Nutrition Research Reviews

cambridge.org/nrr

Effects of active compounds and their metabolites associated with coffee consumption on neurodegenerative disease

Dorota Koníčková[1,2], Kateřina Menšíková[1,2], Lucie Plíhalová[3] and Petr Kaňovský[1,2]

[1]Department of Neurology, Faculty of Medicine and Dentistry, Palacky University, Olomouc, Czech Republic; [2]Department of Neurology, University Hospital Olomouc, Olomouc, Czech Republic and [3]Department of Chemical Biology, Palacky University, Olomouc, Czech Republic

Review Article

Cite this article: Koníčková D, Menšíková K, Plíhalová L, and Kaňovský P (2024). Effects of active compounds and their metabolites associated with coffee consumption on neurodegenerative disease. *Nutrition Research Reviews*, page 1 of 6. doi: 10.1017/S0954422424000349

Received: 26 April 2024
Revised: 19 September 2024
Accepted: 12 November 2024

Keywords:
bioactive compounds; caffeine; coffee; neurodegenerative diseases

Corresponding author:
Dorota Koníčková;
Email: dorota.konickova@upol.cz

Abstract

Coffee is one of the most known and consumed beverages worldwide. Only three species are used in commercial coffee production, that is, *Coffea arabica* L. (Arabica coffee), *Coffea canephora* Pierre ex A. Froehner (Robusta coffee) and *Coffea liberica* Hiern (Excelsa coffee). The world population consumes approximately two billion cups of coffee per day, making it an important commercial resource of bioactive compounds in world markets. High interest in coffee consumption described in the literature is due not only to its organoleptic properties (for example, desirable bitterness, amount of flavours and aromas) but also to its ability to stimulate the central nervous system.

It is now known that there are more than 1000 compounds in coffee beverages, several of which have a bioactive activity. Recent studies show that consuming three to four cups of coffee per day, that is, moderate consumption according to the European Food Safety Authority, may be beneficial for health.

The main objective of the proposed review is to provide a comprehensive overview of bioactive compounds in coffee and other caffeine-containing beverages and their effects on neurodegenerative proteinopathies.

Introduction

Coffee typically contains more caffeine than most other beverages. Because it is widely consumed, it contributes significantly to the total caffeine intake of the general population, especially adults. However, its benefits and risks remain controversial. Several studies have shown an association between coffee consumption and improved health, reporting that coffee consumption is associated with a lower risk of several chronic diseases related to inflammatory processes, including neurodegenerative diseases (ND). The health benefits of coffee are largely attributed to its rich phytochemicals. This has been linked to its potent antioxidant, anti-inflammatory and anti-apoptotic effects against several types of ND, including Alzheimer's disease (AD) and Parkinson's disease (PD)[1]. Neurotrophic factors, poly-(ADP-ribose)-polymerase, vascular endothelial growth factor, inflammatory processes and antioxidant defences have been described as the main mechanisms involved in the specific effects of caffeine. In the past two decades, several studies have been conducted to demonstrate various modulatory effects of coffee/caffeine in experimentally induced ND conditions, especially in animal models[2]. As caffeine is a water- and fat-soluble substance, it can easily cross the blood–brain barrier, and once in the brain, it can act on different molecular targets, modulating several pharmacological effects, such as adenosine receptor antagonism, phosphodiesterase inhibition and calcium release blockade, without altering the physiology and homeostasis of the brain parenchyma. Coffee consumption is therefore associated with a lower risk of several chronic pathological conditions related to inflammatory processes, including ND. Research suggests that regular coffee consumption in moderate amounts (for example, three to five cups or 300 mg of coffee) should be able to reduce the overall risk of cognitive impairment by playing a potential protective role in preventing and delaying the onset of ND (for example, reducing the risk of PD by 24% and AD by 64%)[3]. These results support the hypothesis that coffee consumption is a highly protective factor, possibly acting on neurotoxicity associated with oxidative stress, amyloid-mediated neurotoxicity and inflammatory processes. Caffeine is thought to exert neuroprotective and behavioural effects by blocking adenosine A2A and monoamine oxidase B (MAO-B) receptors while inducing tolerance to the impact of the adenosine 1A receptor blockade. The result is higher levels of serotonin and acetylcholine in the central nervous system (CNS). Caffeine may reduce lipid peroxidation by decreasing the production of reactive oxygen species (ROS) such as hydroxyl

radicals and hydrogen. It may also act as an antioxidant by increasing glutathione *S*-transferase activity. In addition, it appears that caffeine may also protect dopaminergic neurons by activating some antioxidant signalling molecules and promoting the activation of transcription factors involved in mitochondrial biogenesis as well as antioxidant and anti-inflammatory pathways[1,3]. However, it is currently difficult to detect and determine its mode of action. Therefore, strong evidence supports the use of caffeine not as a substitute for conventional pharmacological treatments but rather as an adjunct to suppress and manage the neuroinflammatory processes involved in ND[3].

This review is based on a systematic, bibliographic literature search of PubMed, Web of Science, Scopus and Google Scholar, covering articles published from the databases' inception to 2024. The search strategy included combinations of the terms 'coffee', 'caffeine', 'neurodegenerative disease', 'Parkinson's disease', 'Alzheimer's disease' and 'parkinsonism'. In addition, relevant publications were identified and included from the reference lists of the articles.

Bioactive compounds and their composition in coffee

Roasted coffee beans contain more than 1000 bioactive compounds with various physiological effects as well as health benefits[4,5]. Active compounds and their derivatives contained in coffee have several neuroprotective properties that reduce the risk of cognitive decline and neurodegenerative diseases. A growing body of evidence suggests that regular consumption of coffee, as well as tea and dark chocolate (cocoa), may support a reduction in the risk of age-related neurodegenerative disorders. However, the complex array of phytochemicals in these components hinders a clear understanding of the components that influence neuronal plasticity and resilience[6]. Anti-inflammatory (inhibition of the expression of cytokines genes, modulation of nuclear factor kappa-light chain enhancer of activated B cells, regeneration of neurons, neuroplasticity), antioxidant (elimination of free radicals, reduction of oxidative stress), antifibrotic (reduction of oxidative DNA damage, elimination of free radicals), antimicrobial (antimicrobial activity against a range of Gram-positive and Gram-negative bacteria) and anticancer (prevention of initiation of carcinogenesis, antitumoural activity) properties have also been described, leading to reduced mortality and improvements in endocrine, hepatic, gastrointestinal, cardiovascular and cancer diseases[7–10].

The optimal benefits obtained from coffee in pathologies depend on higher daily doses. Existing research believes that coffee has great therapeutic potential in the future, but there is still a need to elucidate the mechanisms of true causal relationships in certain neuropathologies in further studies.

Coffee is a complex blend of many compounds and nutrients that work synergistically together. However, its multidirectional effects and mechanism of action are still poorly understood. The composition of elements in coffee beans varies with the type of coffee, country of origin, growing conditions, roasting conditions, temperature, time, speed, brewing conditions and grind size of coffee beans[11]. Caffeine (CAF) is one of the most important and discussed compounds not only in coffee but also in tea, cola and chocolate of different types and brands. The different abundances and contents of CAF are studied because of its many effects on the organism (genetic polymorphism, sex and metabolic heterogeneity)[12].

The most important compounds of coffee beans are:

1) caffeine (0·5–2·6%): differences between Arabica (0·7–1·4%), Robusta (2·2–2·4%) and Excelsa (0·86–1·13%)
2) theobromine, theophylline (1%)
3) caffeic acid, quinic acid (10%)
4) chlorogenic acid (4–6%)
5) polysaccharides (25–30%)
6) proteins (13%)
7) fats and waxes (0·1–0·8%)
8) water (10–13%)
9) minerals (4%)
10) vitamin B3 (trace amount)[13].

Among the most important physiologically effective compounds are:

1) purine alkaloids – methylxanthines (CAF, theobromine, theophylline and nicotinic acid);
2) polyphenols (chlorogenic acids (CGA) and their derivates such as CAF, quinic acids, phenylindanes, ferulic acid, quercetin, hydroxyhydroquinone and pyrocatechol);
3) fatty acids (eicosanoyl-5-hydroxytryptamine);
4) diterpenoids (cafestol and kahweol);
5) flavonoids (anthocyanins and catechins);
6) lactones;
7) and many other micronutrients such as potassium and magnesium[7,14,15].

Methylxanthines, of which **CAF** (1,3,7-trimethylxanthine) is best studied, have clear effects on neuronal network activity, protecting neurons from dysfunction and promoting sustained cognitive development. Since it is a purine alkaloid, it is described as an antioxidant, capable of protecting against oxidative damage, which is typical of most neurodegenerative diseases. Its mechanism of action is based on the antagonism of different subclasses of adenosine receptors, thereby mediating protection by dopamine receptors, stimulating the central nervous system and enhancing mood and alertness. In addition, it is a phosphodiesterase inhibitor, with a consequent effect on metabolism. It is most commonly associated with neuroprotective effects, mediated by the inhibition of lipid peroxidation and reduction of reactive oxygen species production[14]. CAF has been shown to reduce excitotoxicity, cellular apoptosis and inflammation, as well as partially resolve memory problems. In Alzheimer's disease (AD), CAF has been shown to protect against blood–brain barrier disruption, reducing amyloid beta (Aβ) levels through inhibition of its secretory pathway specifically, demonstrating its anti-inflammatory, antioxidant and mitochondrial activity, as well as neurological stimulation and neuroprotection. α-Tocopherol has demonstrated neuroprotective activity through antioxidant activity and free radical scavenging activity, which has been associated with inhibition of some forms of neurotoxicity and improvement of memory impairment in Parkinson's disease (PD)[5].

Other representatives of methylxanthines are **theobromine** (3,7-dimethylxanthine) and **theophylline** (1,3-dimethylxanthine), also found in tea or chocolate. They show high bioavailability and are associated with hypoglycaemic and neuroprotective benefits. Moreover, theobromine levels inversely correlate with $A\beta_{42}$ levels in patients with AD[6].

CAF metabolites **paraxanthine** (1,7-dimethylxanthine) and **theophylline** (1,3-dimethylxanthine) provide neuroprotection

https://doi.org/10.1017/S0954422424000349 Published online by Cambridge University Press

against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) which induces dopamine loss in the striatum and shows inhibition of dopamine reduction[6]. Whereas paraxanthine is not present in plant extracts, in humans its blood concentrations reach levels comparable or higher than those of CAF. Therefore, it should be considered when investigating the physiological effects of CAF, especially under conditions of chronic intake.

Mancini *et al.*[16] investigated another group of coffee compounds – the **phenylindanes**. Using fluorescence assays to determine the level of inhibition of neurodegenerative protein accumulation, they found that the phenylindanes in dark-roasted coffee exhibited strong inhibitory activity, suggesting the importance of neuroprotection[16].

When coffee undergoes roasting, amino acids and carbohydrates react through a process called the Maillard reaction[17]. Through this, other compounds such as melanoidins and acrylamide are produced. Moreira *et al.*[18] point to **melanoidins** as having high antioxidant activity, especially in scavenging free radicals. These bioactive substances were studied in rats that were given approximately six cups of espresso (1 espresso = 30 ml of caffeine source/60 mg caffeine content in the product) (to give an idea, Fig. 1 summarises the CAF content in caffeine-containing beverages). Melanoidins were able to decrease the concentration of pro-inflammatory cytokines (tumour necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ)) and increase the number of anti-inflammatory substances, such as interleukins (IL).

***β*-Carbolines** harman and norharman are two compounds present in roasted coffee with a known spectrum of physiological effects in the human body. This is a group of chemicals widely found in nature and structurally very similar to the neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), which has been linked to the development of PD. These compounds have recently been investigated for some neuroprotective effects. In particular, β-carbolines can reversibly inhibit monoamine oxidase (MAO) and increase the concentration of neurotransmitters such as dopamine, thus protecting against the neurodegenerative process. Indeed, MAO inhibition is increasingly being reported as an important mechanism for reducing the rate of PD, mainly by reducing the oxidative deamination of key neurotransmitters, including dopamine, the neurotransmitter most affected in this disease. While caffeine is reported to act as an antagonist for the adenosine A2 receptor, blocking the effect of adenosine on the suppression of dopaminergic transmission and, thus, reducing dopamine neurotoxicity, norharman and harman are potent competitive and reversible MAO inhibitors, both in rats and in humans. The high levels of these β-carbolines in roasted coffee place them at the top of the list of suspected compounds likely to influence the course of Parkinson's disease[5,18,19].

Chlorogenic acids (**CGA**) share not only antioxidant properties but also anti-inflammatory effects by inhibiting the expression of cytokine genes and modulating the activation of inflammatory nuclear factor kappa B (NFκB), which is associated with neuronal regeneration, thereby contributing to neuroplasticity. For this reason, together with CAF, they have attributes of neuroprotective properties[20].

Caffeine and Parkinson's disease

Although there are CAF intake doses determined to be not to be associated with adverse effects by Health Canada (400 mg/d for adults (10 g for lethality), 300 mg/d for pregnant women and 2·5 mg/kg/d for children and adolescents), 2·5 mg CAF/kg body weight/d remains an appropriate recommendation[21]. Because CAF is water and lipid soluble, it readily crosses the blood–brain barrier. It produces complex pharmacological effects in the brain, ranging from adenosine receptor antagonism to phosphodiesterase inhibition, and from to GABA receptor blockade and calcium release[22].

CAF levels and their metabolism can be analysed from blood or saliva. Deciphering the molecular networks distinguishing PD from healthy individuals and patients with other, unrelated PD diseases may lead to new insights into pathogenesis and identification of crucial biomarkers. Previous studies have confirmed the involvement of oxidative stress and dyshomoeostasis in catecholamine, tryptophan and CAF metabolism in PD[23]. In the moderate/ advanced PD group, patients with motor complications had significantly reduced basal salivary CAF concentrations, significantly longer disease duration and an increase in the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) compared with those without motor complications, whereas patients with early PD or *de novo* patients did not. There was a negative association with antiparkinsonian medication, supporting the hypothesis that CAF levels in PD are a marker of disease progression[24,25]. Similarly, a protective effect of coffee has also been reported in dementia and AD, with CAF reversing cognitive impairment and reducing amyloid burden. The results of a study by Hong *et al.*[12] suggest that coffee consumption among healthy individuals and patients with PD was significantly associated with a lower hazard ratio for the risk or progression of PD leading to a favourable causal relationship between CAF consumption and the risk of PD. A potential neuroprotective effect of CAF consumption has also been reported in epidemiological case–control studies. Another constituent in coffee, eicosanoyl-5-hydroxytryptamide, is thought to protect against neurodegeneration. A similar effect is also thought to occur with tea consumption. Instead of psychostimulation, CAF antagonises the adenosine A2A receptor. In the CNS, A2A is expressed exclusively in dopaminergic neurons, and activation of the adenosine A2A receptor triggers cAMP-proteinase A, which is dependent on an increase in intracellular calcium and release of glutamate. This suggests that excessive intracellular calcium and glutamate concentrations are responsible for excitotoxicity in neurodegeneration[12].

Mechanism of action of caffeine

Clinically, CAF appears to improve motor symptoms by non-selective antagonism at the adenosine A2A receptor[26]. A2A receptors are predominantly distributed in the putamen, nucleus caudatus, nucleus accumbens and globulus pallidus, while indirectly interacting with dopamine D2 receptors of the basal ganglia. In the study by Ishibashi *et al.*[27], they report that CAF binds to striatal A2A receptors in a dose-dependent manner, with sufficiently occupied receptors obtainable by drinking at least one cup of coffee, equivalent to approximately 100 mg of CAF[27].

Eicosanoyl-5-hydroxytryptamine (**EHT**) is a derivative of serotonin, whereas C_{20} is a saturated eicosanoic fatty acid linked to the serotonin amino group. EHT purified from coffee serves as an agent leading to enhancement of the enzymatic activity of the specific phosphatase, **protein phosphatase 2A** (**PPA2**), which dephosphorylates pathogenic α-synuclein while working synergistically with CAF in PD and dementia with Lewy bodies (DLB). In the case of coffee, PPA2 thus inhibits the methylesterase and remains in a highly active methylated state. This synergy is through

https://doi.org/10.1017/S0954422424000349 Published online by Cambridge University Press

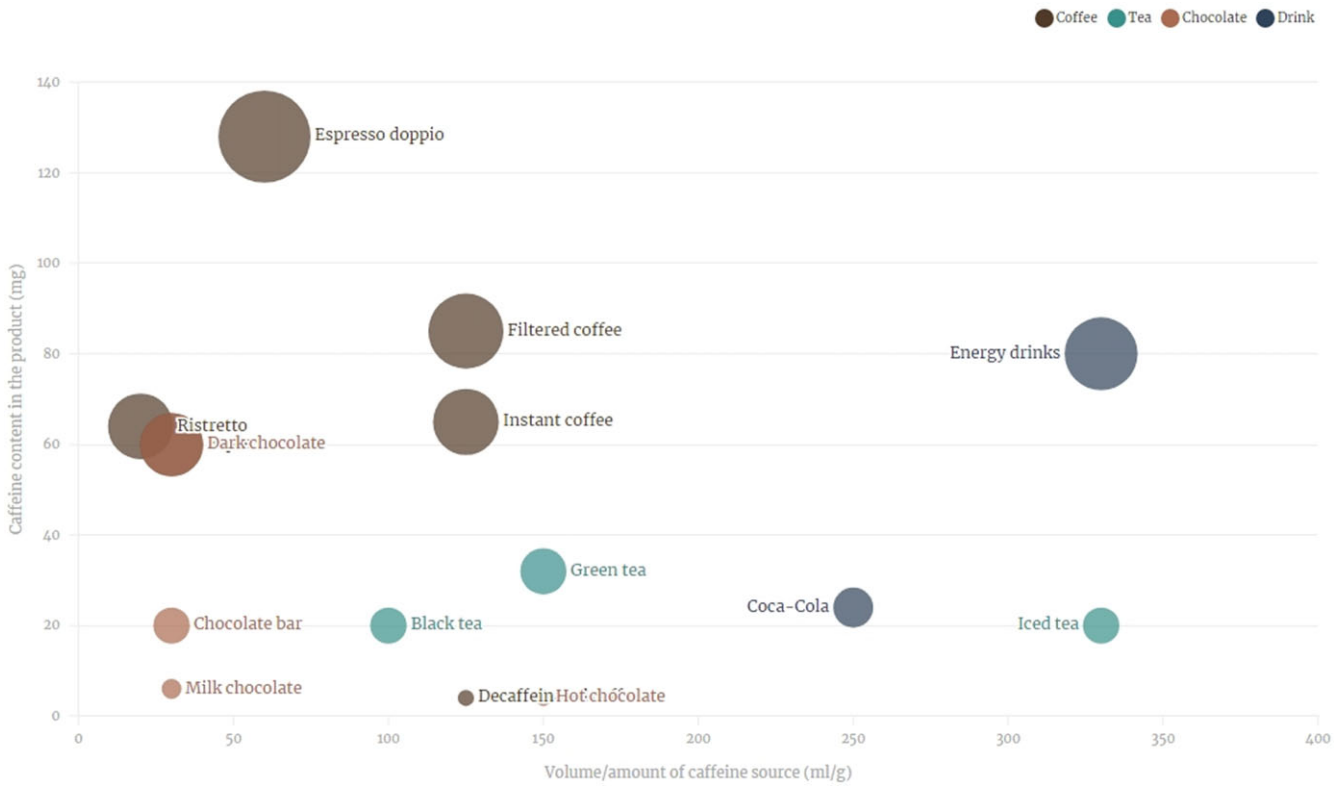

Figure 1. A summary of the ratio of the volume/quantity of the caffeine source to the amount of CAF contained in the product. The amount of CAF (mg) is recorded in individual coffee and other soft drinks, as well as in different types of chocolate. The size of the bubbles represents the amount of CAF in the product. Colour indicates product diversity: dark brown represents coffee drinks; light brown represents chocolate products; green represents tea drinks; and blue represents soft drinks. An interactive version is available at https://public.flourish.studio/visualisation/13411728/.

the enhancement of PPA2, which is dysregulated in the brains of patients with synucleinopathies. EHT is also an inhibitor of PME-1 methylesterase, thereby contributing to an increase in brain PPA2 methylation and phosphatase activity, which reduces the amount of phosphorylated α-synuclein (p-α-syn), improving neuronal integrity, suppressing neuroinflammation and preserving the behavioural phenotype. It also exhibits antioxidant and anti-inflammatory effects.

The catalytic subunit of a specific phosphatase, PP2A, which dephosphorylates α-synuclein, is hypomethylated in the brain of a patient with PD, preventing the assembly of an active trimeric holoenzyme and leading to a decrease in phosphatase activity. This phosphatase deficiency contributes to the accumulation of hyper-phosphorylated α-synuclein, which tends to fibrillate more than unmodified α-synuclein.

CAF is primarily metabolised by cytochrome P450 (CYP), specifically the CYP1A2 and CYP2E1 subunits, protects against the dopaminergic neurotoxin MPTP and acts as an adenosine A2A receptor antagonist. However, in patients with early-onset PD, CAF consumption has no effect on the rate of disease progression nor have any associations between gene polymorphism and frequency of disease onset been confirmed[26]. Co-treatment of CAF with EHT reduces p-α-syn and protects against neuronal damage and neuroinflammation, as such treatment combination significantly reduces the number of p-α-syn immunoreactive cells in the brain and restores neuritic integrity. These results suggest that this treatment has a synergistic effect in protecting neuronal integrity and preventing inflammatory response[28].

A 4-year prospective study by Moccia *et al.*[29] examined the clinical correlates of CAF consumption in a *de novo* patient population, in which they described that greater CAF consumption was associated with reduced deterioration in both motor and non-motor impairment. Concerning motor symptoms, higher CAF product use was associated with lower motor impairments throughout the study period, suggesting that CAF may have a symptomatic effect, possibly delaying an individual's motor impairment. Pathophysiologically, the motor effect of CAF in PD is likely mediated by the inhibition of adenosine A2A receptors in striatopallidal neurons, which determines the improvement of parkinsonian symptoms. Consistent with this, there is another hypothesis that the motor function of patients with PD can be improved by a targeted strategy of incorporating CAF into the development of novel antiparkinsonian drugs. Since antiparkinsonian drugs can competitively affect CAF metabolism, significant improvement in patients with PD undergoing antiparkinsonian treatment has been observed[26]. Also, study results show that patients with PD with higher CAF use presented a reduced need for dopaminergic treatment[29].

Findings studied in mouse models suggest that subtherapeutic doses of CAF and EHT may synergistically act on biochemical and molecular changes in the mouse brain, leading to brain protection in synucleinopathies. This also preserves neuronal integrity and dampens the inflammatory response in phosphatase activity, which is associated with reduced p-α-syn accumulation. Similar biochemical changes are described in a cellular model in which there is a significant increase in PPA2 methylation and

https://doi.org/10.1017/S0954422424000349 Published online by Cambridge University Press

cytoprotection and a decrease in p-α-syn[28]. In addition, antagonism of A2A receptors with selective inhibitors or genetic knock-out mimicked CAF protection in various experimental models of PD. In animal models of PD, caffeine treatment improved oxidative stress, restored striatal and midbrain dopamine depletion, prevented decline in motor activity and muscle strength, and improved norepinephrine levels[30].

Caffeine change modelling tools

Liquid chromatography coupled with mass spectrometry (LC–MS), along with gas chromatography, is a powerful tool for profiling metabolite changes, using four CAF metabolites that have been confirmed as biomarkers of *de novo* PD progression[26].

Conclusion

Coffee consumption is associated with a reduced risk of PD, with CAF generally considered to be a protective agent. Coffee not only reduces the risk of PD, improving overall akinesia for a limited number of months, as shown in a prospective study[20], but also exerts a beneficial antagonistic effect on the adenosine receptor in dopamine-rich areas of the brain, increasing its release and enhancing neurotransmission. This suggests that balanced coffee consumption was associated with slowdown executive dysfunction, as well as a reduced risk of progression to moderate cognitive impairment[1]. Regarding the beneficial effect of coffee, a large multicentre study from three European countries (the Netherlands, Finland and Italy)[3] and associated epidemiological and clinical studies consistently report that coffee/CAF consumption could slow the progression of dementia or reduce the risk of PD, according to a confirmed dose–response pattern of observed disease improvement. In addition, CAF improves the metabolism of amino acids and long-chain polyunsaturated fatty acids, which play an important role in disease development[23] and improves the oxidative system by destroying free radicals on neurons as a consequence of the effect of polyphenols on the body[3]. Another possible explanation for the beneficial effects of coffee may be the increase in the number of bifidobacteria, which are associated with a mitigation of the inflammatory response thereby reducing α-synuclein misfolding in the enteric nervous system, which reduces the risk of PD by limiting the spread of the protein to the brain[7,31]. Although several studies have confirmed the beneficial effects of coffee (reduced need for dopaminergic treatment in patients with higher caffeine consumption) associated with neurodegenerative diseases, further research is needed as it is difficult to detect and determine the exact factor of its effect. If the action of CAF and its beneficial metabolites could be translated into drugs, it would represent a shift towards new therapeutic options and the development of new antiparkinsonian drugs[29].

Acknowledgements. The authors thank Jakub Koníček, MSc. for graphic visualisation and Sarah Elizabeth Victoria Cook MSc. for language editing.

Author contributions. Conceptualisation, D.K., K.M., L.P. and P.K.; writing – original draft preparation, D.K.; writing- review and editing, K.M., P.K. and L.P.; supervision, P.K. and K.M. All authors have read and agreed to the published version of the manuscript.

Financial support. This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Competing interests. The authors report no competing interests to declare.

References

1. Ruggiero M, Calvello R, Porro C, Messina G, Cianciulli A & Panaro MA (2022) Neurodegenerative diseases: can caffeine be a powerful ally to weaken neuroinflammation? *Int J Mol Sci* **23**, 12958. doi: 10.3390/ijms232112958.
2. Sc Y, Muralidhara (2016) Beneficial role of coffee and caffeine in neurodegenerative diseases: a minireview. *AIMS Public Health* **3**, 407–422. doi: 10.3934/publichealth.2016.2.407.
3. Wierzejska R (2017) Can coffee consumption lower the risk of Alzheimer's disease and Parkinson's disease? A literature review. *Arch Med Sci* **13**, 507–514. doi: 10.5114/aoms.2016.63599.
4. Farah A (2019) *Coffee: Consumption and health implications*. London: Royal Society of Chemistry. ISBN 978-1-89907-497-7.
5. Carneiro SM, Beatriz PP, Oliviera M & Alves RC (2021) Neuroprotective properties of coffee: an update. *Trends Food Sci Technol* **113**, 167–171. doi: 10.1016/j.tifs.2021.04.052.
6. Camandola S, Plick N & Mattson MP (2019) Impact of coffee and cacao purine metabolites in neuroplasticity and neurodegenerative disease. *Neurochem Res* **44**, 214–227. doi: 10.1007/s11064-018-2492-0.
7. Wasim S, Kukkar V, Awad VM, *et al.* (2020) Neuroprotective and neurodegenerative aspects of coffee and its active ingredients in view of scientific literature. *Cureus* **12**, e9578. doi: 10.7759/cureus.9578.
8. Attia H, Al-Rasheed N, Mohamed R, *et al.* (2016) The antifibrotic and fibrolytic properties of date fruit extract via modulation of genotoxicity, tissue-inhibitor of metalloproteinases and nuclear factor- kappa B pathway in a rat model of hepatotoxicity. *BMC Complement Altern Med* **16**, 414. doi: 10.1186/s12906-016-1388-2.
9. Martínez-Tomé M, Jiménez-Monreal AM, García-Jiménez L, *et al.* (2011) Assessment of antimicrobial activity of coffee brewed in three different ways from different origins. *Eur Food Res Technol* **233**, 497–505. doi: 10.1007/s00217-011-1539-0.
10. Osarieme ED, Modupe DT & Oluchukwu OP (2019) The anticancer activity of caffeine – a review. *Arch Clin Biomed Res* **3**, 326–342. doi: 10.26502/acbr.50170077.
11. Socała K, Szopa A, Serefko A, *et al.* (2020) Neuroprotective effects of coffee bioactive compounds: a review. *Int J Mol Sci* **22**, 107. doi: 10.3390/ijms22010107.
12. Hong CT, Chan L & Bai CH (2020) The effect of caffeine on the risk and progression of Parkinson's disease: a meta-analysis. *Nutrients* **12**, 1860. doi: 10.3390/nu12061860.
13. Wintgens JN (eds) (2004) *Coffee growing, processing, sustainable production. A guidebook for growers, processors, traders, and researchers*. Germany, Weinheim: Wiley-VCH verlag GmgH& Co.. ISBN 3527307311.
14. Kolahdouzan M & Hamadeh MJ (2017) The neuroprotective effects of caffeine in neurodegenerative diseases. *CNS Neurosci Ther* **23**, 272–290. doi: 10.1111/cns.12684.
15. Li F, Hatamo T & Hattori N (2021) Systematic analysis of the molecular mechanisms mediated by coffee in Parkinson's disease based on network pharmacology approach. *J Funct Foods* **87**, 104764. doi: 10.1016/j.jff.2021.104764.
16. Mancini RS, Wang Y & Weaver DF (2018) Phenylindanes in brewed coffee inhibit amyloid beta and tau aggregation. *Fron Neurosci* **12**, 735. doi: 10.3389/fnins.2018.00735.
17. Martins S, Jongen W & Boekel M (2000) A review of Maillard reaction in food and implications to kinetic modelling. *Trend Food Sci Technol* **11**, 364–373. https://doi.org/10.1016/S0924-2244(01)00022-X.
18. Moreira ASP, Nunes FM, Domingues MR, *et al.* (2012) Coffee melanoidins: structures, mechanisms of formation and potential health impacts. *Food Funct* **3**, 903–915. doi: 10.1039/c2fo30048f.
19. Casal S (2015) *Neuroactive β-carbolines norharman and harman in coffee. Coffee in health and disease prevention*. Cambridge, MA: Academic Press, 737–743. ISBN 9780124095175. https://doi.org/10.1016/B978-0-12-409517-5.00082-6.
20. Kitagawa M, Houzen H & Tashiro K (2007) Effects of caffeine on the freezing of gait in Parkinson's disease. *Mov Disord* **22**, 710–712. doi: 10.1002/mds.21208.

21. Wikoff D, Welsh BT, Henderson R, *et al.* (2017) Systematic review of the potential adverse effects of caffeine consumption in healthy adults, pregnant women, adolescents, and children. *Food Chem Toxicol* **109**, 585–648. doi: 10.1016/j.fct.2017.04.002.
22. Ren X & Chen JF (2020) Caffeine and Parkinson's disease: multiple benefits and emerging mechanisms. *Front Neurosci* **14**, 602697. doi: 10.3389/fnins.2020.602697.
23. Shao Y, Li T, Liu Z, *et al.* (2021) Comprehensive metabolic profiling of Parkinson's disease by liquid chromatography-mass spectrometry. *Mol Neurodeger* **16**, 4. doi: 10.1186/s13024-021-00425-8.
24. Leodori G, De Bartolo MI, Belvisi D, *et al.* (2021) Salivary caffeine in Parkinson's disease. *Sci Rep* **11**, 9823. doi: 10.1038/s41598-021-89168-6.
25. Gökcen BB & Şanlier N (2019) Coffee consumption and disease correlation. *Crit Rev Food Sci Nutr* **59**, 336–348. doi: 10.1080/10408398.2017.1369391.
26. Fujimaki M, Saiki S, Li Y, *et al.* (2018) Serum caffeine and metabolites are reliable biomarkers of early Parkinson disease. *Neurology* **90**, e404–e411. doi: 10.1212/WNL.0000000000004888.
27. Ishibashi K, Miura Y, Wagatsuma K, *et al.* (2022) Adenosine A2A receptor occupancy by caffeine after coffee intake in Parkinson's disease. *Mov Disord* **37**, 853–857. doi: 10.1002/mds.28897.
28. Yan R, Zhang J, Park HJ, *et al.* (2018) Synergistic neuroprotection by coffee components eicosanoyl-5-hydroxytryptamide and caffeine in models of Parkinson's disease and DLB. *Proc Natl Acad Sci USA* **115**, E12053–E12062. doi: 10.1073/pnas.1813365115.
29. Moccia M, Erro R, Picillo M, *et al.* (2016) Caffeine consumption and the 4-year progression of *de novo* Parkinson's disease. *Parkinsonism Relat Disord* **32**, 116–119. doi: 10.1016/j.parkreldis.2016.08.005.
30. Paul K, Chuang YH, Shih IF, *et al.* (2019) The association between lifestyle factors and Parkinson's disease progression and mortality. *Mov Disord* **34**, 58–66. doi: 10.1002/mds.27577.
31. Mulak A & Bonaz B (2015) Brain–gut–microbiota axis in Parkinson's disease. *World J Gastroenterol* **21**, 10609–10620. doi: 10.3748/wjg.v21.i37.10609.

https://doi.org/10.1017/S0954422424000349 Published online by Cambridge University Press