



Possible Health Effects of Caffeinated Coffee Consumption on Alzheimer's Disease and Cardiovascular Disease

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Coffee has been known to have both beneficial and harmful effects upon health. Coffee is one of the most widely consumed beverages, worldwide. Dementia/Alzheimer's disease (AD) and cardiovascular disease (CVD) are public health problems that are rapidly increasing in the aging population. Due to the high consumption of coffee, even small effects on an individual's health could have a large effect on public health. The aim of this review article is to provide an overview of previously published studies of coffee consumption on health. Herein, we focus on epidemiological and experimental findings to investigate whether coffee-drinking habits, and/or the quantity of coffee consumption, have any relationship to CVD, dementia/AD, and other chronic diseases. Although the underlying mechanisms are not fully understood, when comparing coffee drinkers with non-drinkers, moderate doses of caffeine showed protective effects against CVD and AD. We hypothesized that caffeine may be a novel therapy to treat CVD and dementia/AD.

Key words: Caffeine, Cardiovascular disease, Dementia, Alzheimer's disease, Coffee

INTRODUCTION

The coffee plant is an evergreen shrub that grows in tropical and subtropical regions throughout the world. After about four years, coffee plants produce white blossoms and the blossoms produce green coffee berries (Adriana, 2007). It takes 6~9 months for coffee berries to ripen. When ripe, the cherries (ripe coffee berries) are harvested by hand, cleaned, fermented, and hulled, leaving the green coffee beans. The green beans are then roasted (coffee beans), blended, ground, and brewed (Sarah and Alan, 2003). The coffee plant is a genus of the *Rubiaceae* family. The classification of the coffee plant is complicated, as there are many species from which most commercial coffee is obtained, including *Coffea arabica* and the *Coffea canephora* (Robusta) (Mary *et al.*, 2009). Caffeine (1,3,7-trimethylxanthine) is an alkaloid found in coffee beans, tea leaves, and cocoa beans and other plants. It is similar in structure to nucleosides and other xanthines found in vari-

ous natural sources (Fig. 1).

Caffeine is the most widely consumed psychoactive drug in the world and most caffeine is consumed in the form of coffee. The amount of caffeine in food items varies widely, with coffee representing a major source of caffeine intake (71~220 mg caffeine/150 ml). In tea, the caffeine content is 32~42 mg/150 ml and in cocoa the caffeine content is 4 mg/150 ml. The caffeine content per cup also varies greatly, depending upon the serving size (25~190 ml), the preparation method for making coffee (boiled, filtered, espresso, or instant) and the type of coffee used (Arabica or Robusta) (Neha *et al.*, 2009). Depending upon the preparation method, the caffeine content of a cup of coffee ranges from 0.6~3.3 mg/ml for espresso, to 0.7~1.1 mg/ml for boiled or filtered coffee and 0.2~1.0 mg/ml for instant coffee. The average caffeine content in Robusta coffee is about twice as high as the average caffeine content in Arabica coffee. Thus, the range of caffeine content for Robusta coffee is 131~220 mg/150 ml and the range of caffeine content for Arabica coffee is 71~120 mg/150 ml (Nehlig, 1999).

The African word for the coffee plant is *bun*, which then became the *Arabica bun*, meaning both the plant and the berry. Rhazes (850-922 AD), a doctor who lived in Persian

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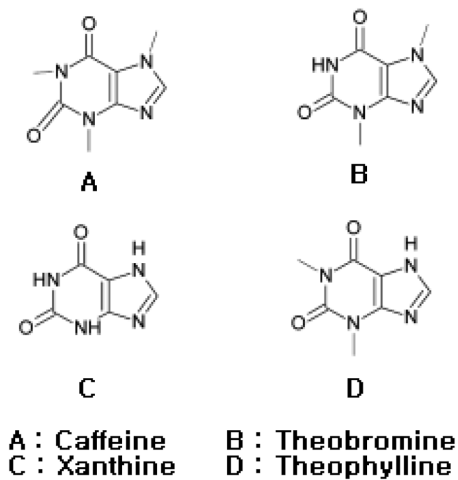


Fig. 1. Structure of caffeine and related molecules.

Iraq, compiled a medical encyclopedia in which he refers to the coffee bean as *bunchum*. His discussion of its healing properties led to the belief that coffee was known as a medicine over a thousand years ago. Similar references appear in the writings of Avicenna (980-1037 AD), another distinguished Muslim physician and philosopher. When used in reference to the beverage, the word ‘coffee’ is a modified form of the Turkish word *Kahveh*, which is derived from the Arabic word, *Kahwa*, which means ‘wine.’ This word derivation reflects the belief that coffee has an effect on people that is similar to the intoxication caused by alcohol. Coffee was also used to treat an astounding variety of ailments, including kidney stones, gout, smallpox, measles, and coughs.

Habitual coffee consumption has been associated with better glucose tolerance in persons without diabetes (Marjo and Miia, 2010). Additionally, coffee contains phenolic compounds with antioxidant properties and may affect the process of atherosclerosis by reducing the risk of LDL-cholesterol and by inhibiting platelet aggregation and thrombogenesis (Bidel and Hu, 2006).

Caffeine displays a broad array of actions on the brain. Recent epidemiological and experimental studies indicate that long-term caffeine intake has beneficial effects against a number of acute and chronic neurological disorders, including stroke, AD, and Parkinson’s disease (PD) (Yukawa *et al.*, 2004).

Conflicting evidence has been found concerning the relationship between caffeinated coffee consumption and the risk of CVD (Dale *et al.*, 2010; Greenberg *et al.*, 2007). A recent study found that moderate consumption of coffee was associated with a lower risk of mortality from CVD (Anderson *et al.*, 2006). On the other hand, the possible health hazards of coffee have been related to its main ingredients, caffeine. The aim of this review is to examine the health effects of caffeinated coffee consumption on CVD

and dementia/AD.

EPIDEMIOLOGICAL AND EXPERIMENTAL FINDING

The longitudinal studies investigating the association between coffee and/or tea consumption and dementia/AD or cognitive function have showed partly inconsistent results (Yohei *et al.*, 2009; Xuesong *et al.*, 2010; Eskelinen *et al.*, 2009). Coffee consumption was categorized into three groups: low (0~2 cups/day), moderate (3~5 cups/day), and high (6 > cups/day). Blood pressure (systolic and diastolic) and body mass index (BMI) were measured and cognitive status was assessed using a three-step protocol for the diagnosis of dementia (a screening, a clinical phase, and a differential diagnostic phase). Recent results from a 21-year follow-up of the Cardiovascular Risk Factors, Aging and Dementia study indicated that drinking three to five cups of coffee per day at midlife (mean age 50.4 years) was associated with a 65% decreased risk of dementia and a 64% decreased risk of AD in later in life. With regard to PD, it was reported 35 years ago that caffeine’s ability to inhibit adenosine receptor activation could lessen a person’s risk of contracting that disease. Subsequent retrospective and prospective epidemiologic studies demonstrated that long-term caffeine intake decreased the risk of developing PD.

A prospective cohort study indicated that no association existed between caffeinated coffee consumption and a higher risk of coronary heart disease (CHD), stroke, or all-cause mortality in both age- and smoking-adjusted analysis and multivariable analysis for lifestyle and other cardiovascular risk factors (Ross *et al.*, 2000; Weili *et al.*, 2009). Another prospective epidemiologic follow-up study indicated that consumption of coffee, green tea, and oolong tea and total caffeine intake was associated with a reduced or mortality from CVD. With regard to strokes among men, when coffee drinkers were compared to non-drinkers of coffee, the multivariable hazards ratio (HR) for those drinking 1~6 cups/week, 1~2 cups/day, and ≥ 3 cups/day were 0.78, 0.67, and 0.45, respectively.

AD, characterized clinically by progressive loss of memory and impaired cognition, is the most common form of irreversible dementia in middle-aged and elderly people. Pathologically, AD is characterized by synaptic loss and neuronal cell death as well as the presence of extracellular amyloid plaques, composed of the amyloid- β (A β) protein and intracellular neurofibrillary tangles. According to the ‘amyloid hypothesis,’ increased levels of A β occur in AD and A β leads to synaptic dysfunction, neuronal cell death, and ultimately, impairment of higher cortical activity, including memory and cognition. Currently, blood-brain barrier (BBB) dysfunction is considered to be one of the earliest pathological events underlying AD.

PD is a chronic neurodegenerative disease characterized

clinically by tremor, imprecise movement, muscular rigidity, and postural instability and pathologically by deficiency of dopaminergic neurons. The cellular and molecular mechanisms underlying the pathogenesis of PD are unclear at present, but PD has been linked to neuroinflammation and oxidative stress.

Coffee is a complex mixture of chemicals including caffeine, phenolic chlorogenic acid, and diterpenes. Caffeine is a natural alkaloid and higher amounts of caffeine are found in coffee than in any other dietary products. Coffee is also a rich source of many other constituents that may contribute to its biological activity including, potassium, niacin, magnesium, and antioxidant substances, such as tocopherols.

Caffeine can block adenosine receptors (A1, A2A, A2B, and A3) distributed among the cellular components of the neurovascular unit and, thereby, it stimulates cholinergic neurons. In mice, it has been shown that both caffeine and adenosine receptor antagonists prevent the accumulation of amyloid- β -peptide (A β) in and around cerebral blood vessels, resulting in cognitive deficits, such as cerebral amyloid angiopathy (CAA). Several characteristics of CAA, which are thought to contribute to acceleration of AD pathology, include impaired neurovascular coupling, loss of cholinergic activity, BBB damages, etc. Recent studies have shown that chronic caffeine consumption reverses cognitive impairment and decreases brain A β levels in AD mice. Chronic caffeine administration has been shown to have neuroprotective effects and is also related to caffeine action as an adenosine receptor antagonist. Diterpenes are natural constituents of coffee beans and, in some studies, they have been associated with an increased risk of high serum total and LDL-cholesterol concentrations. However, the method by which the coffee is brewed may affect its cholesterol-raising effect and filtering the coffee removes most of the diterpenes (Dale *et al.*, 2010).

In randomized trials, the consumption of unfiltered coffee, such as boiled or French press coffee, increased serum LDL-cholesterol concentrations, whereas paper-filtered coffee did not have substantial effects on cholesterol concentration levels (Zhang *et al.*, 2009).

The effect of coffee on CVD remains debated because the underlying mechanisms of its action are complex and involve several behavioral risk factors. Caffeine appears to affect blood pressure (BP) through adenosine receptor inhibition and an increased release of select neurotransmitters. Caffeine levels peak 30~120 min after oral intake and caffeine's half-life is 3~6 hrs. Caffeine tolerance diminishes the acute effect of caffeine on BP and most of evidence suggests that regular intake of caffeinated coffee does not increase the risk of hypertension (Ranheim and Halvorsen, 2005).

CONCLUSION

Our findings suggest that moderate coffee consumption

may decrease the risk of dementia/AD and PD, later in life. This review does not support the hypothesis that habitual consumption of caffeinated coffee increases the risk of CVD and mortality from CVD. However the moderate consumption of coffee and caffeine intake was associated with a lower risk of mortality from CVD.

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