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Review

Smoking, coffee intake, and Parkinson's disease: Potential protective mechanisms and components

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ABSTRACT

Parkinson's disease (PD) is a common progressive neurodegenerative disease characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc). Environmental and lifestyle factors, such as smoking and coffee drinking, have been associated with a decreased risk for PD. However, the biological mechanisms underlying protective effects on PD are still not fully understood. It has been suggested that non-nicotine components in cigarette smoke and non-caffeine components in coffee may contribute to this protective effect. The aim of this review was to explore candidate molecules and mechanisms behind the effects of smoking and coffee drinking on PD by integrating findings from previous studies. By cross-referencing an index of tobacco constituents and a list of coffee constituents with existing literature on natural compounds and their structural analogs that show inhibitory activities against monoamine oxidase B, catechol *O*-methyltransferase, and α-synuclein fibrillation, we have identified tobacco and coffee components that inhibit these targets. Furthermore, tobacco and coffee components potentially play roles in suppressing neuroinflammation, activating the Nrf2 pathway as natural activators, and altering the gut microbiome. This review suggests that the phenolic compounds from tobacco and coffee investigated may contribute to the low incidence of PD in smokers and coffee drinkers, showing moderate to strong potential as therapeutic interventions. The current review suggests that multifunctional molecules found in coffee and cigarette smoke may have potential neuroprotective effects, but none of the data indicates that multifunctionality is required for these effects. This review will deepen our understanding of how smoking and coffee drinking are linked to a reduced risk of PD and will also be important in elucidating the mechanisms underlying the protective effects of smoking and coffee drinking on PD.

1. Introduction

The worldwide prevalence of Parkinson's disease (PD) has increased twofold in the past 25 years, with over 8.5 million people estimated to have PD in 2019 (World Health Organization, 2024). The etiology of PD remains unknown, but a combination of age-associated, genetic, and environmental factors appears to contribute to its development and progression (Tansey et al., 2022). The most significant risk factor for PD is age, with a median onset age of 60 years (Jankovic and Tan, 2020). Currently, four autosomal dominant genes (*LRRK2*, *CHCHD2*, *VPS35*, and *SNCA*) and three autosomal recessive genes (*PARKIN*, *DJ1*, and *PINK1*) are identified as monogenic causes of PD (Ben-Shlomo et al., 2024). However, no genetic cause has been identified in 90 % of PD cases (Ascherio and Schwarzschild, 2016). On the other hand, research conducted through epidemiological studies indicates that the development and progression of PD is significantly influenced by behavioural and environmental factors (Ascherio and Schwarzschild, 2016). In particular, smoking and coffee drinking are well known to have a negative association with PD (Hernán et al., 2002). This association may arise from non-nicotine components in cigarette smoke (Jankovic and Tan, 2020; Rose et al., 2024) and non-caffeine components in coffee (Colombo and Papetti, 2020; Socała et al., 2020). For example, Trinh et al. (2010) found that decaffeinated coffee and nicotine-free tobacco extracts, but not caffeine or nicotine alone, provide neuroprotection via a nuclear factor erythroid 2-related factor 2 (Nrf2)-dependent mechanism in fly PD models. This finding implies that Nrf2-activating components in coffee and tobacco may contribute to the decreased risk of PD in smokers and coffee drinkers. The potential mechanisms for the effects of smoking encompass inhibition of monoamine oxidase B (MAO B) and α-synuclein (α-syn) fibrillation, disruption of the gut microbiome, and antioxidant responses via low levels (5 %–9 %) of carbon monoxide (Derkinderen et al., 2014; Hong et al., 2009; Quik, 2004; Rose et al.,

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2024; Scheperjans et al., 2015; Tsuang et al., 2010). The effects of coffee drinking include inactivation of A_{2A} adenosine receptor, inhibition of α-syn fibrillation, changes in the gut microbiome, inhibition of protein phosphatase 2 A (PP2A), and suppression of neuroinflammation (Chen et al., 2001; Derkinderen et al., 2014; Fazili and Naeem, 2015; Murata et al., 2023; Yan et al., 2018). Since the role of MAO B in dopamine (DA) degradation has been controversial (Nam et al., 2022) and some coffee components are reported to have an inhibitory effect on COMT (Akhtar et al., 2020), we propose that inhibition of catechol *O*-methyltransferase (COMT) is an alternative mechanism for smoking and coffee components to reduce risk of development of PD in smokers and coffee drinkers.

Understanding the candidate molecules and mechanisms underlying the protective effects of smoking and coffee drinking on PD is not only important for gaining insights into these effects, but also crucial for treatment and delaying progression of PD. The objective of this review is to discuss candidate molecules and mechanisms for the effects of smoking and coffee drinking on PD. The protective effects of tobacco and coffee bioactive components in *in vitro* and *in vivo* models of PD are summarized and reviewed. An index of chemical constituents of tobacco and tobacco smoke (Rodgman and Perfetti, 2013), along with a list of chemical constituents of green and roasted coffee (Spiller, 2019), have been used to identify compounds targeting MAO B, COMT, and α-syn fibrillization, as well as the activation of the Nrf2 pathway, suppression of neuroinflammation, and modulation of gut microbiota. These indices were crossmatched with existing literature that reports on natural compounds and their structural analogs known to affect these targets.

2. Therapeutic targets for Parkinson's disease

Parkinson's disease (PD) is one of most common progressive neurodegenerative diseases with the loss of dopaminergic (DAergic) neurons in the substantia nigra pars compacta (SNpc) (Dauer and Przedborski, 2003; Rai and Singh, 2020). The clinical features of PD include both motor (tremor, bradykinesia, rigidity, postural instability, and slow activities of daily living) and non-motor symptoms (cognitive impairment, sensory symptoms, sleep disorders, depression and other behavioural and psychiatric problems), which help distinguish it from other parkinsonian disorders (Jankovic, 2008). Current medications for PD primarily target the DAergic pathway and include levodopa (L-DOPA, which is converted to DA in the neuron), DA agonists, and DA degradation inhibitors such as monoamine oxidase B (MAO B) inhibitors and catechol-*O*-methyl transferase (COMT) inhibitors (Balestrino and Schapira, 2020). However, these treatments are symptomatic and unable to prevent the progression of PD (Li and Song, 2022). While current treatments cannot prevent the progression of PD, therapies aiming to prevent or delay its progression could benefit from a deeper understanding of PD's pathological features and the development of multifunctional molecules that can simultaneously target and control various disease factors (Savelieff et al., 2018). Examples of drugs for the

Table 1
Examples of drugs for the treatment of motor symptoms in Parkinson's disease.

Class	Inhibitor	Symptomatic monotherapy	Symptomatic adjunct therapy in early or stable PD patients	Treatment of motor fluctuations (F) or dyskinesia (D); prevention or delay of motor fluctuations (f) or dyskinesia (d)
		Efficacy conclusions and implications for clinical practice		
Dopamine precursor/ dopa decarboxylase inhibitor	Levodopa/carbidopa (standard formulation)	+		+ (F)
	Levodopa/carbidopa (extended release)	+		+ (F)
	Levodopa/carbidopa (intestinal Infusion)			+ (F)
Ergot dopamine agonists[a]	Bromocriptine (Parlodel)	+ /-	+ /-	+ /- (F); I (f); + /- (d)
	Cabergoline	+		+ /- (F); + (f, d)
Non-ergot dopamine agonists	Pramipexole (ER) (Mirapex ER)	+	+	+ (F)
	Apomorphine[b] (Apokyn)			+ (F)
	Ropinirole (immediate release)	+	+	+ (F); I (f); + (d)
Irreversible MAOBIs	Selegiline (Zelapar)	+	I	+ (F); I (f); - (d)
	Rasagiline (Azilect)	+	+	+ (F)
Reversible MAOBIs	Safinamide (Xadago)		-	+ (F)
	Zonisamide (Zonegran)		+	+ (F); I (D)
COMTIs	Entacapone (Comtan)	-	-	+ (F); - (f, d)
	Opicapone (Ongentys)	-		+ (F)
	Tolcapone (Tasmar)	-	Efficacious and unlikely useful	+ (F)
Adenosine A_{2A} antagonist	Istradefylline (Nourianz)	-		+ /- (F)
Other drugs	Antimuscarinics	Likely efficacious and clinically useful	Likely efficacious and clinically useful	
	Amantadine (Gocovri)	+ /-	+ /-	I (F); + (D)
	Clozapine (Clozaril)			+ (D)

+ : efficacious and clinically useful; -: not useful; + /-: likely efficacious and possibly useful; I: insufficient evidence and investigational. The most recent Evidence-Based Medicine (EBM) review by Fox et al. (2018) and another review by Foltynie et al. (2024) were used to update the treatment options for motor symptoms in Parkinson's disease. Drug names (presented in brackets) usually available in the U.S. (https://www.accessdata.fda.gov/scripts/cder/daf/). COMTIs: catechol *O*-methyltransferase inhibitors; ER: extended release; MAOBIs: monoamine oxidase B inhibitors.

[a] Due to side effects, such as cardiac fibrosis, ergot dopamine agonists are less commonly used for treating Parkinson's disease.

[b] Apomorphine sublingual film offered an effective, on-demand therapy for managing off episodes in Parkinson's disease (Olanow et al., 2020).

treatment of motor symptoms in PD are shown in Table 1, which summarizes options for monotherapy, adjunct therapy, and treatments for motor fluctuations (Foltynie et al., 2024; Fox et al., 2018; Jankovic and Tan, 2020). For prevention or delay of disease progression in PD, the efficacy conclusions and implications for clinical practice of the following interventions are "insufficient evidence" and "investigational, " respectively:

DA agonists (eg, ropinirol), L-DOPA/peripheral decarboxylase inhibitor (eg, standard immediate release (IR) formulation), and MAO B inhibitors (eg, selegiline and rasagiline) (Fox et al., 2018). There are additional strategies targeting oxidative-stress, mitochondrial dysfunction, and excitotoxicity (Pires et al., 2017), as well as Wnt/β-catenin signaling pathway (Ramakrishna et al., 2023), along with non-DAergic neurotransmitter systems, for the treatment of PD. These systems include glutamate, gamma-aminobutyric acid (GABA), noradrenaline (NA), acetylcholine, serotonin (5-HT), adenosine, and histamine (Kalia et al., 2013).

2.1. Monoamine oxidase B

Monoamine oxidase (MAO; EC 1.4.3.4) is a flavin adenine dinucleotide (FAD) dependent enzyme that catalyze the oxidative deamination of monoamine substrates, including neurotransmitters such as serotonin, DA, norepinephrine, epinephrine, and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which can cause symptoms of PD (Youdim and Bakhle, 2006). There are two isoenzymes, MAO A and B, located in the outer membrane of mitochondria, with different substrate specificity and with different inhibitor sensitivity (Shih, 2018). MAO A is predominantly localized in catecholaminergic neurons, while MAO B is found mainly in serotonergic neurons, histaminergic neurons, and astrocytes, a subtype of glial cells (Jones and Raghanti, 2021).

Traditionally, MAO A and B have been considered to mediate DA degradation. DA is degraded by MAO A in presynaptic neurons, while MAO B catalyzes synaptic DA which is taken up by surrounding glial cells (Tan et al., 2022). One hypothesis is that MAO B-mediated DA metabolism in astrocytes not only leads to DA depletion but also produce the harmful metabolic byproducts, including DOPAL, H_2O_2 and MPP^+, which cause DA neuronal cell death and/or senescence (Santin et al., 2021). Consequently, MAO B inhibitors have been proposed for use in the treatment of PD, both to inhibit DA degradation and to prevent the formation of neurotoxic DA metabolites (Santin et al., 2021). However, the question as to whether MAO B is involved in DA degradation in the living brain has been controversial (reviewed in Nam et al. 2022). Recent studies have shown that MAO A mainly mediates DA degradation in the brain, while MAO B mediates aberrant gamma-aminobutyric acid (GABA) synthesis and hydrogen peroxide (H_2O_2) production of reactive astrocytes, which are important in the pathogenesis of PD (Cho et al., 2021; Nam et al., 2022). This excessive GABA synthesis leads to aberrant tonic inhibition of DA neurons in the SNpc in animal models of PD (Heo et al., 2020). These findings suggest that the therapeutic efficacy of MAO B inhibitors in PD could be linked to blocking astrocytic GABA synthesis rather than blocking DA degradation (Cho et al., 2021). Moreover, since MAO B mediates GABA synthesis in reactive astrocytes in brain diseases, inhibiting GABA synthesis through MAO B inhibition could be a promising therapeutic target not only for various diseases such as PD, stroke, depression, obesity and Alzheimer's disease (AD), but also for a potential treatment for posttraumatic stress disorder and ageing (Koh and Lee, 2024). A recent study found that in both neuronal cells and primary astrocytes, MAO B expression was significantly increased by the loss of *DJ1* (PARK7), one of the autosomal recessive genes linked to PD (Liu et al., 2023). Understanding the role of MAO B in PD will be important for elucidating PD pathogenesis as well as for enhancing the therapeutic potential of MAO B inhibitors.

3. Non-genetic risk factors for PD: smoking and coffee drinking

Previously, an umbrella review of 75 unique meta-analyses conducted on non-genetic risk factors for PD showed that two factors, constipation (RR 2.30, 95 % CI 2.02– 2.63) and physical activity (HR 0.66, 95 % CI 0.57–0.78) were categorized as Class 1 (convincing evidence) (Bellou et al., 2016). Additionally, five risk factors, anxiety or depression (RR 1.86, 95 % CI 1.64–2.10), beta-blockers (RR 1.28, 95 % CI 1.19–1.39), head injury (OR 1.55, 95 % CI 1.33–1.81), serum uric acid (OR 0.39, 95 % CI 0.27–0.57), and smoking (RR 0.64, 95 % CI 0.60–0.69) were categorized as Class 2 (highly suggestive evidence). Factors categorized as Class 3 (suggestive evidence) include coffee drinking (RR 0.67, 95 % CI 0.58–0.76), ibuprofen (RR 0.73, 95 % CI 0.62–0.85), pesticides (OR 1.62, 95 % CI 1.40–1.88), dairy products intake (RR 1.40, 95 % CI 1.20–1.63), alcohol intake (RR 0.75, 95 % CI 0.66–0.85), calcium channel blockers (RR 0.78, 95 % CI 0.67–0.90), welding (RR 0.86, 95 % CI 0.80 – 0.92), rural living (OR 1.32, 95 % CI 1.18–1.48), and farming (OR 1.30, 95 % CI 1.16 –1.46). All other risk factors were categorized as Class 4 (weak evidence) and NS (non-significant). Fig. 1A shows odds ratios/relative risks/hazard ratios and 95 % confidence intervals for PD and 16 risk factors.

3.1. Smoking

Smoking not only contributes to major causes of death such as lung cancer, chronic obstructive pulmonary disease (COPD), coronary heart disease, miscarriage, and fetal underdevelopment but also elevates the risk of stroke, blindness, deafness, back pain, osteoporosis, and peripheral vascular disease, which can result in amputation (West, 2017). Additionally, smoking has been linked with an increased risk for several conditions: AD (RR 1.37, 95 % CI 1.23–1.52, current/ever vs. never smokers, 31 studies) (Beydoun et al., 2014), vascular dementia (RR 1.35, 95 % CI 0.90–2.02, current smokers vs. never/nonsmokers) (Peters et al., 2008), depression (OR 1.43, 95 % CI 1.20–1.70, current smoking, prevalent symptoms; OR 1.50, 95 % CI 1.14–1.98, current smoking, incident symptoms) (Hahad et al., 2022), schizophrenia (OR 2.27, 95 % CI 1.67–3.08, lifetime smoking) (Wootton et al., 2020), bipolar disorder (OR 1.46, 95 % CI 1.28–1.66, smoking initiation; OR 1.72, 95 % CI 1.29–2.28, lifetime smoking) (Vermeulen et al., 2021), ADHD (OR 3.72, 95 % CI 3.10–4.44, smoking initiation) (Treur et al., 2021), cataract (OR 1.47, 95 % CI 1.36–1.59, current smoking) (Kai et al., 2024), and COVID-19 progression (OR 1.91, 95 % CI 1.42–2.59, current/former vs. never smokers, 19 studies) (Patanavanich and Glantz, 2020) (Fig. 1B). However, smoking was linked with a decreased risk for PD. Notably, there was a significant inverse dose–response association for the number of pack-years (one pack year is defined as one packet of 20 cigarettes smoked per day for one Class 1 (C1): convincing evidence; Class 2 (C2): highly suggestive evidence; Class 3 (C3): suggestive evidence; HR: hazard ratio; OR: odds ratio; RR: risk ratio; OR/RR/HR = 1: there is no variation in odds, risk, or hazard; OR/RR/HR > 1: an increase in odds, risk, or hazard; OR/RR/HR < 1: a decrease in odds, risk, or hazard. The bar graph was generated using GraphPad Prism software (version 8.4.3; GraphPad Software Inc., San Diego, CA) with data from Bellou et al. (2016) and others in Sections 3.1 and 3.2. year) smoked (RR 0.66, 95 % CI 0.49–0.88, smoking of ≤ 30 pack-years, 3 studies; RR 0.39, 95 % CI 0.29–0.53, smoking of > 30 pack-years, 4 studies) (Li et al., 2015) and the duration of smoking (HR 0.84, 95 % CI 0.67–1.07, smoking for < 20 years; HR 0.73, 95 % CI 0.56–0.96, smoking for 20–29 years; HR 0.54, 95 % CI 0.43–0.66, smoking for > 30 years) (Gallo et al., 2019) (Fig. 1B). Li et al. (2015) conducted a meta-analysis of 61 case-control and 8 cohort studies, revealing an inverse relationship between cigarette smoking and PD. This suggests that effective drug development for PD could utilize chemical substances obtained from tobacco-derived sources. However, while many studies focus on nicotine, clinical trials on PD that have examined its effects have shown nonsignificant results, indicating the need for further research on non-nicotine compounds and

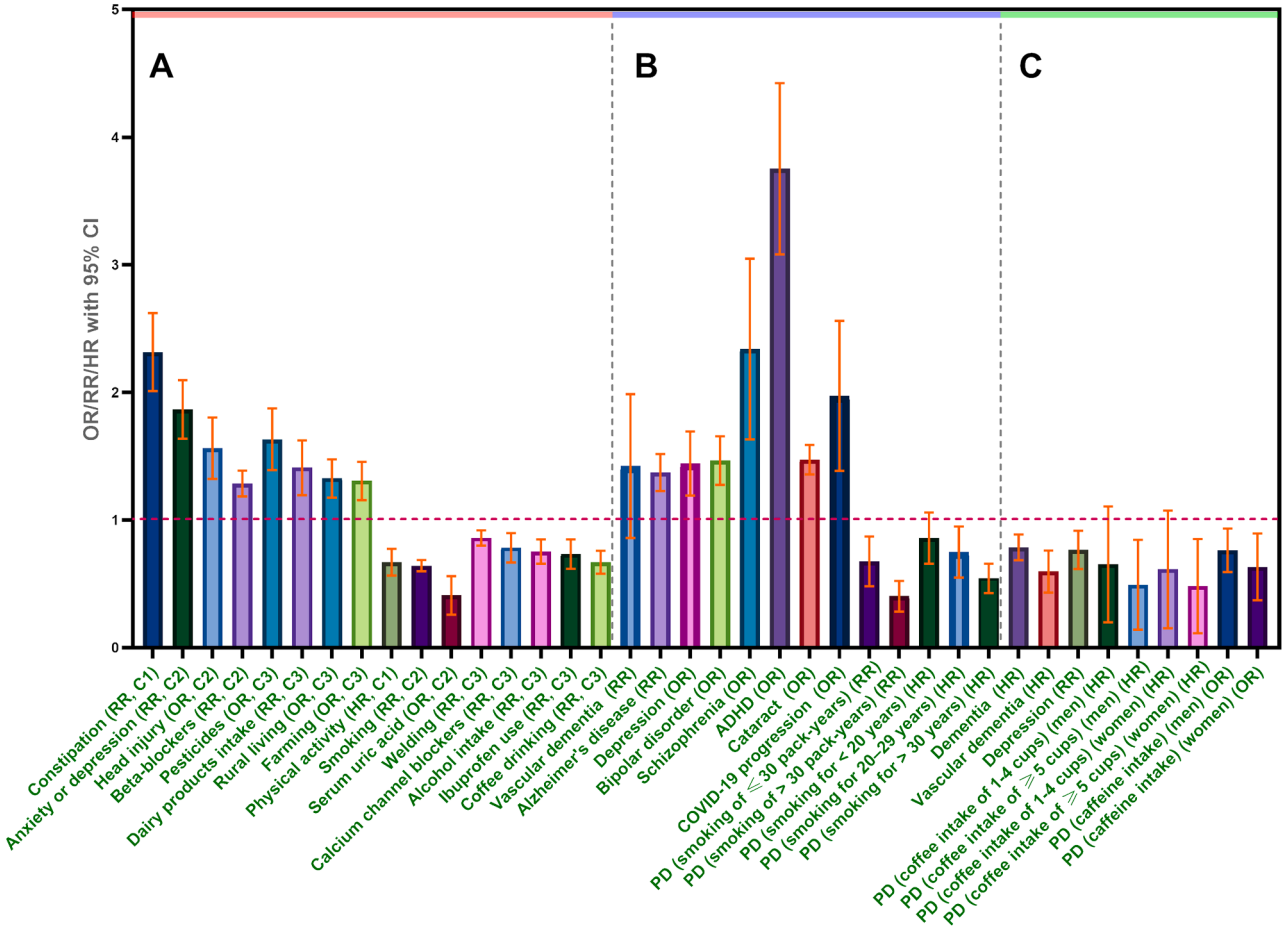

Fig. 1. Non-genetic risk factors for Parkinson's disease (A), and impacts of smoking (B) and coffee drinking (C) on Parkinson's disease and other conditions.

their biological mechanisms (Yoon et al., 2023).

3.2. Coffee drinking

Coffee drinking has been linked with a decreased risk for several conditions: dementia (HR 0.78, 95 % CI 0.69–0.89, ground coffee intake of 1–3 cups/day vs. none) (Zhang et al., 2022), vascular dementia (HR 0.58, 95 % CI 0.44–0.77, ground coffee intake of 1–3 cups/day vs. none) (Zhang et al., 2022), depression (RR 0.76, 95 % CI 0.62–0.92, coffee intake for the highest vs. lowest) (Wang et al., 2016), and PD in both men (HR 0.55, 95 % CI 0.26–1.15, coffee intake of 1–4 cups/day; HR 0.41, 95 % CI 0.19–0.88, coffee intake of $\geq$ 5 cups/day) and women (HR 0.50, 95 % CI 0.22–1.12, coffee intake of 1–4 cups/day; HR 0.39, 95 % CI 0.17–0.89, coffee intake of $\geq$ 5 cups/day) (Hu et al., 2007) (Fig. 1C). Additionally, there was an inverse association between caffeine intake and PD in both men (OR 0.75, 95 % CI 0.60–0.94) and women (OR 0.60, 95 % CI 0.39–0.91) (Liu et al., 2012) (Fig. 1C). Extensive research on the health effects of coffee consumption suggests that its benefits on human health stem from a complex mixture of bioactive compounds, including alkaloids (caffeine and trigonelline), phenolic acids (chlorogenic acids), diterpenes (cafestol and kahweol), and melanoidins, which might act as physiologically effective agents (Socała et al., 2020). While many studies focus on caffeine and its analogs/derivatives for their potential roles, particularly in AD and PD, coffee is also abundant in polyphenols, especially chlorogenic acids, caffeic acid, and ferulic acid, along with quinic acid, and quercetin. The roles of these non-caffeine compounds in various pathologies still need further clarification (Colombo and Papetti, 2020).

4. Molecular mechanisms in PD: Smoking and coffee consumption

As shown in Fig. 1, 16 of 75 risk factors showed Class 1, Class 2, and Class 3 evidence of association with PD (Fig. 1). Among these risk factors, 8 factors (pesticides, dairy products intake, constipation, depression, traumatic brain injury, rural living, farming, beta-blockers) exhibited a positive association with PD, while other 8 factors (smoking, coffee intake, serum uric acid, physical activity, moderate alcohol intake, NSAIDs, calcium channel blockers, welding) showed a negative association with PD. Many candidate molecules and molecular mechanisms underlying these environmental and lifestyle factors for PD have been suggested (Table 2). Among candidate molecules, clinical trials of nicotine, caffeine, and urate have been tested, but there was no evidence for benefit of treatment in PD yet (Table 2).

For this review, we used not only an alphabetical index of tobacco components and a list of coffee components to search for candidate molecules targeting MAO B, COMT, and α-syn fibrillization, but also to investigate the activation of the Nrf2 pathway, suppression of neuroinflammation, and modulation of gut microbiota. We identified bioactive components by comparing these indices with existing literature (Di Giovanni et al., 2010; Engelbrecht et al., 2019; Feng et al., 2022; Gugler and Dengler, 1973; Guldberg, 1975; Hong et al., 2022; Kumar et al., 2014; Ono and Yamada, 2006; Senger et al., 2016; Tao et al., 2005; Zhao et al., 2021).

4.1. MAO B inhibition by tobacco or coffee compounds

MAO B increases with age in the human brain (Fowler et al., 1997)

Table 2
Candidate molecules and molecular mechanisms for environmental risk factors in Parkinson's Disease.

Factors (non-genetic)	Molecules/ products	Mechanisms of action or hypotheses	References
Positive association			
Pesticides	Paraquat	Mitochondrial dysfunction, ROS production, ↑ α-syn aggregation, ↑ lipid peroxidation, ↓ GSH, ↓ nigral DAergic neurons	(Goldman, 2014)
	Rotenone	Mitochondrial dysfunction, ROS production, ↑ α-syn aggregation, ↓ ATP production, impairment of proteasome function, microglial activation, ↓ nigral DAergic neurons	(Goldman, 2014)
Dairy products intake	Dairy proteins	Antiuricemic effect of dairy proteins (↓ serum urate levels)	(Hughes et al., 2017)
Constipation	α-Synuclein	α-syn aggregates in the ENS, early microbiome dysbiosis, changes in intestinal homeostasis	(Anis et al., 2022)
Depression		A risk factor for PD/ depression is a prodromal condition of PD	(Aarsland et al., 2012)
Traumatic brain injury		Inflammation, metabolic dysregulation, and protein accumulation	(Delic et al., 2020)
Rural living, farming,		Factors linked to pesticide exposure show inconsistent or little correlation with PD	(Freire and Koifman, 2012)
Beta-blockers	Propranolol	↑ *SNCA* mRNA, ↑ α-syn protein concentrations	(Hopfner et al., 2020; Mittal et al., 2017)
Negative association			
Smoking	Tobacco	↓ α-Syn fibrillation, ↓ MAO B, changes in the gut microbiome, antioxidant responses via low levels of CO	(Derkinderen et al., 2014; Hong et al., 2009; Quik, 2004; Rose et al., 2024; Scheperjans et al., 2015; Tsuang et al., 2010)
	Nicotine	One-year transdermal treatment in early PD failed in clinical trial (NCT01560754)	(Oertel et al., 2023)
Coffee intake	Coffee	Neuroprotection by inactivation of A_{2A} adenosine receptor (caffeine), changes in the gut microbiome, ↑ enzymatic activity of PP2A that dephosphorylates α-syn (cotreatment with EHT and caffeine), suppression of neuroinflammation.	(Chen et al., 2001; Derkinderen et al., 2014; Fazili and Naeem, 2015; Murata et al., 2023; Yan et al., 2018)
	Caffeine	No evidence for sustained symptomatic benefit on parkinsonism in PD (NCT01738178)	(Postuma et al., 2017)
Serum uric acid	Uric acid (urate)	↓ Oxidative stress (activation of the Nrf2 pathway), effect on striatal DA activity in women (positive correlation)	(Bakshi et al., 2015; Oh et al., 2020)
		No causal link between plasma urate and PD risk	(Kia et al., 2018; Kobylecki et al., 2018)
		No clinical benefit was found from two-year urate-elevating inosine treatment in early PD (NCT02642393)	(Bluett et al., 2021)
Physical activity		↑ Plasma uric acid levels, ↑BDNF, ↓ GFAP	(Paillard et al., 2015; Weisskopf et al., 2007)
Moderate alcohol intake	Beer, red wine	beer: urate-raising effects, free radical scavenger (purine); red wine: neuroprotective role (flavonoids)	(Commenges et al., 2000; Gaffo et al., 2010; Jung et al., 2023)
NSAIDs	Ibuprofen	↓ Inflammation (*LRRK2*-associated PD), activation of PPARγ, ↓ oxidative stress (an antioxidant)	(Ascherio and Schwarzschild, 2016; Kieburtz and Wunderle, 2013; San Luciano et al., 2020; Singh et al., 2021)
Calcium channel blockers	Dihydro-pyridine	Attenuation of mitochondrial oxidant stress by blockade of calcium channel	(Ascherio and Schwarzschild, 2016; Surmeier, 2007)
		Three-year treatment with immediate-release isradipine (an L-type calcium channel blocker) did not slow early PD progression (NCT02168842)	(Parkinson Study GroupSTEADY-PD III Investigators, 2020)
Welding	Mn	No link was found between welding, exposure to Mn, and PD. The expected link likely stemmed from the confounders (eg, smoking, the healthy worker effect, or the effect of exposure dose)	(Dirandeh et al., 2022)

and in neurodegenerative diseases such as PD, AD, progressive supranuclear palsy, multiple system atrophy, Huntington's disease, and amyotrophic lateral sclerosis (Meyer and Braga, 2022). However, smokers have low levels of MAO B (40 %; $P < 0.0002$) in the brain compared to non-smokers for the five brain regions (basal ganglia, thalamus, cerebellum, cingulate gyrus, and frontal cortex) (Fowler et al., 1996).

Among MAO inhibitors in tobacco or tobacco smoke, reversible and selective inhibitors primarily of human MAO B include trans,trans-farnesol, menadione (2-methyl-1,4-naphthoquinone), 1,4-naphthoquinone, scopoletin, and diosmetin (Table 3). Farnesol and menadione were found to be the most potent inhibitors of human MAO B with K_i values in the nanomolar range. Norharman and harman are potent, reversible MAO inhibitors found in coffee and cigarette smoke (Dixon Clarke and Ramsay, 2011). In particular, harman is a condensation product of acetaldehyde with tryptamine or tryptophan and may be produced endogenously (Talhout et al., 2007).

Recently, six new MAO inhibitors (catechol, 4-methylcatechol, 4-ethylcatechol, hydroquinone, α-linolenic acid, and linoleic acid) have been identified in tobacco smoke that inhibit human MAO A and MAO B isoenzymes (Hong, 2023) (Table 3). Notably, 4-methylcatechol and 4-ethylcatechol exhibited significant time-dependent inhibition of MAO B. After 1 h preincubation, both compounds displayed MAO B inhibitory activity with IC_{50} values in the low micromolar range. Moreover, mainstream cigarette smoke condensate includes considerable quantities of catechol (195 μg/cigarette), 4-methylcatechol (38 μg/cigarette), 4-ethylcatechol (28 μg/cigarette), and hydroquinone

Table 3
In vitro inhibitory effects on MAO B, COMT, and α-synuclein fibrillation, as well as activation of the Nrf_2 pathway, modulation of gut microbiota, and other neuroprotective effects by components of tobacco (T), tobacco smoke (S), green coffee (G), and roasted coffee (R).

Compound	Class	T/S/G/R	IC_{50} or K_i or EC_{50} values (μM)[a]		References
			MAO B	α-Syn/COMT/Observed Effects	
Nicotine	Alkaloid	T, S		Inhibits α-syn oligomerisation and fibrillization	(Hong et al., 2009; Kardani et al., 2017)
Caffeine	Alkaloid	T, S, G, R	IC_{50} 5080 K_i 3830	Attenuates the toxicity of α-syn aggregates	(Kardani and Roy, 2015; Petzer et al., 2013)
Trigonelline	Alkaloid	G, R		Inhibits α-syn fibrillization, Nrf2 pathway activator	(Arlt et al., 2013; Ghanem et al., 2021)
Harman	β-carboline	T, S, R	K_i 5.89 (rat brain)		(Miralles et al., 2005)
Norharman	β-carboline	T, S, R	IC_{50} 4.68, K_i 1.12		(Herraiz and Chaparro, 2005)
2-Naphthylamine	Amine	S	K_i 40.2 (mouse brain)		(Hauptmann and Shih, 2001)
Diethylnitrosamine	Amine	T, S	K_i 51.5 (rat liver)		(Obata et al., 1989; van der Toorn et al., 2019)
TMN	Quinone	T, S	K_i 6 (human liver)		(Khalil et al., 2000)
Menadione	Quinone	S	K_i 0.4	Inhibits α-syn fibrillization (EC_{50} 18)	(Cerqueira et al., 2011; da Silva et al., 2013)
1,4-Naphthoquinone	Quinone	S	K_i 1.5		(Cerqueira et al., 2011)
1,4-Benzoquinone	Quinone	S	IC_{50} 10.2		(Mostert et al., 2017)
Catechol	Phenol	T, S, R	IC_{50} 31.3	First generation COMTI, ↑ DA, Nrf2 pathway activator	(Hong, 2023; Kiss and Soares-da-Silva, 2014; Senger et al., 2016; Walker et al., 2012)
4-Methylcatechol[b]	Phenol	S, R	IC_{50} 32.1	Nrf2 pathway activator	(Hong, 2023; Senger et al., 2016)
4-Ethylcatechol[c]	Phenol	S, R	IC_{50} 21.9	Nrf2 pathway activator	(Hong, 2023; Senger et al., 2016)
4-Vinylcatechol	Phenol	S, R		Nrf2 pathway activator	(Senger et al., 2016)
Hydroquinone	Phenol	T, S, R	IC_{50} 19.7	Inhibits α-syn fibrillization, Nrf2 pathway activator	(Hong et al., 2009; Hong, 2023; Senger et al., 2016)
Eugenol	Phenol	T, S, R	IC_{50} 288, K_i 211		(Tao et al., 2005)
Isoeugenol	Phenol	T, S, G	IC_{50} 102		(Zhang et al., 2019)
MHQ	Phenol	S	IC_{50} 8.9		(Tao et al., 2005)
Pyrogallol	Phenol	T, S, R		Inhibits α-syn and Aβ fibrillization, COMT: K_i 13 (rat), ↑ DA	(Di Giovanni et al., 2010; Guldberg, 1975; Walker et al., 2012)
Gallic acid	Phenol	T, S, R		Inhibits α-syn fibrillization, COMT: K_i 70 (rat), modulates of gut microbiota-derived metabolites	(Di Giovanni et al., 2010; Feng et al., 2022; Guldberg, 1975)
Vanillin	Phenol	T, S, G, R	No inhibition at 15		(Zhang et al., 2019)
β-asarone	Phenol	T	IC_{50} 362		(Tao et al., 2005)
Resveratrol	Phenol	T	IC_{50} 30.77	Inhibits α-syn fibrillization, Nrf2 pathway activator	(Rubiolo et al., 2008; Yáñez et al., 2006; Zhang et al., 2018)
CAPE	Phenol	R	IC_{50} 0.1	COMTI, Nrf2 pathway activator	(Lee et al., 2010; Takao et al., 2017; Zhu et al., 2009)
Ferulic acid	Phenolic acid	T, S, G, R	K_i 24.0	Inhibits α-syn fibrillization (EC_{50} 0.75) and destabilizes preformed α-syn fibrils (EC_{50} 4.76), first generation COMTI, Nrf2 pathway activator	(Badavath et al., 2016; Ma et al., 2010; Ono and Yamada, 2006; Yalcin and Bayraktar, 2010)
Protocatechuic acid	Phenolic acid	T, S	IC_{50} 300 (rat)	Inhibits α-syn fibrillization and destabilizes of preformed α-syn fibrils, first generation COMTI, Nrf2 pathway activator	(Hornedo-Ortega et al., 2016; Kim et al., 2012; Kiss and Soares-da-Silva, 2014; Varì et al., 2011)
Caffeic acid	Phenolic acid	T, S, G, R	IC_{50} 247.7	Inhibits α-syn fibrillization, first generation COMTI	(de Mello Andrade et al., 2016; Di Giovanni et al., 2010; Kiss and Soares-da-Silva, 2014)
Chlorogenic acid	Phenolic acid	T, S, G, R	IC_{50} 191.4	Inhibits α-syn oligomerization, COMT: IC_{50} 6.17 (rat), ↑ DA, modulates of gut microbiota-derived metabolites	(de Mello Andrade et al., 2016; Engelbrecht et al., 2019; Teraoka et al., 2012; Walker et al., 2012; Xie et al., 2021)
Quercetin	Flavonoid	T, S, G, R	IC_{50} 10.89, K_i 7.95	Inhibits α-syn fibrillization, COMT: K_i 8.4 (rat), COMT: IC_{50} 1.38, modulates gut microbiota	(Di Giovanni et al., 2010; Duda-Chodak, 2012; Guldberg, 1975; Lee et al., 2001; Zhao et al., 2021)
Kaempferol	Flavonoid	T, S, G, R	IC_{50} 20.4	Inhibits α-syn fibrillization (EC_{50} 0.55) and destabilizes preformed α-syn fibrils (EC_{50} 12.99), COMTI (mixed type noncompetitive) Nrf2 pathway activator	(Deng and West, 2011; Gao et al., 2010; Guldberg, 1975; Ono and Yamada, 2006)
Quercitrin	Flavonoid	T, S, G	IC_{50} 19.06, K_i 21.01		(Lee et al., 2001)
Myricetin	Flavonoid	G	IC_{50} 59.34	Inhibits α-syn fibrillization (EC_{50} 0.21) and destabilizes preformed α-syn fibrils (EC_{50} 0.24), COMT: IC_{50} 0.96	(Larit et al., 2018; Ono and Yamada, 2006; Zhao et al., 2021)
Dihydromyricetin	Flavonoid	G		COMT: IC_{50} 3.73, modulates of gut microbiota-derived metabolites	(Dong et al., 2021; Zhao et al., 2021)
Myricitrin	Flavonoid	T	40 % inhibition at 61.91 (mouse brain)	COMT: IC_{50} 7.26	(Banerjee et al., 2022; Zhao et al., 2021)
Isoquercitrin	Flavonoid	T	IC_{50} 11.64, K_i 2.72		(Lee et al., 2001)
Rutin	Flavonoid	T, S, G, R	IC_{50} 3.89, K_i 1.83	COMT: IC_{50} 25.3 (rat), K_i 30 (rat), Inhibits α-syn fibrillization	(Engelbrecht et al., 2019; Guldberg, 1975; Lee et al., 2001; Meng et al., 2009)
Naringenin	Flavonoid	T, G	IC_{50} 288 (rat liver)	COMT: IC_{50} 54 (human liver), modulates gut microbiota	(Duda-Chodak, 2012; Gugler and Dengler, 1973; Olsen et al., 2008)

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Table 3 (*continued*)

Compound	Class	T/S/G/R	IC_{50} or K_i or EC_{50} values (μM)[a]		References
			MAO B	α-Syn/COMT/Observed Effects	
Naringin	Flavonoid	T	IC_{50} 44.6	COMT: 21.1 % inhibition at 20 (human liver)	(2016; Gugler and Dengler, 1973)
Isorhamnetin	Flavonoid	G		COMT: 51.8 % inhibition at 20 (human liver)	(Gugler and Dengler, 1973)
Taxifolin	Flavonoid	G		COMT: IC_{50} 18 (human liver)	(Gugler and Dengler, 1973)
Diosmetin	Flavonoid	T	IC_{50} 1.58		(Carradori et al., 2016)
Catechin	Flavonoid	G	IC_{50} > 100, IC_{50} 88.6 (rat brain)	Inhibits α-syn fibrillization (EC_{50}0.84) and destabilizes preformed α-syn fibrils (EC_{50} 13.58), COMT: K_i 30 (rat), COMT: IC_{50} 0.86 (rat), modulates gut microbiota	(Engelbrecht et al., 2019; Guldberg, 1975; Hou et al., 2005; Huang et al., 2016; Ono and Yamada, 2006)
Epicatechin	Flavonoid	G	IC_{50} 58.9 (rat brain)	Inhibits α-syn fibrillization (EC_{50} 0.80) and destabilizes preformed α-syn fibrils (EC_{50} 11.38), COMT: IC_{50} 3.1 (human liver), modulates gut microbiota	(Hou et al., 2005; Kang et al., 2013; Ono and Yamada, 2006; Zeng et al., 2024)
Scopoletin	Coumarin	T, S	K_i 20.7, K_i 22.6 (rat)	Inhibits α-syn fibrillization, Nrf2 pathway activator	(Basu et al., 2016; Chang et al., 2015; Rane et al., 2021)
Isoquinoline	Azaarene	T, S	K_i 60.7 (human synaptosomes)		(Naoi and Nagatsu, 1987)
Cembranoids	Terpene	T, S		Neuroprotection activity	(Ferchmin et al., 2009; Yan et al., 2016)
Kahweol	Terpene	G, R		Nrf2 pathway activator, ↓ 6-OHDA-induced ROS generation and caspase−3 activity, ↓ COX−2	(Hwang and Jeong, 2008; Kim et al., 2004)
Cafestol	Terpene	G, R		Nrf2 pathway activator, ↓ COX−2	(Kim et al., 2004; McMahon et al., 2001)
Trans,trans-farnesol	Terpenoid	T, S	K_i 0.80 (human liver)	Modulates gut microbiome	(Khalil et al., 2006; Sell et al., 2022)
α-Linolenic acid	n−3 PUFA	T, S, G, R	IC_{50} 31.9	Modulates gut microbiota	(Gao et al., 2020; Hong, 2023; Zhuang et al., 2018)
Linoleic acid	n−6 PUFA	T, S, G, R	IC_{50} 43.7	Modulates gut microbiota	(Hong, 2023; Zhuang et al., 2018)
EHT	Fatty acid amide	R		Inhibits α-syn phosphorylation and aggregation, ↑ PP2A methylation and cytoprotection (cotreatment of SH-SY5Y cells with EHT and caffeine)	(Lee et al., 2011; Yan et al., 2018)

[b,c] For comparability with other compounds, IC_{50} with no preincubation is given for the catechols. If the species is not mentioned in the Table, the sources of the MAO B and COMT enzymes are always human recombinant MAO B and human recombinant S-COMT, respectively. The EC_{50} values are described as the concentrations of the tested compounds that inhibit α-syn fibrils formation to 50 % of the control value or the concentrations that destabilize preformed α-syn fibrils to 50 % of the control value. 6-OHDA: 6-hydroxydopamine; CAPE: caffeic acid phenylethyl ester; COMTI: catechol *O*-methyltransferase inhibitor; COX-2: cyclooxygenase-2; EHT: Eicosanoyl-5-hydroxytryptamide; MHQ: 2-Methoxyhydroquinone; Nrf2: nuclear factor erythroid 2-related factor 2; TMN: 2,3,6-trimethyl-1,4-naphthoquinone.

[a] The IC_{50} and K_i values reported for the inhibition of MAO B and COMT are not directly compared, as they have been measured in different tissues under various experimental settings.

(121.5 μg/cigarette) (Smith and Hansch, 2000). These compounds may play a crucial role in the inhibition of MAO B in smokers. One of these new MAO inhibitors, α-linolenic acid, is an n-3 polyunsaturated fatty acid (PUFA). There is growing evidence indicating that n–3 PUFAs can help ameliorate PD symptoms (Avallone et al., 2019; Bousquet et al., 2011; Hernando et al., 2019). n–3 PUFAs are considered to have a positive effect on PD due to anti-inflammatory, antioxidative, and neuroprotective properties (Li and Song, 2022). A case-control study reported that PD patients had lower PUFA intake (P = 0.024), compared with healthy controls, based on 24-hour dietary recalls and 3-day dietary records (Ådén et al., 2011).

BDNF: brain-derived neurotrophic factor; DA: dopamine; EHT: eicosanoyl-5-hydroxytryptamide; ENS: enteric nervous system; GFAP: glial fibrillary acidic protein; GSH: L-glutathione; Nrf2: NF-E2-related factor 2; NSAIDs: Non-steroidal anti-infl ammatory drugs; *LRRK2*: leucine rich repeat kinase 2; PP2A: protein phosphatase 2A; PPARγ: Peroxisome proliferator–activated receptor γ; ROS: reactive oxygen species; *SNCA*: α-synuclein gene.

Green coffee (*Coffea arabica and Coffea canephora*) contains numerous flavonoids, including quercetin, kaempferol, quercitrin, myricetin, dihydromyricetin (ampelopsin), isorhamnetin, taxifolin, rutin, naringenin, catechin, and epicatechin (Mannino et al., 2023). Flavonoids in green coffee that inhibit MAO B include quercetin, quercitrin, myricetin, rutin, naringenin, catechin, and epicatechin (Table 3). The content of polyphenolic compounds and caffeine in coffee beans was measured under different roasting conditions using HPLC analysis (Król et al., 2020). The authors found that organic coffee beans contained major bioactive compounds, including caffeine (4.61 mg/g), gallic acid (1.45 mg/g), chlorogenic acid (5.94 mg/g), caffeic acid (0.058 mg/g), rutin (0.103 mg/g), quercetin (0.11 mg/g), and kaempferol (0.14 mg/g). Among these, chlorogenic acid, caffeic acid, rutin, quercetin, and kaempferol show inhibitory activity on human MAO B, with rutin being the most potent compound (Table 3). The coffee ingredient caffeic acid phenylethyl ester (CAPE) is a degradation product of chlorogenic acid (Kalthoff et al., 2020) and a potent human MAO B inhibitor with an IC_{50} value in the nanomolar range (Takao et al., 2017) (Table 3).

Taken together, these results suggest that MAO B inhibition by the non-nicotine components from tobacco smoke and coffee may contribute to the low incidence of PD in smokers and coffee drinkers.

4.2. *Inhibition of α-synuclein fibrillation*

A neuronal protein, α-syn, plays a key role in the PD pathophysiology by aggregating into oligomers and fibrils, and forming Lewy bodies and Lewy neurites in the gastrointestinal tract, brainstem, and higher brain regions. This process contributes to mitochondrial, lysosomal, and synaptic dysfunction, immune activation, and neuroinflammation in PD (Morris et al., 2024). Therapeutic intervention targeting α-syn toxicity span different stages of its pathways, including α-syn synthesis, aggregation, propagation, degradation, and active immunization (Wong and Krainc, 2017). In addition, α-syn fibrillation is an important therapeutic target in the treatment of PD (Follmer, 2014).

Using *in vitro* and the well-validated yeast cell models, it has been found that nicotine inhibits aggregation of α-syn, while caffeine attenuates the toxicity of α-syn aggregates, providing a potential explanation for the inverse relationships between PD and cigarette smoking and coffee consumption reported in epidemiological studies (Kardani and Roy, 2015; Kardani et al., 2017) (Table 3). Furthermore, Hong et al. (2009) reported that nicotine and hydroquinone found in cigarette smoke inhibit α-syn fibrillization in a dose-dependent manner.

In α-syn-transgenic mice, eicosanoyl-5-hydroxytryptamide (EHT), a

coffee component, inhibited PP2A demethylation and prevented both α-syn aggregation and α-syn phosphorylation at Serine 129, which promotes oligomer formation and fibrillization *in vitro*. The authors suggested that EHT exposure via coffee intake may contribute to its potential benefits in reducing PD risk (Lee et al., 2011).

Catechol-containing compounds from tobacco smoke and coffee blocked the fibril formation of α-syn and β-amyloid (Aβ). Pyrogallol, gallic acid, caffeic acid, and quercetin have displayed inhibition of α-syn and Aβ fibrillization, showing that the catechol moiety in these compounds is fundamental for the anti-amyloidogenic activity (Di Giovanni et al., 2010) (Table 3). Antioxidant compounds such as ferulic acid, myricetin, kaempferol, catechin, and epicatechin inhibit the formation of α-syn fibrils and destabilize preformed α-syn fibrils and the most potent compound was myricetin (Ono and Yamada, 2006) (Table 3).

4.3. COMT inhibition by tobacco or coffee compounds

Catechol *O*-methyltransferase (COMT, EC 2.1.1.6) catalyzes the *O*-methylation metabolism of catecholamine neurotransmitters DA, epinephrine, and norepinephrine (Brancher et al., 2021). This reaction involves transferring the methyl group from the cofactor S-adenosyl-L-methionine (SAMe) to a hydroxyl group of catechols, facilitated by a magnesium ion (Tunbridge et al., 2006). COMT also catalyzes the *O*-methylation of the DA precursor L-DOPA into 3-methoxy-L-DOPA (3-OMD), therefore preventing its further conversion into DA (Finberg, 2019). In both central nervous system (CNS) and all peripheral tissue, COMT is expressed. COMT inhibition reduces the metabolite of L-DOPA, 3-OMD, and increases L-DOPA levels transported into the CNS (Regensburger et al., 2023).

Catechol-containing compounds from tobacco smoke or coffee that inhibit COMT include catechol, pyrogallol, CAPE, gallic acid, ferulic acid, protocatechuic acid, caffeic acid, quercetin, and rutin, chlorogenic acid, myricetin, myricitrin, catechin, and epicatechin (Table 3). Among them, catechol, pyrogallol, gallic acid, ferulic acid, protocatechuic acid, caffeic acid, quercetin, and rutin are early COMT inhibitors (categorised as first-generation inhibitors) (Kiss and Soares-da-Silva, 2014; Yalcin and Bayraktar, 2010), which are much less effective than nitrocatechol-type COMT inhibitors such as entacapone, tolcapone, and nitecapone in animal studies (Männistö and Kaakkola, 1999). Pyrogallol, gallic acid, quercetin, rutin, and catechin have been evaluated for rat liver COMT inhibitory activities and the most potent compound was quercetin with K_i value in the low micromolar range (Guldberg, 1975) (Table 3). Forty natural compounds including catechin, chlorogenic acid, and rutin were selected to assess the dual inhibitory activity against rat liver COMT and recombinant human MAO B (Engelbrecht et al., 2019). Catechin, chlorogenic acid, and rutin inhibited COMT with IC_{50} values of 0.86, 6.17 and 25.3 μM, respectively (Table 3). Also, a recent study found that two flavonoids myricetin and myricitrin are both potent human COMT inhibitors with IC_{50} values of 0.96 and 7.26 μM, respectively (Zhao et al., 2021) (Table 3).

4.4. Suppression of neuroinflammation

Neuroinflammation in the CNS is a response including all cell types (neurons, macroglia, and microglia), and its first indication is microglia activation (Shabab et al., 2017). Microglia can be classified into two distinct types, M1 phenotype and M2 phenotype (Tang and Le, 2016). Under pathological conditions in PD, activated M1 (pro-inflammatory) microglia release pro-inflammatory mediators that stimulate astrocytes, causing increased production of pro-inflammatory factors, nitric oxide, and superoxide radicals, which contribute to the degeneration of DAergic neurons (Wang et al., 2015a). Table 4 summarises the suggested neuroprotective and anti-inflammatory effects of bioactive components from tobacco and coffee in *in vivo* models of PD, as discussed in the following section.

Table 4
Potential neuroprotective effects of tobacco (T), tobacco smoke (S), green coffee (G), and roasted coffee (R) components in *in vivo* models of Parkinson's disease.

Compound	T/S/G/R	PD models/Animals	Observed Effects	References
Nicotine	T, S	MPTP, C57BL/6 mouse	↑ p-ERK/ERK, ↓ iNOS and IL−6, ↓ p-JNK/JNK	(Ruan et al., 2023)
		MPTP, SIRT6 transgenic mouse	↓ SIRT6	(Nicholatos et al., 2018)
Caffeine	T, S, G, R	MPTP, C57BL/6 mouse	↓ MPTP-induced DAergic toxicity, A_{2A} adenosine receptor inactivation	(Chen et al., 2001)
		Rotenone, Wistar rat	↑ GSH (antioxidation) and SOD, ↓ TNF-α, MDA (oxidative stress), and NO,	(Khadrawy et al., 2017)
Trigonelline	G, R	6-OHDA, Wistar rat	↓ MDA	(Mirzaie et al., 2016)
TMN	T, S	MPTP, C57BL/6 mouse	↑ DA	(Castagnoli et al., 2003)
Eugenol	T, S, R	MPTP, Swiss albino mouse	↑ GSH, ↓ MDA	(Vora et al., 2022)
		6-OHDA, Wistar rat	↑ GSH, ↓ NO_2/NO_3 (nitrosative stress), ↓ TBARS (lipid peroxidation)	(Moreira Vasconcelos et al., 2020)
Vanillin	T, S, G	Rotenone, Wistar rat	↑ DA, ↑ GSH, ↑ Antioxidant enzymes (GPx, CAT, and SOD), ↓ TBARS	(Dhanalakshmi et al., 2016)
		6-OHDA, Wistar rat	↑ DA	(Abuthawabeh et al., 2020)
β-asarone	T	MPTP, C57BL/6 mouse	↑ TH+ cells, ↓ MALAT1 and α-syn	(Zhang et al., 2016)
CAPE	R	MPTP, C57BL/6 mouse	↑ TH+ cells, ↓ iNOS and caspase−1 expression	(Fontanilla et al., 2011)
		6-OHDA, Wistar rat	↑ Locomotor activity and motor performance	(Soner et al., 2021)
Ferulic acid	T, S, G, R	MPTP, C57BL/6 mouse	↓ Bax/Bcl2, ↑ antioxidation, ↓ apoptosis	(Nagarajan et al., 2015)
		Rotenone, Wistar rat	↓ COX−2 and iNOS, ↓ Pro-inflammatory cytokines (IL−1β, IL−6, and TNF-α), ↓ Iba−1 and GFAP	(Ojha et al., 2015)
Caffeic acid	T, S, G, R	Rotenone, Swiss albino mouse	↓ Inflammatory mediators (COX−2, iNOS, and NF-κB)	(Zaitone et al., 2019)
		MPTP, C57BL/6 mouse	↑ DA, DOPAC, and HVA, ↓ COX−2, iNOS, and GFAP, ↓ NO and PGE_2	(Tsai et al., 2011)
Chlorogenic acid	T, S, G, R	MPTP, Swiss albino mouse	↓ iNOS, TNF-α, and NF-κB, ↓ GFAP, ↑ TH	(Singh et al., 2018)
		Rotenone, C57BL/6 mouse	↑ GLP−1	(Sharma et al., 2022)
Quercetin	T, S, G, R	6-OHDA, Wistar rat	↑ SOD, GPx, CAT, ↓ MDA, ↓ AChE activity	(Sriraksa et al., 2012)
		Rotenone, Albino rat	↑ DA, Beclin−1, ↓ MDA, CHOP, TrxR activity	(El-Horany et al., 2016)

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Table 4 (*continued*)

Compound	T/S/G/R	PD models/Animals	Observed Effects	References
		Rotenone, Wistar rat	↓ IL−1β, TNF-α, NF-κB, and IκKB	(Josiah et al., 2022)
Kaempferol	T, S, G, R	MPTP, C57BL/6 mouse	↑ DA and DOPAC, ↑ SOD and GSH-PX activity, ↓ MDA	(Li and Pu, 2011)
		Rotenone, Albino rat	↑GSH, SOD, GPx, and CAT, ↓ Lipid peroxidation, IL−6, and TNF-α	(Pan et al., 2020)
Rutin	T, S, G	6-OHDA, Wistar rat	↑ DA and DOPAC, ↑ GPx, GR, CAT, and SOD, ↓NO	(Moshahid Khan et al., 2012)
Resveratrol	T	Rotenone, Wistar rat	↑ DA, ↓ CHOP and GRP78, ↓ caspase−3 activity	(Gaballah et al., 2016)
		MPTP, C57BL/6 N mouse	↑ TH+ cells, ↓ α-syn	(Wang et al., 2015b)
		6-OHDA, Sprague–Dawley rat	↓ COX−2, ↓TNF-α	(Jin et al., 2008)
DHM	G	MPTP, C57BL/6 J mouse	↓ GSK−3β	(Ren et al., 2016)
Myricitrin	T, G, R	MPTP, C57BL/6 mouse	↑ DA	(Banerjee et al., 2022)
Naringenin	T, G	MPTP, C57BL/6 J mouse	↑ DAT and TH, ↑ DA, DOPAC, and HVA, ↑ GSH and SOD, ↓ α-syn, ↓ IL−1β and TNF-α, ↓NO	(Mani et al., 2018)
Naringin	T	6-OHDA, C57BL/6 mouse	↑ mTORC1 activity, ↓ microglial activation	(Kim et al., 2016)
		Rotenone, Wistar rat	↑ DA, DOPAC, and HVA, ↑ GPx and GR, ↓ cytochrome-C, caspase−9, and caspase−3	(Garabadu and Agrawal, 2020)
Esculetin	T, S	MPTP, C57BL/6 J mouse	↑ TH+ cells, ↑ GSH, ↓ caspase−3 activity	(Subramaniam and Ellis, 2013)
α-Linolenic acid	T, S, G, R	6-OHDA, *C. elegans*	↓ DAergic neurodegeneration and movement disorder	(Shashikumar et al., 2015)
EHT	R	MPTP, C57BL/6 mouse	↓ Iba−1 and GFAP, ↓ p-JNK/JNK, ↑ GSH/GSSG	(Lee et al., 2013)
Cafestol	G, R	CncRNAi *Drosophila*	Nrf2-activator	(Trinh et al., 2010)

List of Abbreviations: CAPE: caffeic acid phenylethyl ester; CAT: catalase; CHOP: C/EBP homologous protein; COX-2: cyclooxygenase-2; DAT: dopamine transporter; DHM: Dihydromyricetin; DOPAC: 3,4-dihydroxyphenylacetic acid; EHT: Eicosanoyl-5-hydroxytryptamide; ERK: extracellular signal-regulated kinase; GFAP: glial fibrillary acidic protein; GLP-1: glucagon-like peptide 1; GPx: glutathione peroxidase; GR: glutathione reductase; GRP78: glucose-regulated protein 78; GSH: L-glutathione; GSH-PX: glutathione peroxidase; GSK-3β: glycogen synthase kinase-3 beta; GSSG: oxidized glutathione; HVA: homovanillic acid; Iba-1: anti-ionized calcium-binding adaptor molecule-1; IκKB: IkappaB kinase beta; iNOS: inducible nitric oxide synthase; JNK: c-Jun NH_2-terminal kinase; MALAT1: metastasis associated lung adenocarcinoma transcript 1;MDA: malondialdehyde; mTORC1: mammalian target of rapamycin complex 1; NF-κB: nuclear factor kappa B; Nrf2: nuclear factor erythroid 2-related factor 2; 2 PGE_2: prostaglandin E_2; SIRT6: a member of the sirtuin family of NAD^+-dependent deacetylases; p-ERK: phosphorylated ERK; p-JNK: phosphorylated-JNK; SOD: superoxide dismutase; TBARS: thiobarbituric acid reactive substances; TH: tyrosine hydroxylase; TH+ cells: nigral dopaminergic neurons; TMN: 2,3,6-trimethyl-1,4-naphthoquinone.

4.4.1. Alkaloids

Epidemiological and basic research studies on the role of nicotine in protecting against PD suggest that nicotine administration may slow down and/or stop disease progression in early PD, as nicotine acts on nicotinic acetylcholine receptors (nAChRs) (Quik et al., 2012). A recent study on the neuroprotective effects of nicotine on PD found that nicotine pretreatment reduced microglia activation, as well as inducible nitric oxide synthase (iNOS) and interleukin-6 (IL- 6) expression in the substantia nigra and striatal regions of MPTP-induced PD models (Ruan et al., 2023). Another study found that nicotine not only suppressed SIRT6, a member of the sirtuin family of NAD^+-dependent deacetylases, *in vitro* and *in vivo* but also indicated that SIRT6 contributes to the pathogenesis and inflammation found in PD. This implies that by accelerating the degradation of SIRT6, nicotine can offer neuroprotective benefits (Nicholatos et al., 2018).

In a rotenone-induced PD model, caffeine reduced the elevated levels of tumor necrosis factor-α (TNF-α) in the midbrain and the striatum (+19 % and +29 %, respectively), demonstrating caffeine's anti-inflammatory effect (Khadrawy et al., 2017). The authors suggested that this effect could result from caffeine's ability to inhibit TNF-α gene expression and reduce the number of activated microglia. Trigonelline (1-*N*-methylnicotinic acid) is a pyridine alkaloid and a nicotinic acid metabolite present in coffee beans (Ashihara et al., 2015). It can cross the blood-brain barrier and has been shown to have antidiabetic, neuroprotective, and antioxidant effects (Liang et al., 2023). Regarding PD, Mirzaie et al. (2016) found that pretreatment with trigonelline in 6-hydroxydopamine (6-OHDA)-lesioned rats enhances the viability of SNpc neurons, prevents apoptosis, as well as restores the level of malondialdehyde (MDA), suggesting potential benefits for early PD management.

4.4.2. Phenols and phenolic acids

Using the LPS-treated BV-2 microglial cells and C57BL/6 mice, catechol inhibited nuclear factor kappa B (NF-κB) activation in microglia, leading to a significant suppression of lipopolysaccaride (LPS)-induced production of inflammation-related mediators, including nitric oxide (NO), cytokines, and chemokines. However, future studies are needed to explore whether catechol also suppresses neuroinflammation in PD caused by α-syn (Murata et al., 2023). Eugenol (4-allyl-2-methoxyphenol) and its link with L-DOPA were investigated in a 6-OHDA-induced PD model because eugenol has been extensively studied for its anti-inflammatory and antioxidant effects. Moreira Vasconcelos et al. (2020) demonstrated that combination of eugenol and L-DOPA enhances reduced glutathione (GSH) level more than L-DOPA alone and showed that this combination was promising in comparison to conventional treatment.

Chlorogenic acid and its metabolites, including caffeic acid, ferulic acid, and quinic acid, are widely recognized for their antioxidant activities, which play a crucial role in their neuroprotective effects (Colombo and Papetti, 2020). Chlorogenic acid (3-*O*-caffeoylquinic acid), an ester of caffeic acid and quinic acid, is a main phenolic acid in coffee with potential health benefits, including antioxidant and anti-inflammatory effects, as well as anti-diabetic, anti-bacterial, anti-carcinogenic, and anti-obesity effects (Tajik et al., 2017). In MPTP-intoxicated mice, chlorogenic acid significantly decreased pro-inflammatory mediators, like TNF-α and IL-1β, and blocked astrocyte activation. Additionally, it significantly increased levels of anti-inflammatory cytokine interleukin-10 (IL-10), showing potential benefits in treating the inflammatory condition linked with PD (Singh et al., 2018). To examine whether the neuroprotective effect of caffeic acid is dependent on its reported anti-inflammatory properties, microglial activity was assessed in rotenone-induced Parkinsonian mice (Zaitone et al., 2019). In this model, treatment with caffeic acid led to a reduction in microglial activation and decreased the expression of inflammatory mediators, including COX-2, iNOS, and NF-kB. Ferulic acid decreased activation of anti-ionized calcium-binding adaptor

molecule-1 (Iba-1) and glial fibrillary acidic protein (GFAP), as well as levels of cyclooxygenase-2 (COX-2) and iNOS, interleukin-1β (IL-1β), IL-6, and TNF-α, suggesting that neuroprotective effect occurs via its antioxidant and anti-inflammatory properties (Ojha et al., 2015).

4.4.3. Flavonoids

In a rotenone-induced PD model, quercetin (20 mg/kg) significantly decreased the expression of genes, including IL-1β, TNF-α, NF-κB, and IkappaB kinase beta (IκKB), suggesting that quercetin's anti-inflammatory effect is mediated through the regulation of the canonical NF-κB pathway (Josiah et al., 2022). In a 6-OHDA-induced PD model, naringin treatment significantly reduced not only the number of Iba1-positive microglia but also the level of IL-1β, suggesting that its potential anti-neuroinflammatory activities could contribute to neuroprotective effects in the adult brain (Kim et al., 2016). In lipopolysaccharide (LPS)-treated mice, dihydromyricetin elevated the level of IL-10 while decreasing the level of pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6 (Hou et al., 2015). Additionally, it reduced the phosphorylation levels of NF-κB, IκKB, p38 mitogen-activated protein kinase (MAPK), and JNK, showing potential benefits in treating inflammatory-related diseases. In a PD model using MPTP, dihydromyricetin administration markedly alleviates MPTP-induced behavioural deficits and loss of DAergic neurons (Ren et al., 2016). Furthermore, Ren and colleagues found that dihydromyricetin dose- and time-dependently enhanced the phosphorylation of glycogen synthase kinase-3 beta (GSK-3β), indicating a potential link to dihydromyricetin-induced protection of DAergic neurons. GSK3 exists in two isoforms (GSK3α and GSK3β) that regulate many cellular functions and is a potential therapeutic target for conditions such as psychiatric diseases, neurological diseases, inflammatory diseases, and cancer (Beurel et al., 2015).

4.4.4. Other compounds

EHT is a fatty acid derivative of serotonin (Yan et al., 2018) and a minor constituent present in coffee, recognized for its antioxidant and anti-inflammatory activities (Colombo and Papetti, 2020). In an MPTP PD model, the neuroprotective effect of EHT was examined (Lee et al., 2013). Lee and coworkers suggested that EHT has significant neuroprotective effects through multiple mechanisms: strong anti-inflammatory effect both *in vivo* and in cultured primary glial cells, direct antioxidant action, and modulated PP2A activity.

4.5. Disruption of the gut microbiome

Research on the gastrointestinal microbiome (GM) in PD indicates that changes in GM composition may lead to the spread of α-syn aggregates from the gut to the brain and potentially contribute to PD pathogenesis (Lubomski et al., 2020). There is a hypothesis that cigarette and coffee consumption decrease the risk of PD by altering the gut microbiota composition, which mitigates intestinal inflammation and results in reduced misfolding of α-syn in enteric nerves (Derkinderen et al., 2014). The gut microbiota composition differs significantly between current smokers and never smokers, while it is similar between never smokers and former smokers (Lee et al., 2018).

Farnesol, a potent and selective human MAO B inhibitor present in tobacco and tobacco smoke, has been reported to modify the composition of the gut microbiome (Sell et al., 2022). It notably decreases the Firmicutes:Bacteroidetes (F/B) ratio, which several studies have indicated is elevated in inflammatory gut diseases. Recently, Feng and coworkers reported that dietary compounds like gallic acid, chlorogenic acid, and dihydromyricetin can modulate gut microbiota-derived metabolites through their interaction with gut microbiota (Feng et al., 2022) (Table 3). These metabolites, including short-chain fatty acids (SCFAs) and bile acids (BAs), are important not only for maintaining host homeostasis but also for the development of diseases such as PD. Furthermore, smoking enhances the integrity of the large intestine barrier by potentially increasing the levels of Bacteroides and Prevotella, while decreasing the levels of Firmicutes and Actinobacteria (Hirayama et al., 2023). On the other hand, coffee led to higher levels of anti-inflammatory Bifidobacteria, while reducing the levels of Clostridium spp. and Escherichia coli, which penetrate the gut mucosa in PD (Scheperjans et al., 2015). Other components from tobacco and coffee that modulate gut microbiota include quercetin, naringenin, catechin, epicatechin, α-linolenic acid, and linoleic acid (Table 3).

4.6. Nrf2 pathway activation by tobacco and coffee compounds

Components in coffee and tobacco that activate the Nrf2 pathway may contribute to the decreased risk of PD in smokers and coffee drinkers (Trinh et al., 2010). One of the primary defence strategies against oxidative or electrophilic stress involves activating the Nrf2 pathway (Kumar et al., 2014), which helps protect disorders such as cancer and neurodegeneration (Senger et al., 2016). We report that catechol, 4-methylcatechol, 4-ethylcatechol, and 4-vinylcatechol, and hydroquinone are natural Nrf2 activators found in coffee and tobacco smoke (Table 3). Catechol, 4-methylcatechol, 4-ethylcatechol, and 4-vinylcatechol are formed via rapid decarboxylation of chlorogenic acid during coffee roasting (Ou, 2021). Senger and coworkers found that 4-methylcatechol, 4-ethylcatechol, and 4-vinylcatechol are potent activators of the Nrf2 pathway, showing potency comparable to that of sulforaphane, a well-characterized Nrf2 inducer (Senger et al., 2016). Recently, it has also been reported that coffee components such as catechol, and 4-ethylcatechol, and hydroquinone inhibit LPS-induced activation of NF-κB and activate Nrf2, demonstrating anti-inflammatory activity (Funakoshi-Tago et al., 2022; Funakoshi-Tago et al., 2020). It was suggested that catechol is the primary component contributing to the anti-inflammatory effects of coffee, as it has a higher concentration of catechol compared to 4-ethylcatechol and hydroquinone. Other natural Nrf2 activators found in components of coffee and tobacco include trigonelline, kahweol, cafestol, resveratrol, protocatechuic acid, ferulic acid, kaempferol, scopoletin, and CAPE (Table 3). As such, these compounds could be promising candidates for therapeutic intervention in PD.

5. Limitations

This review has several limitations. Firstly, the identification of non-nicotine and non-caffeine components from tobacco and coffee was achieved through literature-based cross-referencing with known inhibitors of MAO B, COMT, and α-syn fibrillation, which may overlook novel mechanisms. Protective effects of these components have been observed in both *in vitro* and *in vivo* models of PD, including MPTP, 6-OHDA, and rotenone-induced models. However, further research is needed to validate these findings and assess their efficacy and selectivity compared to existing treatments. Notably, polyphenols like chlorogenic acid and quercetin are promising candidates for treating PD (Acıkara et al., 2022; Gao et al., 2023). They share structural features, such as the catechol group, with established PD treatments like entacapone and opicapone. However, their exact mechanisms of action and therapeutic relevance in PD require further investigation. Secondly, most identified compounds lack data on bioavailability, pharmacokinetic analyses, and blood-brain barrier permeability. While compounds like chlorogenic acids in coffee are highly bioaccessible, only trace nano-molar levels of these compounds have been found in the bloodstream, raising questions about their potential to reach CNS targets (Wu et al., 2022). Moreover, limited data on toxicity or dose-response profiles complicate the evaluation of their therapeutic application. Thirdly, as mentioned in Section 4.6, the Nrf2 pathway helps protect against oxidative stress, which is linked to disorders like neurodegeneration. Mechanisms such as Nrf2 activation and MAO B inhibition, and modulation of gut microbiota, are implicated in neuroprotection, their long-term safety remains unclear. For example, while the adverse effects of MAO B inhibitors may be

milder compared to those of dopamine agonists (Giladi et al., 2016), and the MAO B inhibitor rasagiline has been proven safe and effective for long-term use, both as monotherapy and in combination with levodopa (Tan et al., 2022), many Nrf2 activators interact with cysteine residues on Keap1, often leading to off-target effects and toxicity (Li et al., 2020). Fourthly, strong evidence indicates that smoking and coffee consumption may reduce the risk of PD by improving gut health and reducing inflammation (Derkinderen et al., 2014; Zhu et al., 2022). For example, farnesol can decrease the Firmicutes:Bacteroidetes ratio. However, the role of gut microbiota modulation in PD risk reduction requires further investigation. Lastly, as mentioned in Table 2, cotreatment with EHT and caffeine increased PP2A activity, which dephosphorylates α-syn. EHT synergizes with caffeine to provide neuroprotection in mouse models of PD (Yan et al., 2018). Similarly, Hogg (2016) suggested that several tobacco-derived substances may contribute to the MAO inhibition observed in smokers through additive or synergistic effects. While individual components may provide benefits, their combined effects could lead to stronger neuroprotective benefits, which requires further research to fully understand their potential.

6. Conclusion and future directions

PD is a common progressive neurodegenerative disease, and current medications are only symptomatic and unable to prevent its progression. It has been suggested for a long time that two lifestyle factors, smoking and coffee drinking, are associated with a reduced risk of PD. Identifying candidate molecules and mechanisms underlying the protective effects of smoking and coffee drinking on PD is important for understanding these effects and for the treatment and progression of PD. This review summarized the protective effects of tobacco and coffee bioactive components in both *in vitro* and *in vivo* models of PD and categorized them based on their biological targets and molecular structure. The potential common mechanisms for the effects of smoking and coffee drinking include inhibition of MAO B, COMT, and α-syn fibrillation, changes in the gut microbiome, activation of the Nrf2 pathway, and suppression of neuroinflammation.

We have shown that bioactive components from tobacco and coffee, including alkaloids like nicotine and caffeine, phenolic compounds such as phenols, phenolic acids, flavonoids, and other components like esculetin, α-linolenic acid, TMN, EHT, and cafestol have potential neuroprotective effects in *in vivo* models of PD. Additionally, many candidate molecules from tobacco and coffee are multifunctional molecules that primarily target MAO B, COMT, and α-syn fibrillization. These molecules also may play a role in activating the Nrf2 pathway, suppressing neuroinflammation, and modulation of gut microbiota. Whilst these findings could plausibly explain the inverse link between smoking, coffee drinking, and PD, it is not clear whether the compounds identified in tobacco and coffee reduce the development and progression of PD, or only alleviate symptoms. Current data suggest both possibilities, but further research is needed to understand their long-term impact on disease progression. Future studies could explore the pathological role of MAO B in PD. Understanding of the role of MAO B in PD will not only be important for elucidating PD pathogenesis, but also for understanding the potential neuroprotective effects of MAO B inhibitors. Further studies on the development of multifunctional molecules targeting MAO B, COMT, and α-syn fibrillization, as well as the activation of the Nrf2 pathway, suppression of neuroinflammation, and modulation of gut microbiota, are essential for the effective treatment of PD.

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CRediT authorship contribution statement

Sa Weon Hong: Writing – original draft, Conceptualization. **Penelope Truman:** Writing – review & editing, Conceptualization. **Rachel Page:** Writing – review & editing, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

References

Aarsland, D., Påhlhagen, S., Ballard, C.G., Ehrt, U., Svenningsson, P., 2012. Depression in Parkinson disease—epidemiology, mechanisms and management. Nat. Rev. Neurol. 8, 35–47. https://doi.org/10.1038/nrneurol.2011.189.

Abuthawabeh, R., Abuirmeileh, A.N., Alzoubi, K.H., 2020. The beneficial effect of vanillin on 6-hydroxydopamine rat model of Parkinson's disease. Restor. Neurol. Neurosci. 38, 369–373. https://doi.org/10.3233/rnn-201028.

Acıkara, O.B., Karatoprak, G., Yücel, Ç ., Akkol, E.K., Sobarzo-Sánchez, E., Khayatkashani, M., Kamal, M.A., Kashani, H.R., 2022. A critical analysis of quercetin as the attractive target for the treatment of Parkinson's disease. CNS Neurol. Disord. -Drug Targets 21, 795–817. https://doi.org/10.2174/1871527320666211206122407.

Ådén, E., Carlsson, M., Poortvliet, E., Stenlund, H., Linder, J., Edström, M., Forsgren, L., Håglin, L., 2011. Dietary intake and olfactory function in patients with newly diagnosed Parkinson's disease: a case-control study. Nutr. Neurosci. 14, 25–31. https://doi.org/10.1179/174313211X12966635733312.

Akhtar, M.J., Yar, M.S., Grover, G., Nath, R., 2020. Neurological and psychiatric management using COMT inhibitors: A review. Bioorg. Chem. 94, 103418. https://doi.org/10.1016/j.bioorg.2019.103418.

Anis, E., Xie, A., Brundin, L., Brundin, P., 2022. Digesting recent findings: gut alpha-synuclein, microbiome changes in Parkinson's disease. Trends Endocrinol. Metab. 33, 147–157. https://doi.org/10.1016/j.tem.2021.11.005.

Arlt, A., Sebens, S., Krebs, S., Geismann, C., Grossmann, M., Kruse, M., Schreiber, S., Schäfer, H., 2013. Inhibition of the Nrf2 transcription factor by the alkaloid trigonelline renders pancreatic cancer cells more susceptible to apoptosis through decreased proteasomal gene expression and proteasome activity. Oncogene 32, 4825–4835. https://doi.org/10.1038/onc.2012.493.

Ascherio, A., Schwarzschild, M.A., 2016. The epidemiology of Parkinson's disease: risk factors and prevention. Lancet Neurol. 15, 1257–1272. https://doi.org/10.1016/S1474-4422(16)30230-7.

Ashihara, H., Ludwig, I.A., Katahira, R., Yokota, T., Fujimura, T., Crozier, A., 2015. Trigonelline and related nicotinic acid metabolites: occurrence, biosynthesis, taxonomic considerations, and their roles in planta and in human health. Phytochem. Rev. 14, 765–798. https://doi.org/10.1007/s11101-014-9375-z.

Avallone, R., Vitale, G., Bertolotti, M., 2019. Omega-3 fatty acids and neurodegenerative diseases: new evidence in clinical trials. Int. J. Mol. Sci. 20, 4256. https://doi.org/10.3390/ijms20174256.

Badavath, V.N., Baysal, İ., Uçar, G., Mondal, S.K., Sinha, B.N., Jayaprakash, V., 2016. Monoamine oxidase inhibitory activity of ferulic acid amides: curcumin-based design and synthesis. Arch. Pharm. 349, 9–19. https://doi.org/10.1002/ardp.201500317.

Bakshi, R., Zhang, H., Logan, R., Joshi, I., Xu, Y., Chen, X., Schwarzschild, M.A., 2015. Neuroprotective effects of urate are mediated by augmenting astrocytic glutathione synthesis and release. Neurobiol. Dis. 82, 574–579. https://doi.org/10.1016/j.nbd.2015.08.022.

Balestrino, R., Schapira, A.H.V., 2020. Parkinson disease. Eur. J. Neurol. 27, 27–42. https://doi.org/10.1111/ene.14108.

Banerjee, C., Nandy, S., Chakraborty, J., Kumar, D., 2022. Myricitrin–a flavonoid isolated from the Indian olive tree (Elaeocarpus floribundus)–inhibits Monoamine oxidase in the brain and elevates striatal dopamine levels: therapeutic implications against Parkinson's disease. Food Funct. 13, 6545–6559. https://doi.org/10.1039/D2FO00734G.

Basu, M., Mayana, K., Xavier, S., Balachandran, S., Mishra, N., 2016. Effect of scopoletin on monoamine oxidases and brain amines. Neurochem. Int. 93, 113–117. https://doi.org/10.1016/j.neuint.2016.01.001.

Bellou, V., Belbasis, L., Tzoulaki, I., Evangelou, E., Ioannidis, J.P., 2016. Environmental risk factors and Parkinson's disease: an umbrella review of meta-analyses. Park. Relat. Disord. 23, 1–9. https://doi.org/10.1016/j.parkreldis.2015.12.008.

Ben-Shlomo, Y., Darweesh, S., Llibre-Guerra, J., Marras, C., San Luciano, M., Tanner, C., 2024. The epidemiology of Parkinson's disease. Lancet 403, 283–292. https://doi.org/10.1016/S0140-6736(23)01419-8.
Beurel, E., Grieco, S.F., Jope, R.S., 2015. Glycogen synthase kinase-3 (GSK3): regulation, actions, and diseases. Pharmacol. Ther. 148, 114–131. https://doi.org/10.1016/j.pharmthera.2014.11.016.
Beydoun, M.A., Beydoun, H.A., Gamaldo, A.A., Teel, A., Zonderman, A.B., Wang, Y., 2014. Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis. BMC Public Health 14, 1–33. https://doi.org/10.1186/1471-2458-14-643.
Bluett, B., Togasaki, D.M., Mihaila, D., Evatt, M., Rezak, M., Jain, S., Schwarzschild, M. A., Ascherio, A., Casaceli, C., Curhan, G.C., 2021. Effect of urate-elevating inosine on early Parkinson disease progression: the SURE-PD3 randomized clinical trial. JAMA 326, 926–939. https://doi.org/10.1001/jama.2021.10207.
Bousquet, M., Calon, F., Cicchetti, F., 2011. Impact of omega-3 fatty acids in Parkinson's disease. Ageing Res. Rev. 10, 453–463. https://doi.org/10.1016/j.arr.2011.03.001.
Brancher, J.A., Bertoli, F.Md.P., Michels, B., Lopes-Faturri, A., Pizzatto, E., Losso, E.M., Orsi, J.S., Feltrin de Souza, J., Küchler, E.C., Wambier, L.M., 2021. Is catechol-O-methyltransferase gene associated with temporomandibular disorders? A systematic review and meta-analysis. Int. J. Paediatr. Dent. 31, 152–163. https://doi.org/10.1111/ipd.12721.
Carradori, S., Gidaro, M.C., Petzer, Al, Costa, G., Guglielmi, P., Chimenti, P., Alcaro, S., Petzer, J.P., 2016. Inhibition of human monoamine oxidase: biological and molecular modeling studies on selected natural flavonoids. J. Agric. Food Chem. 64, 9004–9011. https://doi.org/10.1021/acs.jafc.6b03529.
Castagnoli, K., Petzer, J.B., Steyn, S.J., van der Schyf, C.J., Castagnoli Jr, N., 2003. Inhibition of human MAO-A and MAO-B by a compound isolated from flue-cured tobacco leaves and its neuroprotective properties in the MPTP mouse model of neurodegeneration. Inflammopharmacology 11, 183–188. https://doi.org/10.1163/156856003765764353.
Cerqueira, E.C., Netz, P.A., Diniz, C., do Canto, V.P., Follmer, C., 2011. Molecular insights into human monoamine oxidase (MAO) inhibition by 1, 4-naphthoquinone: Evidences for menadione (vitamin K3) acting as a competitive and reversible inhibitor of MAO. Biorg. Med. Chem. 19, 7416–7424. https://doi.org/10.1016/j.bmc.2011.10.049.
Chang, W.-C., Wu, S.-C., Xu, K.-D., Liao, B.-C., Wu, J.-F., Cheng, A.-S., 2015. Scopoletin protects against methylglyoxal-induced hyperglycemia and insulin resistance mediated by suppression of advanced glycation endproducts (AGEs) generation and anti-glycation. Molecules 20, 2786–2801. https://doi.org/10.3390/molecules20022786.
Chen, J.-F., Xu, K., Petzer, J.P., Staal, R., Xu, Y.-H., Beilstein, M., Sonsalla, P.K., Castagnoli, K., Castagnoli Jr, N., Schwarzschild, M.A., 2001. Neuroprotection by caffeine and A (2A) adenosine receptor inactivation in a model of Parkinson's disease. J. Neurosci. 21, RC143. https://doi.org/10.1523/jneurosci.21-10-j0001.2001.
Cho, H.-U., Kim, S., Sim, J., Yang, S., An, H., Nam, M.-H., Jang, D.-P., Lee, C.J., 2021. Redefining differential roles of MAO-A in dopamine degradation and MAO-B in tonic GABA synthesis. Exp. Mol. Med. 53, 1148–1158. https://doi.org/10.1038/s12276-021-00646-3.
Colombo, R., Papetti, A., 2020. An outlook on the role of decaffeinated coffee in neurodegenerative diseases. Crit. Rev. Food Sci. Nutr. 60, 760–779. https://doi.org/10.1080/10408398.2018.1550384.
Commenges, D., Scotet, V., Renaud, S., Jacqmin-Gadda, H., Barberger-Gateau, P., Dartigues, J.-F., 2000. Intake of flavonoids and risk of dementia. Eur. J. Epidemiol. 16, 357–363. https://doi.org/10.1023/A:1007614613771.
Dauer, W., Przedborski, S., 2003. Parkinson's disease: mechanisms and models. Neuron 39, 889–909. https://doi.org/10.1016/s0896-6273(03)00568-3.
Delic, V., Beck, K.D., Pang, K.C., Citron, B.A., 2020. Biological links between traumatic brain injury and Parkinson's disease. Acta Neuropathol. Commun. 8, 1–16. https://doi.org/10.1186/s40478-020-00924-7.
Deng, S., West, B.J., 2011. Antidepressant effects of noni fruit and its active principals. Asian J. Med. Sci. 3, 79–83.
van der Toorn, M., Koshibu, K., Schlage, W.K., Majeed, S., Pospisil, P., Hoeng, J., Peitsch, M.C., 2019. Comparison of monoamine oxidase inhibition by cigarettes and modified risk tobacco products. Toxicol. Rep. 6, 1206–1215. https://doi.org/10.1016/j.toxrep.2019.11.008.
Derkinderen, P., Shannon, K.M., Brundin, P., 2014. Gut feelings about smoking and coffee in Parkinson's disease. Mov. Disord. 29, 976–979. https://doi.org/10.1002/mds.25882.
Dhanalakshmi, C., Janakiraman, U., Manivasagam, T., Justin Thenmozhi, A., Essa, M.M., Kalandar, A., Khan, M.A.S., Guillemin, G.J., 2016. Vanillin attenuated behavioural impairments, neurochemical deficts, oxidative stress and apoptosis against rotenone induced rat model of Parkinson's disease. Neurochem. Res. 41, 1899–1910. https://doi.org/10.1007/s11064-016-1901-5.
Di Giovanni, S., Eleuteri, S., Paleologou, K.E., Yin, G., Zweckstetter, M., Carrupt, P.-A., Lashuel, H.A., 2010. Entacapone and tolcapone, two catechol O-methyltransferase inhibitors, block fibril formation of α-synuclein and β-amyloid and protect against amyloid-induced toxicity. J. Biol. Chem. 285, 14941–14954. https://doi.org/10.1074/jbc.M109.080390.
Dirandeh, E., Palizgir, A., Kassiri, N., Palizgir Sr, A., 2022. An overview of the relationship between occupational manganese exposure and Parkinsonism. Cureus 14. https://doi.org/10.7759/cureus.32161.
Dixon Clarke, S.E., Ramsay, R.R., 2011. Dietary inhibitors of monoamine oxidase A. J. Neural Transm. (Vienna) 118, 1031–1041. https://doi.org/10.1007/s00702-010-0537-x.
Dong, S., Zhu, M., Wang, K., Zhao, X., Hu, L., Jing, W., Lu, H., Wang, S., 2021. Dihydromyricetin improves DSS-induced colitis in mice via modulation of fecal-bacteria-related bile acid metabolism. Pharmacol. Res. 171, 105767. https://doi.org/10.1016/j.phrs.2021.105767.
Duda-Chodak, A., 2012. The inhibitory effect of polyphenols on human gut microbiota. J. Physiol. Pharmacol. 63, 497–503.
El-Horany, H.E., El-latif, R.N.A., ElBatsh, M.M., Emam, M.N., 2016. Ameliorative effect of quercetin on neurochemical and behavioral deficits in rotenone rat model of Parkinson's disease: modulating autophagy (quercetin on experimental Parkinson's disease). J. Biochem. Mol. Toxicol. 30, 360–369. https://doi.org/10.1002/jbt.21821.
Engelbrecht, I., Petzer, J.P., Petzer, A., 2019. Evaluation of selected natural compounds as dual inhibitors of catechol-O-methyltransferase and monoamine oxidase. Cent. Nerv. Syst. Agents Med. Chem. 19, 133–145. https://doi.org/10.2174/1871524919666190619090852.
Fazili, N.A., Naeem, A., 2015. Anti-fibrillation potency of caffeic acid against an antidepressant induced fibrillogenesis of human α-synuclein: Implications for Parkinson's disease. Biochimie 108, 178–185. https://doi.org/10.1016/j.biochi.2014.11.011.
Feng, W., Liu, J., Cheng, H., Zhang, D., Tan, Y., Peng, C., 2022. Dietary compounds in modulation of gut microbiota-derived metabolites. Front. Nutr. 9, 939571. https://doi.org/10.1039/C9FO00213H.
Ferchmin, P., Pagán, O.R., Ulrich, H., Szeto, A.C., Hann, R.M., Eterović, V.A., 2009. Actions of octocoral and tobacco cembranoids on nicotinic receptors. Toxicon 54, 1174–1182. https://doi.org/10.1016/j.toxicon.2009.02.033.
Finberg, J.P., 2019. Inhibitors of MAO-B and COMT: their effects on brain dopamine levels and uses in Parkinson's disease. J. Neural Transm. 126, 433–448. https://doi.org/10.1007/s00702-018-1952-7.
Follmer, C., 2014. Monoamine oxidase and α-synuclein as targets in Parkinson's disease therapy. Expert Rev. Neurother. 14, 703–716. https://doi.org/10.1586/14737175.2014.920235.
Foltynie, T., Bruno, V., Fox, S., Kühn, A.A., Lindop, F., Lees, A.J., 2024. Medical, surgical, and physical treatments for Parkinson's disease. Lancet 403, 305–324. https://doi.org/10.1016/S0140-6736(23)01429-0.
Fontanilla, C., Ma, Z., Wei, X., Klotsche, J., Zhao, L., Wisniowski, P., Dodel, R., Farlow, M., Oertel, W., Du, Y., 2011. Caffeic acid phenethyl ester prevents 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine-induced neurodegeneration. Neuroscience 188, 135–141. https://doi.org/10.1016/j.neuroscience.2011.04.009.
Fowler, J., Volkow, N., Wang, G.-J., Logan, J., Pappas, N., Shea, C., MacGregor, R., 1997. Age-related increases in brain monoamine oxidase B in living healthy human subjects. Neurobiol. Aging 18, 431–435. https://doi.org/10.1016/S0197-4580(97)00037-7.
Fowler, J.S., Volkow, N.D., Wang, G.J., Pappas, N., Logan, J., MacGregor, R., Alexoff, D., Shea, C., Schlyer, D., Wolf, A.P., Warner, D., Zezulkova, I., Cilento, R., 1996. Inhibition of monoamine oxidase B in the brains of smokers. Nature 379, 733–736. https://doi.org/10.1038/379733a0.
Fox, S.H., Katzenschlager, R., Lim, S.Y., Barton, B., De Bie, R.M.A., Seppi, K., Coelho, M., Sampaio, C., 2018. International Parkinson and movement disorder society evidence-based medicine review: update on treatments for the motor symptoms of Parkinson's disease. Mov. Disord. 33, 1248–1266. https://doi.org/10.1002/mds.27372.
Freire, C., Koifman, S., 2012. Pesticide exposure and Parkinson's disease: epidemiological evidence of association. Neurotoxicology 33, 947–971. https://doi.org/10.1016/j.neuro.2012.05.011.
Funakoshi-Tago, M., Nonaka, Y., Tago, K., Takeda, M., Ishihara, Y., Sakai, A., Matsutaka, M., Kobata, K., Tamura, H., 2020. Pyrocatechol, a component of coffee, suppresses LPS-induced inflammatory responses by inhibiting NF-κB and activating Nrf2. Sci. Rep. 10, 2584. https://doi.org/10.1038/s41598-020-59380-x.
Funakoshi-Tago, M., Matsutaka, M., Hokimoto, S., Kobata, K., Tago, K., Tamura, H., 2022. Coffee ingredients, hydroquinone, pyrocatechol, and 4-ethylcatechol exhibit anti-inflammatory activity through inhibiting NF-κB and activating Nrf2. J. Funct. Foods 90, 104980. https://doi.org/10.1016/j.jff.2022.104980.
Gaballah, H.H., Zakaria, S.S., Elbatsh, M.M., Tahoon, N.M., 2016. Modulatory effects of resveratrol on endoplasmic reticulum stress-associated apoptosis and oxido-inflammatory markers in a rat model of rotenone-induced Parkinson's disease. Chem. Biol. Interact. 251, 10–16. https://doi.org/10.1016/j.cbi.2016.03.023.
Gaffo, A.L., Roseman, J.M., Jacobs, D.R., Lewis, C.E., Shikany, J.M., Mikuls, T.R., Jolly, P.E., Saag, K.G., 2010. Serum urate and its relationship with alcoholic beverage intake in men and women: findings from the Coronary Artery Risk Development in Young Adults (CARDIA) cohort. Ann. Rheum. Dis. 69, 1965–1970. https://doi.org/10.1136/ard.2010.129429.
Gallo, V., Vineis, P., Cancellieri, M., Chiodini, P., Barker, R.A., Brayne, C., Pearce, N., Vermeulen, R., Panico, S., Bueno-de-Mesquita, B., 2019. Exploring causality of the association between smoking and Parkinson's disease. Int. J. Epidemiol. 48, 912–925. https://doi.org/10.1093/ije/dyy230.
Gao, S.S., Choi, B.-M., Chen, X.Y., Zhu, R.Z., Kim, Y., So, H., Park, R., Sung, M., Kim, B.-R., 2010. Kaempferol suppresses cisplatin-induced apoptosis via inductions of heme oxygenase-1 and glutamate-cysteine ligase catalytic subunit in HEI-OC1 cells. Pharm. Res. 27, 235–245. https://doi.org/10.1007/s11095-009-0003-3.
Gao, X., Chang, S., Liu, S., Peng, L., Xie, J., Dong, W., Tian, Y., Sheng, J., 2020. Correlations between α-linolenic acid-improved multitissue homeostasis and gut microbiota in mice fed a high-fat diet, 20 Msystems 5, e00391. https://doi.org/10.1128/msystems.00391-20.
Gao, X., Zhang, B., Zheng, Y., Liu, X., Rostyslav, P., Finiuk, N., Sik, A., Stoika, R., Liu, K., Jin, M., 2023. Neuroprotective effect of chlorogenic acid on Parkinson's disease like

symptoms through boosting the autophagy in zebrafish. Eur. J. Pharmacol. 956, 175950. https://doi.org/10.1016/j.ejphar.2023.175950.
Garabadu, D., Agrawal, N., 2020. Naringin exhibits neuroprotection against rotenone-induced neurotoxicity in experimental rodents. Neuromolecular Med. 22, 314–330. https://doi.org/10.1007/s12017-019-08590-2.
Ghanem, S.S., Fayed, H.S., Zhu, Q., Lu, J.-H., Vaikath, N.N., Ponraj, J., Mansour, S., El-Agnaf, O.M., 2021. Natural alkaloid compounds as inhibitors for alpha-synuclein seeded fibril formation and toxicity. Molecules 26, 3736. https://doi.org/10.3390/molecules26123736.
Giladi, N., Asgharnejad, M., Bauer, L., Grieger, F., Boroojerdi, B., 2016. Rotigotine in combination with the MAO-B inhibitor selegiline in early Parkinson's disease: a post hoc analysis. J. Park. Dis. 6, 401–411. https://doi.org/10.3233/JPD-150758.
Goldman, S.M., 2014. Environmental toxins and Parkinson's disease. Annu. Rev. Pharmacol. Toxicol. 54, 141–164. https://doi.org/10.1146/annurev-pharmtox-011613-135937.
Gugler, R., Dengler, H., 1973. Inhibition of human liver catechol-O-methyltransferase by flavonoids. Naunyn-Schmiede 'S. Arch. Pharmacol. 276, 223–233. https://doi.org/10.1007/BF00501194.
Guldberg, H.C., 1975. Catecol-o-methyl transferase: pharmacological aspects and physiological role. Phermacol. Rev. 27, 135–206.
Hahad, O., Beutel, M., Gilan, D.A., Michal, M., Schulz, A., Pfeiffer, N., König, J., Lackner, K., Wild, P., Daiber, A., 2022. The association of smoking and smoking cessation with prevalent and incident symptoms of depression, anxiety, and sleep disturbance in the general population. J. Affect. Disord. 313, 100–109. https://doi.org/10.1016/j.jad.2022.06.083.
Hauptmann, N., Shih, J.C., 2001. 2-Naphthylamine, a compound found in cigarette smoke, decreases both monoamine oxidase A and B catalytic activity. Life Sci. 68, 1231–1241. https://doi.org/10.1016/s0024-3205(00)01022-5.
Heo, J.Y., Nam, M.-H., Yoon, H.H., Kim, J., Hwang, Y.J., Won, W., Woo, D.H., Lee, J.A., Park, H.-J., Jo, S., 2020. Aberrant tonic inhibition of dopaminergic neuronal activity causes motor symptoms in animal models of Parkinson's disease. e279 Curr. Biol. 30, 276–291. https://doi.org/10.1016/j.cub.2019.11.079.
Hernán, M.A., Takkouche, B., Caamaño-Isorna, F., Gestal-Otero, J.J., 2002. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. Ann. Neurol. 52, 276–284. https://doi.org/10.1002/ana.10277.
Hernando, S., Requejo, C., Herran, E., Ruiz-Ortega, J.A., Morera-Herreras, T., Lafuente, J. V., Ugedo, L., Gainza, E., Pedraz, J.L., Igartua, M., 2019. Beneficial effects of n-3 polyunsaturated fatty acids administration in a partial lesion model of Parkinson's disease: the role of glia and NRf2 regulation. Neurobiol. Dis. 121, 252–262. https://doi.org/10.1016/j.nbd.2018.10.001.
Herraiz, T., Chaparro, C., 2005. Human monoamine oxidase is inhibited by tobacco smoke: beta-carboline alkaloids act as potent and reversible inhibitors. Biochem Biophys. Res Commun. 326, 378–386. https://doi.org/10.1016/j.bbrc.2004.11.033.
Hirayama, M., Nishiwaki, H., Hamaguchi, T., Ohno, K., 2023. Gastrointestinal disorders in Parkinson's disease and other Lewy body diseases. npj Park. 'S. Dis. 9, 71. https://doi.org/10.1038/s41531-023-00511-2.
Hogg, R.C., 2016. Contribution of monoamine oxidase inhibition to tobacco dependence: a review of the evidence. Nicotine Tob. Res 18, 509–523. https://doi.org/10.1093/ntr/ntv245.
Hong, D.-P., Fink, A.L., Uversky, V.N., 2009. Smoking and Parkinson's disease: does nicotine affect α-synuclein fibrillation? Biochim. Biophys. Acta 1794, 282–290. https://doi.org/10.1016/j.bbapap.2008.09.026.
Hong, S.W., 2023. Biochemical characterisation of six novel monoamine oxidase inhibitors identified in tobacco smoke: a thesis presented in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Health Sciences at Massey University. EMBARGOED to 18 July 2024. Massey University, Wellington, New Zealand.
Hong, S.W., Teesdale-Spittle, P., Page, R., Truman, P., 2022. A review of monoamine oxidase (MAO) inhibitors in tobacco or tobacco smoke. Neurotoxicology 93, 163–172. https://doi.org/10.1016/j.neuro.2022.09.008.
Hopfner, F., Höglinger, G.U., Kuhlenbaeumer, G., Pottegård, A., Wod, M., Christensen, K., Tanner, C.M., Deuschl, G., 2020. β-adrenoreceptors and the risk of Parkinson's disease. Lancet Neurol. 19, 247–254. https://doi.org/10.1016/S1474-4422(19)30400-4.
Hornedo-Ortega, R., Alvarez-Fernandez, M.A., Cerezo, A.B., Richard, T., Troncoso, A.Ma, Garcia-Parrilla, Ma.C., 2016. Protocatechuic acid: inhibition of fibril formation, destabilization of preformed fibrils of amyloid-β and α-synuclein, and neuroprotection. J. Agric. Food Chem. 64, 7722–7732. https://doi.org/10.1021/acs.jafc.6b03217.
Hou, W.-C., Lin, R.-D., Chen, C.-T., Lee, M.-H., 2005. Monoamine oxidase B (MAO-B) inhibition by active principles from Uncaria rhynchophylla. J. Ethnopharmacol. 100, 216–220. https://doi.org/10.1016/j.jep.2005.03.017.
Hou, X., Tong, Q., Wang, W., Shi, C., Xiong, W., Chen, J., Liu, X., Fang, J., 2015. Suppression of inflammatory responses by dihydromyricetin, a flavonoid from Ampelopsis grossedentata, via inhibiting the activation of NF-κB and MAPK signaling pathways. J. Nat. Prod. 78, 1689–1696. https://doi.org/10.1021/acs.jnatprod.5b00275.
Hu, G., Bidel, S., Jousilahti, P., Antikainen, R., Tuomilehto, J., 2007. Coffee and tea consumption and the risk of Parkinson's disease. Mov. Disord. 22, 2242–2248. https://doi.org/10.1002/mds.21706.
Huang, J., Chen, L., Xue, B., Liu, Q., Ou, S., Wang, Y., Peng, X., 2016. Different flavonoids can shape unique gut microbiota profile in vitro. J. Food Sci. 81, H2273–H2279. https://doi.org/10.1111/1750-3841.13411.
Hughes, K.C., Gao, X., Kim, I.Y., Wang, M., Weisskopf, M.G., Schwarzschild, M.A., Ascherio, A., 2017. Intake of dairy foods and risk of Parkinson disease. Neurology 89, 46–52. https://doi.org/10.1212/WNL.0000000000004057.
Hwang, Y.P., Jeong, H.G., 2008. The coffee diterpene kahweol induces heme oxygenase-1 via the PI3K and p38/Nrf2 pathway to protect human dopaminergic neurons from 6-hydroxydopamine-derived oxidative stress. FEBS Lett. 582, 2655–2662. https://doi.org/10.1016/j.febslet.2008.06.045.
Jankovic, J., 2008. Parkinson's disease: clinical features and diagnosis. J. Neurol. Neurosurg. Psychiatry 79, 368–376. https://doi.org/10.1136/jnnp.2007.131045.
Jankovic, J., Tan, E.K., 2020. Parkinson's disease: Etiopathogenesis and treatment. J. Neurol. Neurosurg. Psychiatry. https://doi.org/10.1136/jnnp-2019-322338.
Jin, F., Wu, Q., Lu, Y.-F., Gong, Q.-H., Shi, J.-S., 2008. Neuroprotective effect of resveratrol on 6-OHDA-induced Parkinson's disease in rats. Eur. J. Pharmacol. 600, 78–82. https://doi.org/10.1016/j.ejphar.2008.10.005.
Jones, D.N., Raghanti, M.A., 2021. The role of monoamine oxidase enzymes in the pathophysiology of neurological disorders. J. Chem. Neuroanat. 114, 101957. https://doi.org/10.1016/j.jchemneu.2021.101957.
Josiah, S.S., Famusiwa, C.D., Crown, O.O., Lawal, A.O., Olaleye, M.T., Akindahunsi, A.A., Akinmoladun, A.C., 2022. Neuroprotective effects of catechin and quercetin in experimental Parkinsonism through modulation of dopamine metabolism and expression of IL-1β, TNF-α, NF-κB, IκKB, and p53 genes in male Wistar rats. Neurotoxicology 90, 158–171. https://doi.org/10.1016/j.neuro.2022.03.004.
Jung, S.Y., Chun, S., Cho, E.B., Han, K., Yoo, J., Yeo, Y., Yoo, J.E., Jeong, S.M., Min, J.-H., Shin, D.W., 2023. Changes in smoking, alcohol consumption, and the risk of Parkinson's disease. Front. Aging Neurosci. 15. https://doi.org/10.3389/fnagi.2023.1223310.
Kai, J.-Y., Zhou, M., Li, D.-L., Zhu, K.-Y., Wu, Q., Zhang, X.-F., Pan, C.-W., 2024. Smoking, dietary factors and major age-related eye disorders: an umbrella review of systematic reviews and meta-analyses. Br. J. Ophthalmol. 108, 51–57. https://doi.org/10.1136/bjo-2022-322325.
Kalia, L.V., Brotchie, J.M., Fox, S.H., 2013. Novel nondopaminergic targets for motor features of Parkinson's disease: review of recent trials. Mov. Disord. 28, 131–144. https://doi.org/10.1002/mds.25273.
Kalthoff, S., Paulusch, S., Rupp, A., Holdenrieder, S., Hartmann, G., Strassburg, C.P., 2020. The coffee ingredients caffeic acid and caffeic acid phenylethyl ester protect against irinotecan-induced leukopenia and oxidative stress response. Br. J. Pharmacol. 177, 4193–4208. https://doi.org/10.1111/bph.15162.
Kang, K.S., Yamabe, N., Wen, Y., Fukui, M., Zhu, B.T., 2013. Beneficial effects of natural phenolics on levodopa methylation and oxidative neurodegeneration. Brain Res. 1497, 1–14. https://doi.org/10.1016/j.brainres.2012.11.043.
Kardani, J., Roy, I., 2015. Understanding caffeine's role in attenuating the toxicity of α-synuclein aggregates: Implications for risk of Parkinson's disease. ACS Chem. Neurosci. 6, 1613–1625. https://doi.org/10.1021/acschemneuro.5b00158.
Kardani, J., Sethi, R., Roy, I., 2017. Nicotine slows down oligomerisation of α-synuclein and ameliorates cytotoxicity in a yeast model of Parkinson's disease. Biochim. Biophys. Acta - Mol. Basis Dis. 1863, 1454–1463. https://doi.org/10.1016/j.bbadis.2017.02.002.
Khadrawy, Y.A., Salem, A.M., El-Shamy, K.A., Ahmed, E.K., Fadl, N.N., Hosny, E.N., 2017. Neuroprotective and therapeutic effect of caffeine on the rat model of Parkinson's disease induced by rotenone. J. Diet. Suppl. 14, 553–572. https://doi.org/10.1080/19390211.2016.1275916.
Khalil, A.A., Steyn, S., Castagnoli Jr, N., 2000. Isolation and characterization of a monoamine oxidase inhibitor from tobacco leaves. Chem. Res. Toxicol. 13, 31–35. https://doi.org/10.1021/tx990146f.
Khalil, A.A., Davies, B., Castagnoli Jr, N., 2006. Isolation and characterization of a monoamine oxidase B selective inhibitor from tobacco smoke. Biorg. Med. Chem. 14, 3392–3398. https://doi.org/10.1016/j.bmc.2005.12.057.
Kia, D.A., Noyce, A.J., White, J., Speed, D., Nicolas, A., collaborators, I., Burgess, S., Lawlor, D.A., Davey Smith, G., Singleton, A., 2018. Mendelian randomization study shows no causal relationship between circulating urate levels and Parkinson's disease. Ann. Neurol. 84, 191–199. https://doi.org/10.1002/ana.25294.
Kieburtz, K., Wunderle, K.B., 2013. Parkinson's disease: evidence for environmental risk factors. Mov. Disord. 28, 8–13. https://doi.org/10.1002/mds.25150.
Kim, H.D., Jeong, K.H., Jung, U.J., Kim, S.R., 2016. Naringin treatment induces neuroprotective effects in a mouse model of Parkinson's disease in vivo, but not enough to restore the lesioned dopaminergic system. J. Nutr. Biochem. 28, 140–146. https://doi.org/10.1016/j.jnutbio.2015.10.013.
Kim, J.H., Kim, G.H., Hwang, K.H., 2012. Monoamine oxidase and dopamine β-hydroxylase inhibitors from the fruits of Gardenia jasminoides. Biomol. Ther. (Seoul.) 20, 214. https://doi.org/10.4062/biomolther.2012.20.2.214.
Kim, J.Y., Jung, K.S., Jeong, H.G., 2004. Suppressive effects of the kahweol and cafestol on cyclooxygenase-2 expression in macrophages. FEBS Lett. 569, 321–326. https://doi.org/10.1016/j.febslet.2004.05.070.
Kiss, L.E., Soares-da-Silva, P., 2014. Medicinal chemistry of catechol O-methyltransferase (COMT) inhibitors and their therapeutic utility. J. Med. Chem. 57, 8692–8717. https://doi.org/10.1021/jm500572b.
Kobylecki, C.J., Nordestgaard, B.G., Afzal, S., 2018. Plasma urate and risk of Parkinson's disease: a Mendelian randomization study. Ann. Neurol. 84, 178–190. https://doi.org/10.1002/ana.25292.
Koh, W., Lee, C.J., 2024. Diagnostic and therapeutic potential of tonic gamma-aminobutyric acid from reactive astrocytes in brain diseases. Clin. Transl. Med. 14. https://doi.org/10.1002/ctm2.1642.
Król, K., Gantner, M., Tatarak, A., Hallmann, E., 2020. The content of polyphenols in coffee beans as roasting, origin and storage effect. Eur. Food Res. Technol. 246, 33–39. https://doi.org/10.1007/s00217-019-03388-9.
Kumar, H., Kim, I.-S., More, S.V., Kim, B.-W., Choi, D.-K., 2014. Natural product-derived pharmacological modulators of Nrf2/ARE pathway for chronic diseases. Nat. Prod. Rep. 31, 109–139. https://doi.org/10.1039/C3NP70065H.

Larit, F., Elokely, K.M., Chaurasiya, N.D., Benyahia, S., Nael, M.A., León, F., Abu-Darwish, M.S., Efferth, T., Wang, Y.-H., Belouahem-Abed, D., 2018. Inhibition of human monoamine oxidase A and B by flavonoids isolated from two Algerian medicinal plants. Phytomedicine 40, 27–36. https://doi.org/10.1016/j.phymed.2017.12.032.

Lee, K.-W., Chen, W., Junn, E., Im, J.-Y., Grosso, H., Sonsalla, P.K., Feng, X., Ray, N., Fernandez, J.R., Chao, Y., 2011. Enhanced phosphatase activity attenuates α-synucleinopathy in a mouse model. J. Neurosci. 31, 6963–6971. https://doi.org/10.1523/JNEUROSCI.6513-10.2011.

Lee, K.-W., Im, J.-Y., Woo, J.-M., Grosso, H., Kim, Y.-S., Cristovao, A.C., Sonsalla, P.K., Schuster, D.S., Jalbut, M.M., Fernandez, J.R., 2013. Neuroprotective and anti-inflammatory properties of a coffee component in the MPTP model of Parkinson's disease. Neurotherapeutics 10, 143–153. https://doi.org/10.1007/s13311-012-0165-2.

Lee, M.-H., Lin, R.-D., Shen, L.-Y., Yang, L.-L., Yen, K.-Y., Hou, W.-C., 2001. Monoamine oxidase B and free radical scavenging activities of natural flavonoids in Melastoma candidum D. Don. J. Agric. Food Chem. 49, 5551–5555. https://doi.org/10.1021/jf010622j.

Lee, S.H., Yun, Y., Kim, S.J., Lee, E.-J., Chang, Y., Ryu, S., Shin, H., Kim, H.-L., Kim, H.-N., Lee, J.H., 2018. Association between cigarette smoking status and composition of gut microbiota: population-based cross-sectional study. J. Clin. Med. 7, 282. https://doi.org/10.3390/jcm7090282.

Lee, Y., Shin, D.-h, Kim, J.-H., Hong, S., Choi, D., Kim, Y.-J., Kwak, M.-K., Jung, Y., 2010. Caffeic acid phenethyl ester-mediated Nrf2 activation and IκB kinase inhibition are involved in NFκB inhibitory effect: structural analysis for NFκB inhibition. Eur. J. Pharmacol. 643, 21–28. https://doi.org/10.1016/j.ejphar.2010.06.016.

Li, P., Song, C., 2022. Potential treatment of Parkinson's disease with omega-3 polyunsaturated fatty acids. Nutr. Neurosci. 25, 180–191. https://doi.org/10.1080/1028415x.2020.1735143.

Li, Q., Xing, S., Chen, Y., Liao, Q., Li, Q., Liu, Y., He, S., Feng, F., Chen, Y., Zhang, J., 2020. Reasonably activating Nrf2: A long-term, effective and controllable strategy for neurodegenerative diseases. Eur. J. Med. Chem. 185, 111862. https://doi.org/10.1016/j.ejmech.2019.111862.

Li, S., Pu, X.-P., 2011. Neuroprotective effect of kaempferol against a 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine-induced mouse model of Parkinson's disease. Biol. Pharm. Bull. 34, 1291–1296. https://doi.org/10.1248/bpb.34.1291.

Li, X., Li, W., Liu, G., Shen, X., Tang, Y., 2015. Association between cigarette smoking and Parkinson's disease: a meta-analysis. Arch. Gerontol. Geriatr. 61, 510–516. https://doi.org/10.1016/j.archger.2015.08.004.

Liang, Y., Dai, X., Cao, Y., Wang, X., Lu, J., Xie, L., Liu, K., Li, X., 2023. The neuroprotective and antidiabetic effects of trigonelline: A review of signaling pathways and molecular mechanisms. Biochimie 206, 93–104. https://doi.org/10.1016/j.biochi.2022.10.009.

Liu, L.-l, Han, Y., Zhang, Z.-j, Wang, Y.-q, Hu, Y.-w, Kaznacheyeva, E., Ding, J.-q, Guo, D.-k, Wang, G.-h, Li, B., 2023. Loss of DJ-1 function contributes to Parkinson's disease pathogenesis in mice via RACK1-mediated PKC activation and MAO-B upregulation. Acta Pharmacol. Sin. 44, 1948–1961. https://doi.org/10.1038/s41401-023-01104-8.

Liu, R., Guo, X., Park, Y., Huang, X., Sinha, R., Freedman, N.D., Hollenbeck, A.R., Blair, A., Chen, H., 2012. Caffeine intake, smoking, and risk of Parkinson disease in men and women. Am. J. Epidemiol. 175, 1200–1207. https://doi.org/10.1093/aje/kwr451.

Lubomski, M., Tan, A.H., Lim, S.-Y., Holmes, A.J., Davis, R.L., Sue, C.M., 2020. Parkinson's disease and the gastrointestinal microbiome. J. Neurol. 267, 2507–2523. https://doi.org/10.1007/s00415-019-09320-1.

Ma, Z.-C., Hong, Q., Wang, Y.-G., Tan, H.-L., Xiao, C.-R., Liang, Q.-D., Zhang, B.-L., Gao, Y., 2010. Ferulic acid protects human umbilical vein endothelial cells from radiation induced oxidative stress by phosphatidylinositol 3-kinase and extracellular signal-regulated kinase pathways. Biol. Pharm. Bull. 33, 29–34. https://doi.org/10.1248/bpb.33.29.

Mani, S., Sekar, S., Barathidasan, R., Manivasagam, T., Thenmozhi, A.J., Sevanan, M., Chidambaram, S.B., Essa, M.M., Guillemin, G.J., Sakharkar, M.K., 2018. Naringenin decreases α-synuclein expression and neuroinflammation in MPTP-induced Parkinson's disease model in mice. Neurotox. Res. 33, 656–670. https://doi.org/10.1007/s12640-018-9869-3.

Mannino, G., Kunz, R., Maffei, M.E., 2023. Discrimination of green coffee (Coffea arabica and Coffea canephora) of different geographical origin based on antioxidant activity, high-throughput metabolomics, and DNA RFLP fingerprinting. Antioxidants 12, 1135. https://doi.org/10.3390/antiox12051135.

Männistö, P.T., Kaakkola, S., 1999. Catechol-O-methyltransferase (COMT): biochemistry, molecular biology, pharmacology, and clinical efficacy of the new selective COMT inhibitors. Pharmacol. Rev. 51, 593–628.

McMahon, M., Itoh, K., Yamamoto, M., Chanas, S.A., Henderson, C.J., McLellan, L.I., Wolf, C.R., Cavin, C., Hayes, J.D., 2001. The Cap 'n'Collar basic leucine zipper transcription factor Nrf2 (NF-E2 p45-related factor 2) controls both constitutive and inducible expression of intestinal detoxification and glutathione biosynthetic enzymes. Cancer Res 61, 3299–3307.

de Mello Andrade, J.M., dos Santos Passos, C., Rubio, M.A.K., Mendonça, J.N., Lopes, N. P., Henriques, A.T., 2016. Combining in vitro and in silico approaches to evaluate the multifunctional profile of rosmarinic acid from Blechnum brasiliense on targets related to neurodegeneration. Chem. Biol. Inter. 254, 135–145. https://doi.org/10.1016/j.cbi.2016.06.005.

Meng, X., Munishkina, L.A., Fink, A.L., Uversky, V.N., 2009. Molecular mechanisms underlying the flavonoid-induced inhibition of α-synuclein fibrillation. Biochemistry 48, 8206–8224. https://doi.org/10.1021/bi900506b.

Meyer, J.H., Braga, J., 2022. Development and clinical application of positron emission tomography imaging agents for monoamine oxidase B. Front. Neurosci. 15, 773404. https://doi.org/10.3389/fnins.2021.773404.

Miralles, A., Esteban, S., Sastre-Coll, A., Moranta, D., Asensio, V.J., García-Sevilla, J.A., 2005. High-affinity binding of β-carbolines to imidazoline I2B receptors and MAO-A in rat tissues: norharman blocks the effect of morphine withdrawal on DOPA/noradrenaline synthesis in the brain. Eur. J. Pharmacol. 518, 234–242. https://doi.org/10.1016/j.ejphar.2005.06.023.

Mirzaie, M., Khalili, M., Kiasalari, Z., Roghani, M., 2016. Neuroprotective and antiapoptotic potential of trigonelline in a striatal 6-hydroxydopamine rat model of Parkinson's disease. Neurophysiology 48, 176–183. https://doi.org/10.1007/s11062-016-9586-6.

Mittal, S., Bjørnevik, K., Im, D.S., Flierl, A., Dong, X., Locascio, J.J., Abo, K.M., Long, E., Jin, M., Xu, B., 2017. β2-Adrenoreceptor is a regulator of the α-synuclein gene driving risk of Parkinson's disease. Science 357, 891–898. https://doi.org/10.1126/science.aaf3934.

Moreira Vasconcelos, C.F., da Cunha Ferreira, N.M., Hardy Lima Pontes, N., de Sousa dos Reis, T.D., Basto Souza, R., Aragão Catunda Junior, F.E., Vasconcelos Aguiar, L.M., Maranguape Silva da Cunha, R., 2020. Eugenol and its association with levodopa in 6-hydroxydopamine-induced hemiparkinsonian rats: Behavioural and neurochemical alterations. Basic Clin. Pharmacol. Toxicol. 127, 287–302. https://doi.org/10.1111/bcpt.13425.

Morris, H.R., Spillantini, M.G., Sue, C.M., Williams-Gray, C.H., 2024. The pathogenesis of Parkinson's disease. Lancet 403, 293–304. https://doi.org/10.1016/S0140-6736(23)01478-2.

Moshahid Khan, M., Raza, S.S., Javed, H., Ahmad, A., Khan, A., Islam, F., Safhi, M.M., Islam, F., 2012. Rutin protects dopaminergic neurons from oxidative stress in an animal model of Parkinson's disease. Neurotox. Res. 22, 1–15. https://doi.org/10.1007/s12640-011-9295-2.

Mostert, S., Petzer, A., Petzer, J.P., 2017. The evaluation of 1,4-benzoquinones as inhibitors of human monoamine oxidase. Eur. J. Med Chem. 135, 196–203. https://doi.org/10.1016/j.ejmech.2017.04.055.

Murata, T., Tago, K., Miyata, K., Moriwaki, Y., Misawa, H., Kobata, K., Nakazawa, Y., Tamura, H., Funakoshi-Tago, M., 2023. Suppression of neuroinflammation by coffee component pyrocatechol via inhibition of NF-κB in microglia. Int. J. Mol. Sci. 25, 316. https://doi.org/10.3390/ijms25010316.

Nagarajan, S., Chellappan, D.R., Chinnaswamy, P., Thulasingam, S., 2015. Ferulic acid pretreatment mitigates MPTP-induced motor impairment and histopathological alterations in C57BL/6 mice. Pharm. Biol. 53, 1591–1601. https://doi.org/10.3109/13880209.2014.993041.

Nam, M.-H., Sa, M., Ju, Y.H., Park, M.G., Lee, C.J., 2022. Revisiting the role of astrocytic MAOB in Parkinson's disease. Int. J. Mol. Sci. 23, 4453. https://doi.org/10.3390/ijms23084453.

Naoi, M., Nagatsu, T., 1987. Quinoline and quninaldine as naturally-occurring inhibitors specific for type-a monoamine-oxidase. Life Sci. 40, 1075–1082. https://doi.org/10.1016/0024-3205(87)90570-4.

Nicholatos, J.W., Francisco, A.B., Bender, C.A., Yeh, T., Lugay, F.J., Salazar, J.E., Glorioso, C., Libert, S., 2018. Nicotine promotes neuron survival and partially protects from Parkinson's disease by suppressing SIRT6. Acta Neuropathol. Commun. 6, 1–18. https://doi.org/10.1186/s40478-018-0625-y.

Obata, T., Yamashita, H., Egashira, T., Yamanaka, Y., 1989. Effect of diethylnitrosamine on monoamine oxidase in rat liver. Jpn. J. Pharmacol. 49, 151–153. https://doi.org/10.1254/jjp.49.151.

Oertel, W.H., Müller, H.-H., Unger, M.M., Schade-Brittinger, C., Balthasar, K., Articus, K., Brinkman, M., Venuto, C., Tracik, F., Eberling, J., 2023. Transdermal nicotine treatment and progression of early Parkinson's disease. NEJM Evid. 2, EVIDoa2200311. https://doi.org/10.1056/EVIDoa2200311.

Oh, Y.S., Kim, J.S., Yoo, S.W., Hwang, E.J., Lyoo, C., Lee, K.S., 2020. Gender difference in the effect of uric acid on striatal dopamine in early Parkinson's disease. Eur. J. Neurol. 27, 258–264. https://doi.org/10.1111/ene.14070.

Ojha, S., Javed, H., Azimullah, S., Abul Khair, S.B., Haque, M.E., 2015. Neuroprotective potential of ferulic acid in the rotenone model of Parkinson's disease. Drug Des. Devel. Ther. 5499–5510. https://doi.org/10.2147/DDDT.S90616.

Olanow, C.W., Factor, S.A., Espay, A.J., Hauser, R.A., Shill, H.A., Isaacson, S., Pahwa, R., Leinonen, M., Bhargava, P., Sciarappa, K., 2020. Apomorphine sublingual film for off episodes in Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 study. Lancet Neurol. 19, 135–144. https://doi.org/10.1016/S1474-4422(19)30396-5.

Olsen, H.T., Stafford, G.I., van Staden, J., Christensen, S.B., Jager, A.K., 2008. Isolation of the MAO-inhibitor naringenin from Mentha aquatica L. J. Ethnopharmacol. 117, 500–502. https://doi.org/10.1016/j.jep.2008.02.015.

Ono, K., Yamada, M., 2006. Antioxidant compounds have potent anti-fibrillogenic and fibril-destabilizing effects for α-synuclein fibrils in vitro. J. Neurochem 97, 105–115. https://doi.org/10.1111/j.1471-4159.2006.03707.x.

Ou, J., 2021. Incorporation of polyphenols in baked products. Adv. Food Nutr. Res. Elsevier, pp. 207–252.

Paillard, T., Rolland, Y., de Souto Barreto, P., 2015. Protective effects of physical exercise in Alzheimer's disease and Parkinson's disease: a narrative review. J. Clin. Neurol. 11, 212. https://doi.org/10.3988/jcn.2015.11.3.212.

Pan, X., Liu, X., Zhao, H., Wu, B., Liu, G., 2020. Antioxidant, anti-inflammatory and neuroprotective effect of kaempferol on rotenone-induced Parkinson's disease model of rats and SH-S5Y5 cells by preventing loss of tyrosine hydroxylase. J. Funct. Foods 74, 104140. https://doi.org/10.1016/j.jff.2020.104140.

Parkinson Study GroupSTEADY-PD III Investigators, 2020. Isradipine versus placebo in early Parkinson disease: a randomized trial. Ann. Intern. Med. 172, 591–598. https://doi.org/10.7326/M19-2534.

Patanavanich, R., Glantz, S.A., 2020. Smoking is associated with COVID-19 progression: a meta-analysis. Nicotine Tob. Res. 22, 1653–1656. https://doi.org/10.1093/ntr/ntaa082.
Peters, R., Poulter, R., Warner, J., Beckett, N., Burch, L., Bulpitt, C., 2008. Smoking, dementia and cognitive decline in the elderly, a systematic review. BMC Geriatr. 8, 1–7. https://doi.org/10.1186/1471-2318-8-36.
Petzer, A., Pienaar, A., Petzer, J.P., 2013. The interactions of caffeine with monoamine oxidase. Life Sci. 93, 283–287. https://doi.org/10.1016/j.lfs.2013.06.020.
Pires, A.O., Teixeira, F.G., Mendes-Pinheiro, B., Serra, S.C., Sousa, N., Salgado, A.J., 2017. Old and new challenges in Parkinson's disease therapeutics. Prog. Neurobiol. 156, 69–89. https://doi.org/10.1016/j.pneurobio.2017.04.006.
Postuma, R.B., Anang, J., Pelletier, A., Joseph, L., Moscovich, M., Grimes, D., Furtado, S., Munhoz, R.P., Appel-Cresswell, S., Moro, A., 2017. Caffeine as symptomatic treatment for Parkinson disease (Café-PD) A randomized trial. Neurology 89, 1795–1803. https://doi.org/10.1212/WNL.0000000000004568.
Quik, M., 2004. Smoking, nicotine and Parkinson's disease. Trends Neurosci. 27, 561–568. https://doi.org/10.1016/j.tins.2004.06.008.
Quik, M., Perez, X.A., Bordia, T., 2012. Nicotine as a potential neuroprotective agent for Parkinson's disease. Mov. Disord. 27, 947–957. https://doi.org/10.1002/mds.25028.
Rai, S.N., Singh, P., 2020. Advancement in the modelling and therapeutics of Parkinson's disease. J. Chem. Neuroanat. 104, 101752. https://doi.org/10.1016/j.jchemneu.2020.101752.
Ramakrishna, K., Nalla, L.V., Naresh, D., Venkateswarlu, K., Viswanadh, M.K., Nalluri, B. N., Chakravarthy, G., Duguluri, S., Singh, P., Rai, S.N., 2023. WNT-β catenin signaling as a potential therapeutic target for neurodegenerative diseases: current status and future perspective. Diseases 11, 89. https://doi.org/10.3390/diseases11030089.
Rane, A.R., Paithankar, H., Hosur, R.V., Choudhary, S., 2021. Modulation of α-synuclein fibrillation by plant metabolites, daidzein, fisetin and scopoletin under physiological conditions. Int. J. Biol. Macromol. 182, 1278–1291. https://doi.org/10.1016/j.ijbiomac.2021.05.071.
Regensburger, M., Ip, C.W., Kohl, Z., Schrader, C., Urban, P.P., Kassubek, J., Jost, W.H., 2023. Clinical benefit of MAO-B and COMT inhibition in Parkinson's disease: practical considerations. J. Neural Transm. 130, 847–861. https://doi.org/10.1007/s00702-023-02623-8.
Ren, Z.-x, Zhao, Y.-f, Cao, T., Zhen, X.-c, 2016. Dihydromyricetin protects neurons in an MPTP-induced model of Parkinson's disease by suppressing glycogen synthase kinase-3 beta activity. Acta Pharmacol. Sin. 37, 1315–1324. https://doi.org/10.1038/aps.2016.42.
Rodgman, A., Perfetti, T.A., 2013. The Chemical Components of Tobacco and Tobacco Smoke. CRC Press.
Rose, K.N., Schwarzschild, M.A., Gomperts, S.N., 2024. Clearing the Smoke: What Protects Smokers from Parkinson's Disease? Mov. Disord. 39, 267–272. https://doi.org/10.1002/mds.29707.
Ruan, S., Xie, J., Wang, L., Guo, L., Li, Y., Fan, W., Ji, R., Gong, Z., Xu, Y., Mao, J., 2023. Nicotine alleviates MPTP-induced nigrostriatal damage through modulation of JNK and ERK signaling pathways in the mice model of Parkinson's disease. Front. Pharmacol. 14, 1088957. https://doi.org/10.3389/fphar.2023.1088957.
Rubiolo, J.A., Mithieux, G., Vega, F.V., 2008. Resveratrol protects primary rat hepatocytes against oxidative stress damage:: Activation of the Nrf2 transcription factor and augmented activities of antioxidant enzymes. Eur. J. Pharmacol. 591, 66–72. https://doi.org/10.1016/j.ejphar.2008.06.067.
San Luciano, M., Tanner, C.M., Meng, C., Marras, C., Goldman, S.M., Lang, A.E., Tolosa, E., Schüle, B., Langston, J.W., Brice, A., 2020. Nonsteroidal anti-inflammatory use and LRRK2 Parkinson's disease penetrance. Mov. Disord. 35, 1755–1764. https://doi.org/10.1002/mds.28189.
Santin, Y., Resta, J., Parini, A., Mialet-Perez, J., 2021. Monoamine oxidases in age-associated diseases: New perspectives for old enzymes. Ageing Res. Rev. 66, 101256. https://doi.org/10.1016/j.arr.2021.101256.
Savelieff, M.G., Nam, G., Kang, J., Lee, H.J., Lee, M., Lim, M.H., 2018. Development of multifunctional molecules as potential therapeutic candidates for Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis in the last decade. Chem. Rev. 119, 1221–1322. https://doi.org/10.1021/acs.chemrev.8b00138.
Scheperjans, F., Pekkonen, E., Kaakkola, S., Auvinen, P., 2015. Linking smoking, coffee, urate, and Parkinson's disease–a role for gut microbiota? J. Park. Dis. 5, 255–262. https://doi.org/10.3233/JPD-150557.
Sell, L.B., Ramelow, C.C., Kohl, H.M., Hoffman, K., Bains, J.K., Doyle, W.J., Strawn, K.D., Hevrin, T., Kirby, T.O., Gibson, K.M., 2022. Farnesol induces protection against murine CNS inflammatory demyelination and modifies gut microbiome. Clin. Immunol. 235, 108766. https://doi.org/10.1016/j.clim.2021.108766.
Senger, D.R., Li, D., Jaminet, S.-C., Cao, S., 2016. Activation of the Nrf2 cell defense pathway by ancient foods: disease prevention by important molecules and microbes lost from the modern western diet. PLoS One 11, e0148042. https://doi.org/10.1371/journal.pone.0148042.
Shabab, T., Khanabdali, R., Moghadamtousi, S.Z., Kadir, H.A., Mohan, G., 2017. Neuroinflammation pathways: a general review. Int. J. Neurosci. 127, 624–633. https://doi.org/10.1080/00207454.2016.1212854.
Sharma, N., Soni, R., Sharma, M., Chatterjee, S., Parihar, N., Mukarram, M., Kale, R., Sayyed, A.A., Behera, S.K., Khairnar, A., 2022. Chlorogenic acid: a polyphenol from coffee rendered neuroprotection against rotenone-induced Parkinson's disease by GLP-1 secretion. Mol. Neurobiol. 59, 6834–6856. https://doi.org/10.1007/s12035-022-03005-z.
Shashikumar, S., Pradeep, H., Chinnu, S., Rajini, P., Rajanikant, G., 2015. Alpha-linolenic acid suppresses dopaminergic neurodegeneration induced by 6-OHDA in C. elegans. Physiol. Behav. 151, 563–569. https://doi.org/10.1016/j.physbeh.2015.08.025.
Shih, J.C., 2018. Monoamine oxidase isoenzymes: genes, functions and targets for behavior and cancer therapy. J. Neural Transm. 125, 1553–1566. https://doi.org/10.1007/s00702-018-1927-8.
da Silva, F.L., Cerqueira, E.C., de Freitas, M.S., Gonçalves, D.L., Costa, L.T., Follmer, C., 2013. Vitamins K interact with N-terminus α-synuclein and modulate the protein fibrillization in vitro. Exploring the interaction between quinones and α-synuclein. Neurochem. Int. 62, 103–112. https://doi.org/10.1016/j.neuint.2012.10.001.
Singh, A., Tripathi, P., Singh, S., 2021. Neuroinflammatory responses in Parkinson's disease: relevance of Ibuprofen in therapeutics. Inflammopharmacology 29, 5–14. https://doi.org/10.1007/s10787-020-00764-w.
Singh, S.S., Rai, S.N., Birla, H., Zahra, W., Kumar, G., Gedda, M.R., Tiwari, N., Patnaik, R., Singh, R.K., Singh, S.P., 2018. Effect of chlorogenic acid supplementation in MPTP-intoxicated mouse. Front. Pharmacol. 9, 757. https://doi.org/10.3389/fphar.2018.00757.
Smith, C.J., Hansch, C., 2000. The relative toxicity of compounds in mainstream cigarette smoke condensate. Food Chem. Toxicol. 38, 637–646. https://doi.org/10.1016/S0278-6915(00)00051-X.
Socała, K., Szopa, A., Serefko, A., Poleszak, E., Wlaź, P., 2020. Neuroprotective effects of coffee bioactive compounds: a review. Int. J. Mol. Sci. 22, 107. https://doi.org/10.3390/ijms22010107.
Soner, B.C., Acikgoz, E., Inan, S.Y., Ayla, S., Sahin, A.S., Oktem, G., 2021. Neuroprotective effect of intrastriatal caffeic acid phenethyl ester treatment in 6-OH dopamine model of Parkinson's Disease in rats. Park. 'S. Dis. 2021, 5553480. https://doi.org/10.1155/2021/5553480.
Spiller, M.A., 2019. The chemical components of coffee. Caffeine 97–161.
Sriraksa, N., Wattanathorn, J., Muchimapura, S., Tiamkao, S., Brown, K., Chaisiwamongkol, K., 2012. Cognitive-enhancing effect of quercetin in a rat model of Parkinson's disease induced by 6-hydroxydopamine. Evid. Based Complement. Altern. Med. 2012. https://doi.org/10.1155/2012/823206.
Subramaniam, S.R., Ellis, E.M., 2013. Neuroprotective effects of umbelliferone and esculetin in a mouse model of Parkinson's disease. J. Neurosci. Res. 91, 453–461. https://doi.org/10.1002/jnr.23164.
Surmeier, D.J., 2007. Calcium, ageing, and neuronal vulnerability in Parkinson's disease. Lancet Neurol. 6, 933–938. https://doi.org/10.1016/S1474-4422(07)70246-6.
Tajik, N., Tajik, M., Mack, I., Enck, P., 2017. The potential effects of chlorogenic acid, the main phenolic components in coffee, on health: a comprehensive review of the literature. Eur. J. Nutr. 56, 2215–2244. https://doi.org/10.1007/s00394-017-1379-1.
Takao, K., Toda, K., Saito, T., Sugita, Y., 2017. Synthesis of amide and ester derivatives of cinnamic acid and its analogs: evaluation of their free radical scavenging and monoamine oxidase and cholinesterase inhibitory activities. Chem. Pharm. Bull. 65, 1020–1027. https://doi.org/10.1248/cpb.c17-00416.
Talhout, R., Opperhuizen, A., van Amsterdam, J.G., 2007. Role of acetaldehyde in tobacco smoke addiction. Eur. Neuropsychopharmacol. 17, 627–636. https://doi.org/10.1016/j.euroneuro.2007.02.013.
Tan, Y.-Y., Jenner, P., Chen, S.-D., 2022. Monoamine oxidase-B inhibitors for the treatment of Parkinson's disease: past, present, and future. J. Park. Dis. 12, 477–493. https://doi.org/10.3233/JPD-212976.
Tang, Y., Le, W., 2016. Differential roles of M1 and M2 microglia in neurodegenerative diseases. Mol. Neurobiol. 53, 1181–1194. https://doi.org/10.1007/s12035-014-9070-5.
Tansey, M.G., Wallings, R.L., Houser, M.C., Herrick, M.K., Keating, C.E., Joers, V., 2022. Inflammation and immune dysfunction in Parkinson disease. Nat. Rev. Immunol. 22, 657–673. https://doi.org/10.1038/s41577-022-00684-6.
Tao, G., Irie, Y., Li, D.J., Keung, W.M., 2005. Eugenol and its structural analogs inhibit monoamine oxidase A and exhibit antidepressant-like activity. Bioorg. Med Chem. 13, 4777–4788. https://doi.org/10.1016/j.bmc.2005.04.081.
Teraoka, M., Nakaso, K., Kusumoto, C., Katano, S., Tajima, N., Yamashita, A., Zushi, T., Ito, S., Matsura, T., 2012. Cytoprotective effect of chlorogenic acid against α-synuclein-related toxicity in catecholaminergic PC12 cells. J. Clin. Biochem. Nutr. 51, 122–127. https://doi.org/10.3164/jcbn.D-11-00030.
Treur, J.L., Demontis, D., Smith, G.D., Sallis, H., Richardson, T.G., Wiers, R.W., Børglum, A.D., Verweij, K.J., Munafò, M.R., 2021. Investigating causality between liability to ADHD and substance use, and liability to substance use and ADHD risk, using Mendelian randomization. Addict. Biol. 26, e12849. https://doi.org/10.1111/adb.12849.
Trinh, K., Andrews, L., Krause, J., Hanak, T., Lee, D., Gelb, M., Pallanck, L., 2010. Decaffeinated coffee and nicotine-free tobacco provide neuroprotection in Drosophila models of Parkinson's disease through an NRF2-dependent mechanism. J. Neurosci. 30, 5525–5532. https://doi.org/10.1523/JNEUROSCI.4777-09.2010.
Tsai, S.-j, Chao, C.-y, Yin, M.-c, 2011. Preventive and therapeutic effects of caffeic acid against inflammatory injury in striatum of MPTP-treated mice. Eur. J. Pharmacol. 670, 441–447. https://doi.org/10.1016/j.ejphar.2011.09.171.
Tsuang, D., Larson, E.B., Li, G., Shofer, J.B., Montine, K.S., Thompson, M.L., Sonnen, J. A., Crane, P.K., Leverenz, J.B., Montine, T.J., 2010. Association between lifetime cigarette smoking and Lewy body accumulation. Brain Pathol. 20, 412–418. https://doi.org/10.1111/j.1750-3639.2009.00296.x.
Tunbridge, E.M., Harrison, P.J., Weinberger, D.R., 2006. Catechol-o-methyltransferase, cognition, and psychosis: Val158Met and beyond. Biol. Psychiatry 60, 141–151. https://doi.org/10.1016/j.biopsych.2005.10.024.
Varì, R., D'Archivio, M., Filesi, C., Carotenuto, S., Scazzocchio, B., Santangelo, C., Giovannini, C., Masella, R., 2011. Protocatechuic acid induces antioxidant/detoxifying enzyme expression through JNK-mediated Nrf2 activation in murine macrophages. J. Nutr. Biochem. 22, 409–417. https://doi.org/10.1016/j.jnutbio.2010.03.008.

Vermeulen, J.M., Wootton, R.E., Treur, J.L., Sallis, H.M., Jones, H.J., Zammit, S., van den Brink, W., Goodwin, G.M., De Haan, L., Munafò, M.R., 2021. Smoking and the risk for bipolar disorder: evidence from a bidirectional Mendelian randomisation study. Br. J. Psychiatry 218, 88–94. https://doi.org/10.1192/bjp.2019.202.

Vora, U., Vyas, V.K., Wal, P., Saxena, B., 2022. Effects of eugenol on the behavioral and pathological progression in the MPTP-induced Parkinson's disease mouse model. Drug Discov. Ther. 16, 154–163. https://doi.org/10.5582/ddt.2022.01026.

Walker, J., Rohm, B., Lang, R., Pariza, M., Hofmann, T., Somoza, V., 2012. Identification of coffee components that stimulate dopamine release from pheochromocytoma cells (PC-12). Food Chem. Toxicol. 50, 390–398. https://doi.org/10.1016/j.fct.2011.09.041.

Wang, L., Shen, X., Wu, Y., Zhang, D., 2016. Coffee and caffeine consumption and depression: A meta-analysis of observational studies. Aust. N. Z. J. Psychiatry 50, 228–242. https://doi.org/10.1177/0004867415603131.

Wang, Q., Liu, Y., Zhou, J., 2015a. Neuroinflammation in Parkinson's disease and its potential as therapeutic target. Transl. Neurodegener. 4, 1–9. https://doi.org/10.1186/s40035-015-0042-0.

Wang, Z.-H., Zhang, J.-L., Duan, Y.-L., Zhang, Q.-S., Li, G.-F., Zheng, D.-L., 2015b. MicroRNA-214 participates in the neuroprotective effect of Resveratrol via inhibiting α-synuclein expression in MPTP-induced Parkinson's disease mouse. Biomed. Pharmacother. 74, 252–256. https://doi.org/10.1016/j.biopha.2015.08.025.

Weisskopf, M., O'reilly, E., Chen, H., Schwarzschild, M., Ascherio, A., 2007. Plasma urate and risk of Parkinson's disease. Am. J. Epidemiol. 166, 561–567. https://doi.org/10.1093/aje/kwm127.

West, R., 2017. Tobacco smoking: Health impact, prevalence, correlates and interventions. Psychol. Health 32, 1018–1036. https://doi.org/10.1080/08870446.2017.1325890.

Wong, Y.C., Krainc, D., 2017. α-synuclein toxicity in neurodegeneration: mechanism and therapeutic strategies. Nat. Med. 23, 1–13. https://doi.org/10.1038/nm.4269.

Wootton, R.E., Richmond, R.C., Stuijfzand, B.G., Lawn, R.B., Sallis, H.M., Taylor, G.M., Hemani, G., Jones, H.J., Zammit, S., Smith, G.D., 2020. Evidence for causal effects of lifetime smoking on risk for depression and schizophrenia: a Mendelian randomisation study. Psychol. Med. 50, 2435–2443. https://doi.org/10.1017/S0033291719002678.

World Health Organization, 2024. Parkinson disease: Fact sheets. ⟨https://www.who.int/news-room/fact-sheets/detail/parkinson-disease⟩ (accessed 23 Jul 2024).

Wu, H., Gu, J., Amrit, B., Nawaz, M.A., Barrow, C.J., Dunshea, F.R., Suleria, H.A., 2022. Effect of processing on bioaccessibility and bioavailability of bioactive compounds in coffee beans. Food Biosci. 46, 101373. https://doi.org/10.1016/j.fbio.2021.101373.

Xie, M.G., Fei, Y.Q., Wang, Y., Wang, W.Y., Wang, Z., 2021. Chlorogenic acid alleviates colon mucosal damage induced by a high-fat diet via gut microflora adjustment to increase short-chain fatty acid accumulation in rats. Oxid. Med. Cell. Longev. 2021, 3456542. https://doi.org/10.1155/2021/3456542.

Yalcin, D., Bayraktar, O., 2010. Inhibition of catechol-O-methyltransferase (COMT) by some plant-derived alkaloids and phenolics. J. Mol. Catal. B: Enzym. 64, 162–166. https://doi.org/10.1016/j.molcatb.2009.04.014.

Yan, N., Du, Y., Liu, X., Zhang, H., Liu, Y., Zhang, P., Gong, D., Zhang, Z., 2016. Chemical structures, biosynthesis, bioactivities, biocatalysis and semisynthesis of tobacco cembranoids: An overview. Ind. Crops Prod. 83, 66–80. https://doi.org/10.1016/j.indcrop.2015.12.031.

Yan, R., Zhang, J., Park, H.-J., Park, E.S., Oh, S., Zheng, H., Junn, E., Voronkov, M., Stock, J.B., Mouradian, M.M., 2018. Synergistic neuroprotection by coffee components eicosanoyl-5-hydroxytryptamide and caffeine in models of Parkinson's disease and DLB. Proc. Natl. Acad. Sci. 115, E12053–E12062. https://doi.org/10.1073/pnas.1813365115.

Yáñez, M., Fraiz, N., Cano, E., Orallo, F., 2006. Inhibitory effects of cis-and trans-resveratrol on noradrenaline and 5-hydroxytryptamine uptake and on monoamine oxidase activity. Biochem. Biophys. Res. Commun. 344, 688–695. https://doi.org/10.1016/j.bbrc.2006.03.190.

Yoon, S.Y., Park, Y.H., Lee, S.C., Suh, J.H., Yang, S.N., Kang, D.R., Kim, Y.W., 2023. Association between smoking and all-cause mortality in Parkinson's disease. NPJ. Park. Dis. 9, 59. https://doi.org/10.1038/s41531-023-00486-0.

Youdim, M.B., Bakhle, Y., 2006. Monoamine oxidase: isoforms and inhibitors in Parkinson's disease and depressive illness. Br. J. Pharmacol. 147, S287–S296. https://doi.org/10.1038/sj.bjp.0706464.

Zaitone, S.A., Ahmed, E., Elsherbiny, N.M., Mehanna, E.T., El-Kherbetawy, M.K., ElSayed, M.H., Alshareef, D.M., Moustafa, Y.M., 2019. Caffeic acid improves locomotor activity and lessens inflammatory burden in a mouse model of rotenone-induced nigral neurodegeneration: Relevance to Parkinson's disease therapy. Pharmacol. Rep. 71, 32–41. https://doi.org/10.1016/j.pharep.2018.08.004.

Zeng, H., Liu, C., Wan, L., Peng, L., Wen, S., Fang, W., Chen, H., Wang, K., Yang, X., Huang, Ja, 2024. (−)-Epicatechin ameliorates type 2 diabetes mellitus by reshaping the gut microbiota and Gut–Liver axis in GK rats. Food Chem. 447, 138916. https://doi.org/10.1016/j.foodchem.2024.138916.

Zhang, L.-f, Yu, X.-l, Ji, M., Liu, S.-y, Wu, X.-l, Wang, Y.-j, Liu, R.-t, 2018. Resveratrol alleviates motor and cognitive deficits and neuropathology in the A53T α-synuclein mouse model of Parkinson's disease. Food Funct. 9, 6414–6426. https://doi.org/10.1039/C8FO00964C.

Zhang, Q.-S., Wang, Z.-H., Zhang, J.-L., Duan, Y.-L., Li, G.-F., Zheng, D.-L., 2016. Beta-asarone protects against MPTP-induced Parkinson's disease via regulating long non-coding RNA MALAT1 and inhibiting α-synuclein protein expression. Biomed. Pharmacother. 83, 153–159. https://doi.org/10.1016/j.biopha.2016.06.017.

Zhang, Y., Yang, H., Li, S., Cao, Z., Li, W.-D., Yan, T., Wang, Y., 2022. Association of coffee and genetic risk with incident dementia in middle-aged and elderly adults. Nutr. Neurosci. 25, 2359–2368. https://doi.org/10.1080/1028415X.2021.1966868.

Zhang, Z., Hamada, H., Gerk, P.M., 2019. Selectivity of dietary phenolics for inhibition of human monoamine oxidases A and B. Biomed. Res Int 2019, 8361858. https://doi.org/10.1155/2019/8361858.

Zhao, D.-F., Fan, Y.-F., Yu, H.-N., Hou, F.-b, Xiang, Y.-W., Wang, P., Ge, G.-B., Yang, L., Xu, J.-G., 2021. Discovery and characterization of flavonoids in vine tea as catechol-O-methyltransferase inhibitors. Fitoterapia 152, 104913. https://doi.org/10.1016/j.fitote.2021.104913.

Zhu, B.T., Wang, P., Nagai, M., Wen, Y., Bai, H.-W., 2009. Inhibition of human catechol-O-methyltransferase (COMT)-mediated O-methylation of catechol estrogens by major polyphenolic components present in coffee. J. Steroid Biochem. Mol. Biol. 113, 65–74. https://doi.org/10.1016/j.jsbmb.2008.11.011.

Zhu, M., Liu, X., Ye, Y., Yan, X., Cheng, Y., Zhao, L., Chen, F., Ling, Z., 2022. Gut microbiota: a novel therapeutic target for Parkinson's disease. Front. Immunol. 13, 937555. https://doi.org/10.3389/fimmu.2022.937555.

Zhuang, P., Shou, Q., Wang, W., He, L., Wang, J., Chen, J., Zhang, Y., Jiao, J., 2018. Essential fatty acids linoleic acid and α-linolenic acid sex-dependently regulate glucose homeostasis in obesity. Mol. Nutr. Food Res. 62, 1800448. https://doi.org/10.1002/mnfr.201800448.