Journal of Gerontology & Geriatric Research

Hugel, et al., J Gerontol Geriatr Res 2015, 4:4
DOI: 10.4172/2167-7182.1000233

Research Aticle Open Access

The Effects of Coffee Consumption on Cognition and Dementia Diseases

Hugel HM*, Yu T and Jackson N

School of Applied Sciences and Health Innovations Research Institute, RMIT University, Melbourne, Victoria 3001 Australia

***Corresponding author:** Hugel HM, School of Applied Sciences RMIT University, Melbourne, GPO Box 2476V Melbourne Victoria 3001 Australia, Tel: +61-3-9925-2626; Fax: +61-3-9925-3747; E-mail: helmut.hugel@rmit.edu.au

Rec date: Jun 28, 2015; **Acc date:** Jul 20, 2015; **Pub date:** Jul 23, 2015

Abstract

Normal aging is accompanied by diminishing motor and cognitive performances that are exacerbated or accelerated in neurodegenerative diseases such as Alzheimer's disease (AD) or Parkinson's disease (PD). Coffee/caffeine is regularly consumed by many people around the world providing a psychoactive stimulant resulting in enhanced alertness, arousal and improvement of cognitive performance. This review presents the science surrounding coffee, caffeine and its impact on cognition for the elderly. There is now considerable knowledge obtained from epidemiological evidence and animal studies, that 3 to 5 cups of caffeine-coffee improves-corrects, positively changes the trajectory of age-related neurodegenerative decline, supporting the healthy aging effects of coffee consumption for dementia prevention and AD. With time, life doesn't get better by chance - it gets better by change.

Keywords: Caffeine; Healthy aging; Neurodegeneration; Neuroprotection

Introduction

Alzheimer's disease (AD) is the most common disease of aging, currently incurable with a long and progressive course. The first defined pathological features of AD are extracellular amyloid plaques and intracellular neurofibrillary tangles in the hippocampus. Studies related to autosomal dominant AD [1] found that the disease process starts 20 years prior to the onset of dementia. The incremental neuronal damage caused by non-sequestered amyloid oligomers is the early pathological event and accumulates over time eventually leading to neurodegeneration and then widespread cognitive impairment [2,3]. Therefore for aging societies, AD is no longer a growing threat but a global health problem and it is a problem for and of our age. The World Health Organization [4] reported that in 2010 an estimated 35.6 million people were suffering from dementia and the 2050 projection of people living with dementia is 115 million. Now every 4 seconds there is a reported case of dementia. The biggest challenge facing scientists is the human brain and sustaining healthy brain aging.

Nature is not only inspirational, but may have created therapeutic agents for combating AD. Plant derived dietary-medicinal compounds termed nutraceuticals represent classes of molecules/phytochemicals that are generally less potent and have fewer side effects than pharmaceuticals. A snapshot of some nutraceuticals [5-18] in common usage to combat AD is shown in Figure 1. The multiple binding modes of EGCG, curcumin and resveratrol to Aβ, specifically to the 17-42 peptide [19,20] portion, derived from sequential cleavage of APP by α-, γ-secretases present in AD amyloid plaques has been described using computational studies. This indicated that the dominant interaction occurs with the central hydrophobic core region involving Aβ residues [17-21] with the implication that these nutraceuticals may interfere with Aβ oligomerization. The nutraceutical aromatic ring hydrophobic π-π interactions with like residues of the Aβ peptide can inhibit the early stages of the molecular recognition-structural transition of the monomers that results in the formation of amyloid protein toxicity.

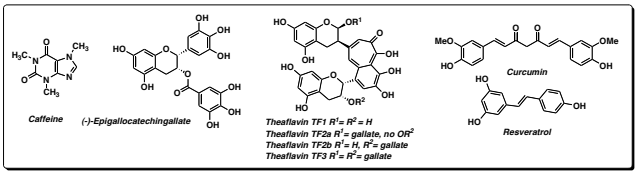


Figure 1: Some nutraceuticals that reduce Aβ toxicity in AD.

Caffeine Characteristics

Caffeine in coffee is the most popular natural drug in the world [21,22] with more than 2.25 billion cups consumed daily. Some of its characteristic effects are listed in Table 1. It has multiple molecular targets [23] and therefore exhibits many affects, and is regarded as a safe substance for most people. It can easily pass the BBB and it appears to directly affect cognitive processes. This review examines the evidence and the surrounding science of coffee, its consumption and its therapeutic value to combat neurocognitive impairments and AD with aging.

There are many compounds present in coffee [24] with caffeine, caffeic acid and chlorogenic acid (CGA) the three most abundant components. For a regular coffee consumer [three cups per day] this amounts to an approximate daily intake of 500 mg, 500 mg, 1000 mg of these natural products [25-27]. Coffee roasting via the Maillard reaction converts some free CGAs into melanoidin-CGAs combinations, with this bound form contributing 25-47% of the brews antioxidant activity [28]. The potential formation of polyphenol-protein complexes with simultaneous coffee-milk consumption [29] may limit the bioavailability of CGAs and trans-cinnamic acid derivatives. Computational studies of the various mechanisms by which caffeine and caffeic acid are involved in scavenging hydroxyl

free radicals concluded that radical adduct formation as the most likely mechanism involved. However it was found that caffeine is inefficient in directly scavenging oxygen superoxide anion, $O_2^{\bullet-}$ and methylperoxyl $\bullet OOCH_3$ radicals and most likely other alkylperoxyl radicals. The C8 atom for caffeine [30] and the phenolic-C4-atom of caffeic acid [31] are the most reactive sites for adduct formation with hydroxyl radicals that are further stabilized by resonance delocalization.

Caffeine characteristics	Caffeine conclusions
Caffeine absorption from the GI tract is rapid [32,33]	Peak concentration is reached after 30 minutes of ingestion with a half-life period of approximately 4 h.
One effect of caffeine is in the lengthening the post firing duration in the hippocampus [34,35]	This effect lasts longer than the changes induced by caffeine on the EEG.
Caffeine and persuasion [36]	Evidence exists for caffeine increasing the systematic processing of persuasive messages.
Does the ingestion of a controlled amount of caffeine improve Working Memory? [37]	Caffeine was associated with a significant increase in alertness. Significantly shorter response times were recorded with caffeine compared to placebo.
Does caffeine consumption improve cognition? Does caffeine improve accuracy? Large-scale studies need to be undertaken to affirm caffeine's possible effectiveness on specific cognitive functions and working memory	Functional magnetic resonance imaging data suggests an effect on brain areas engaged in specific cognitive processes rather than a general effect due to the influence of caffeine on the vasculature [38] Caffeine had no significant effect on cognitive performance.
Elderly women [65 years and older] who drank three cups of coffee or more a day had better [less cognitive decline] working and storage memory compared to controls [39]	Caffeine has fewer side effects than other treatments for cognitive decline, and it requires a relatively small amount for a beneficial effect. The benefits increased with age -- coffee drinkers being 30 percent less likely to have memory decline at age 65 and rising to 70 percent less likely over age 80.
A longer study is required to examine if caffeine prevents dementia; perhaps caffeine slows the dementia process rather than preventing it.	Caffeine consumers did not seem to have lower rates of dementia.
The effects of caffeine and SCH58261, a selective A2A receptor antagonist, on memory impairment and oxidative stress generated by aging in rats were investigated [40]	The age-related memory deficit was reversed by treatment with caffeine or SCH58261. Treatment also significantly normalized oxygen and nitrogen reactive species levels that are increased in brains of aged rats.
Examination of the effects of ingesting a performance bar, containing caffeine, before and during cycling exercise on physical and cognitive performance [41]	Caffeine in a performance bar can significantly improve endurance performance and complex cognitive ability during and after exercise.
Can low caffeine consumption enhance both vigilance and the executive control of visual attention? Examination of the effects of four caffeine doses (0 mg, 100 mg, 200 mg, 400 mg) on low- and high-level visual attention [42]	Habitual consumers of only high doses [400 mgs] of caffeine can produce beneficial changes in visual attention. These results carry implications for the theorized interactions between caffeine, adenosine and dopamine in brain regions mediating visual attention.

Table 1: Caffeine characteristics.

Coffee may reduce the risk of T2DM

Evidence from epidemiological research suggests that coffee consumption is inversely related with the risk of type 2 diabetes mellitis (T2DM). Recent in vitro studies of the suppression of oligomerization and fibrillization of human islet amyloid polypeptide (hIAPP), a key indicator of T2DM by 3-caffeoylquinic acid supports this assertion [43]. This is not without precedence since the green tea polyphenol (-)-epigallocatechin-3-gallate (EGCG) and black tea theaflavins (Figure 1) can inhibit the toxic amyloid aggregation [10] of Aβ in AD and α-synuclein in PD. Further studies are required to determine the molecular mechanisms of the coffee constituents on inhibition of the toxic aggregation of hIAPP.

Neuroprotective actions of caffeine

Snapshots of the neuroprotective impacts attributed to caffeine are presented in Scheme 1 and are summarized here:

Caffeine consumption in stressful situations inversely correlates with the incidence of depression [44].

In A2AR transgenic mice subjected to chronic unpredicatble stress, (CUS) caffeine inhibited stress pathologies analogous to the functions of A2AR antagonists. CUS promoted A2AR activity in synapses – implicating A2AR blockers as a protocol to control the affect of chronic strss on brain disfunction [45].

Analysis of 11 randomized placebo-controlled human studies of acute effects of tea constituents L-theanine and (-)-epigallocatechin gallate, without or with caffeine, on cognitive function and mood were alertness, calmness, and contentedness. A major effect correlated with the caffeine dose [46].

The blockade of A2ARs may be useful in brain disorders including ischemia, epilepsy, Huntington's disease, or AD [47].

Caffeine, and coffee antioxidants are hydroxyl radical scavengers [27,28].

Consumption of coffee was significantly related to slower cognitive decline [48].

Chronic caffeine administration to APP transgenic mice significantly improved cognitive performance and reduced levels of Aβ40 and Aβ42 production [49] The intake also caused an attenuation in PS1 and BACE1 protein expression.

Not only caffeine but also the bioactive compounds in coffee consumed in reasonable amounts, may reduce both motor and cognitive deficits in aging [50].

Is a non-selective A1 and A2 adenosine receptor antagonist leads to increased cognitive performance with habitual consumption [51].

Is neuroprotective toward Aβ induced neurotoxicity in cultured neurons of rats [51].

Is protective against Aβ induced neuronal damage in mice [52].

Stimulates acetylcholine release via blockade of A1 adenosine receptor [53,54].

Prevented neuronal damage, synaptotoxicity and cognitive deficit in rats induced by Aβ, comparable to the actions of the A2 adenosine receptor antagonist SCH 58261 [55].

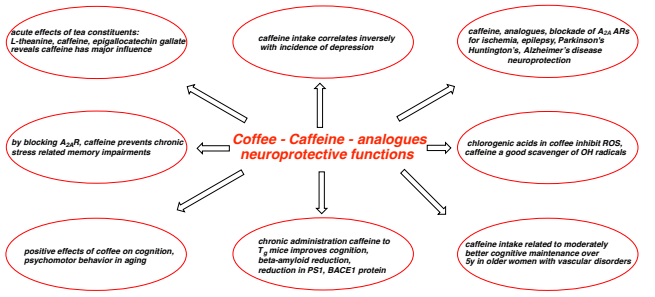
Has been shown to attenuate Aβ production in APPswe mice [49,56] and also a high cholesterol-fed rabbit model of sporadic AD [57].

Modulates tau phosphorylation in human neuroblastoma SHSY5Y cells via Akt pathway, regulating the activity of the tau kinase glycogen synthase kinase 3β [58].

Stimulates an increase in Aβ production from ryanodine receptor-regulated intracellular calcium release channels [59].

In cellular models [60,61] to probe neurodegeneration and cell death evoked by Aβ and aggregated tau, caffeine was the most promising therapeutic drug candidate showing high efficacy in both the APP (77%) and tau-induced models (72%) recovery.

Studies have indicated [62] that the immunomodulatory actions of caffeine are mediated via nonselective inhibition of cyclic adenosine monophosphate (cAMP)–phosphodiesterase (PDE). It raises intracellular cAMP, activates PKA [63,64] inhibits TNF-α [60,65] leukotriene synthesis [66] and reduces inflammation. The claim that many of these effects occur at concentrations that are relevant to normal human coffee consumption is controversial [62].



Scheme 1: Snapshot of the neuroprotective actions of coffee – caffeine – analogues.

A2A antagonists and the receptor pathways of PD

The neurological effects of caffeine are due in large part to its activity at human hA2A receptors, which are abundant in the nucleus accumbens, olfactory tubercle, and striatum, where they are co-localized with dopamine D2 receptors [67]. Epidemiological studies [68] have illustrated that caffeine consumption is associated with a decreased risk of developing PD making A2A adenosine receptors an important pharmacological target for PD therapy. Furthermore antagonists of A2A receptors in the striatum can potentiate the response of dopamine agonists acting at D2 receptors in the same location. Indeed preclinical and clinical studies have provided evidence of the ability of A2A antagonists such as istradefylline, an analogue of caffeine (Scheme 3) improvement in the mobility of PD patients [69-72] by enhancing the therapeutic effects of L-DOPA and reduce motor complications such as wearing off, dyskinesias and on/off phenomena deriving from its pulsatile long-term treatment [73,74]. It has been established that A2A receptors are co-expressed with dopaminergic D2 receptors in striatopallidal GABA neurons, where they form hetero-dimeric complexes able to decrease the D2 affinity for dopamine when the A2A receptors are stimulated [70, 75,76]. The A2A antagonists therefore enhance the therapeutic index of L-DOPA and D2 agonists by blocking the A2A receptors in these A2A– D2 heteromers [76,77] Moreover, A2A antagonists are able to reduce the L-DOPA induced dyskinesias by restoring the appropriate balance between A2A receptors and D2 receptors [78-80]. The neuroprotective effects of A2A antagonists are considered as potentially useful in preventing the onset and development of PD [81-83] The A2A antagonists emerge, therefore, as a class of efficacious antiparkinsonian drugs for the future, whose co-administration with L-DOPA appears significant for both the early stage and long-term treatment of PD.

There is a productive focus to discover selective and potent A2A antagonists for drug development that either alone or as multi-target antiparkinsonian strategies for the treatment of neurodegenerative movement disorder.

Human Studies of the effects of coffee consumption on dementia and AD (Table 2)

Human Studies	Outcomes
Findings of two large cross-sectional population studies investigated regular coffee intake [84,85].	Improvement of cognitive performance in older subjects (55+).
The Maastricht Aging Study in southern Netherlands [86]	Confirmed the link between coffee consumption and enhancement of cognitive function in healthy individuals.
Survey of coffee drinking habits 20 years prior AD diagnosis [87]	AD patients consumed less caffeine than age-matched individuals without AD.
Canadian Study of Health & Aging survey of 4,615 subjects, 5-year follow up with 194 AD plus 3,894 healthy controls [88]	Concluded that regular coffee drinking is related to a reduced risk of developing AD.
The FINE study of 667 healthy men born [1900-1920] in Finland, Italy, Netherlands [89]	Confirmed that the men with intake of 3 cups of coffee had the least cognitive decline.
The French Three Cities studied of the coffee drinking habits of 4,197 women, 2,820 men [39] The protective effect of caffeine was observed to increase with age.	Found that women without dementia drinking over 3 cups of coffee per day, the psycho-stimulant properties of caffeine appear to reduce cognitive decline, especially at higher ages. No impact was observed on dementia incidence.
The Cardiovascular Risk Factors, Aging, and Dementia study examined the causal connection between coffee/tea intake at midlife and consequent development of dementia [90]	The coffee drinkers at midlife were 65% less likely to develop dementia and AD in later life relative to persons drinking little or no coffee. Scope of study: 1,409 aged 65-79; 21-year follow up with 61 cases demented, 48 AD patients.
Studies on a cohort of 648 Portugal subjects aged >65 years was conducted to quantify the association between caffeine intake and cognitive decline [91]	Cognitive evaluations indicated that caffeine intake >62 mg/day supported the negative association between caffeine and cognitive decline in women.
Despite methodological heterogeneities, the systematic review and meta-analysis of four studies [89] published [2004] suggests an inverse relation of coffee consumption and AD.	However the shortcomings of the epidemiological studies that found a trend towards a protective cognitive effect of caffeine, precluded formation of robust and definitive statements to be made.

The latest case-control studies of 124 elderly (65-88 years) subjects equated blood plasma caffeine values [92,93] with dementia progression rates.	The incidence of dementia was higher in subjects with plasma caffeine levels below 1200 ng/mL (≈6 μM) and the analysis of 3 cytokine biomarkers [GCSF, IL-10 and IL-6] were also found to be lower.

Table 2: The evaluation of human coffee consumption studies on dementia and AD.

Summary

Low doses of caffeine non selectively block inhibitory adenosine A1 and A2A receptors resulting in increases in CNS activity and stimulation.

Adenosine A2A is co-localized with DA receptors and occurs mainly in the striatum. The antagonistic A2A-D2 receptor interactions underlie the anti-PD effects of caffeine and those of more potent A2A antagonists.

Structure based drug design, fragment based drug design and other technologies have injected a new productive focus into A2A antagonist discovery.

Epidemiological data reveal that caffeine appears to reduce cognitive decline in the elderly, has fewer side effects, with relatively small amounts providing a beneficial effect. Importantly, the cognitive benefits increase with age - coffee drinkers being 30 percent less likely to have memory decline at age 65 and rising to 70 percent less likely over age 80.

The mechanisms and influences of dietary molecules such as caffeine/coffee on brain health, mental function and cognitive ability are not completely understood. Further research on how natural products influence cognition will help to optimize the nature of diets to increase and extend the longevity of mental fitness with aging and resist dementia and AD.

There are limited and inconsistent findings from longitudinal studies. Many of the studies that proposed a causal relationship between coffee consumption or plasma caffeine levels with incident mild cognitive impairment and its progression to dementia were too limited to draw any conclusion [94].

Coffee is readily available, low in cost with multiple benefits. Caffeine's prophylactic effects in slowing cognitive decline are promising in humans, and compelling in animal studies.

The impact of potential caffeine-coffee molecular synergies on biomarker patterns and their changes with aging needs further investigation and should be included in further studies [95].

In vitro and pre-clinical animal models have identified and suggested potential neuroprotective mechanisms of action of some or many of the bioactive components of coffee, however to the best of our knowledge, no evidence has been gathered from randomized controlled trials.

It is difficult to obtain definitive evidence for the cognitive corrections and brain-benefits derived from caffeine consumption, as there are currently no adenosine receptor antagonists or therapeutic options approved for the treatment of patients with dementia or AD to compare and evaluate the affects of caffeine on these receptors.

As the global growth of dementia continues, coffee can turn down dementia. However this needs to be confirmed with RCT evidence. More translational research is needed to make available FDA approved A1A, A2A receptor antagonists. In the meantime we should encourage safe and regular coffee consumption [3 cups daily] be included with other dietary health approaches across the lifespan, for neuroprotection and for promotion of healthier old age.

Acknowledgments

The work presented in this perspective is part of our ongoing interdisciplinary research collaboration with colleagues at RMIT University and around the globe. We are grateful for their contributions of high quality research to study dementia and AD. There is sufficient scientific evidence to suggest that making small changes such as increasing coffee consumption by the elderly will make a big positive cognitive impact and providing the healthy way to 'living longer, living better' aged care welfare strategy for our society. This is an innovative self-help way of preventing cognitive decline, fighting dementia and AD that empowers the aged, enabling them to cope with a better cognitive future. The low cost-high benefit, and the direct human impact of this natural product, has quite enormous future implications for everyone.

References

1. Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, et al. (2012) Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med 367: 795-804.
2. Narayan P, Holmström KM, Kim DH, Whitcomb DJ, Wilson MR, et al. (2014) Rare individual amyloid-Î² oligomers act on astrocytes to initiate neuronal damage. Biochemistry 53: 2442-2453.
3. Yau WY, Tudorascu DL, McDade EM, Ikonomovic S, James JA, et al. (2015) Longitudinal assessment of neuroimaging and clinical markers in autosomal dominant Alzheimer's disease: a prospective cohort study. Lancet Neurol 14: 804-813.
4. www.who.int/mediacentre/news/releases/2012/dementia
5. Georgiou NA, Garssen J, Witkamp RF (2011) Pharma-nutrition interface: the gap is narrowing. Eur J Pharmacol 651: 1-8.
6. Mori T, Rezai-Zadeh K, Koyama N, Arendash GW, Yamaguchi H, et al. (2012) Tannic acid is a natural Î²-secretase inhibitor that prevents cognitive impairment and mitigates Alzheimer-like pathology in transgenic mice. J Biol Chem 287: 6912-6927.
7. Mancuso C, Siciliano R, Barone E, Preziosi P (2012) Natural substances and Alzheimer's disease: from preclinical studies to evidence based medicine. Biochim Biophys Acta 1822: 616-624.
8. Ehrnhoefer DE, Bieschke J, Boeddrich A, Herbst M, Masino L, et al. (2008) EGCG redirects amyloidogenic polypeptides into unstructured, off-pathway oligomers. Nat Struct Mol Biol 15: 558-566.
9. Hügel HM, Jackson N (2012) Redox chemistry of green tea polyphenols: therapeutic benefits in neurodegenerative diseases. Mini Rev Med Chem 12: 380-387.
10. Grelle G, Otto A, Lorenz M, Frank RF, Wanker EE, et al. (2011) Black tea theaflavins inhibit formation of toxic amyloid-Î² and Î±-synuclein fibrils. Biochemistry 50: 10624-10636.
11. Hügel HM, Jackson N (2014) Herbs and Dementia: a focus on Chinese and other traditional herbs. Martin, C. and Preedy, V. (eds.), Diet and Nutrition in Dementia and Cognitive Decline. Elsevier Acad ISBN 12-407824.
12. Dragicevic N, Smith A, Lin X, Yuan F, Copes N, et al. (2011) Green tea epigallocatechin-3-gallate (EGCG) and other flavonoids reduce Alzheimer's amyloid-induced mitochondrial dysfunction. J Alzheimers Dis 26: 507-521.
13. Hügel HM, Jackson N (2014) Danshen diversity defeating dementia. Bioorg Med Chem Lett 24: 708-716.

14. Liao KK, Wu MJ, Chen PY, Huang SW, Chiu SJ, et al. (2012) Curcuminoids promote neurite outgrowth in PC12 cells through MAPK/ERK- and PKC-dependent pathways. J Agric Food Chem 60: 433-443.
15. Han YS, Zheng WH, Bastianetto S, Chabot JG, Quirion R (2004) Neuroprotective effects of resveratrol against ß-amyloid-induced neurotoxicity in rat hippocampal neurons: Involvement of protein kinase C. Br. J Pharmacol 141: 997-1005.
16. Ono K, Lei LL, Takamura Y, Yoshiike Y, Zhu L, et al. (2012) Phenolic Compounds Prevent Amyloid-Protein Oligomerization and Synaptic Dysfunction by Site Specific Binding. J Biol Chem 287: 14631–14643.
17. Hügel HM (2015) Brain Food for Alzheimer-Free Ageing: Focus on Herbal Medicines. Adv Exp Med Biol 863: 95-116.
18. Lau FC, Shukitt-Hale B, Joseph JA (2005) The beneficial effects of fruit polyphenols on brain aging. Neurobiol Aging 26 Suppl 1: 128-132.
19. Wang SH, Dong XY, Sun Y (2012) Thermodynamic analysis of the molecular interactions between amyloid Î²-protein fragments and (-)-epigallocatechin-3-gallate. J Phys Chem B 116: 5803-5809.
20. Streltsov VA, Varghese JN, Masters CL, Nuttall SD (2011) Crystal structure of the amyloid-Î² p3 fragment provides a model for oligomer formation in Alzheimer's disease. J Neurosci 31: 1419-1426.
21. Fredholm BB, Bättig K, Holmén J, Nehlig A, Zvartau EE (1999) Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. Pharmacol Rev 51: 83-133.
22. Rosso A, Mossey J, Lippa CF (2008) Caffeine: neuroprotective functions in cognition and Alzheimer's disease. Am J Alzheimers Dis Other Demen 23: 417-422.
23. Yu L, Coelho JE, Zhang X, Fu Y, Tillman A, et al. (2009) Uncovering multiple molecular targets for caffeine using a drug target validation strategy combining A2A receptor knockout mice with microarray profiling. Physiol Genomics 37: 199-210.
24. Wei F, Furihata K, Hu F, Miyakawa T, Tanokura M (2011) Two-dimensional 1H-13C nuclear magnetic resonance (NMR)-based comprehensive analysis of roasted coffee bean extract. J Agric Food Chem 59: 9065-9073.
25. Farah A, Donangelo CM (2006) Phenolic compounds in coffee. Braz J Plant Physiol 18: 23-26.
26. Yoshida Y, Hayakawa M, Niki E (2008) Evaluation of the antioxidant effects of coffee and its components using the biomarkers hydroxyoctadecadienoic acid and isoprostane. J Oleo Sci 57: 691-697.
27. Ferruzzi MG (2010) The influence of beverage composition on delivery of phenolic compounds from coffee and tea. Physiol Behav 100: 33-41.
28. Perrone D, Farah A, Donangelo CM (2012) Influence of coffee roasting on the incorporation of phenolic compounds into melanoidins and their relationship with antioxidant activity of the brew. J Agric Food Chem 60: 4265-4275.
29. Duarte GS, Farah A (2011) Effect of simultaneous consumption of milk and coffee on chlorogenic acids' bioavailability in humans. J Agric Food Chem 59: 7925-7931.
30. León-Carmona JR, Galano A (2011) Is caffeine a good scavenger of oxygenated free radicals? J Phys Chem B 115: 4538-4546.
31. Leopoldini M, Chiodo SG, Russo N, Toscano M (2011) Detailed Investigation of the OH Radical Quenching by Natural Antioxidant Caffeic Acid Studied by Quantum Mechanical Models. J Chem Theory Comput 7: 4218-4233.
32. Marks V, Kelly JF (1973) Absorption of caffeine from tea, coffee, and coca cola. Lancet 1: 827.
33. Papadelis C, Kourtidou-Papadeli C, Vlachogiannis E, Skepastianos P, Bamidis P, et al. (2003) Effects of mental workload and caffeine on catecholamines and blood pressure compared to performance variations. Brain Cogn 51: 143-154.
34. Bruce M, Scott N, Lader M, Marks V (1986) The psychopharmacological and electrophysiological effects of single doses of caffeine in healthy human subjects. Br J Clin Pharmacol 22: 81-87.
35. Deslandes AC, Veiga H, Cagy M, Piedade R, Pompeu F, et al. (2005) Effects of caffeine on the electrophysiological, cognitive and motor responses of the central nervous system. Braz J Med Biol Res 38: 1077-1086.
36. Martin PY, Laing J, Martin R, Mitchell M (2005) Caffeine, cognition, and persuasion: Evidence for caffeine increasing the systematic processing of persuasive messages. J App Soc Psych 35: 160-182.
37. Valladares L, Verlag VDM (2009) Effects of Caffeine on Cognitive Tasks: A double-blind study of healthy subjects performing working memory n-back tasks. ISBN 10: 3639163737.
38. Koppelstaetter F, Poeppel TD, Siedentopf CM, Ischebeck A, Verius M, et al. (2008) Does caffeine modulate verbal working memory processes? An fMRI study. Neuroimage 39: 492-499.
39. Ritchie K, Carrière I, de Mendonca A, Portet F, Dartigues JF, et al. (2007) The neuroprotective effects of caffeine: a prospective population study (the Three City Study). Neurology 69: 536-545.
40. Leite MR, Wilhelm EA, Jesse CR, Brandão R, Nogueira CW (2011) Protective effect of caffeine and a selective A2A receptor antagonist on impairment of memory and oxidative stress of aged rats. Exp Gerontol 46: 309-315.
41. Hogervorst E, Bandelow S, Schmitt J, Jentjens R, Oliveira M, et al. (2008) Caffeine improves physical and cognitive performance during exhaustive exercise. Med Sci Sports Exerc 40: 1841-1851.
42. Brunyé TT, Mahoney CR, Lieberman HR, Giles GE, Taylor HA (2010) Acute caffeine consumption enhances the executive control of visual attention in habitual consumers. Brain Cogn 74: 186-192.
43. Cheng B, Liu X, Gong H, Huang L, Chen H, et al. (2011) Coffee Components Inhibit Amyloid Formation of Human Islet Amyloid Polypeptide in Vitro: Possible link between Coffee Consumption and Diabetes Mellitus. J Agric Food Chem 59: 13147-13155.
44. Smith AP (2009) Caffeine, cognitive failures and health in a non-working community sample. Hum Psychopharmacol 24: 29-34.
45. Kaster MP, Machado NJ, Silva HB, Nunes A, Ardais AP, et al. (2015) Caffeine acts through neuronal adenosine A2A receptors to prevent mood and memory dysfunction triggered by chronic stress. Proc Natl Acad Sci U S A 112: 7833-7838.
46. Camfield DA, Stough C, Farrimond J, Scholey AB (2014) Acute effects of tea constituents L-theanine, caffeine, and epigallocatechin gallate on cognitive function and mood: a systematic review and meta-analysis. Nutr Rev 72: 507-522.
47. Preti D, Baraldi PG, Moorman AR, Borea PA, Varani K (2015) History and Perspectives of A2A Adenosine Receptor Antagonists as Potential Therapeutic Agents. Med Res Rev 35: 790-848.
48. Vercambre MN, Berr C, Ritchie K, Kang JH (2013) Caffeine and cognitive decline in elderly women at high vascular risk. J Alzheimers Dis 35: 413-421.
49. Arendash GW, Schleif W, Rezai-Zadeh K, Jackson EK, Zacharia LC, et al. (2006) Caffeine protects Alzheimer's mice against cognitive impairment and reduces brain beta-amyloid production. Neuroscience 142: 941-952.
50. Shukitt-Hale B, Miller MG, Chu YF, Lyle BJ, Joseph JA (2013) Coffee, but not caffeine, has positive effects on cognition and psychomotor behavior in aging. Age (Dordr) 35: 2183-2192.
51. Dall'Igna OP, Porciúncula LO, Souza DO, Cunha RA, Lara DR (2003) Neuroprotection by caffeine and adenosine A2A receptor blockade of beta-amyloid neurotoxicity. Br J Pharmacol 138: 1207-1209.
52. Dall'Igna OP, Fett P, Gomes MW, Souza DO, Cunha RA, et al. (2007) Caffeine and adenosine A(2a) receptor antagonists prevent beta-amyloid (25-35)-induced cognitive deficits in mice. Exp Neurol 203: 241-245.
53. Broad RM, Fredholm BB (1996) A, but not A2A, adenosine receptors modulate electrically stimulated [14C]acetylcholine release from rat cortex. J Pharmacol Exp Ther 277: 193-197.
54. Carter AJ, O'Connor WT, Carter MJ, Ungerstedt U (1995) Caffeine enhances acetylcholine release in the hippocampus in vivo by a selective interaction with adenosine A1 receptors. J Pharmacol Exp Ther 273: 637-642.
55. Canas PM, Porciu´ncula,LO, Cunha GMA, Silva CG, Machado NJ, et al. (2009) Adenosine A2A Receptor Blockade Prevents Synaptotoxicity and

Memory Dysfunction Caused by Amyloid Peptides via p38 Mitogen-Activated Protein Kinase Pathway. J Neurosci 29: 14741–14751.

56. Arendash GW, Mori T, Cao C, Mamcarz M, Runfeldt M, et al. (2009) Caffeine reverses cognitive impairment and decreases brain amyloid-beta levels in aged Alzheimer's disease mice. J Alzheimers Dis 17: 661-680.
57. Prasanthi JR, Dasari B, Marwarha G, Larson T, Chen X, et al. (2010) Caffeine protects against oxidative stress and Alzheimer's disease-like pathology in rabbit hippocampus induced by cholesterol-enriched diet. Free Radic Biol Med 49: 1212-1220.
58. Currais A, Kato K, Canuet L, Ishii R, Tanaka T, et al. (2011) Caffeine modulates tau phosphorylation and affects Akt signaling in postmitotic neurons. J Mol Neurosci 43: 326-332.
59. Querfurth HW, Jiang J, Geiger JD, Selkoe DJ (1997) Caffeine stimulates amyloid beta-peptide release from beta-amyloid precursor protein-transfected HEK293 cells. J Neurochem 69: 1580-1591.
60. Stoppelkamp S, Bell HS, Palacios-Filardo J, Shewan DA, Riedel G, et al. (2011) In vitro modelling of Alzheimer's disease: degeneration and cell death induced by viral delivery of amyloid and tau. Exp Neurol 229: 226-237.
61. Marwarha G, Ghribi O (2012) Cellular model of Alzheimer's disease--relevance to therapeutic testing. Exp Neurol 233: 733-739.
62. Horrigan LA, Kelly JP, Connor TJ (2006) Immunomodulatory effects of caffeine: friend or foe? Pharmacol Ther 111: 877-892.
63. Essayan DM (2001) Cyclic nucleotide phosphodiesterases. J Allergy Clin Immunol 108: 671-680.
64. Deree J, Martins JO, Melbostad H, Loomis WH, Coimbra R (2008) Insights into the regulation of TNF-alpha production in human mononuclear cells: the effects of non-specific phosphodiesterase inhibition. Clinics (Sao Paulo) 63: 321-328.
65. Marques LJ, Zheng L, Poulakis N, Guzman J, Costabel U (1999) Pentoxifylline inhibits TNF-alpha production from human alveolar macrophages. Am J Respir Crit Care Med 159: 508-511.
66. Peters-Golden M, Canetti C, Mancuso P, Coffey MJ (2005) Leukotrienes: underappreciated mediators of innate immune responses. J Immunol 174: 589-594.
67. Svenningsson P, Le Moine C, Fisone G, Fredholm BB (1999) Distribution, biochemistry and function of striatal adenosine A2A receptors. Prog Neurobiol 59: 355-396.
68. Schwarzschild MA, Chen JF, Ascherio A (2002) Caffeinated clues and the promise of adenosine A(2A) antagonists in PD. Neurology 58: 1154-1160.
69. Marcellino D, Lindqvist E, Schneider M, Müller CE, Fuxe K, et al. (2010) Chronic A2A antagonist treatment alleviates parkinsonian locomotor deficiency in MitoPark mice. Neurobiol Dis 40: 460-466.
70. Knebel W, Rao N, Uchimura T, Mori A, Fisher J, et al. (2011) Population pharmacokinetic analysis of istradefylline in healthy subjects and in patients with Parkinson's disease. J Clin Pharmacol 51: 40-52.
71. Hodgson RA, Bedard PJ, Varty GB, Kazdoba TM, Di Paolo T, et al. (2010) Preladenant, a selective A(2A) receptor antagonist, is active in primate models of movement disorders. Exp Neurol 225: 384-390.
72. Hauser RA, Cantillon M, Pourcher E, Micheli F, Mok V, et al. (2011) Preladenant in patients with Parkinson's disease and motor fluctuations: a phase, double-blind, randomised trial. Lancet Neurol 10: 221-229.
73. Simola N, Morelli M, Pinna A (2008) Adenosine A2A receptor antagonists and Parkinson's disease: state of the art and future directions. Curr Pharm Des 14: 1475-1489.
74. Blanchet PJ, Calon F, Morissette M, Hadj Tahar A, Bélanger N, et al. (2004) Relevance of the MPTP primate model in the study of dyskinesia priming mechanisms. Parkinsonism Relat Disord 10: 297-304.
75. Ferré S, Ciruela F, Woods AS, Lluis C, Franco R (2007) Functional relevance of neurotransmitter receptor heteromers in the central nervous system. Trends Neurosci 30: 440-446.
76. Fuxe K, Ferré S, Genedani S, Franco R, Agnati LF (2007) Adenosine receptor-dopamine receptor interactions in the basal ganglia and their relevance for brain function. Physiol Behav 92: 210-217.
77. Fuxe K, Marcellino D, Genedani S, Agnati L (2007) Adenosine A(2A) receptors, dopamine D(2) receptors and their interactions in Parkinson's disease. Mov Disord 22: 1990-2017.
78. Antonelli T, Fuxe K, Agnati L, Mazzoni E, Tanganelli S, et al. (2006) Experimental studies and theoretical aspects on A2A/D2 receptor interactions in a model of Parkinson's disease. Relevance for L-dopa induced dyskinesias. J Neurol Sci 248: 16-22.
79. Fuxe K Marcellino D, Rivera A, Diaz-Cabiale Z, Filip M, Gago B, et al. (2008) Receptor - Receptor Interactions within Receptor Mosaics. Impact on Neuropsychopharmacology Brain Res Rev 58: 415-452.
80. Fuxe K, Marcellino D, Leo G, Agnati LF (2010) Molecular integration via allosteric interactions in receptor heteromers. A working hypothesis. Curr Opin Pharmacol 10: 14-22.
81. Morelli M, Wardas J (2001) Adenosine A(2a) receptor antagonists: potential therapeutic and neuroprotective effects in Parkinson's disease. Neurotox Res 3: 545-556.
82. Xu K, Bastia E, Schwarzschild M (2005) Therapeutic potential of adenosine A(2A) receptor antagonists in Parkinson's disease. Pharmacol Ther 105: 267-310.
83. Alessandro Dalpiaz A, Cacciari B, Vicentini CB, Bortolotti F, Spalluto G, et al. (2012) A Novel Conjugated Agent between Dopamine and an A2A Adenosine Receptor Antagonist as a Potential Anti-Parkinson Multitarget Approach. Mol Pharmaceutics 9: 591–604.
84. Jarvis MJ (1993) Does caffeine intake enhance absolute levels of cognitive performance? Psychopharmacology (Berl) 110: 45-52.
85. Johnson-Kozlow M, Kritz-Silverstein D, Barrett-Connor E, Morton D (2002) Coffee consumption and cognitive function among older adults. Am J Epidemiol 156: 842-850.
86. van Boxtel MP, Schmitt JA, Bosma H, Jolles J (2003) The effects of habitual caffeine use on cognitive change: a longitudinal perspective. Pharmacol Biochem Behav 75: 921-927.
87. Maia L, de Mendonça A (2002) Does caffeine intake protect from Alzheimer's disease? Eur J Neurol 9: 377-382.
88. Lindsay J, Laurin D, Verreault R, Hébert R, Helliwell B, et al. (2002) Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. Am J Epidemiol 156: 445-453.
89. van Gelder BM, Buijsse B, Tijhuis M, Kalmijn S, Giampaoli S, et al. (2007) Coffee consumption is inversely associated with cognitive decline in elderly European men: the FINE Study. Eur J Clin Nutr 61: 226-232.
90. Eskelinen MH, Ngandu T, Tuomilehto J, Soininen H, Kivipelto M (2009) Midlife coffee and tea drinking and the risk of late-life dementia: a population-based CAIDE study. J Alzheimers Dis 16: 85-91.
91. Santos C, Lunet N, Azevedo A, de Mendonça A, Ritchie K, et al. (2010) Caffeine intake is associated with a lower risk of cognitive decline: a cohort study from Portugal. J Alzheimers Dis 20 Suppl 1: S175-185.
92. Santos C, Costa J, Santos J, Vaz-Carneiro A, Lunet N (2010) Caffeine intake and dementia: systematic review and meta-analysis. J Alzheimers Dis 20 Suppl 1: S187-204.
93. Cao C, Loewenstein DA, Lin X, Zhang C, Wang L, et al. (2012) High Blood caffeine levels in MCI linked to lack of progression to dementia. J Alzheimers Dis 30: 559-572.
94. Panza F, Solfrizzi V, Barulli MR, Bonfiglio C, Guerra V, et al. (2015) Coffee, tea, and caffeine consumption and prevention of late-life cognitive decline and dementia: a systematic review. J Nutr Health Aging 19: 313-328.
95. Carman AJ, Dacks PA, Lane RF, Shineman DW, Fillit HM (2014) Current evidence for the use of coffee and caffeine to prevent age-related cognitive decline and Alzheimer's disease. J Nutr Health Aging 18: 383-392.