International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

ARTICLE TITLE	THE NEUROPROTECTIVE POTENTIAL OF COFFEE COMPOUNDS IN THE PREVENTION AND PROGRESSION OF NEURODEGENERATIVE DISORDERS: A SYSTEMATIC REVIEW FOCUSING ON ALZHEIMER'S AND PARKINSON'S DISEASES
DOI	https://doi.org/10.31435/ijitss.2(50).2026.5914
RECEIVED	24 March 2026
ACCEPTED	17 June 2026
PUBLISHED	23 June 2026
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

THE NEUROPROTECTIVE POTENTIAL OF COFFEE COMPOUNDS IN THE PREVENTION AND PROGRESSION OF NEURODEGENERATIVE DISORDERS: A SYSTEMATIC REVIEW FOCUSING ON ALZHEIMER'S AND PARKINSON'S DISEASES

Agnieszka Jóźwicka *(Corresponding Author, Email: agnieszka.jozwicka@onet.eu)*
Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland
ORCID ID: 0009-0008-1130-1518

Wojciech Janikowski
Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland
ORCID ID: 0009-0008-4078-9698

Ewa Bąkowska
Medical University of Lublin, Aleje Racławickie 1, 20-059 Lublin, Poland
ORCID ID: 0009-0007-4135-9748

Aleksandra Stępka
Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland
ORCID ID: 0009-0007-5034-0037

Lena Jaworowicz
Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland
ORCID ID: 0009-0008-4210-7216

Weronika Plichtowicz-Kordowska
Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland
ORCID ID: 0009-0009-7713-8597

Karina Lewandowska
Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland
ORCID ID: 0009-0004-5298-1426

Sara Awad
Samodzielny Publiczny Szpital Kliniczny im. prof. W. Orłowskiego CMKP, Warsaw, Mazovia, Poland
ORCID ID: 0009-0004-0942-6240

Paweł Szymonek
SPZOZ w Lubartowie, ul. Cicha 10, 21-100 Lubartów, Poland
ORCID ID: 0009-0002-6345-7721

Adam Zysk
Warsaw Southern Hospital, Warsaw, Poland
ORCID ID: 0009-0006-0425-2493

ABSTRACT

Background: Neurodegenerative disorders (NDDs), particularly Alzheimer's disease (AD) and Parkinson's disease (PD), present a profound and growing global health burden with a notable lack of disease-modifying therapies. Emerging epidemiological and preclinical evidence suggests that habitual coffee consumption may confer significant neuroprotective benefits, driven by its complex matrix of bioactive phytochemicals.
Objective: This systematic review aims to critically evaluate the efficacy and underlying molecular mechanisms of coffee-derived compounds in the prevention and progression of Alzheimer's and Parkinson's diseases.
Methods: A comprehensive literature search was conducted across PubMed and Google Scholar databases using predefined Medical Subject Headings (MeSH) and keywords. The review synthesized data from epidemiological cohorts, clinical trials, and preclinical models focusing on caffeine and non-caffeine constituents, such as chlorogenic acids and phenylindanes.
Results: Coffee exerts neuroprotective effects through a synergistic, multi-target approach. Caffeine primarily acts via adenosine A2A receptor antagonism, enhancing dopaminergic signaling and reducing excitotoxicity, which strongly correlates with a reduced risk of PD (relative risk ranging from 0.65 to 0.80). Non-caffeine constituents provide robust antioxidant and anti-inflammatory activity, upregulating the Nrf2 pathway and directly inhibiting the aggregation of amyloid-beta, tau, and alpha-synuclein proteins. While epidemiological evidence for PD is highly consistent, data regarding AD is more variable; however, regular midlife coffee consumption is significantly associated with a reduced risk of late-life cognitive decline. Individual responses are notably modulated by genetic polymorphisms (e.g., CYP1A2).
Conclusion: Coffee represents a potent, biologically plausible dietary intervention with significant potential to mitigate NDD pathology. While its multifaceted mechanisms position it as a promising neuroprotective agent, particularly against PD, further rigorous randomized controlled trials are essential to establish causality and define optimal, personalized consumption guidelines.

KEYWORDS

Coffee, Neuroprotection, Alzheimer's Disease, Parkinson's Disease, Caffeine, Chlorogenic Acid

CITATION

Agnieszka Jóźwicka, Wojciech Janikowski, Ewa Bąkowska, Aleksandra Stępka, Lena Jaworowicz, Weronika Plichtowicz-Kordowska, Karina Lewandowska, Sara Awad, Paweł Szymonek, Adam Zysk. (2026) The Neuroprotective Potential of Coffee Compounds in the Prevention and Progression of Neurodegenerative Disorders: a Systematic Review Focusing on Alzheimer's and Parkinson's Diseases. *International Journal of Innovative Technologies in Social Science*. 2(50). doi: 10.31435/ijitss.2(50).2026.5914

1. Introduction

Neurodegenerative disorders (NDDs), with Alzheimer's disease (AD) and Parkinson's disease (PD) being the most prevalent, represent an escalating and formidable challenge to global public health [1–3]. As the global population ages, the socioeconomic and healthcare burdens associated with these debilitating conditions are expanding exponentially. The pathophysiology of AD is classically hallmarked by the extracellular accumulation of amyloid-beta plaques and the formation of intracellular neurofibrillary tangles composed of hyperphosphorylated tau proteins. These pathological events drive progressive synaptic dysfunction, severe neuronal loss, and irreversible cognitive decline [1–3]. Conversely, PD is characterized by the preferential and progressive degeneration of dopaminergic neurons residing in the substantia nigra pars compacta, coupled with the propagation of intracellular inclusions known as Lewy bodies, which are primarily composed of misfolded alpha-synuclein aggregates [4–6]. Because the currently available pharmacotherapies for both of these devastating conditions are predominantly symptomatic and entirely lack disease-modifying efficacy, identifying modifiable lifestyle factors that can successfully halt, delay, or prevent neurodegeneration has become a primary focus of modern preventative medicine and neurobiology [7, 8].

Over the past two decades, extensive epidemiological data have consistently revealed a compelling inverse relationship between habitual, long-term coffee consumption and the incidence of several NDDs [9–11]. As one of the most universally consumed beverages across the globe, coffee is not merely a mild central nervous system stimulant; rather, it is a highly complex and pharmacologically active phytochemical matrix

comprising thousands of distinct bioactive compounds [15, 16]. Furthermore, population-based cohort studies have repeatedly demonstrated that moderate consumers typically exhibit a slower rate of cognitive decline compared to abstainers, reinforcing the hypothesis that sustained exposure to this beverage confers substantial long-term neurophysiological benefits. Historically, the primary focus of research was directed almost exclusively toward caffeine (1,3,7-trimethylxanthine), the principal psychoactive constituent of the beverage. Caffeine exerts its well-documented neuroprotective effects primarily through the non-selective antagonism of adenosine A2A receptors in the brain, which subsequently modulates neurotransmitter release and limits excitatory neurotoxicity [12–14]. However, emerging preclinical and clinical evidence strongly highlights the critical, independent contributions of other intrinsic non-caffeine phytomolecules [15, 16].

Among these diverse constituents, polyphenols such as chlorogenic acids and their primary metabolite, caffeic acid, have garnered significant scientific attention. Additionally, specific diterpenes, including cafestol and kahweol, alongside phenylindanes—which are unique compounds formed during the extensive roasting process of coffee beans—have demonstrated robust biological activity [17, 18]. These non-caffeine fractions exhibit potent antioxidant and anti-inflammatory properties, effectively mitigating oxidative stress by upregulating endogenous defense systems, such as the Nrf2/ARE signaling pathway. Furthermore, they are capable of modulating profound neuroinflammatory responses by suppressing the activation of microglia and astrocytes, thereby reducing the localized release of neurotoxic pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) [19].

Crucially, recent in vitro and in vivo models suggest that these specific phytochemicals may possess direct disease-modifying capabilities. For instance, certain coffee derivatives have been shown to directly interfere with and inhibit the oligomerization and fibrillogenesis of amyloid-beta, tau, and alpha-synuclein proteins, effectively preventing the formation of toxic oligomers that drive neuronal death [20]. This targeted disruption of protein aggregation pathways highlights a critical therapeutic avenue, as controlling the spread of misfolded proteins is paramount to halting disease progression at a fundamental level. Despite these highly promising molecular findings, the seamless translation of these complex mechanisms into definitive, universally applicable clinical recommendations remains significantly complicated. The existing scientific literature is fraught with heterogeneous study designs, highly variable coffee preparation and brewing methods, differing roast profiles, and confounding individual genetic interactions, such as polymorphisms in the *CYP1A2* gene responsible for caffeine metabolism. Therefore, a highly comprehensive and critically updated synthesis of the current body of literature is essential to bridge the gap between basic science and clinical application. This systematic review aims to meticulously evaluate the neuroprotective potential of various coffee-derived compounds in both the prevention and progression of Alzheimer’s and Parkinson’s diseases. By comprehensively dissecting both the large-scale epidemiological correlations and the specific underlying molecular mechanisms, this review seeks to determine whether specific coffee phytomolecules can be effectively leveraged as viable, evidence-based, non-pharmacological interventions in the ongoing global fight against progressive neurodegeneration.

2. Methodology

A comprehensive literature search was performed across the PubMed and Google Scholar databases to identify relevant studies on the neuroprotective potential of coffee compounds in the prevention and progression of neurodegenerative disorders, with a specific focus on Alzheimer's and Parkinson's diseases. The search strategy utilized combinations of the following keywords and Medical Subject Headings (MeSH): "coffee," "caffeine," "chlorogenic acid," "neuroprotection," "Alzheimer's disease," "Parkinson's disease," "cognitive decline," and "disease progression". Search terms were combined using Boolean operators (AND, OR) to ensure an exhaustive retrieval of evidence.

3. Results

3.1 Mechanisms of Action of Coffee in the Context of Neurodegenerative Disorders

The neuroprotective effects of coffee are mediated through a complex interplay of bioactive compounds acting across multiple converging molecular pathways. While caffeine has historically been considered the principal active compound, recent evidence emphasizes that the overall neuroprotective profile of coffee results from synergistic interactions between caffeine and non-caffeine phytochemicals [16, 21]. Caffeine exerts its central effects primarily through the non-selective antagonism of adenosine receptors, particularly the A2A subtype, which is highly expressed in the basal ganglia and hippocampus. Experimental studies demonstrate that A2A receptor blockade enhances dopaminergic neurotransmission and reduces glutamate-mediated excitotoxicity, thereby promoting neuronal survival [20, 22]. In animal models of neurodegeneration, A2A receptor inactivation has been associated with a significant attenuation of neuronal loss and improved motor and cognitive outcomes [22].

In addition to its effects on neurotransmission, caffeine exerts potent anti-inflammatory activity. Chronic neuroinflammation, characterized by sustained microglial activation and elevated levels of pro-inflammatory cytokines such as TNF-α and IL-6, is a key contributor to neurodegeneration. Caffeine-mediated A2A receptor antagonism has been shown to suppress microglial activation and reduce inflammatory signaling pathways, leading to decreased neuronal damage [16, 20].

Oxidative stress represents another critical mechanism underlying neurodegenerative processes. Coffee-derived polyphenols, particularly chlorogenic acids, exhibit strong antioxidant activity by scavenging reactive oxygen species and activating endogenous defense systems such as the Nrf2 pathway [18]. These effects contribute to mitochondrial protection and a reduction of apoptosis in neuronal cells. Emerging evidence suggests that coffee compounds may directly interfere with protein aggregation. Phenylindanes formed during coffee roasting have been shown to inhibit amyloid-beta and tau aggregation in vitro, indicating a potential disease-modifying effect [17]. Additionally, caffeine has been implicated in the modulation of autophagic pathways, facilitating the clearance of misfolded proteins [20].

Importantly, these mechanisms are highly interconnected and likely act synergistically. The simultaneous modulation of neurotransmission, inflammation, oxidative stress, and protein aggregation supports the concept of coffee as a multi-target neuroprotective agent [16, 21]. However, it should be noted that the majority of mechanistic evidence is derived from in vitro and animal studies, which may limit direct clinical translation. Furthermore, the magnitude of these effects may vary depending on factors such as coffee preparation methods, roasting degree, and inter-individual variability in caffeine metabolism, particularly related to *CYP1A2* polymorphisms [21].

3.2 Findings on Parkinson's Disease

A substantial body of epidemiological evidence supports a strong inverse association between coffee consumption and the risk of Parkinson's disease. Large prospective cohort studies and meta-analyses consistently report that habitual coffee consumption is associated with a significant reduction in PD risk, with relative risk (RR) estimates typically ranging from 0.65 to 0.80 for high versus low consumption [8, 23, 24]. A dose-response relationship has been demonstrated in several analyses; a meta-analysis by Qi et al. reported that each additional cup of coffee per day was associated with an approximately 3–7% reduction in PD risk, with the strongest protective effect observed at 3–5 cups per day [24]. Similarly, large cohort studies have shown that individuals in the highest caffeine intake categories exhibit up to a 25–30% lower risk of developing PD compared to non-consumers (HR ≈ 0.70–0.75) [23].

Recent biomarker-based studies further strengthen these findings, demonstrating that higher prediagnostic plasma caffeine metabolite levels are associated with a significantly reduced risk of Parkinson's disease, supporting a biological basis for the observed epidemiological associations [25]. Sex-specific differences have also been observed; the protective association between caffeine intake and PD appears to be more consistent in men, while results in women are less robust, potentially due to interactions between caffeine metabolism and estrogen levels. Hormonal status, including the use of hormone replacement therapy, may further modulate these effects [8].

Mechanistic studies provide strong biological support for these epidemiological findings. In animal models, caffeine administration significantly attenuates dopaminergic neuron loss induced by neurotoxins such as MPTP, reducing neuronal degeneration and improving motor outcomes [22, 26]. These effects are primarily mediated through A2A receptor antagonism, which modulates basal ganglia circuitry and enhances dopaminergic signaling. The translational relevance of this pathway is underscored by the clinical development

of selective A2A receptor antagonists, such as istradefylline, which has been approved as an adjunctive therapy in Parkinson's disease [27]. Additional pathways, including anti-inflammatory effects, modulation of synaptic plasticity, and potential interactions with the gut-brain axis, may further contribute to the observed neuroprotective effects. Genetic variability, particularly in the *CYP1A2* and *ADORA2A* genes, may also influence individual susceptibility to caffeine's effects [21]. Despite the overall consistency of findings, some heterogeneity remains across studies, potentially reflecting differences in study design, population characteristics, and assessment of coffee intake. Reverse causation, related to prodromal PD symptoms influencing caffeine consumption, also cannot be entirely excluded. Taken together, the available evidence strongly supports a protective association between coffee consumption and Parkinson's disease risk.

3.3 Findings on Alzheimer's Disease and Cognitive Decline

The association between coffee consumption and Alzheimer's disease is supported by a growing but less consistent body of evidence compared to Parkinson's disease. Several longitudinal studies and meta-analyses suggest that moderate coffee consumption is associated with a reduced risk of cognitive decline and dementia, particularly when exposure occurs during midlife [9, 28]. For example, findings from the CAIDE study indicate that individuals consuming 3–5 cups of coffee per day in midlife had approximately a 60–65% lower risk of developing dementia or Alzheimer's disease later in life (OR ≈ 0.35–0.40) [9]. Meta-analyses of prospective cohort studies have reported a pooled relative risk reduction of approximately 15–20% for moderate coffee consumers compared to low or non-consumers [28]. Recent systematic reviews further suggest that higher caffeine intake (>200 mg/day) is associated with a reduced risk of cognitive decline and may delay progression from mild cognitive impairment to Alzheimer's disease, although effect sizes remain moderate and are influenced by genetic and lifestyle factors [29].

At the molecular level, caffeine has been shown to modulate key pathological processes associated with AD. Experimental studies demonstrate that caffeine reduces amyloid-beta production by influencing secretase activity and inhibits tau hyperphosphorylation, thereby mitigating two central features of AD pathology [14, 20]. Non-caffeine compounds also contribute significantly to neuroprotection. Polyphenols such as chlorogenic acids exhibit antioxidant and anti-inflammatory effects, which may reduce oxidative stress and neuroinflammation, both of which are implicated in cognitive decline [18, 30]. Additionally, coffee consumption has been associated with improved cerebral perfusion and enhanced neuronal resilience. Neuroimaging studies provide further support for these observations; higher coffee intake has been associated with lower amyloid-beta deposition in the brain, as measured by PET imaging, suggesting a direct effect on disease pathology [19]. Furthermore, umbrella reviews of meta-analyses involving large populations suggest that coffee consumption is associated with an approximately 10% reduction in dementia risk (RR ≈ 0.90), although heterogeneity across studies remains moderate [31].

However, inconsistencies across studies remain a significant limitation. Variability in results may be attributed to differences in study design, duration of follow-up, genetic factors, and the timing of consumption. Notably, midlife coffee consumption appears to demonstrate stronger protective associations than late-life intake [9, 32]. Furthermore, the relationship between coffee consumption and cognitive outcomes appears to be nonlinear, with moderate intake conferring benefits and excessive intake potentially leading to adverse effects such as sleep disruption.

4. Discussion

An additional critical aspect that warrants further consideration is the role of lifestyle clustering and residual confounding in observational studies investigating coffee consumption. Individuals who consume coffee regularly may differ systematically from non-consumers in terms of diet quality, socioeconomic status, physical activity, and other health-related behaviors. Although most large cohort studies attempt to adjust for these variables, the possibility of residual confounding cannot be entirely excluded, particularly in long-term observational designs [33].

Moreover, reverse causation represents a significant methodological challenge, especially in Parkinson's disease research. Prodromal symptoms of PD, such as hyposmia, depression, and gastrointestinal dysfunction, may precede clinical diagnosis by years and could influence behavioral patterns, including reduced coffee consumption. This may partially explain the observed inverse association between caffeine intake and PD risk, although longitudinal studies with extended follow-up periods suggest that this effect does not fully account for the relationship [8].

Another important consideration is the heterogeneity in coffee composition. Coffee is not a standardized product, and its chemical profile varies depending on bean type, roasting degree, brewing method, and preparation techniques. For instance, espresso, filtered coffee, and boiled coffee differ significantly in their concentrations of caffeine, diterpenes, and polyphenols. These variations may influence biological activity and contribute to the inconsistencies observed across studies [15]. The issue of dosage also remains insufficiently resolved. While moderate consumption appears to confer neuroprotective benefits, excessive intake may lead to adverse effects, including sleep disturbances, anxiety, and cardiovascular complications. Sleep disruption, in particular, has been linked to impaired glymphatic clearance of amyloid-beta, suggesting that excessive caffeine consumption could paradoxically exacerbate neurodegenerative processes [34]. Therefore, identifying an optimal therapeutic window for coffee consumption is essential.

In addition, genetic variability plays a crucial role in modulating the effects of coffee. Polymorphisms in genes involved in caffeine metabolism (e.g., *CYP1A2*) and adenosine receptor signaling (e.g., *ADORA2A*) may lead to substantial inter-individual differences in response to caffeine intake. Slow metabolizers, for example, may experience prolonged exposure to caffeine, potentially altering both its beneficial and adverse effects [35]. This highlights the importance of incorporating genetic profiling into future research to better understand personalized responses.

The gut-brain axis has also emerged as a potential mediator of coffee's neuroprotective effects. Coffee consumption has been shown to influence gut microbiota composition, promoting the growth of beneficial bacterial species and reducing systemic inflammation. Given the growing evidence linking gut dysbiosis to neurodegenerative diseases, particularly Parkinson's disease, this pathway represents a promising area for future investigation [36].

From a translational perspective, the identification of specific bioactive compounds responsible for neuroprotection opens new avenues for therapeutic development. Compounds such as phenylindanes, chlorogenic acids, and caffeine derivatives may serve as candidates for the development of nutraceuticals or pharmacological agents targeting key pathological mechanisms, including protein aggregation and neuroinflammation [37]. However, translating these findings into clinical applications requires rigorous validation in human trials.

Finally, it is important to emphasize that coffee consumption should be considered within the broader context of dietary and lifestyle patterns. Neurodegenerative diseases are multifactorial, and single dietary components are unlikely to exert strong effects in isolation. Instead, coffee may contribute to neuroprotection as part of a comprehensive approach encompassing diet, physical activity, and other environmental factors [38].

5. Conclusions

This systematic review provides a comprehensive evaluation of the current evidence on the neuroprotective potential of coffee and its bioactive compounds in the prevention and progression of neurodegenerative disorders, with particular emphasis on Alzheimer's disease and Parkinson's disease. The findings support the hypothesis that habitual, moderate coffee consumption is associated with a reduced risk of Parkinson's disease and may contribute to the attenuation of cognitive decline and Alzheimer's disease pathology. The strongest and most consistent evidence is observed in Parkinson's disease, where epidemiological findings are supported by robust mechanistic data and clinical translation through adenosine A2A receptor-targeted therapies. In contrast, while the evidence in Alzheimer's disease is less consistent, multiple experimental and observational studies indicate that coffee-derived compounds may modulate key pathogenic processes, including amyloid-beta accumulation, tau pathology, oxidative stress, and neuroinflammation.

Importantly, the neuroprotective effects of coffee appear to arise from the synergistic action of multiple bioactive compounds rather than caffeine alone. Polyphenols, diterpenes, and roasting-derived compounds such as phenylindanes contribute to a broad spectrum of biological activities, reinforcing the concept of coffee as a multi-target neuroprotective agent. Despite these promising findings, several limitations must be acknowledged. The predominance of observational studies limits causal inference, while variability in coffee composition, dosage, timing of exposure, and individual genetic factors complicates the interpretation of results. Therefore, although coffee represents a widely accessible and potentially beneficial lifestyle factor, current evidence does not yet support its use as a formal preventive or therapeutic intervention.

Future research should focus on well-designed randomized controlled trials and longitudinal studies to establish causality and define optimal consumption patterns. Additionally, advances in precision nutrition,

metabolomics, and microbiome research may facilitate the development of personalized dietary recommendations and targeted therapeutic strategies based on coffee-derived compounds. In conclusion, coffee represents a biologically plausible and globally relevant modifiable factor with potential neuroprotective effects. While further high-quality evidence is required, its multifaceted mechanisms of action and consistent epidemiological associations position it as a promising component in strategies aimed at reducing the burden of neurodegenerative diseases.

Author's contribution

Here we present a detailed description of author's contribution to the creation of this manuscript. Conceptualization Wojciech Janikowski, Ewa Bąkowska, and Agnieszka Jóźwicka; methodology, Aleksandra Stępka; software, Weronika Plichtowicz- Kordowska; check, Lena Jaworowicz, Adam Zysk, Maria Wieczorek, Aleksandra Stępka and Agnieszka Jóźwicka; formal analysis, Karina Lewandowska, Sara Awad; investigation, Wojciech Janikowski; resources, Maria Wieczorek, Sara Awad; data curation, Ewa Bąkowska, Paweł Szymonek; writing - rough preparation, Agnieszka Jóźwicka, Adam Zysk; writing - review and editing Weronika Plichtowicz- Kordowska, Wojciech Janikowski; visualization, Paweł Szymonek, Agnieszka Jóźwicka; supervision, Lena Jaworowicz; project administration, Wojciech Janikowski.

All authors have read and agreed with the published version of the manuscript.

REFERENCES

1. Scheltens, P., De Strooper, B., Kivipelto, M., et al. (2021). Alzheimer's disease. *Lancet, 397*(10284), 1577–1590. https://doi.org/10.1016/S0140-6736(20)32205-4
2. Knopman, D. S., Amieva, H., Petersen, R. C., et al. (2021). Alzheimer disease. *Nature Reviews Disease Primers, 7*(1), 33. https://doi.org/10.1038/s41572-021-00269-y
3. Long, J. M., & Holtzman, D. M. (2019). Alzheimer disease: An update on pathobiology and treatment strategies. *Cell, 179*(2), 312–339. https://doi.org/10.1016/j.cell.2019.09.001
4. Bloem, B. R., Okun, M. S., & Klein, C. (2021). Parkinson's disease. *Lancet, 397*(10291), 2284–2303. https://doi.org/10.1016/S0140-6736(21)00218-X
5. Poewe, W., Seppi, K., Tanner, C. M., et al. (2017). Parkinson disease. *Nature Reviews Disease Primers, 3*, 17013. https://doi.org/10.1038/nrdp.2017.13
6. Kalia, L. V., & Lang, A. E. (2015). Parkinson's disease. *Lancet, 386*(9996), 896–912. https://doi.org/10.1016/S0140-6736(14)61393-3
7. Yiannopoulou, K. G., & Papageorgiou, S. G. (2013). Current and future treatments for Alzheimer's disease. *Therapeutic Advances in Neurological Disorders, 6*(1), 19–33. https://doi.org/10.1177/1756285612461679
8. Ascherio, A., & Schwarzschild, M. A. (2016). The epidemiology of Parkinson's disease: Risk factors and prevention. *Lancet Neurology, 15*(12), 1257–1272. https://doi.org/10.1016/S1474-4422(16)30230-7
9. Eskelinen, M. H., 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. *Journal of Alzheimer's Disease, 16*(1), 85–91. https://doi.org/10.3233/JAD-2009-0920
10. Ross, G. W., Abbott, R. D., Petrovitch, H., et al. (2000). Association of coffee and caffeine intake with the risk of Parkinson disease. *JAMA, 283*(20), 2674–2679. https://doi.org/10.1001/jama.283.20.2674
11. Liu, Q. P., Wu, Y. F., Cheng, H. Y., et al. (2016). Habitual coffee consumption and risk of cognitive decline/dementia: A systematic review and meta-analysis of prospective cohort studies. *Nutrition, 32*(6), 628–636. https://doi.org/10.1016/j.nut.2015.11.015
12. Xu, K., Bastia, E., & Schwarzschild, M. A. (2005). Therapeutic potential of adenosine A2A receptor antagonists in Parkinson's disease. *Pharmacology & Therapeutics, 105*(3), 267–310. https://doi.org/10.1016/j.pharmthera.2004.10.007
13. Wierzejska, R. (2017). Can coffee consumption lower the risk of Alzheimer's disease and Parkinson's disease? A literature review. *Archives of Medical Science, 13*(3), 507–514. https://doi.org/10.5114/aoms.2016.63599
14. Arendash, G. W., Schleif, W., Rezai-Zadeh, K., et al. (2006). Caffeine protects Alzheimer's mice against cognitive impairment and reduces brain beta-amyloid production. *Neuroscience, 142*(4), 941–952. https://doi.org/10.1016/j.neuroscience.2006.07.021
15. Ludwig, I. A., Clifford, M. N., Lean, M. E., Ashihara, H., & Crozier, A. (2014). Coffee: Biochemistry and potential health benefits. *Food & Function, 5*(8), 1695–1717. https://doi.org/10.1039/c4fo00042k
16. Kolb, H., Kempf, K., & Martin, S. (2020). Health effects of coffee: Mechanism unraveled? *Nutrients, 12*(6), 1842. https://doi.org/10.3390/nu12061842
17. Mancini, R. S., Wang, Y., & Weaver, D. F. (2018). Phenylindanes in brewed coffee inhibit amyloid-beta and tau aggregation. *Frontiers in Neuroscience, 12*, 735. https://doi.org/10.3389/fnins.2018.00735

18. Heitman, E., & Ingram, D. K. (2017). Cognitive and neuroprotective effects of chlorogenic acid. *Nutritional Neuroscience, 20*(1), 32–39. https://doi.org/10.1179/1476830514Y.0000000146
19. Kim, J. W., Byun, M. S., Yi, D., et al. (2019). Coffee consumption and reduced amyloid-beta deposition in the human brain. *Translational Psychiatry, 9*(1), 270. https://doi.org/10.1038/s41398-019-0604-5
20. Ren, X., & Chen, J. F. (2020). Caffeine and Parkinson's disease: Multiple benefits and emerging mechanisms. *Frontiers in Neuroscience, 14*, 602697. https://doi.org/10.3389/fnins.2020.602697
21. Grosso, G., Godos, J., Galvano, F., & Giovannucci, E. L. (2017). Coffee, caffeine, and health outcomes: An umbrella review. *Annual Review of Nutrition, 37*, 131–156. https://doi.org/10.1146/annurev-nutr-071816-064941
22. Chen, J. F., Xu, K., Petzer, J. P., et al. (2001). Neuroprotection by caffeine and A(2A) receptor inactivation in a model of Parkinson's disease. *Journal of Neuroscience, 21*(10), RC143. https://doi.org/10.1523/JNEUROSCI.21-10-j0001.2001
23. Liu, R., Guo, X., Park, Y., et al. (2012). Caffeine intake, smoking, and risk of Parkinson disease in men and women. *American Journal of Epidemiology, 175*(11), 1200–1207. https://doi.org/10.1093/aje/kwr451
24. Qi, H., & Li, S. (2014). Dose-response meta-analysis on coffee, tea and caffeine consumption with risk of Parkinson's disease. *Geriatrics & Gerontology International, 14*(2), 430–439. https://doi.org/10.1111/ggi.12123
25. Zhao, Y., Lai, Y., Konijnenberg, H., et al. (2024). Association of coffee consumption and prediagnostic caffeine metabolites with incident Parkinson disease in a population-based cohort. *Neurology, 102*(8), e209201. https://doi.org/10.1212/WNL.0000000000209201
26. Chen, X., Lan, X., Roche, I., et al. (2008). Caffeine protects against MPTP-induced blood-brain barrier dysfunction in mouse striatum. *Journal of Neurochemistry, 107*(4), 1147–1157. https://doi.org/10.1111/j.1471-4159.2008.05697.x
27. Chen, J. F., & Cunha, R. A. (2020). The belated US FDA approval of the adenosine A2A receptor antagonist istradefylline for treatment of Parkinson's disease. *NPJ Parkinson's Disease, 6*, 13. https://doi.org/10.1007/s11302-020-09694-2
28. Panza, F., Solfrizzi, V., Barulli, M. R., et al. (2015). Coffee, tea, and caffeine consumption and prevention of late-life cognitive decline and dementia: A systematic review. *Journal of Nutrition, Health & Aging, 19*(3), 313–328. https://doi.org/10.1007/s12603-014-0563-8
29. Ashfaq, Z., Younas, Z., Nathaniel, E., et al. (2025). Association between caffeine intake and Alzheimer's disease progression: A systematic review. *Cureus, 17*(3), e80923. https://doi.org/10.7759/cureus.80923
30. Gardener, S. L., Rainey-Smith, S. R., Villemagne, V. L., et al. (2021). Higher coffee consumption is associated with slower cognitive decline and less cerebral Aβ-amyloid accumulation over 126 months: Data from the Australian Imaging, Biomarkers, and Lifestyle Study. *Frontiers in Aging Neuroscience, 13*, 744872. https://doi.org/10.3389/fnagi.2021.744872
31. Gill, H., Phan, L., Chen-Li, D., et al. (2024). An umbrella review of meta-analysis to understand the effect of coffee consumption and the relationship between stroke, cardiovascular heart disease, and dementia among its global users. *Journal of Family Medicine and Primary Care, 13*(11), 4785–4795. https://doi.org/10.4103/jfmpc.jfmpc_654_24
32. Pham, K., Mulugeta, A., Zhou, A., O'Brien, J. T., Llewellyn, D. J., & Hyppönen, E. (2022). High coffee consumption, brain volume and risk of dementia and stroke. *Nutritional Neuroscience, 25*(10), 2111–2122. https://doi.org/10.1080/1028415X.2021.1945858
33. Loftfield, E., Freedman, N. D., Graubard, B. I., et al. (2018). Association of coffee drinking with mortality by genetic variation in caffeine metabolism: Findings from the UK Biobank. *JAMA Internal Medicine, 178*(8), 1086–1097. https://doi.org/10.1001/jamainternmed.2018.2425
34. Xie, L., Kang, H., Xu, Q., et al. (2013). Sleep drives metabolite clearance from the adult brain. *Science, 342*(6156), 373–377. https://doi.org/10.1126/science.1241224
35. Cornelis, M. C., & El-Sohemy, A. (2007). Coffee, caffeine, and coronary heart disease. *Current Opinion in Clinical Nutrition and Metabolic Care, 10*(6), 745–751. https://doi.org/10.1097/MOL.0b013e3280127b04
36. Jaquet, M., Rochat, I., Moulin, J., et al. (2009). Impact of coffee consumption on gut microbiota. *International Journal of Food Microbiology, 130*(2), 117–121. https://doi.org/10.1016/j.ijfoodmicro.2009.01.011
37. Higdon, J. V., & Frei, B. (2006). Coffee and health: A review of recent human research. *Critical Reviews in Food Science and Nutrition, 46*(2), 101–123. https://doi.org/10.1080/10408390500400009
38. Scarmeas, N., Anastasiou, C. A., & Yannakoulia, M. (2018). Nutrition and prevention of cognitive impairment. *Lancet Neurology, 17*(11), 1006–1015. https://doi.org/10.1016/S1474-4422(18)30338-7