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Caffeine, chocolate, and adenosine antagonism in Parkinson's disease

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Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disorder. It is generally accepted that dopamine replacement therapy substantially improves motor symptoms; however, there is a worldwide tendency to include nutrients in treatment strategies. In the present review, caffeine and chocolate are discussed. Caffeine use seems to postpone the occurrence of PD in men, and perhaps also in women who do not take postmenopausal hormone replacement therapy. There are contradictory data concerning possible caffeine-induced improvements in PD symptoms. Given that the basic action of caffeine is the antagonism of adenosine receptors, adenosine antagonists may be a new option for treating PD patients. Furthermore, PD patients tend to have increased chocolate consumption; this may be causally related to ingredients such as phenylethylamine. Thus, nutrients such as caffeine and chocolate may play an important role in postponing and/or improving symptoms in PD.

Keywords: Parkinson's disease, caffeine, chocolate, adenosine antagonism

INTRODUCTION

Idiopathic Parkinson's disease (PD) is the second most common neurodegenerative disorder and is rapidly increasing in incidence[1]. It is generally assumed that misfolded α-synuclein is the main constituent of Lewy bodies[2] and is the major player in the etiopathogenesis of PD. Inflammation and oxidative stress also

appear to have an important role in the death of dopaminergic neurons in this disease. Furthermore, PD seems to be a spreading disease[3,4] that affects not only the dopaminergic nigrostriatal system, but also many other parts of the brain and autonomic nervous system[3]. The widespread appearance of misfolded α-synuclein causes the typical motor symptoms associated with PD - akinesia, rigidity, and tremor - and impairs the production and function of other neurotransmitters, thus leading to cognitive, psychiatric, autonomic, and other symptoms. Treatment of PD is mostly focused on repairing imbalances between the direct and indirect pathways (i.e., addressing and substituting the dopaminergic system by administering dopamine replacement therapy).

It would likely be well accepted if readily available and commonly used nutrients were able to improve the symptoms of PD or even postpone its onset. In light of this assumption, the following review focuses on our knowledge of caffeine and chocolate in the control of PD and also reviews the use of adenosine antagonists as a therapeutic approach.

FUNCTION OF CAFFEINE IN THE BRAIN

Caffeine (1,3,7-trimethylxanthine) is the most frequently used psychostimulant worldwide[5]. It is a natural alkaloid and can be found in leaves and seeds (e.g., from coffee and cacao plants), from which it can be extracted. The stimulating effects of the cacao plant were recognized by the Maya culture, which led to its cultivation as early as 1000 BC. Caffeine can cross the blood-brain barrier and exerts its biological effects mainly via the antagonism of adenosine receptors[5]. It inhibits lipid peroxidation and the formation of reactive oxygen species[6,7] and improves mitochondrial function[8]. Caffeine is metabolized in the liver; its main metabolites are paraxanthine, theobromine, and theophylline. In common with its three metabolites, caffeine can cross all biological membranes and be excreted in urine. Because of its lipophilic structure, caffeine can also cross the blood-brain barrier and elicit its effects in the brain. Its blockade of the adenosine A1, A2A, and A3 receptors in glial cells, astrocytes, oligodendrocytes, and neurons modulates the release of dopamine, serotonin, acetylcholine, γ-aminobutyric acid (GABA), adrenaline, and noradrenaline in the nucleus accumbens, hippocampus and other brain regions, including the nigrostriatal system[5,9,10]. Caffeine also inhibits phosphodiesterases and causes calcium release from intracellular storage. Moreover, at moderate doses of 3-5 cups of coffee per day, it improves sleep, learning ability, cognition, and mobility. It thus seems clear that such a substance may have beneficial effects for patients with movement disorders, depression, migraines, or dementia[7,11-14]. Nonetheless, too high a dose of caffeine causes dysphoria, restlessness, nausea, and vomiting. The lethal dose for humans seems to be 100 cups of coffee or 10 g of caffeine per day[15].

CAFFEINE AND PD RISK

There is evidence from animal models that caffeine may reduce the risk of developing PD[16]. The adenosine A2A receptor seems to play a key role in this protection in animal models of PD [e.g., the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model], and an A2A antagonist (KW6002; istradefylline) has been developed to treat patients with PD[17]. The basic mechanism of the protective effect of caffeine/adenosine antagonists in animal models is not yet fully established, but may involve the prevention of blood-brain barrier disruption in addition to neuroprotective and antioxidative effects[18].

The first evidence of a possible neuroprotective effect of caffeine against PD came from the Honolulu Heart Program, in which more than 8000 participants were followed for 30 years or more. A high intake of caffeine (> 784 mg caffeine/day) reduced the risk of developing PD by fivefold[19]. Paganini-Hill[20], who analyzed 395 patients from a retirement community in Southern California, obtained similar results. The author demonstrated that the risk of developing PD was significantly reduced in smokers, hypertensives,

alcohol consumers, and coffee drinkers. The literature at that time pointed toward a tendency for men to benefit more from coffee than women with respect to PD; thus, Ascherio *et al.* prospectively investigated the interplay between estrogen and coffee consumption[21]. They reported that caffeine reduces the risk of PD in women who do not use postmenopausal hormones, but increases the risk among hormone users. These findings suggest that women should avoid caffeine in combination with postmenopausal hormones. A study from Sweden of 415 same-sex twin pairs analyzed the influence of many lifestyle factors - such as smoking, alcohol, area of living, education, and caffeine consumption - on the risk of developing PD[22]. Only smoking was found to have a positive effect. However, a major problem with this study was that, although coffee consumption led to a reduced risk of PD, the finding was not significant; this was likely because the controls also drank relatively high amounts of coffee. In contrast to the findings of Ascherio *et al.*, a large prospective Finnish study demonstrated that caffeine consumption was associated with a lower risk of PD in both men and women[23]. Because tea also contains caffeine, it is noteworthy that a study from Singapore demonstrated positive effects of black tea - but not green tea - on risk reduction in PD[24]. In a further study, Powers *et al.* investigated the effects of a combination of coffee, smoking, and the regular intake of nonsteroidal anti-inflammatory drugs on the risk of developing PD[25]. They found a reduced risk of up to 87% for those who used all three, and their results also indicated dose-dependent effects. Similar results were obtained by Sääksjärvi *et al.*[26]. In another large prospective study involving more than 300,000 participants, caffeine consumption was once again found to be associated with a reduced risk of developing PD in both men and women[27]. A more recent study of more than 900,000 participants reported that 3 cups of coffee per day is the most beneficial for preventing PD[28]. In conclusion, it seems that coffee drinking helps to lower the risk of developing PD. A summary of these studies is provided in Table 1.

CAFFEINE AS A POSSIBLE TREATMENT FOR PATIENTS WITH PD

If caffeine is protective via adenosine receptors, it should also be determined whether it has beneficial effects in patients with established PD. In the Harvard Biomarkers Study, a longitudinal study involving 369 patients with PD - of whom 97 were *de novo* patients - and 197 healthy controls, high caffeine consumption resulted in a delayed need to start levodopa therapy[29]. Patients consumed an average of 296 mg of caffeine per day, and those who consumed less caffeine had a higher prevalence of PD and more rapid disease progression. Higher espresso consumption also correlated with improved motor function [using the Unified Parkinson's Disease Rating Scale (UPDRS)] and non-motor symptoms (using the Nonmotor-Symptoms Questionnaire). Prior to this, Altman *et al.* had reported that caffeine was associated with improved motor and non-motor symptoms in a smaller series of PD patients[30]. Simon *et al.* evaluated the rate of disease progression when creatine, another possible neuroprotective substance, was administered in addition to coffee[31]. This Phase III study involved 1741 PD patients; information about caffeine intake was available from 1549 participants. The influence of caffeine was analyzed using the UPDRS and the observation period was up to 5 years. There was no indication that caffeine had a beneficial effect on PD progression; on the contrary, caffeine combined with creatine was associated with a negative effect. In a randomized, controlled trial, patients with PD of 1-8 years of duration, Hoehn and Yahr stages I-III, and on stable symptomatic therapy were randomized to 200 mg caffeine or placebo capsules twice daily for 6-18 months. There was no improvement in either group (61 participants with placebo and 57 with caffeine) in the Movement Disorder Society UPDRS. There was a slight improvement in somnolence during the first 6 months as well as a slight increase in dyskinesia and worse cognitive testing scores in the caffeine group[32]. Thus, the same research team that observed a positive effect of caffeine (with a decrease in UPDRS of 3.2 points) in a smaller, randomized trial of PD patients who did or did not receive caffeine[33] found in this later study that caffeine was not associated with improvements in the condition of PD patients. The authors themselves stated that this difference may have been caused by different study populations. In the positive trial, patients were older and somnolent, had a longer disease duration, and were more often male. In favor of the negative study, it

Table 1. Caffeine consumption and risk of developing PD

Ross *et al.*, 2000[19]	Honolulu Heart Programme	Caffeine reduced the risk of developing PD
Paganini-Hill *et al.*, 2001[20]	Retirement Community South California	Caffeine and smoking reduced the risk of developing PD
Ascherio *et al.*, 2003[21]		Caffeine reduces the risk of PD in men and in women who do not use postmenopausal hormones
Wirdefeldt *et al.*, 2005[22]	Swedish twin study	Nicotine but not caffeine reduced the risk of developing PD
Hu *et al.*, 2007[23]	Finnish study	Both men and women show a reduced risk of developing PD
Powers *et al.*, 2008[25] Sääksjärvi *et al.*, 2008[26]		If smoking and regular intake of nonsteroidal anti-inflammatory drugs are used in combination with caffeine, the risk of developing PD can be further reduced
Liu *et al.*, 2012[27]		Caffeine reduces the risk of developing PD
Qi*et al.*, 2014[28]		Caffeine reduces the risk of developing PD

PD: Parkinson's disease.

lasted for 6 months compared with 6 weeks in the positive study. In this context, it is surprising that the patients who received caffeine had poorer performance in the Montreal Cognitive Assessment Scale; this finding is contradictory to the normal stimulant effects of caffeine on alertness and cognitive function. Thus, it remains unclear whether caffeine improves motor or/and non-motor symptoms in PD. A summary of the studies is provided in Table 2.

CAFFEINE AS A BIOMARKER FOR PD

Fujimaki *et al.* analyzed the levels of caffeine and 11 of its metabolites in the serum of 108 advanced-stage PD patients and compared them with the levels found in the serum of 31 healthy age- and sex-matched controls[34]. Independent of disease stage, total caffeine intake, or disease severity, the levels of caffeine and nine metabolites - including theophylline, theobromine, and paraxanthine - were decreased in PD patients. Caffeine levels were, on average, 25% of those in healthy controls, theophylline 41%, theobromine 50%, and paraxanthine 42%. No genetic variants in *CYP1A2* or *CYP2E1*, which encode cytochrome P450 enzymes that are primarily involved in metabolizing caffeine in humans, were identified compared with controls. Patients with dyskinesia had lower serum caffeine concentrations than those without dyskinesia. In addition, the authors were unable to detect genetic abnormalities in the gene encoding adenosine A2A receptors. Most of the patients and controls drank 1-3 cups of coffee per day and there was no difference between the two groups in the amount of coffee consumed. The findings of this study suggest that caffeine and its metabolites may be used as biomarkers for PD. A reasonable explanation for this observation may be that caffeine absorption is reduced in PD patients. Ohmichi *et al.* assessed the measurement of theophylline as a possible new biomarker in the serum of PD patients[35]. Theophylline is a major metabolite of caffeine and is advantageous because it can easily be analyzed in most hospitals using standardized immunoassay kits. In addition, theophylline levels are less markedly affected by caffeine intake. The authors measured theophylline concentration in the serum of 31 patients with PD and 33 age-matched controls. On average, PD patients had 50% less theophylline in their serum than control individuals. The only weakness of this study is that it remains uncertain whether theophylline concentration is affected by coffee consumed before blood is drawn; further studies are therefore needed. The same group developed a specific enzyme-linked immunosorbent assay system for detecting caffeine in blood[36]. In a series of 50 PD patients, 50 multiple system atrophy (MSA) patients, and 45 age-matched controls, serum caffeine concentration was significantly lower in PD patients (and, to a lesser extent, MSA patients) than in controls. In a first cohort of only 18 MSA patients, there was no significant difference between MSA patients and controls. Crotty *et al.*

Table 2. Caffeine consumption and Parkinsonian symptoms

Altmanet *al.*, 2011[30]		Caffeine improved both motor and non-motor symptoms in PD patients
Bakshiet *al.*, 2020[29]	Harvard Biomarkers Study	Caffeine use resulted in later start with levodopa. High caffeine intake reduced the progression of the disease and improved motor function
Simon *et al.*, 2015[31]	Creatine phase III study	No improvement of motor symptoms by caffeine and worsening when creatine was added
Postuma *et al.*, 2012[33]		Improvement of UPDRS part III by 3,2 points
Postuma *et al.*, 2017[32]	Café-PD	No improvement of motor symptoms in patients with PD

PD: Parkinson's disease.

studied caffeine, among other analytes, in the cerebrospinal fluid and serum of 118 patients with a pathogenic mutation in the gene encoding leucine-rich repeat kinase 2 (*LRRK2*) and PD, 115 patients with a pathogenic mutation in *LRRK2* but without PD symptoms, 70 idiopathic PD patients without *LRKK2* mutations, and 68 controls[37]. Plasma caffeine concentration was lower in patients with idiopathic or *LRRK2* -positive PD than in unaffected *LRKK2*-positive individuals, and was lower in *LRRK2*-positive PD than in idiopathic PD. It is intriguing that patients with PD and *LRKK2* mutations had lower caffeine and metabolite levels than *LRRK2*-positive carriers without motor symptoms; this was true for both the cerebrospinal fluid and plasma. Notably, the *LRRK2*-positive patients with motor symptoms drank much less caffeine than those without symptoms. Thus, it may be that *LRKK2*-positive patients without PD symptoms drank more caffeine and were protected by attenuation of LRRK2-potentiated α-synuclein pathology. These observations encourage a long-term study on caffeine intake in *LRRK2*-positive carriers. Taken together, caffeine and its metabolites are promising biomarkers for PD.

ADENOSINE ANTAGONISM IN PD

Adenosine is an important neurotransmitter for neuronal maturation/development, sleep and arousal, cognition and memory, and control of respiration[14]. A detailed description of the distribution, biochemistry, and functions of striatal adenosine A2A receptors can be found in Svenningsson *et al.*[38]. In short, the main actions of caffeine in the brain are in adenosine receptor antagonism, intracellular Ca^{2+} release, and GABA receptor modulation[14]. Adenosine receptors can be found in the striatum, globus pallidus, nucleus accumbens, and olfactory bulb. For PD, adenosine A2A receptors in the medium spiny neurons of the striatum are almost exclusively relevant. It thus makes sense to speculate that, similar to caffeine, drugs that antagonize adenosine receptors may be beneficial in PD. In this context, a positron emission tomography study by Ishibashi *et al.* is important; these authors demonstrated a significant occupancy of adenosine A2A receptors after participants drank a cup of coffee (equivalent to 100 mg caffeine)[39]. To date, there is only one licensed A2A receptor antagonist medication: istradefylline. This substance received approval in Japan in 2013 and in the USA in 2019; however, approval was recently denied by the European Medicines Agency. Istradefylline has been investigated in a large Phase II and Phase III clinical research program of about nine trials. On average, a gain of about 45-60 min of ON state and a decrease of about 45-60 min of OFF state have been identified. The most common side effect was dyskinesia, which was able to be overcome by adjusting levodopa dose[40].

CHOCOLATE AND PD

Chocolate, particularly dark chocolate, also contains caffeine. Specifically, 100 g of dark chocolate contains 43 mg of caffeine[41]. Cacao-containing chocolate is highly valued worldwide for its taste and smell, as well as for its psychoactive stimulation. Approximately 20 years ago, I noticed that the bedside cupboard of a

patient of mine - an in-patient who had traveled a long distance - was full of bars of chocolate. He told me that he had not been certain that we could provide him with his favorite chocolate, which improved his PD symptoms. On the basis of this observation, we performed a survey among our PD patients[41] and revealed a significantly higher intake of chocolate in patients than that of their caregivers and partners; this preference for chocolate was independent of the presence or absence of depression. Furthermore, the consumption of other sweets was similar between PD patients and their caregivers and partners. Caffeine may be an underlying reason for this behavior, or perhaps energy production from glucose. The amine phenylethylamine, which can penetrate the blood-brain barrier, may also be responsible for our finding[42], or tryptophane, which is a precursor of serotonin. We favored the idea that phenylethylamine may be the reason for the high intake of chocolate and performed a study in which we compared phenylethylamine content in the blood of patients with PD who had eaten either dark or white chocolate[42]. We tested the effects of 200 g of chocolate containing 80% cacao on the UPDRS motor score at 1 and 3 h in 26 subjects with moderate, non-fluctuating PD. The investigation was a mono-center, single-dose, investigator-blinded cross-over study using cacao-free white chocolate as the placebo. At 1 h after chocolate intake, mean UPDRS motor scores were mildly decreased compared with baseline in both treatment groups; however, only the dark chocolate results were significant [-1.3 (95% confidence interval [CI] 0.18-2.52, repeated measures analysis of variance $F = 4.783$, $P = 0.013$, Bonferroni $P = 0.021$)]. A 2 × 2 cross-over analysis revealed no significant differences between the two treatments [-0.54 ± 0.47 (95%CI: -1.50-0.42), $P = 0.258$]. Similar results were obtained 3 h after intake. Furthermore, β-phenylethylamine blood levels were unaltered. In summary, dark chocolate did not show significant improvements over white (cacao-free) chocolate in terms of PD motor function.

CONCLUSION

Caffeine and its metabolites play an important role in brain function. Caffeine may be neuroprotective against PD and slow the occurrence of this neurodegenerative disease. There are many more studies suggesting that coffee drinking lowers the risk of PD than those that suggest the opposite. However, the existing data on whether coffee, tea, or chocolate intake may improve symptoms in patients with PD are much more ambiguous. Given that caffeine acts mostly via adenosine receptors in many brain regions, further studies with new adenosine antagonists are needed.

DECLARATIONS

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Prof. Reichmann H was invited by EISAI to give lectures on the function of the adenosine antagonist *istradefylline*.

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Not applicable.

REFERENCES

1. Dorsey ER, Bloem BR. The Parkinson pandemic - a call to action. *JAMA Neurol* 2018;75:9-10. DOI PubMed
2. Shahmoradian SH, Lewis AJ, Genoud C, et al. Lewy pathology in Parkinson's disease consists of crowded organelles and lipid membranes. *Nat Neurosci* 2019;22:1099-109. DOI PubMed
3. Braak H, de Vos RA, Bohl J, Del Tredici K. Gastric α-synuclein immunoreactive inclusions in Meissner's and Auerbach's plexuses in cases staged for Parkinson's disease-related brain pathology. *Neurosci Lett* 2006;396:67-72. DOI PubMed
4. Borghammer P. The α-synuclein origin and connectome model (SOC model) of Parkinson's disease: explaining motor asymmetry, non-motor phenotypes, and cognitive decline. *J Parkinsons Dis* 2021;11:455-74. DOI PubMed PMC
5. Solinas M, Ferré S, You Z, Karcz-kubicha M, Popoli P, Goldberg SR. Caffeine induces dopamine and glutamate release in the shell of the nucleus accumbens. *J Neurosci* 2002;22:6321-4. DOI PubMed PMC
6. Devasagayam TP, Kamat JP, Mohan H, Kesavan PC. Caffeine as an antioxidant: inhibition of lipid peroxidation induced by reactive oxygen species. *Biochim Biophys Acta* 1996;1282:63-70. DOI PubMed
7. Schepici G, Silvestro S, Bramanti P, Mazzon E. Caffeine: an overview of its beneficial effects in experimental models and clinical trials of Parkinson's disease. *Int J Mol Sci* 2020;21:4766. DOI PubMed PMC
8. Kolahdouzan M, Hamadeh MJ. The neuroprotective effects of caffeine in neurodegenerative diseases. *CNS Neurosci Ther* 2017;23:272-90. DOI PubMed PMC
9. Olopade FE, Femi-Akinlosotu OM, Adekanmbi AJ, Ighogboja OO, Shokunbi MT. Chronic caffeine ingestion improves motor function and increases dendritic length and arborization in the motor cortex, striatum, and cerebellum. *J Caffeine Adenosine Res* 2021;11:3-14. DOI
10. Sheth S, Brito R, Mukherjea D, Rybak LP, Ramkumar V. Adenosine receptors: expression, function and regulation. *Int J Mol Sci* 2014;15:2024-52. DOI PubMed PMC
11. Fredholm BB, Svenningsson P. Why target brain adenosine receptors? *Parkinsonism Relat Disord* 2020;80 Suppl 1:S3-6. DOI PubMed
12. Camandola S, Plick N, Mattson MP. Impact of coffee and cacao purine metabolites on neuroplasticity and neurodegenerative disease. *Neurochem Res* 2019;44:214-27. DOI PubMed PMC
13. Chen JF, Schwarzschild MA. Do caffeine and more selective adenosine A2A receptor antagonists protect against dopaminergic neurodegeneration in Parkinson's disease? *Parkinsonism Relat Disord* 2020;80 Suppl 1:S45-53. DOI PubMed PMC
14. Ribeiro JA, Sebastião AM. Caffeine and adenosine. *J Alzheimers Dis* 2010;20 Suppl 1:S3-15. DOI PubMed
15. Forth W, Adam O. Coffein: Umgang mit einem Genussmittel, das auch pharmakologische Wirkungen entfalten kann. *Dtsch Arztebl* 2001;98:2816.
16. Schwarzschild MA, Xu K, Oztas E, et al. Neuroprotection by caffeine and more specific A2A receptor antagonists in animal models of Parkinson's disease. *Neurology* 2003;61:S55-61. DOI PubMed
17. Kalda A, Yu L, Oztas E, Chen JF. Novel neuroprotection by caffeine and adenosine A(2A) receptor antagonists in animal models of Parkinson's disease. *J Neurol Sci* 2006;248:9-15. DOI PubMed
18. Chen X, Ghiribi O, Geiger JD. Caffeine protects against disruptions of the blood-brain barrier in animal models of Alzheimer's and Parkinson's disease. *J Alzheimers Dis* 2010;20:S127-41. DOI
19. Ross GW, Abbott RD, Petrovitch H, et al. Association of coffee and caffeine intake with the risk of Parkinson disease. *JAMA* 2000;283:2674-9. DOI PubMed
20. Paganini-Hill A. Risk factors for Parkinson's disease: the leisure world cohort study. *Neuroepidemiology* 2001;20:118-24. DOI PubMed
21. Ascherio A, Chen H, Schwarzschild MA, Zhang SM, Colditz GA, Speizer FE. Caffeine, postmenopausal estrogen, and risk of Parkinson's disease. *Neurology* 2003;60:790-5. DOI PubMed
22. Wirdefeldt K, Gatz M, Pawitan Y, Pedersen NL. Risk and protective factors for Parkinson's disease: a study in Swedish twins. *Ann Neurol* 2005;57:27-33. DOI PubMed
23. Hu G, Bidel S, Jousilahti P, Antikainen R, Tuomilehto J. Coffee and tea consumption and the risk of Parkinson's disease. *Mov Disord* 2007;22:2242-8. DOI PubMed
24. Tan LC, Koh WP, Yuan JM, et al. Differential effects of black versus green tea on risk of Parkinson's disease in the Singapore Chinese Health Study. *Am J Epidemiol* 2008;167:553-60. DOI PubMed PMC

25. Powers KM, Kay DM, Factor SA, et al. Combined effects of smoking, coffee, and NSAIDs on Parkinson's disease risk. *Mov Disord* 2008;23:88-95. DOI PubMed
26. Sääksjärvi K, Knekt P, Rissanen H, Laaksonen MA, Reunanen A, Männistö S. Prospective study of coffee consumption and risk of Parkinson's disease. *Eur J Clin Nutr* 2008;62:908-15. DOI PubMed
27. Liu R, Guo X, Park Y, et al. Caffeine intake, smoking, and risk of Parkinson disease in men and women. *Am J Epidemiol* 2012;175:1200-7. DOI PubMed PMC
28. Qi H, Li S. Dose-response meta-analysis on coffee, tea and caffeine consumption with risk of Parkinson's disease. *Geriatr Gerontol Int* 2014;14:430-9. DOI PubMed
29. Bakshi R, Macklin EA, Hung AY, et al. Associations of lower caffeine intake and plasma urate levels with idiopathic Parkinson's disease in the harvard biomarkers study. *J Parkinsons Dis* 2020;10:505-10. DOI PubMed PMC
30. Altman RD, Lang AE, Postuma RB. Caffeine in Parkinson's disease: a pilot open-label, dose-escalation study. *Mov Disord* 2011;26:2427-31. DOI PubMed
31. Simon DK, Wu C, Tilley BC, et al. Caffeine and progression of Parkinson disease: a deleterious interaction with creatine. *Clin Neuropharmacol* 2015;38:163-9. DOI PubMed PMC
32. Postuma RB, Anang J, Pelletier A, et al. Caffeine as symptomatic treatment for Parkinson disease (Café-PD): a randomized trial. *Neurology* 2017;89:1795-803. DOI PubMed PMC
33. Postuma RB, Lang AE, Munhoz RP, et al. Caffeine for treatment of Parkinson disease: a randomized controlled trial. *Neurology* 2012;79:651-8. DOI PubMed PMC
34. Fujimaki M, Saiki S, Li Y, et al. Serum caffeine and metabolites are reliable biomarkers of early Parkinson disease. *Neurology* 2018;90:e404-11. DOI PubMed PMC
35. Ohmichi T, Kasai T, Kosaka T, et al. Biomarker repurposing: Therapeutic drug monitoring of serum theophylline offers a potential diagnostic biomarker of Parkinson's disease. *PLoS One* 2018;13:e0201260. DOI PubMed PMC
36. Ohmichi T, Kasai T, Shinomoto M, et al. Quantification of blood caffeine levels in patients with Parkinson's disease and multiple system atrophy by caffeine ELISA. *Front Neurol* 2020;11:580127. DOI PubMed PMC
37. Crotty GF, Maciuca R, Macklin EA, et al. Association of caffeine and related analytes with resistance to Parkinson disease among LRRK2 mutation carriers: a metabolomic study. *Neurology* 2020;95:e3428-37. DOI PubMed PMC
38. Svenningsson P, Le Moine C, Fisone G, Fredholm BB. Distribution, biochemistry and function of striatal adenosine A2A receptors. *Prog Neurobiol* 1999;59:355-96. DOI PubMed
39. Ishibashi K, Miura Y, Wagatsuma K, Toyohara J, Ishiwata K, Ishii K. Adenosine A2A receptor occupancy by caffeine after coffee intake in Parkinson's disease. *Mov Disord* 2022;37:853-7. DOI PubMed PMC
40. Hauser RA, Hattori N, Fernandez H, et al. Efficacy of istradefylline, an adenosine A2A receptor antagonist, as adjunctive therapy to levodopa in Parkinson's disease: a pooled analysis of 8 phase 2b/3 trials. *J Parkinsons Dis* 2021;11:1663-75. DOI PubMed PMC
41. Wolz M, Kaminsky A, Löhle M, Koch R, Storch A, Reichmann H. Chocolate consumption is increased in Parkinson's disease. Results from a self-questionnaire study. *J Neurol* 2009;256:488-92. DOI PubMed
42. Wolz M, Schleiffer C, Klingelhöfer L, et al. Comparison of chocolate to cacao-free white chocolate in Parkinson's disease: a single-dose, investigator-blinded, placebo-controlled, crossover trial. *J Neurol* 2012;259:2447-51. DOI PubMed