CAFFEINE AND CHLOROGENIC ACIDS IN COFFEE AND EFFECTS ON SELECTED NEURODEGENERATIVE DISEASES

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ABSTRACT
Much controversy and misunderstanding has surrounded the disputed health impact of coffee consumption. Recent studies now help clarify the pharmacological and neurological health promoting properties of coffee daily intake. Benefits are shown attributable to coffee’s rich phytochemistry that includes (besides caffeine), phenolic compounds, such as chlorogenic acids, diterpenes, trigonelline, minerals, amino acids and other volatile compounds. It is also a powerful disease fighting antioxidant, the primary source of antioxidants in several countries.

The purpose of this article is to review results from current epidemiological and mechanistic studies on the central nervous system attributed to coffee. A primary focus to this review is the activity of caffeine and chlorogenic acids and their implications to CNS health. The discussion will highlight possible molecular mechanisms responsible for the respective pharmacological benefits.

Keywords: caffeine, central nervous system, coffee, chlorogenic acid, Alzheimer’s disease, Parkinsonism, Huntington Chorea, Multiple sclerosis

INTRODUCTION
The activity of caffeine and chlorogenic acids in the central nervous system and their implications to health are of ongoing interest to both researchers and clinicians. Coffee is the leading beverage after water and its trade exceeds US$ 10 billion worldwide. It is also the primary source of dietary antioxidants in some countries such in the U.S. The stimulating aromatic drink is made from an infusion of ground roasted seeds of a fruit that was first cultivated from wild plants in the forests of Ethiopia in a region known as Kaffa, as early as 6th century A.D. Consumption quickly spread into Yemen, Arabia and Egypt. Muslims adopted the beverage and it was exclusively theirs for a thousand years (7th to 17th centuries). Later, coffee was exported to Europe via Italy. Jesuits priests are credited with being the first to introduce coffee seeds into Colombia, today the 3rd largest world producer. Portuguese colonizers brought coffee plants to Brazil, the largest coffee producer and the second largest consumer, surpassed only by USA.

The long debate over the potential benefit or harm of coffee consumption to human health continues but new light is being shed on its unique constituent properties. Previous research primarily focused caffeine’s contents and negative health results. Current studies are now more comprehensive and report health promoting properties of coffee daily intake attributable to coffee’s rich phytochemistry that includes, besides caffeine, phenolic compounds (chlorogenic acids and derivatives) diterpenes (kahweol and cafestol), trigonelline, minerals, amino acids and thousands of volatile compounds.

Chemistry of Coffee
Coffee beans have unique properties. The familiar dark infusion of ground, roasted coffee beans, is a beverage composed of hundreds of potentially beneficial compounds. When roasted at high temperatures, new compounds are formed, such as chlorogenic acid quinides or quinolactones, that have known health benefits. Table 1 summarizes the biologically active primary compounds found in green coffee beans.

The complexity of coffee composition and the variability of its aroma, taste and health properties are affected by numerous factors. Firstly being the composition and origin of the beans. Coffee beans are normally purchased green by the coffee industry. Most of the ground coffee brewed today is a mix of two coffee species — Coffea arabica and Coffea robusta.

Second, the roasting process of the green beans can hold temperatures from 160 - 220°C for the duration of 6 minutes (light roast), 7 minutes (medium roast), 8 minutes (dark roast), 9 or more minutes (very dark roast). The variation in the temperatures and duration of the roasting process will determine the final composition of the roasted coffee (Table 2).

Third, the brewing process such as dripping, percolation, filtration, espresso or others, will influence the final composition, although not so dramatically. Possible variations in these three factors explain why study results with apparently similar products, each generally referred as ‘coffee’, produce varying results with conflicting data and health effect conclusions.

Caffeine
Recent epidemiological and mechanistic studies on the central nervous system (CNS) attributed to daily intake of coffee are enlightening and may cause clinicians to reevaluate their recommendations concerning caffeine use. Two constituent coffee chemical components primarily appear responsible for the respective pharmacological effects: caffeine and chlorogenic acids. Caffeine, or 1, 3, 7-trimethylxanthine, is the most broadly known chemical and it is found in concentrations of 0.5-2% (total chemicals) in...
green coffee beans (See Figure 1). Caffeine is rapidly absorbed from the GI tract after drinking coffee beverages and is freely distributed around the body, easily crossing both the blood-brain barrier and placenta.

The most important mechanism of action by caffeine is the antagonism on adenosine receptors, especially the receptor subtypes A1 and A2 6-8. The A1 receptors are associated with protective or homeostatic functions in tissues while A2 receptors appear to have more regulatory function. A2 receptors are widely expressed in the CNS and thus account for the majority of central effects seen with caffeine consumption.

Adenosine is known to be involved in numerous brain functions including sleep, arousal, anxiety, cognition, memory, and pain perception. It is also implicated in pathologies including stroke, Alzheimer’s disease, Huntington’s disease, Parkinson’s disease, myasthenia gravis, epilepsy, depression and schizophrenia 9, 10. Chronic caffeine treatment causes the up-regulation of A1A receptors due to prolonged receptor antagonism, increasing adenosine sensitivity via this receptor overall. This has been seen to have positive effects on the outcomes of cerebral ischemia patients 11.

These G-protein-coupled receptors act by altering cyclic adenosine monophosphate (cAMP) levels in tissues. Their second important target is the inhibition of phosphodiesterases (PDEs: PDE 1, PDE 4 and PDE 5) responsible for the degradation of cAMP 10. Additionally, caffeine can cause calcium release from intracellular stores 8, 12 and affect GABA3 ionotropic receptors. Taken all proposed mechanisms together, caffeine often produces effects overall similar to beta-adrenergic receptor agonists, which increase cAMP levels, but effects on the immune system are less clear cut and may depend significantly on dosage. For instance, Daly (2007) found that at the very low doses of caffeine that humans typically consume, most of its effects are due to adenosine antagonism 12.

Activation of all the adenosine receptor subtypes (A1, A2A, A2B and A3) have been shown to regulate the production of cytokines and other immunoregulatory molecules and therefore suppress inflammation 13-15. Apparently, some binding to plasma proteins occurs in the blood. In adults only about 1% is excreted unchanged whereas ~80% is metabolized to 1,7-dimethylxanthine; ~10% to 3,7-dimethylxanthine (theobromine); and ~4% 1,3-dimethylxanthine (theophylline). These compounds are further metabolized in the liver to monomethylxanthines and finally to methyl uric acids. In adults, caffeine has a plasma half-life of ~3 to 5 hours which is increased in pregnant women and people with liver disease 14, 15.

Chlorogenic Acids (CGA)

The general term chlorogenic acids or CGA refers to a family of esters of hydroxycinnamic acids, such as caffeic, ferulic and p-coumaric, with quinic acid. Quantitatively, the main CGA subclass in coffee are caffeoylquinic acids (CQA), followed by di-cafeoylquinic (di-CQA) and feruloyl quinic (FQA). Among these compounds 5-CQA accounts for 35% of total CGA in roasted coffee. Total chlorogenic acids are found in concentrations of 6-10% in green coffee beans (See Table 1 and Figure 2). One third of the CGA is absorbed on the guts and metabolized in the liver into various metabolites, which includes hippuric and ferulic acids and related compounds that are excreted by the kidneys. The other 2/3 seems to be hydrolyzed into quinic and caffeic acids 16-18. Similarly to other polyphenols in the human diet, chlorogenic acids have important protective antioxidant properties. Indeed, coffee is the major daily dietary source of antioxidants in many countries 19, 20. It has been shown to perform this protective function in cortical neurons subjected to H2O2-induced apoptosis. This protection is thought to be mediated via inhibiting down-regulation of anti-apoptotic proteins Bel-2 and Bel-X(L) and cleavage of caspase-3 and pro-poly (ADP-ribose) polymerase and additionally up regulation of the anti-oxidant enzyme NADPH quinine oxidoreductase 1 NQO1 21-23.

Although characterization of chlorogenic acid and its metabolites is still an ongoing area of study, researchers found a plasma half-life of ~1.7 hours for chlorogenic acid in rats after oral administration 24.

Coffee and Neurodegenerative Disorders

The most important findings of primary interest to clinicians may relate to coffees relationship to neurodegenerative disorders. A recent review on the neuroprotective effects of caffeine by the Department of Neurology of Boston University School of Medicine provides though provoking details on caffeine modulation of adenosine A2A receptor in the brain 25. Through a series of studies, the in vivo function of adenosine receptors in genetic mouse models revealed the development of neurodegenerative disorders, including, stroke, traumatic brain injury, Alzheimer’s, Parkinson’s and Huntington’s diseases, as well as multiple sclerosis. Using the genetic mouse models the researchers demonstrated a broad spectrum of neuroprotection with chronic treatment with caffeine and other adenosine receptor ligands.

This evidence encouraged the development of various adenosine A2A receptor selective antagonists that are now in advanced clinical phase III trials for Parkinson’s disease. The authors finalize their comments by postulating that the potential benefit of caffeine strongly argues against the common practice by clinicians discouraging regular consumption of caffeine (coffee) in aging populations.

Coffee and Alzheimer’s Disease (AD)

Insidious neurodegenerative disorders such as Alzheimer’s disease are also strongly associated with oxidative stress induced by reactive oxygen species (ROS) including hydrogen peroxide. One of the hallmarks of Alzheimer’s disease is the accumulation of senile plaques composed of amyloid β. Amyloid β plays a critical role in the progression of the disease via generation of ROS such as hydrogen peroxide, which ultimately promotes neuronal apoptosis or cell death 21.

Cho et al (2009) using a PC12 rat pheochromocytoma cell line as a model to study neuronal cell death concluded that decaffeinated instant coffee and chlorogenic acid (CGA) inhibit the hydrogen peroxide-induced apoptotic PC12 cell death and further that CGA was largely responsible for these positive effects 21.

Dall’Igna and co-workers were the first to report an in vitro evidence to suggest that adenosine A2A receptors could be the molecular target responsible for observed beneficial effects of caffeine consumption in the development of AD 26. Animal studies of the effects of caffeine blocking the disruption of blood brain barrier using a rabbit model of AD concluded that caffeine is a safe and readily available drug with
important implications for therapeutic interventions against neurological diseases. A comprehensive review of published observational studies on AD and coffee consumption in populations from North America, Europe and Australia included four observational studies conducted during the period of 1996 to 2004. This meta-analysis showed that pooled risk estimate between coffee consumption and AD to be ~0.73 (95% confidence interval: 0.58-0.92). The researchers concluded that coffee consumption is inversely associated with the risk of AD.

Nine longitudinal studies investigating the association between coffee/tea (delivering caffeine) consumption and dementia or cognitive decline were evaluated by Eskelinen and Kivipelto in 2010. Six of those studies evaluated coffee consumption. Sample populations came from Canada, Netherlands, Finland, Italy and France. Three out of six studies were from Finland, home of the highest per capita coffee consumption in the world (12 kilos in 2011). The authors concluded that moderate coffee consumption may decrease the risk of dementia or AD later in life. Table 3 presents the results of the six studies. The data presented in this table was transcribed from the article of the authors Eskelinen and Kivipelto from Aging Research Center (ARC), Karolinska Institutet, Stockholm, Sweden.

In the U.S., a recent longitudinal study examined the relationship between coffee or tea consumption, gender and change of cognitive function. The study utilized data from Cardiovascular Health Study (CHS) of 4809 participants age 65 years or older. Median follow-up time was 7.9 years. Models were adjusted for age, education, smoking status, clinic site, diabetes, hypertension, stroke, coronary heart disease, depression score and apolipoprotein E (APOE) genotype. Interestingly, the researchers concluded that caffeine consumption was associated with cognitive decline in women, but found no consistent effect for men.

An article published in 2012 by Cao, et al. presents a case-control study of two separate cohorts consisting of 124 individuals (65-88 years-old). Participants were cognitively assessed and a blood sample taken for caffeine biomarker analysis. Subjects were then monitored for cognitive status change over the ensuing 2-4 year period. This case-control study provides the first direct evidence that caffeine/coffee intake is associated with a reduced risk of dementia or delayed onset, particularly for those who already have mild cognitive impairment (MCI).

Results showed that no MCI patients with a blood caffeine level above 1200 ng/ml advanced to AD during the 2-4 year study period. The authors suggested that older adults with MCI who drink moderate levels of coffee (3 cups/day) will not convert to Alzheimer’s disease or will experience a substantial delay.

Coffee and Parkinson’s Disease (PD)

Parkinson’s disease follows AD as the second most common neurodegenerative disease, affecting 1% of the population over 65 years. PD is characterized by the loss of nigrostriatal dopaminergic neurons and consequent imbalance of dopamine in the brain. Bradykinesia, resting tremor, muscular rigidity, gait disturbances, and postural reflex impairment are the cardinal features of this insidious disease. The standard-of-care treatment replacing dopamine with L-dopa to control motor symptoms has not changed in the last 40 years.

Interestingly, recent research by Cheng and Chern (2011) highlights the A2A receptor as an emerging therapeutic target in PD. This receptor appears to have a localization in close proximity to dopamine receptor type 2 (D2R) at the striatopallidal neurons with antagonistic interaction. This recent finding provides the molecular basis for the novel use of A2A receptor antagonists such as caffeine to improve motor activity in the treatment of PD.

Although various recent studies are pointing to A2A receptor antagonists promoting neuroprotection, the mechanism of protection against the loss of dopaminergic neurons still unknown. Some studies have demonstrated that with A2A receptor localization forebrain neurons or other elements such as microglia, the effect is either motor stimulatory or neuroprotective, respectively. Interestingly, the fact that A2A receptor antagonists are non-dopaminergic agents may explain why they do not have tendency to induce dyskinesia, the major limiting factor of the treatment of advanced PD with L-dopa due to chronic stimulation of dopamine receptors.

Tan et al. (2006) investigated the potential interaction of this A2A genetic variant with the quantity of coffee and tea intake and their relationship with the risk of PD. Tan found that the dose dependent protective effect of coffee intake in PD demonstrated by their research team in a previous paper was independent of the 2592C>T A2A genotype. Authors suggested that the pharmacogenetic action of caffeine in PD may be mediated differently from other caffeine-induced neurologic syndromes.

Far more than 90% of caffeine clearance is due to differences in metabolism by cytochrome P450 1A2 (CYP 1A2). A polymorphic variant of CYP1A2 (-163C>A) (rs762551) is associated with high CYP1A2 inducibility. In 2007 Tan and colleagues analyzed the relationship between caffeine intake and risk of PD in both fast and slow caffeine metabolizers in a case-study design, noting that the general population is genetically distributed between fast and slow caffeine metabolizers.

Their study population included 868 subjects, 418 with Parkinson’s disease and 468 without, matched by race, gender and age. A multivariate analysis revealed no evidence of interaction effects of caffeine with the variant CYP1A2 (P=0.956). The authors concluded that the association between caffeine intake and risk of PD was similar observed in both fast and slow caffeine metabolizers, supporting experimental evidence in animal models that both caffeine and its major metabolite, paraxanthine, are neuroprotective. This same conclusion was reported by Facheris et al. in 2008.

Also in 2008, McCulloch et al. explored combined effects of four candidate susceptibility genes and two exposures on Parkinson’s disease (PD) risk; namely: alpha-synuclein (SNCA) promoter polymorphism REP1, microtubule-associated protein tau (MAPT) H1/H2 haplotypes, apolipoprotein E (APOE) epsilon2/epsilon3/epsilon4 polymorphism, ubiquitin carboxy-terminal esterase L1 (UCHL1) S18Y variant, cigarette smoking and caffeinated coffee consumption. Complete data on all six factors on 932 PD patients and 664 control subjects from the NeuroGenetics Research Consortium were analyzed. The researchers concluded that while the individual main effects were modest, each yielding OR < 1.6, the effects were cumulative, with some combinations reaching OR ~ 12.6 (95% CI: 5.9-26.8). This study provided credible evidence for Parkinson’s disease.
the long-held notion that PD risk is modulated by cumulative and interactive effects of genes and exposures. More recently, Popat et al. (2011) revisited the association between pharmacogenetic effects of A2A receptor (ADOR2A) and CYP1A2 polymorphisms, coffee consumption and risk of PD. These researchers found that two ADORA2A polymorphisms were inversely associated with PD risk, but no association was found with CYP1A2 variants. However, the coffee-PD association was strongest among slow metabolizers of caffeine who were homozygous carriers of the CYP1A2 polymorphisms\(^8\).

Another interesting study by Powers et al. (2008) composed of subjects from the NeuroGenetics Research Consortium examined the combined effects of smoking, coffee, and NSAIDs on Parkinson's disease risk. Smoking, coffee, and over–the–counter NSAID use as individual factors exhibited significantly reduced risks of 20% to 30%. The two-way and three-way combinations were associated with risk reduction of 37% to 49%, and 62%, respectively. Provocatively, persons who were at the highest exposure strata for smoking and coffee and used NSAIDs had an estimated 87% reduction in risk (OR = 0.13, 95% CI = 0.06–0.29). The authors concluded that whether this finding reflects true biologic protection needs to be investigated further\(^9\).

A more recent genome-wide association and interaction study (GWAIS) from the NeuroGenetics Research Consortium by Hamza et al. (2011) analyzed each SNP's main-effect plus its interaction with coffee. Researchers used genome-wide genotype data and lifetime caffeinated-coffee-consumption data on 1,458 persons with PD and 931 without PD. Their study identified a glutamate receptor gene GRIN2A as a Parkinson's disease modifier gene via interaction with coffee\(^6\).

It appears that GRIN2A encodes an NMDA-glutamate-receptor subunit and regulates excitatory neurotransmission in the brain. Both adenosine antagonists (caffeine-like) and glutamate antagonists (GRIN2A-related) are being tested in clinical trials for treatment of PD.

The association of coffee drinking, cigarette smoking and risk of Parkinson’s disease has been focus of several epidemiological studies. These include those by Hernan et al. (2002); Marder and Logroscino (2002); James (2003); and Tan et al. (2003)\(^10\,\,57\,\,59\).

The systematic review by Hernan et al. summarizes epidemiological evidence on the association involving cigarette smoking was based on 44 case-control and 4 cohort studies, and for coffee drinking, 8 case-control and 5 cohort studies. Results comparing with never smokers, the relative risk of Parkinson's disease was 0.59 (95% CI, 0.54–0.63) for ever smokers, 0.80 (95% CI, 0.69–0.93) for past smokers, and 0.39 (95% CI, 0.32–0.47) for current smokers.\(^7\)

The relative risk per 10 additional pack-years was 0.84 (95% CI, 0.81-0.88) in case-control studies and 0.78 (95% CI, 0.73–0.84) in cohort studies. Compared with non-coffee drinkers, relative risk of Parkinson's disease was 0.69 (95% CI, 0.59–0.80) for coffee drinkers. The relative risk per three additional cups of coffee per day was 0.75 (95% CI, 0.64–0.86) in case-control studies and 0.68 (95% CI, 0.46–1.00) in cohort studies. This meta-analysis shows that there is strong epidemiological evidence that smokers and coffee drinkers have a lower risk of Parkinson's disease.

In 2003 Ragonese investigated the association between cigarette smoking, alcohol drinking, coffee consumption and Parkinson's disease (PD) by means of a questionnaire and interview of 150 PD patients and 150 matched controls. He found an inverse association between coffee drinkers (>81 cups/year vs. none: OR = 0.20, 95% CI = 0.08–0.47, p < or = 0.0001) and PD. Another finding was an inverse association between alcohol drinking (ever vs. never OR = 0.61, 95% CI = 0.39–0.97, p = 0.037) and coffee consumption (ever vs. never OR = 0.16, 95% CI 0.05-0.46, p = 0.0001) and PD\(^6\).

The association of coffee consumption and gender in PD was the focus of another large study where researchers prospectively assessed the relation between coffee consumption and Parkinson's disease mortality among participants in the Cancer Prevention Study II\(^6\). For the CPS II, a cohort of over 1 million people, were initially assessed in 1982. Parkinson's disease was listed as a cause of death in 909 men and 340 women. After adjustment for age, smoking, and alcohol intake, coffee consumption was inversely associated with Parkinson's disease mortality in men (p (trend) = 0.01) but not in women (p = 0.6). In women, this association was dependent on postmenopausal estrogen use; the relative risk for women drinking 4 or more cups (600 ml) of coffee per day compared with nondrinkers was 0.47 (95% confidence interval: 0.27, 0.80; p = 0.006) among never users and 1.31 (95% confidence interval: 0.75, 2.30; p = 0.34) among users. These results suggest that caffeine reduces the risk of Parkinson's disease, but that this hypothetical beneficial effect may be prevented by use of estrogen replacement therapy.

In 2007 Kandinov et al. conducted a retrospective study conducted among 278 consecutive PD patients to determine how these factors (coffee consumption and cigarette smoking) affect the rate of progression of the disease\(^6\). The results showed that disease progression was not affected by cigarette smoking, tea or coffee consumption. In their conclusion they suggested that these variables do not have a disease modifying effect in already diagnosed PD patients.

**Coffee and Huntington's Disease**

Huntington's disease (HD) is an inherited, slowly progressing neurodegenerative disease. Initial symptoms include problems with mood and cognition followed by a lack of coordination and jerky movements, eventually declining into dementia as the neurodegeneration progresses. The disease is thought to be due principally, especially in its early stages, to the loss of local GABAergic inhibitory neurons, known as medium spiny neurons (MSNs), in the basal ganglia. The functions of the basal ganglia are still not totally understood but it is known that they are involved in motivation, motor control and coordination\(^6\).\(^4\). As HD progresses this loss of inhibition results in inappropriately excessive dopaminergic synaptic release. HD can be thought of as roughly the opposite situation that is seen with Parkinson’s disease where dopamine levels are reduced in the basal ganglia.\(^6\)

Interestingly, caffeine’s antagonism of adenosine receptors can counteract the dopaminergic synaptic release excessiveness in HD\(^6\).\(^8\).

Huntington’s disease is due to an autosomal dominant mutation of the protein huntingtin\(^6\). This protein interacts with over a 100 others and has multiple functions\(^6\). It is known that mutant huntingtin causes the death of MSNs\(^6\).\(^8\). Recent research has implicated that abnormal intracellular calcium release from the endoplasmic reticulum is of clinical importance in HD\(^6\). It is well documented that excessive intracellular calcium levels are toxic to neurons and forms the
Multiple sclerosis (MS) is an inflammatory condition of the central nervous system (CNS) characterized by the loss of myelin sheaths surrounding nerves. The disease is primarily an autoimmune condition due to misrecognition of self-antigens by the immune system. Currently, two general theories have been proposed. The first, termed the infection hypothesis, posits that a viral infection in early life may trigger the disease after prolonged exposure to environmental or stress factors. The other hypothesis, named the prevalence hypothesis, is that predetermines an inappropriate immune response to environmental antigens, both of foreign (type 2) and self-identifying/infected cells (type 1) 80. It appears that MS is primarily an autoimmune condition due to mis-recognition of myelin basic protein and proteolipid protein have been suggested as candidate too 81. Recent data have suggested myelin lipids, rather than proteins, may be involved.

Coffee and Multiple Sclerosis

Multiple sclerosis (MS) is an inflammatory condition affecting the CNS that results in the loss of the insulating myelin sheaths that surround neuronal axons, the axons that are vital for proper transmission of action potentials. The disease currently is classified as an autoimmune condition in which the patient’s own immune system misrecognizes myelin, or a component of myelin, as foreign and attacks it. In the process, the cells that produce myelin can be damaged, limiting the ability of the brain to repair damaged myelin. Research indicates MS may be due to oligodendrocyte dysfunction. Oligodendrocytes are the CNS glia responsible for producing myelin 80. As MS does not appear to have specific targets, patients can exhibit diverse symptoms depending on what part or parts of the CNS are affected 81. It is generally accepted that central to the development of MS is due to immunological insult. Currently two general theories have been proposed. The hygiene hypothesis suggests it is the lack of early exposure to several pathogens that predetermines an inappropriate response later in life 81. The other hypothesis, named the prevalence hypothesis, is due to a pathogen more common in areas of high MS incidence where some individuals eventually develop the disease after prolonged exposure to environmental or stress factors or following certain diseases such as measles, rubella and mumps 82.

Of clinical importance, changes to the human leukocyte antigen (HLA) system genes on chromosome 6 that is the major histocompatibility complex (MHC) are linked with increased risk of MS. The MHC receptors are involved in antigen recognition, both of foreign (type 2) and self-identifying/infected cells (type 1) 81. It appears that MS is primarily an autoimmune condition due to mis-recognition of myelin basic protein and proteolipid protein have been suggested as candidate too 83. Recent data have suggested myelin lipids, rather than proteins, may be involved. Significant research studies on MS patients have revealed that their macrophages and microglia had reduced levels and activity of adenosine A1A receptors, which leads to inflammatory responses similar to those seen in MS. Findings suggest that caffeine-induced up regulation of A1A receptors seems to suppress this 84, 85. Chen and Chern (2011) reviewed the current evidence for the effects of methylxanthines and adenosine receptors in general, including the effects of caffeine (a xanthine) and concluded that caffeine indeed appears to have applicable neuroprotective properties especially with respect to the most common neurodegenerative disorders including MS 85. This is supported by a study in Europe by D’hooghe et al. (2011) who also concluded that coffee was inversely associated with the progression of relapsing (discrete attacks) MS but not in progressive MS 86. Still, there is some conflicting evidence concerning caffeine intake and MS. A study by Massa et al. (2013) did not support an association with caffeine intake and MS 87, yet little research directly concerned chlorogenic acid and MS has been performed.

Table 1: Coffee Chemical composition of green beans 88

<table>
<thead>
<tr>
<th>Components</th>
<th>Arabica</th>
<th>Robusta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>1.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Trigonelline</td>
<td>1.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Minerals (41%/K)</td>
<td>4.2</td>
<td>4.4</td>
</tr>
<tr>
<td>Acids Chlorogenic (total)</td>
<td>6.5</td>
<td>10.0</td>
</tr>
<tr>
<td>Aliphatics</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Quinic</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Sugars Sacarose</td>
<td>8.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Reductors</td>
<td>0.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Polysaccharides</td>
<td>44.0</td>
<td>48.0</td>
</tr>
<tr>
<td>Lignin</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Pexit</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Proteins</td>
<td>11.0</td>
<td>11.0</td>
</tr>
<tr>
<td>Free aminoacids</td>
<td>0.3</td>
<td>0.8</td>
</tr>
<tr>
<td>Lipids</td>
<td>16.0</td>
<td>10.0</td>
</tr>
</tbody>
</table>

Table 2: Composition of roasted coffee beans (medium degree of roasting) 89

<table>
<thead>
<tr>
<th>Components</th>
<th>Content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>1.3</td>
</tr>
<tr>
<td>Lipids</td>
<td>17.0</td>
</tr>
<tr>
<td>Proteins³</td>
<td>10.0</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>38.0</td>
</tr>
<tr>
<td>Trigonelline, Niacin</td>
<td>1.0</td>
</tr>
<tr>
<td>Aliphatic acids</td>
<td>2.4</td>
</tr>
<tr>
<td>Chlorogenic acids</td>
<td>2.7</td>
</tr>
<tr>
<td>Volatile compounds</td>
<td>0.1</td>
</tr>
<tr>
<td>Minerals</td>
<td>4.5</td>
</tr>
<tr>
<td>Melanoidins³</td>
<td>23.0</td>
</tr>
</tbody>
</table>

³Based on solids. Water content varies between 1-5%; ³Calculated as sum of the amino acids after acid hydrolysis; ³Calculated as the difference
### Table 3: Six out of nine longitudinal studies where the association of coffee/caffeine intake and dementia/AD/cognitive function was examined*

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Study Design Follow-up</th>
<th>Coffee/caffeine Intake</th>
<th>Covariates</th>
<th>Outcome &amp; results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindsay et al., 2002, CSHA, Canada</td>
<td>N=4088, ≥65 years, 60.7% women</td>
<td>5-year</td>
<td>Daily coffee drinking</td>
<td>Age, gender, education</td>
<td>Decreased risk of AD by 31%</td>
</tr>
<tr>
<td>van Boxtel et al. 2003, MAAS, Netherlands</td>
<td>N=1376 24-81 years (mean:50.2 years-old)</td>
<td>6-year</td>
<td>0, 1-3, 4-6, 7-10, ≥10 cups of coffee/day</td>
<td>Age, gender, education, housing, occupation, smoking, alcohol, Perceived health</td>
<td>Faster locomotive speed; Ns for cognitive decline</td>
</tr>
<tr>
<td>van Gelder et al. 2007, FINE, Finland, Italy, Netherlands</td>
<td>N=676 (101 Finnish, 239 Italians, 336 Dutch) Only elderly men</td>
<td>10-year</td>
<td>0, 1, 2, 3, 4, ≥4 cups of coffee/day</td>
<td>Age, education, country, alcohol, smoking, physical activity, cognitive function</td>
<td>Men who consumed coffee had a 2x smaller 10-year cognitive decline</td>
</tr>
<tr>
<td>Ritchie et al., 2007, Three city study, France</td>
<td>N=7017; ≥65 years 59.8% women</td>
<td>3.5-year</td>
<td>Daily caffeine intake from coffee</td>
<td>Age, gender, study center</td>
<td>Fewer declines in verbal cognitive function to a lesser extent in visualspatial memory in women but not in men with over 3 cups/day</td>
</tr>
<tr>
<td>Eskelinen et al., 2009, CAIDE, Finland</td>
<td>N= 1409 Mean age: 50.4 62% women</td>
<td>21-year</td>
<td>0-2, 3-5, &gt;5 cups of coffee/day</td>
<td>Age, gender, follow-up, residence, midlife smoking, SBP, serum total cholesterol, BMI, physical activity</td>
<td>Decreased risk of dementia by 65% and AD by 64% with daily coffee intake of 3-5 cups.</td>
</tr>
<tr>
<td>Laitala et al., 2009, Finnish Twin Cohort Study, Finland</td>
<td>N=2606 Middle-aged twins, mean age of 46-52; 48% women</td>
<td>28-year</td>
<td>0-3, 3-5, 5-8, &gt;8 cups of coffee/day</td>
<td>Age, education, gender</td>
<td>Ns for coffee and cognitive performance, MCI or dementia</td>
</tr>
</tbody>
</table>

Abbreviations: AD=Alzheimer’s disease; BMI=body mass index; CAIDE=Cardiovascular Risk Factors, Aging and Dementia Study; CSHA=Canadian Study of Health and Aging; FINE=Finland, Italy and Netherlands Elderly Study; MAAS=Maastricht Aging Study; MCI=mild cognitive impairment; Ns=not significant; SBP=systolic blood pressure.


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**Figure 1: Caffeine Chemical Structure**

**Figure 2: Chlorogenic acids – a family of esters of hydroxycinnamic acids (such as caffeic acid) and quinic acid. Caffeoylquinic acids are the most abundant and are present as 3 forms of isomers, esterified at positions 3, 4 or 5.**
CONCLUSION
The controversial role of coffee in the human health has long been a topic of interest, conjecture and misunderstanding. Provocative research now suggests that the pervasive humble beverage, once the domain of only a select few, may hold positive clinical benefits well beyond the well-known satisfying and stimulating effects already celebrated by millions worldwide. Clearly, trustworthy data now indicates that the study of the antioxidant and various other effects of the chemical constituents of coffee as it relates to the neuronal activities of the brain and to several inflammatory-related diseases. Studies as those mentioned in this review indicate that the beneficial aspects of compounds inherent to coffee warrants detailed further studies and perhaps reevaluation by clinicians of recommendations concerning caffeine. Further on, it is necessary to address one important factor that might be an answer for so many controversies in respect to coffee and health preventative effects. There is a need to standardize coffees utilized on clinical and animal studies. After all, we cannot continue neglecting the composition of the coffee and referring to ‘coffee’ as a single and simple product. Coffee industry has to evolve and start labeling their products with a minimum chemical composition and start compromising to stick within a concentration range of the major components in coffee.

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