species such as theaflavins and thearubigins that are poorly absorbed in the upper digestive tract and predominantly persist to the colon where they undergo bioconversions by resident microbiota. In doing so, tea polyphenols modulate gut microbial diversity.

In order to study the complex interactions between dietary polyphenols and the human superorganism, modelling tools are applied that use validated gut models. The *in vitro* impact of black tea polyphenols on the composition of the colonic microbiota can now well be assessed by microbiomics technologies. Nutrikinetic modeling of longitudinally acquired metabolic profiles has been proven critical for defining nutritional phenotypes related to gut microbial bioconversion capacity and establishing relations between gut microbial functionality and circulating metabolites. As an ever-increasing body of evidence suggests that the beneficial GI microbiota play a role in health and wellness, tea may prove to be a dietary component that provides a beneficial pre- or probiotic effect.

Molecular Targets of Tea Polyphenols
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Green and black teas contain different biologically active polyphenolic compounds that might offer protection against a variety of human diseases. Promising experimental and clinical data have demonstrated protective effects, but limited information exists on how these beneficial effects of tea polyphenols are mediated at the cellular level.

Evidence is accumulating that catechins in green tea as well as theaflavins and thearubigins from black tea are the substances responsible for the physiological effects of tea. The green tea catechin EGCG (epigallocatechin-3-gallate) is generally considered to be the biologically most active compound *in vitro*. The modification of the activity of various growth factors, transcription factors and protein kinases is a common mechanism involved in the molecular effects of tea polyphenols.

In addition, tea polyphenols exert direct and indirect antioxidant effects at the cellular level. These include direct scavenging of free radicals, chelating of metal ions, and inhibition of cellular ROS generating enzymes and cytokine production at one hand and induction of intracellular free radical scavenging enzymes on the other hand. As well,

the generation of reactive oxygen species by tea polyphenols was observed in a number of *in vitro* experiments.

Tea Consumption and Risk of Cardiovascular Disease
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Randomized human clinical trials are necessary to determine if tea and how much tea is needed to provide a cardiovascular benefit. However, as these types of studies are not always feasible, epidemiological studies are often used to assess if there are strong or weak associations between a dietary component and cardiovascular disease.

A literature review of 18 publications of observational epidemiologic studies reporting on tea consumption and cardiovascular disease outcomes, representing worldwide populations including subjects from Australia, the United States and Europe, support animal and laboratory data that demonstrate a preventive effect of tea exposure on stroke outcomes, and are remarkably homogeneous. The studies include a wide range of tea consumption, from light tea drinking to heavy tea drinking populations and include populations of consumers of black, green and oolong teas.

Impact of Tea on Functional Measures of Cardiovascular Health
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Dietary flavonoids have been found to slow the development of cardiovascular disease in animal models. In humans, an inverse relationship between flavonoid intake and cardiovascular disease has been described in different epidemiological surveys and retrospective analyses, while few case-control or clinical trials have been completed.

One case-control study found that individuals who drank one cup of tea or more per day (n=192) had a 44% reduction in the risk for myocardial infarction. In another study, moderate (<14 cups of tea per week, n=615) and heavy tea drinkers ($\geq$14 cups of tea per week, n=266) had 31% and 39% risk factor adjusted reductions in mortality, respectively. In addition, other data show that myocardial infarction was estimated to decrease by 11% with an increase in tea consumption of three cups of tea per day.

Data show that flavonoids improve endothelial function. In vitro studies provided evidence for direct effects of flavonoids from tea on endothelium, resulting in vasorelaxation. In addition, results from human studies show that black tea ingestion is able to reduce both systolic and diastolic blood pressure levels, starting from ingestion of one single cup of tea per day.

In another human study with hypertensive subjects, moderate consumption of black tea protected against adverse effects of flow-mediated dilation (FMD) after a fat load. The vascular benefits of tea are also reflected in blood pressure lowering, and improved endothelial function as well as peripheral arterial hemodynamics under fasted and postprandial conditions.

Tea and Cancer: Potential Mechanisms of Prevention
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Laboratory studies have shown that tea and tea constituents, both polyphenols and to a lesser extent caffeine, have cancer preventive activity in a number of animal models and at different stages of the carcinogenic process. For example dietary administration of green tea extract inhibits lung tumorigenesis in mice. In most studies, polyphenols have been reported to be the major active constituents in tea, although in some studies, caffeine has been shown to exert potent cancer preventive activity. Recent animal model studies have focused on the potentiation of the cancer preventive effects of tea by other dietary compounds or in combination with pharmaceutical agents.

A number of potential mechanisms have been proposed for the cancer preventive activities of tea and tea components based on *in vitro* studies. These mechanisms remain largely untested *in vivo*, although there are some exceptions including induction of phase II drug metabolizing enzymes and modulation of insulin-like growth factor signaling. There is evidence to suggest that polyphenol-induced oxidative stress may play a role in the anticancer activity of EGCG. Our laboratory and others have demonstrated that EGCG-induced oxidative stress is critical for inhibition of cell growth and induction of apoptosis.

In conclusion, although there is ample laboratory data demonstrating the preclinical cancer preventive activity of tea and tea constituents, the underlying mechanism(s) of action remain unclear and the efficacy of tea for cancer prevention in humans remains to be conclusively demonstrated.

Role for Tea in Chemoprevention: Observational Evidence
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Green tea contains high concentrations of tea polyphenols including (-)-epigallocatechin-3-gallate (EGCG). Both green tea extracts and EGCG have shown inhibitory effect against the development, progress, and growth of carcinogen-induced tumors in animal models at various organ sites. Epidemiological studies, however, have provided more inconsistent results. Future prospective observational studies with biomarkers of exposure and clinical trials are required to provide definitive evidence for

the hypothesized beneficial effect of tea consumption on cancer development in humans.

When studies control for potential confounders, an inverse association between high consumption of green tea and risk for certain cancers is reported. Green tea consumption was associated with statistically significantly reduced risk of esophageal cancer in men and women who did not consume either alcohol or tobacco products. Epidemiological studies have also demonstrated an inverse, albeit moderate, association between green tea consumption and lung cancer. In population-based studies, the association between green tea consumption and risk for breast, prostate and bladder cancer is inconsistent yet clinical data suggests green tea may offer protection against these cancers, as well.

Can Tea Intake Aid Weight Loss?
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Obesity is the biggest public health threat impacting the world. As a complex disease, its causes and treatments are multifactorial, and it likely will require many treatments to help reverse the incidence rates of overweight and obesity. In addition to being calorie-free, green tea may provide benefits for those trying to lose weight and maintain a healthy weight.

Several studies have evaluated the potential role of green tea catechins and caffeine on obesity prevention. It has been shown that green tea can increase energy expenditure by 4-5% and fat oxidation by 10-16 percent. A daily increase in thermogenesis of approximately 95 calories can eventually lead to substantial weight loss.

Results from meta-analyses reveal that a catechin-caffeine mixture and caffeine-only treatment showed a stimulating effect on energy expenditure and a catechin-caffeine mixture also showed a stimulating effect on fat oxidation compared with placebo. Energy expenditure measured over 24 hours and fat oxidation was increased on average with 0.5kJ/mg and 0.02g/mg for catechin-caffeine mixtures and 0.4kJ/mg and 0.01g/mg for the caffeine-only treatment. It was also shown that catechin-caffeine mixtures have a positive effect on weight loss and on weight maintenance.

Tea and Bone Health: Steps Forward in Translational Nutrition
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Osteoporosis, a degenerative bone disease, is characterized by low bone mass and microstructural deterioration of bone tissue that results in bone fragility and an increased susceptibility to fractures, especially of the hip, spine and wrist. Oxidative

stress (excessive reactive oxygen species) is considered to be responsible for contributing to the etiology of various degenerative diseases, including osteoporosis.

Recent research suggests that bone mineral density is positively associated with tea consumption that might optimize bone health. The bioactive components in tea might benefit bone health in terms of maintaining higher bone mineral density and reducing fracture risk. Specifically, green tea appeared to benefit bone health more than black or oolong tea. Research shows that the bioactive components of green tea increase bone formation (osteoblastogenesis) and has been found to reduce bone resorption (osteoclastogenesis).

These significant beneficial effects on bone suggest that green tea polyphenols might serve as an effective dietary supplement to mitigate bone loss in patients with low bone mass. Future studies with humans should be conducted for longer periods of time and should be monitored via validated biomarkers, and efficacy in terms of bone mass and micro-architecture should be evaluated through advanced imaging technology.

Effects of Tea on Cognitive Performance

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Tea has historically been associated with cognitive benefits such as mental clarity and concentration. Recent findings attribute these benefits to caffeine and theanine, two constituents of tea. Collectively, the studies demonstrate that black tea helps to improve cognitive functioning and, in particular, attention.

Performance benefits of tea have been reported when comparing tea to water and coffee with or without caffeine over the course of a day. Results showed improvements in performance and alertness after caffeine, as well as tentative evidence of beneficial effects of tea over caffeinated water. Other studies investigated the effects of black tea on attention and a self-report measure of alertness. Results indicated that accuracy on the attention-switching tests was improved after tea and subjects felt more alert.

More recent studies have sought to study the impact of tea on psychological wellbeing. A cross-sectional study showed that participants who consumed more tea felt less tired and reported higher levels of work performance. In another study, tea consumption was found to positively impact mood and complex problem solving, compared to water.