



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

Santos Roseane Maria Maia^{1*}, Hunter Tracy², Wright Nick³, Lima Darcy Roberto Andrade⁴

¹Assistant Professor, South University School of Pharmacy, Savannah, GA, USA

²Professor, Wingate University School of Pharmacy, Wingate, NC, USA

³Assistant Professor, Wingate University School of Pharmacy, Wingate, NC, USA

⁴Professor, Instituto de Neurologia, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

*Corresponding Author Email: rsantos@southuniversity.edu

DOI: 10.7897/2277-4572.02443

Published by Moksha Publishing House. Website www.mokshaph.com

All rights reserved.

Received on: 28/05/13 Revised on: 26/06/13 Accepted on: 28/06/13

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: coffee, central nervous system caffeine, 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 worldwide¹. It is also the primary source of dietary antioxidants in some countries such in the U.S². This 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 USA³.

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, aminoacids 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 benefits⁴. 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)⁵.

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-trimethylpurine-2,6-dione (C₈H₁₀N₄O₂; also known as 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 A2⁶⁻⁸. 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 A_{1A} 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 patients¹¹.

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 cAMP¹⁰. Additionally, caffeine can cause calcium release from intracellular stores^{6,12} and affect GABA_A 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 antagonism¹².

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 inflammation¹³⁻¹⁵. 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-caffeoylquinic (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 acids¹⁶⁻¹⁸.

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 Bcl-2 and Bcl-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 NQO1²¹⁻²³.

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 administration²⁴.

Coffee and Neurodegenerative Disorders

The most important findings of primary interest to clinicians may relate to coffee's 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 A_{2A} receptor in the brain²⁵. 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 A_{2A} 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 death²¹.

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 effects²¹.

Dall'Igna and co-workers were the first to report an *in vitro* evidence to suggest that adenosine A_{2A} receptors could be the molecular target responsible for observed beneficial effects of caffeine consumption in the development of AD²⁶. 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^{27,28}.

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 AD²⁹.

Nine longitudinal studies investigating the association between coffee/tea (delivering caffeine) consumption and dementia or cognitive decline were evaluated by Eskelinen and Kivipelto in 2010³⁰. 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)³¹. 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 article of the authors Eskelinen and Kivipelto from Aging Research Center (ARC), Karolinska Institutet, Stockholm, Sweden³⁰.

In the U.S., a recent longitudinal study examined the relationship between coffee or tea consumption, gender and change of cognitive function³². 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)³³. 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 brain³⁴⁻³⁶, 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 years³⁷⁻³⁹.

Interestingly, recent research by Cheng and Chern (2011) highlights the A_{2A} receptor as an emerging therapeutic target in PD²⁵. 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 A_{2A} receptor antagonists such as caffeine to improve motor activity in the treatment of PD⁴⁰⁻⁴³.

Although various recent studies are pointing to A_{2A} receptor antagonists promoting neuroprotection, the mechanism of protection against the loss of dopaminergic neurons still unknown. Some studies have demonstrated that with A_{2A} receptor localization forebrain neurons or other elements such as microglia, the effect is either motor stimulatory or neuroprotective, respectively⁴⁴. Interestingly, the fact that A_{2A} 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^{25,45-48}.

Tan et al. (2006) investigated the potential interaction of this A_{2A} genetic variant with the quantity of coffee and tea intake and their relationship with the risk of PD⁴⁹. 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 > Tins A_{2A} genotype⁵⁰. 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 metabolizers⁵¹. Their study population included 886 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 similarly 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 2008⁵².

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 consumption⁵³. 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

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 A_{2A} receptor (ADORA2A) and CYP 1A2 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 CYP 1A2 variants. However, the coffee-PD association was strongest among slow metabolizers of caffeine who were homozygous carriers of the CYP1A2 polymorphisms⁵⁴.

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 further⁵⁵.

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 coffee⁵⁶.

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)^{50, 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 smokers⁵⁷.

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, $p < 0.0001$) 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 PD⁶⁰.

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 II⁶¹. 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 disease⁶². 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^{63, 64}. 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 ganglia⁶⁵. Interestingly, caffeine's antagonism of adenosine receptors can counteract the dopaminergic synaptic release excessiveness in HD⁶⁻⁸.

Huntington's disease is due to an autosomal dominant mutation of the protein Huntingtin⁶⁶. This protein interacts with over a 100 others and has multiple functions⁶⁷. It is known that mutant Huntingtin causes the death of MSNs^{68, 69}. Recent research has implicated that abnormal intracellular calcium release from the endoplasmic reticulum is of clinical importance in HD⁷⁰. It is well documented that excessive intracellular calcium levels are toxic to neurons and forms the

basis of glutamate-induced excitotoxicity observed in stroke^{71, 72}. Studies on cultured mouse MSNs have implicated mutant Huntingtin in this calcium dysfunction and suggested antagonizing ryanodine receptors which mediates calcium-induced calcium release from intracellular stores. The authors used a high dose of caffeine (2.5mM) to potentiate calcium release caused by glutamate on MSNs and the ryanodine antagonist dantrolene to counter¹². This suggests that excessive caffeine consumption may be harmful for HD patients.

Additionally, Huntingtin has been shown to increase transcription of brain-derived neurotrophic factor (BDNF). This is of clinical significance as it is thought that decreased levels of BDNF may contribute initially for the loss of the GABAergic MSNs in the basal ganglia⁷³⁻⁷⁶. Studies with animal models have given apparently conflicting results concerning the involvement of adenosine receptors in this disease. This is due to the fact that the particular A_{2A} receptor subtype expressed in basal ganglia (A_{2A}) appears to have different functions depending on its location, pre- or postsynaptic, and therefore can be both neuroprotective and neurotoxic⁷⁷. A_{2A} receptor activation can facilitate BDNF activity in the brain⁷⁸. This effect can help compensate for diminished BDNF function seen in HD and is postulated as yet another mechanism whereby caffeine may have a negative influence. Popoli and colleagues did an extensive review in 2007 on the conflicting role of adenosine receptors in HD⁷⁸.

There appears to be scarce research into the clinical effect of chlorogenic acid on HD. This is not surprising as although previous researchers suggested that, as in Alzheimer's disease, inflammation is also involved in HD progression⁷⁹.

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 mis-recognizes 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 myelin⁸⁰. As MS does not appear to have specific targets, patients can exhibit diverse symptoms depending on what part or parts of the CNS are affected⁸¹.

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 life⁸¹. 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 mumps⁸².

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 too⁸³. 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 A_{1A} receptors, which leads to inflammatory responses similar to those seen in MS. Findings suggest that caffeine-induced up regulation of A_{1A} 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 MS²⁵. 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 MS⁸⁶. 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 MS⁸⁷, yet little research directly concerned chlorogenic acid and MS has been performed.

Table 1: Coffee Chemical composition of green beans⁸⁸

Components	% on dry basis	
	Arabica	Robusta
Caffeine	1.2	2.2
Trigonelline	1.0	0.7
Minerals (41%=K)	4.2	4.4
Acids: Chlorogenic (total)	6.5	10.0
Aliphatics	1.0	1.0
Quinic	0.4	0.4
Sugars: Sacarose	8.0	4.0
Reductors	0.1	0.4
Polysaccharides	44.0	48.0
Lignin	3.0	3.0
Pectin	2.0	2.0
Proteins	11.0	11.0
Free aminoacids	0.5	0.8
Lipids	16.0	10.0

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

Components	Content (%) ^a	
	Arabica	Robusta
Caffeine	1.3	2.4
Lipids	17.0	11.0
Proteins ^b	10.0	10.0
Carbohydrates	38.0	41.5
Trigonelline, Niacin	1.0	0.7
Aliphatic acids	2.4	2.5
Chlorogenic acids	2.7	3.1
Volatile compounds	0.1	0.1
Minerals	4.5	4.7
Melanoidins ^c	23.0	23.0

^a Based on solids. Water content varies between 1-5%;

^b Calculated as sum of the amino acids after acid hydrolysis;

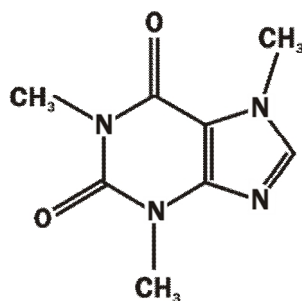
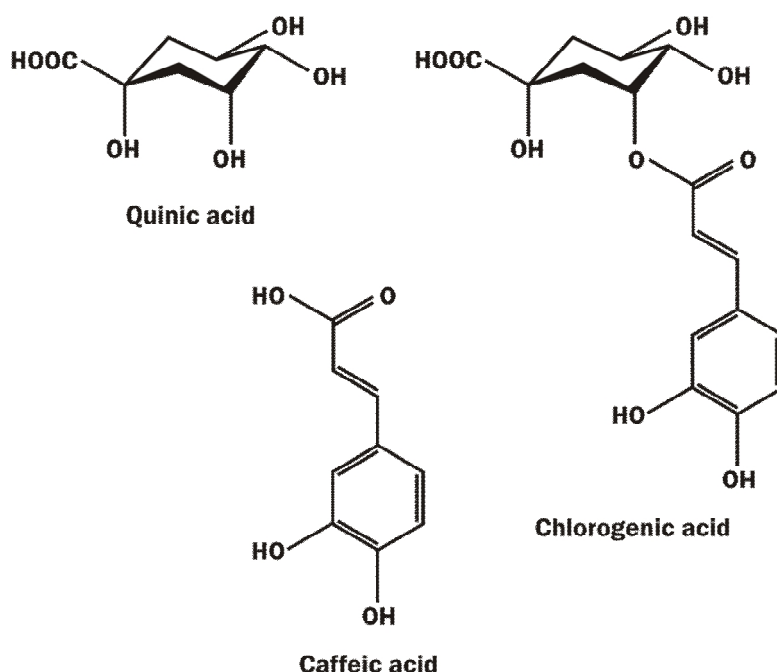
^c Calculated as the difference

Table 3: Six out of nine longitudinal studies where the association of coffee/caffeine intake and dementia/AD/cognitive function was examined*

Study	Sample	Study Design Follow-up	Coffee/caffeine Intake	Covariates	Outcome & results
Lindsay et al. 2002, CSHA, Canada ⁹⁰	N=4088, ≥65 years, 60.7% women	5-year	Daily coffee drinking	Age, gender, education	Decreased risk of AD by 31%
van Boxtel et al. 2003, MAAS, Netherlands ⁹¹	N=1376 24-81 years (mean:50.2 years-old) 48.5% women	6-year	0, 1-3, 4-6, 7- 10, ≥10 cups of coffee/day	Age, gender, education, housing, occupation, smoking, alcohol, Perceived health	Faster locomotive speed; Ns for cognitive decline
van Gelder et al. 2007, FINE, Finland, Italy , Netherlands ⁹²	N=676 (101 Finnish, 239 Italians, 336 Dutch) Only elderly men	10-year	0, 1, 2, 3, 4, >4 cups of coffee/day	Age, education, country, alcohol, smoking, physical activity, cognitive function	Men who consumed coffee had a 2x smaller 10-year cognitive decline
Ritchie et al., 2007, Three city study, France ⁹³	N=7017; ≥65 years 59.8% women	3.5-year	Daily caffeine intake from coffee	Age, gender, study center	Fewer declines in verbal cognitive function to a lesser extent in visuospatial memory in women but not in men with over 3 cups/day
Eskelinen et al., 2009, CAIDE, Finland ⁹⁴	N= 1409 Mean age: 50.4 62% women	21-year	0-2, 3-5, >5 cups of coffee/day	Age, gender, follow-up, residence, midlife smoking, SBP, serum total cholesterol, BMI, physical activity	Decreased risk of dementia by 65% and AD by 64% with daily coffee intake of 3-5 cups.
Laitala et al., 2009, Finnish Twin Cohort Study, Finland ⁹⁵	N=2606 Middle-aged twins, mean age of 46-52; 48% women	28-year	0-3, 3-5, 5-8, >8 cups of coffee/day	Age, education, gender	Ns for coffee and cognitive performance, MCI or dementia

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.

*Transcribed from Table 1, page S170, Journal of Alzheimer's Disease 20(2010) S167-S174.

**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 inherit to coffee warrants detailed further studies and perhaps revaluation 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.

ACKNOWLEDGEMENT


We thank Mrs. Valerie Yaghn, Library Director of South University Savannah Campus for helping to search over various databases for updated material in support to the present manuscript.

REFERENCES

- Butt MS, Sultan MT. Coffee and its consumption: benefits and risks. *Crit Rev Food Sci Nutr*. 2011;51(4):363-73. Epub 2011/03/25.
- Coffee is the number one source of antioxidants. 2005 [06/24/2103]; Available from: <http://phys.org/news6067.html#jCp>.
- Santos RMM, Lima DRA. Coffee a revolutionary drink for pleasure and health. . Pittsburgh, PA: Xlibris; 2007.
- Trugo LC, Macrae, R. A Study of the Effect of roasting on the chlorogenic acid composition of coffee using HPLC. *Food Chemistry*. 1984;15:219-27.
- Farah A, de Paulis T, Moreira DP, Trugo LC, Martin PR. Chlorogenic acids and lactones in regular and water-decaffeinated arabica coffees. *J Agric Food Chem*. 2006;54(2):374-81.
- Daly JW. Caffeine analogs: biomedical impact. *Cellular and molecular life sciences* : CMLS. 2007;64(16):2153-69. Epub 2007/05/22.
- Ferre S. An update on the mechanisms of the psychostimulant effects of caffeine. *Journal of neurochemistry*. 2008;105(4):1067-79. Epub 2007/12/20.
- Fredholm BB, Battig K, Holmen J, Nehlig A, Zvartau EE. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacological reviews*. 1999;51(1):83-133. Epub 1999/03/02.
- Ribeiro JA, Sebastiao AM. Caffeine and adenosine. *Journal of Alzheimer's disease* : JAD. 2010;20 Suppl 1:S3-15. Epub 2010/02/19.
- Sebastiao AM, Ribeiro JA. Adenosine receptors and the central nervous system. *Handbook of experimental pharmacology*. 2009(193):471-534. Epub 2009/07/30.
- Bona E, Aden U, Fredholm BB, Hagberg H. The effect of long term caffeine treatment on hypoxic-ischemic brain damage in the neonate. *Pediatric research*. 1995;38(3):312-8. Epub 1995/09/01.
- Chen X, Wu J, Lvovskaya S, Herndon E, Supnet C, Bezprozvanny I. Dantrolene is neuroprotective in Huntington's disease transgenic mouse model. *Molecular neurodegeneration*. 2011;6:81. Epub 2011/11/29.
- Daly JW. Caffeine analogs: biomedical impact. *Cell Mol Life Sci*. 2007;64:2153-69.
- al. Re. *Pharmacology*. 5 th ed: Churchill Livingstone; 2003.
- NCBI, NLM, NIH. PUBCHEM COMPOUND. Bethesda, MD2004; Available from: <http://www.pubchem.ncbi.nlm.nih.gov>.
- Gonthier MP, Verny MA, Besson C, Remesy C, Scalbert A. Chlorogenic acid bioavailability largely depends on its metabolism by the gut microflora in rats. *J Nutr*. 2003;133(6):1853-9. Epub 2003/05/29.
- Monteiro M, Farah A, Perrone D, Trugo LC, Donangelo C. Chlorogenic acid compounds from coffee are differentially absorbed and metabolized in humans. *J Nutr*. 2007;137(10):2196-201. Epub 2007/09/22.
- Olthof MR, Hollman PC, Katan MB. Chlorogenic acid and caffeic acid are absorbed in humans. *J Nutr*. 2001;131(1):66-71. Epub 2001/02/24.
- Ishimoto H, Tai A, Yoshimura M, Amakura Y, Yoshida T, Hatano T, et al. Antioxidative properties of functional polyphenols and their metabolites assessed by an ORAC assay. *Bioscience, biotechnology, and biochemistry*. 2012;76(2):395-9. Epub 2012/02/09.
- Tsuchiya T, Suzuki O, Igarashi K. Protective effects of chlorogenic acid on paraquat-induced oxidative stress in rats. *Bioscience, biotechnology, and biochemistry*. 1996;60(5):765-8. Epub 1996/05/01.
- Cho ES, Jang YJ, Hwang MK, Kang NJ, Lee KW, Lee HJ. Attenuation of oxidative neuronal cell death by coffee phenolic phytochemicals. *Mutat Res*. 2009;661(1-2):18-24. Epub 2008/11/26.
- Chu YF, Brown PH, Lyle BJ, Chen Y, Black RM, Williams CE, et al. Roasted coffees high in lipophilic antioxidants and chlorogenic acid lactones are more neuroprotective than green coffees. *J Agric Food Chem*. 2009;57(20):9801-8. Epub 2009/09/24.
- Kim JB, Lee S, Shim J, Kim HW, Jang YJ, Yang H, et al. Caffeinated coffee, decaffeinated coffee, and the phenolic phytochemical chlorogenic acid up-regulate NQO1 expression and prevent H2O2-induced apoptosis in primary cortical neurons. *Neurochemical Int*. 2009;60(5):466-74.
- Qi W, Zhao T, Yang WW, Wang GH, Yu H, Zhao HX, et al. Comparative pharmacokinetics of chlorogenic acid after oral administration in rats. *J Pharm Anal*. 2011;1(4):270-74.
- Chen JF, Chern Y. Impacts of methylxanthines and adenosine receptors on neurodegeneration: human and experimental studies. *Handbook of experimental pharmacology*. 2011(200):267-310. Epub 2010/09/23.
- Dall'Igna OP, Porciuncula LO, Souza DO, Cunha RA, Lara DR. Neuroprotection by caffeine and adenosine A2A receptor blockade of beta-amyloid neurotoxicity. *British journal of pharmacology*. 2003;138(7):1207-9. Epub 2003/04/25.
- Chen X, Gawryluk JW, Wagener JF, Ghribi O, Geiger JD. Caffeine blocks disruption of blood brain barrier in a rabbit model of Alzheimer's disease. *Journal of neuroinflammation*. 2008;5:12. Epub 2008/04/05.
- Chen X, Lan X, Roche I, Liu R, Geiger JD. Caffeine protects against MPTP-induced blood-brain barrier dysfunction in mouse striatum. *Journal of neurochemistry*. 2008;107(4):1147-57. Epub 2008/09/24.
- Barranco Quintana JL, Allam MF, Serrano Del Castillo A, Fernandez-Crehuet Navajas R. Alzheimer's disease and coffee: a quantitative review. *Neurol Res*. 2007;29(1):91-5. Epub 2007/04/12.
- Eskelinen MH, Kivipelto M. Caffeine as a protective factor in dementia and Alzheimer's disease. *Journal of Alzheimer's disease* : JAD. 2010;20 Suppl 1:S167-74. Epub 2010/02/26.
- Current Worldwide Coffee Consumption per capita. www.wri.org: Chartsbin.com; [updated 02/08/201106/24/2013]; Available from: <http://www.chartsbin.com/view/581>.
- Arab L, Biggs ML, O'Meara ES, Longstreth WT, Crane PK, Fitzpatrick AL. Gender differences in tea, coffee, and cognitive decline in the elderly: the Cardiovascular Health Study. *Journal of Alzheimer's disease* : JAD. 2011;27(3):553-66. Epub 2011/08/16.
- Cao C, Loewenstein DA, Lin X, Zhang C, Wang L, Duara R, et al. High Blood caffeine levels in MCI linked to lack of progression to dementia. *J Alzheimers Dis*. 2012;30(3):559-72. Epub 2012/03/21.
- Gongora-Alfaro JL. [Caffeine as a preventive drug for Parkinson's disease: epidemiologic evidence and experimental support]. *Revista de neurologia*. 2010;50(4):221-9. Epub 2010/03/04. La cafeina como un farmaco preventivo de la enfermedad de Parkinson: evidencias epidemiologicas y sustrato experimental.
- Lang AE, Lozano AM. Parkinson's Disease. First of two parts. *N Engl J Med*. 1998a;339:1130-43.
- Lang AE, Lozano AM. Parkinson's Disease. Second of two parts. *N Engl J Med*. 1998b;339:1044-53.
- Goetz CG, Poewe W, Rascol O, Sampaio C. Evidence-based medical review update: pharmacological and surgical treatments of Parkinson's disease: 2001 to 2004. *Movement disorders* : official journal of the Movement Disorder Society. 2005;20(5):523-39. Epub 2005/04/09.
- Lang AE, Obeso JA. Challenges in Parkinson's disease: restoration of the nigrostriatal dopamine system is not enough. *Lancet neurology*. 2004;3(5):309-16. Epub 2004/04/22.
- Rascol O, Goetz C, Koller W, Poewe W, Sampaio C. Treatment interventions for Parkinson's disease: an evidence based assessment. *Lancet*. 2002;359(9317):1589-98. Epub 2002/06/06.
- Ferre S, von Euler G, Johansson B, Fredholm BB, Fuxe K. Stimulation of high-affinity adenosine A2 receptors decreases the affinity of dopamine D2 receptors in rat striatal membranes. *Proceedings of the National Academy of Sciences of the United States of America*. 1991;88(16):7238-41. Epub 1991/08/15.

41. Richardson PJ, Gubitz AK, Freeman TC, Dixon AK. Adenosine receptor antagonists and Parkinson's disease: actions of the A2A receptor in the striatum. *Advances in neurology*. 1999;80:111-9. Epub 1999/07/20.
42. Richardson PJ, Kase H, Jenner PG. Adenosine A2A receptor antagonists as new agents for the treatment of Parkinson's disease. *Trends in pharmacological sciences*. 1997;18(9):338-44. Epub 1997/11/05.
43. Schwarzschild MA, Agnati L, Fuxe K, Chen JF, Morelli M. Targeting adenosine A2A receptors in Parkinson's disease. *Trends in neurosciences*. 2006;29(11):647-54. Epub 2006/10/13.
44. Yu L, Shen HY, Coelho JE, Araujo IM, Huang QY, Day YJ, et al. Adenosine A2A receptor antagonists exert motor and neuroprotective effects by distinct cellular mechanisms. *Annals of neurology*. 2008;63(3):338-46. Epub 2008/02/27.
45. Grondin R, Bedard PJ, Hadj Tahar A, Gregoire L, Mori A, Kase H. Antiparkinsonian effect of a new selective adenosine A2A receptor antagonist in MPTP-treated monkeys. *Neurology*. 1999;52(8):1673-7. Epub 1999/05/20.
46. Kanda T, Jackson MJ, Smith LA, Pearce RK, Nakamura J, Kase H, et al. Adenosine A2A antagonist: a novel antiparkinsonian agent that does not provoke dyskinesia in parkinsonian monkeys. *Annals of neurology*. 1998;43(4):507-13. Epub 1998/04/18.
47. Kanda T, Jackson MJ, Smith LA, Pearce RK, Nakamura J, Kase H, et al. Combined use of the adenosine A(2A) antagonist KW-6002 with L-DOPA or with selective D1 or D2 dopamine agonists increases antiparkinsonian activity but not dyskinesia in MPTP-treated monkeys. *Experimental neurology*. 2000;162(2):321-7. Epub 2000/03/31.
48. Kanda T, Tashiro T, Kuwana Y, Jenner P. Adenosine A2A receptors modify motor function in MPTP-treated common marmosets. *Neuroreport*. 1998;9(12):2857-60. Epub 1998/10/06.
49. Tan EK, Lu ZY, Fook-Chong SM, Tan E, Shen H, Chua E, et al. Exploring an interaction of adenosine A2A receptor variability with coffee and tea intake in Parkinson's disease. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2006;141B(6):634-6. Epub 2006/07/11.
50. Tan EK, Tan C, Fook-Chong SM, Lum SY, Chai A, Chung H, 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):163-7. Epub 2003/11/11.
51. Tan EK, Chua E, Fook-Chong SM, Teo YY, Yuen Y, Tan L, et al. Association between caffeine intake and risk of Parkinson's disease among fast and slow metabolizers. *Pharmacogenet Genomics*. 2007;17(11):1001-5. <http://dx.doi.org/10.1097/FPC.0b013e3282f09265>
52. Facheris MF, Schneider NK, Lesnick TG, de Andrade M, Cunningham JM, Rocca WA, et al. Coffee, caffeine-related genes, and Parkinson's disease: a case-control study. *Mov Disord*. 2008;23(14):2033-40. Epub 2008/09/02.
53. McCulloch CC, Kay DM, Factor SA, Samii A, Nutt JG, Higgins DS, et al. Exploring gene-environment interactions in Parkinson's disease. *Human genetics*. 2008;123(3):257-65. Epub 2008/01/23.
54. Popat RA, Van Den Eeden SK, Tanner CM, Kamel F, Umbach DM, Marder K, et al. Coffee, ADORA2A, and CYP1A2: the caffeine connection in Parkinson's disease. *Eur J Neurol*. 2011;18(5):756-65. Epub 2011/02/02.
55. Powers KM, Kay DM, Factor SA, Zabetian CP, Higgins DS, Samii A, et al. Combined effects of smoking, coffee, and NSAIDs on Parkinson's disease risk. *Mov Disord*. 2008;23(1):88-95. Epub 2007/11/08.
56. Hamza TH, Chen H, Hill-Burns EM, Rhodes SL, Montimurro J, Kay DM, et al. Genome-wide gene-environment study identifies glutamate receptor gene GRIN2A as a Parkinson's disease modifier gene via interaction with coffee. *PLoS genetics*. 2011;7(8):e1002237. Epub 2011/08/31.
57. Hernan MA, Takkouche B, Caamano-Isorna F, Gestal-Otero JJ. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. *Annals of neurology*. 2002;52(3):276-84. Epub 2002/09/03.
58. James WH. Coffee drinking, cigarette smoking, and Parkinson's disease. *Annals of neurology*. 2003;53(4):546; author reply Epub 2003/04/01.
59. Marder K, Logroscino G. The ever-stimulating association of smoking and coffee and Parkinson's disease. *Annals of neurology*. 2002;52(3):261-2. Epub 2002/09/03.
60. Ragonese P, Salemi G, Morgante L, Aridon P, Epifanio A, Buffa D, et al. A case-control study on cigarette, alcohol, and coffee consumption preceding Parkinson's disease. *Neuroepidemiology*. 2003;22(5):297-304. Epub 2003/08/07.
61. Ascherio A, Weisskopf MG, O'Reilly EJ, McCullough ML, Calle EE, Rodriguez C, et al. Coffee consumption, gender, and Parkinson's disease mortality in the cancer prevention study II cohort: the modifying effects of estrogen. *American journal of epidemiology*. 2004;160(10):977-84. Epub 2004/11/04.
62. Kandinov B, Giladi N, Kerczyn AD. The effect of cigarette smoking, tea, and coffee consumption on the progression of Parkinson's disease. *Parkinsonism & related disorders*. 2007;13(4):243-5. Epub 2007/02/06.
63. Crossman AR. Functional anatomy of movement disorders. *Journal of anatomy*. 2000;196 (Pt 4):519-25. Epub 2000/08/03.
64. Montoya A, Price BH, Menear M, Lepage M. Brain imaging and cognitive dysfunctions in Huntington's disease. *Journal of psychiatry & neuroscience : JPN*. 2006;31(1):21-9. Epub 2006/02/24.
65. Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. *Trends in neurosciences*. 1989;12(10):366-75. Epub 1989/10/01.
66. Walker FO. Huntington's disease. *Lancet*. 2007;369(9557):218-28. Epub 2007/01/24.
67. Goehler H, Lalowski M, Stelzl U, Waelter S, Stroedicke M, Worm U, et al. A protein interaction network links GIT1, an enhancer of huntingtin aggregation, to Huntington's disease. *Molecular cell*. 2004;15(6):853-65. Epub 2004/09/24.
68. Bauer PO, Nukina N. The pathogenic mechanisms of polyglutamine diseases and current therapeutic strategies. *Journal of neurochemistry*. 2009;110(6):1737-65. Epub 2009/08/05.
69. Vonsattel JP, Myers RH, Stevens TJ, Ferrante RJ, Bird ED, Richardson EP, Jr. Neuropathological classification of Huntington's disease. *Journal of neuropathology and experimental neurology*. 1985;44(6):559-77. Epub 1985/11/01.
70. Tang TS, Tu H, Chan EY, Maximov A, Wang Z, Wellington CL, et al. Huntingtin and huntingtin-associated protein 1 influence neuronal calcium signaling mediated by inositol(1,4,5) triphosphate receptor type 1. *Neuron*. 2003;39(2):227-39. Epub 2003/07/23.
71. Choi DW. Calcium-mediated neurotoxicity: relationship to specific channel types and role in ischemic damage. *Trends in neurosciences*. 1988;11(10):465-9. Epub 1988/10/01.
72. Lipton SA, Rosenberg PA. Excitatory amino acids as a final common pathway for neurologic disorders. *The New England journal of medicine*. 1994;330(9):613-22. Epub 1994/03/03.
73. Diogenes MJ, Assaife-Lopes N, Pinto-Duarte A, Ribeiro JA, Sebastiao AM. Influence of age on BDNF modulation of hippocampal synaptic transmission: interplay with adenosine A2A receptors. *Hippocampus*. 2007;17(7):577-85. Epub 2007/04/11.
74. Diogenes MJ, Fernandes CC, Sebastiao AM, Ribeiro JA. Activation of adenosine A2A receptor facilitates brain-derived neurotrophic factor modulation of synaptic transmission in hippocampal slices. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2004;24(12):2905-13. Epub 2004/03/27.
75. Fontinha BM, Diogenes MJ, Ribeiro JA, Sebastiao AM. Enhancement of long-term potentiation by brain-derived neurotrophic factor requires adenosine A2A receptor activation by endogenous adenosine. *Neuropharmacology*. 2008;54(6):924-33. Epub 2008/04/04.
76. Zuccato C, Ciammola A, Rigamonti D, Leavitt BR, Goffredo D, Conti L, et al. Loss of huntingtin-mediated BDNF gene transcription in Huntington's disease. *Science*. 2001;293(5529):493-8. Epub 2001/06/16.
77. Blum D, Galas MC, Pintor A, Brouillet E, Ledent C, Muller CE, et al. A dual role of adenosine A2A receptors in 3-nitropropionic acid-induced striatal lesions: implications for the neuroprotective potential of A2A antagonists. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2003;23(12):5361-9. Epub 2003/07/02.
78. Popoli P, Blum D, Martire A, Ledent C, Ceruti S, Abbracchio MP. Functions, dysfunctions and possible therapeutic relevance of adenosine A2A receptors in Huntington's disease. *Progress in neurobiology*. 2007;81(5-6):331-48. Epub 2007/02/17.
79. Messmer K, Reynolds GP. Increased peripheral benzodiazepine binding sites in the brain of patients with Huntington's disease. *Neuroscience letters*. 1998;241(1):53-6. Epub 1998/03/21.
80. Nakahara J, Maeda M, Aiso S, Suzuki N. Current concepts in multiple sclerosis: autoimmunity versus oligodendroglialopathy. *Clinical reviews in allergy & immunology*. 2012;42(1):26-34. Epub 2011/12/23.
81. Compston A, Coles A. Multiple sclerosis. *Lancet*. 2008;372(9648):1502-17. Epub 2008/10/31.
82. Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part II: Noninfectious factors. *Annals of neurology*. 2007;61(6):504-13. Epub 2007/05/12.
83. Compston A, Coles A. Multiple sclerosis. *Lancet*. 2002;359(9313):1221-31. Epub 2002/04/17.
84. Johnston JB, Silva C, Gonzalez G, Holden J, Warren KG, Metz LM, et al. Diminished adenosine A1 receptor expression on macrophages in brain and blood of patients with multiple sclerosis. *Annals of neurology*. 2001;49(5):650-8. Epub 2001/05/19.
85. Mayne M, Shepel PN, Jiang Y, Geiger JD, Power C. Dysregulation of adenosine A1 receptor-mediated cytokine expression in peripheral blood mononuclear cells from multiple sclerosis patients. *Annals of neurology*. 1999;45(5):633-9. Epub 1999/05/13.

85. D'Hooghe M B, Haentjens P, Nagels G, De Keyser J. Alcohol, coffee, fish, smoking and disease progression in multiple sclerosis. *European journal of neurology : the official journal of the European Federation of Neurological Societies*. 2012;19(4):616-24. Epub 2011/11/29.
86. Massa J, O'Reilly EJ, Munger KL, Ascherio A. Caffeine and alcohol intakes have no association with risk of multiple sclerosis. *Mult Scler*. 2013;19(1):53-8. Epub 2012/05/30.
87. Santos RMaL, Darcy R. *An Unashamed Defense of Coffee: 101 reasons to drink coffee without guilt*. USA: XLibris; 2009. 351 p.
88. Belitz HD, Grosch W, Schieberle P. *Food Chemistry*. Heidelberg, Germany: Springer; 2009.
89. Lindsay J, Laurin D, Verreault R, Hebert R, Helliwell B, Hill GB, et al. Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. *Am J Epidemiol*. 2002;156(5):445-53. Epub 2002/08/28.
90. Van Boxtel MP, Schmitt JA, Bosma H, Jolles J. The effects of habitual caffeine use on cognitive change: a longitudinal perspective. *Pharmacology, biochemistry, and behavior*. 2003;75(4):921-7. Epub 2003/09/06.
91. Van Gelder BM, Buijsse B, Tijhuis M, Kalmijn S, Giampaoli S, Nissinen A, et al. Coffee consumption is inversely associated with cognitive decline in elderly European men: the FINE Study. *Eur J Clin Nutr*. 2007;61(2):226-32. Epub 2006/08/25.
92. Ritchie K, Carriere I, de Mendonca A, Portet F, Dartigues JF, Rouaud O, et al. The neuroprotective effects of caffeine: a prospective population study (the Three City Study). *Neurology*. 2007;69(6):536-45. Epub 2007/08/08.
93. Eskelinen MH, Ngandu T, Tuomilehto J, Soininen H, Kivipelto M. Midlife coffee and tea drinking and the risk of late-life dementia: a population-based CAIDE study. *Journal of Alzheimer's disease : JAD*. 2009;16(1):85-91. Epub 2009/01/23.
94. Laitala VS, Kaprio J, Koskenvuo M, Raiha I, Rinne JO, Silventoinen K. Coffee drinking in middle age is not associated with cognitive performance in old age. *Am J Clin Nutr*. 2009;90(3):640-6. Epub 2009/07/10.

<p>QUICK RESPONSE CODE</p> 	<p>ISSN (Online) : 2277 -4572</p> <hr/> <p>Website http://www.jpsionline.com </p>
---	--

How to cite this article:

Santos Roseane Maria Maia, Hunter Tracy, Wright Nick, Lima Darcy Roberto Andrade. Caffeine and chlorogenic acids in coffee and effects on selected neurodegenerative diseases. *J Pharm Sci Innov*. 2013; 2(4): 9-17.