Review

From Clinical to Basic Research: The Neuroprotective Effects and Mechanisms of Caffeine

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Abstract: Caffeine is the most widely used psychoactive substance in the world, is present in various beverages such as coffee, tea, and energy drinks. Its basic chemical structure contains methylxanthine active components. As a non-selective central adenosine receptor antagonist, caffeine exerts a broad range of pharmacological effects, including antioxidant, anti-inflammatory, and neuroprotective functions. Epidemiological studies and clinical reports suggest that caffeine consumption is closely associated with a reduced risk of neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, and dementia. Additionally, caffeine has shown potential benefits in regulating cognitive function, improving depressive symptoms, and reducing the risk of stroke. Although the neuroprotective mechanisms of caffeine remain unclear, current research has revealed that it exerts its effects through multiple signaling pathways, including the inhibition of adenosine A_{2A} receptors, the suppression of neuroinflammation, and the modulation of synaptic plasticity. This paper discusses the recent advancements in research on the neuroprotective effects of caffeine and explores its potential mechanisms and applications in Alzheimer's disease, Parkinson's disease, stroke, and depression.

Keywords: caffeine; Alzheimer's disease; Parkinson's disease; stroke; depression

1. Introduction

Caffeine is the most popular and widely consumed psychoactive substance globally. Commonly found in foods such as coffee, tea, and chocolate, and is also frequently added to various foods and beverages, including sodas and energy drinks, to enhance alertness and improve work efficiency. In the United States, 85% of adults consume caffeine daily, with an average intake of 135 milligrams per day [1]. Caffeine has been extensively studied and proven to have potential protective effects against various diseases [2]. Clinically, it is primarily used for the treatment of apnea in premature infants [3] and pain management [4]. Recent studies suggests that caffeine can reduce the risk of coronary heart disease [5], cancer [6], type 2 diabetes [7], cirrhosis and hepatocellular carcinoma [8,9], In the central nervous system, caffeine has demonstrated neuroprotective effects, including improvements in Alzheimer's disease(AD) [10,11], Parkinson's disease(PD) [12], stroke, depression and other neurodegenerative diseases [13]. Although caffeine is widely consumed worldwide, its potential therapeutic value in AD, PD, and other cognitive disorders has only recently been studied in detail. In this review, we aim to explore the neuroprotective effects of caffeine in neurodegenerative diseases such as AD, PD, stroke, and depression. We systematically reviewed the literature to highlight the mechanisms through which caffeine exerts its potential therapeutic effects. A comprehensive search was conducted using the following databases: PubMed, Scopus, Web of Science and Google Scholar. The search was performed using key terms such as 'Caffeine', 'Alzheimer's Disease', 'Parkinson's Disease', 'Depression', 'Stroke', 'Neuroprotection' and 'Central Nervous System Injury'. After screening abstracts and titles for relevance and removing duplicates, 97 studies were included in this review.

2. Metabolism of Caffeine

Caffeine, chemically known as 1,3,7-trimethylxanthine, is a commonly occurring xanthine alkaloid. Pure caffeine is a white, intensely bitter powder [14]. After oral ingestion of 5–8 mg/kg by adults, it is rapidly and completely absorbed in the gastrointestinal tract, reaching peak plasma concentrations within 30 to 60 min. The peak levels can persist for up to 120 min, and caffeine is quickly distributed throughout all body fluids (including

plasma, saliva, bile, cerebrospinal fluid, breast milk, semen, and umbilical cord blood) and all tissues and organs [15]. Caffeine's high lipid solubility enables it to cross the blood-brain barrier. The concentration of caffeine in the brain begins to increase within 5 min of ingestion, reaching nearly the same peak concentration as in plasma [16]. Caffeine is primarily metabolized in the liver, producing various purine and uric acid derivatives, including paraxanthine (about 80%), theophylline (approximately 7%), and theobromine (around 12%) [17]. These metabolites are further broken down into uric acid and are eventually excreted in the urine. "Several cytochrome P450 enzymes participate in caffeine metabolism, including CYP1A2, CYP1A1, CYP2E1, and CYP3A, but hepatic CYP1A2 is primarily responsible for its clearance. CYP1A2 exhibits genetic polymorphism, meaning individual variations or exposure to its inducers can influence caffeine metabolism [18,19].

3. Caffeine's Antagonistic Effect on Central Adenosine Receptors

Caffeine's primary pharmacological effects, such as mental stimulation, heightened bodily sensitivity, and its protective effects on cognitive function and neurological diseases, are primarily attributed to its non-specific antagonism of central adenosine receptors (AR) [20,21]. Adenosine, a precursor and metabolite of adenine nucleotides, is an important neuromodulator. ARs are a group of G protein-coupled receptors, which are classified into A_1R, $A_{2A}R$, $A_{2B}R$ and A_3R subtypes based on their affinity for adenosine [22]. Adenosine is widely present in the body, and its receptors are broadly expressed. By either activating or inhibiting adenylate cyclase, adenosine influences cyclic adenosine monophosphate (cAMP) levels and subsequent phosphorylation of related target proteins. However, the complex actions of adenosine signaling remain incompletely understood [23]. Caffeine's antagonistic effect occurs only when ARs are activated. A_3R has significantly lower affinity for caffeine compared to the other three subtypes, and $A_{2B}R$ is only activated under pathological conditions with high adenosine concentrations. Therefore, A_1R and $A_{2A}R$ are generally regarded as caffeine's primary targets within the central nervous system (CNS) [24]. The development of tolerance to long-term caffeine consumption is also thought to be related to A_1R [25]. Adenosine $A_{2A}R$ receptors are predominantly located in the striatum, hippocampus, and basal ganglia, and they act on neurons, astrocytes, and microglia to achieve neuroprotective effects through several mechanisms: (1). Involvement in the release of neurotransmitters such as glutamate [26], γ-aminobutyric acid (GABA) [27], acetylcholine, and dopamine [28]; (2). Regulation of synaptic plasticity [29]; (3). Participation in various activation signaling pathways that influence memory and cognitive function [30]; (4). Involvement in neuroinflammation, oxidative stress [31], and cell death.

4. Caffeine and Alzheimer's Disease (AD)

Dementia is characterized by acquired chronic or progressive cognitive impairment, with causes including AD, vascular dementia, Lewy body dementia, and mixed dementia, with AD accounting for over 70% of cases. Dietary alkaloids like caffeine have been shown to improve memory in behavioral models and modulate the mechanisms underlying the cognitive benefits, such as glucose metabolism, gut microbiota, vasculopathy, neuroinflammation, and oxidative stress [32]. A case-control study by Maia and de Mendonça found that increased caffeine consumption was associated with a 60% reduction in AD risk (the average caffeine intake of healthy individuals was 199–136 mg/day, compared to 74–98 mg/day for Alzheimer's patients) [33]. Prospective studies have reached similar conclusions. In the Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) study, Eskelinen and colleagues followed 1409 individuals aged 65–79 years (534 men and 875 women) for an average of 21 years. They found that moderate coffee drinkers (3–5 cups per day) had a significantly lower risk of developing AD and dementia compared to low coffee consumers (0 to 2 cups per day), with a risk reduction of 62–64% for AD and 65–70% for dementia. These findings suggest that coffee consumption in midlife may reduce the risk of developing dementia or AD later in life [34]. Several meta-analyses have been conducted, including a large-scale prospective study from France involving 4197 women and 2820 men aged 65 and older, examining the relationship between caffeine intake, cognitive ability, and dementia. The results showed no association between caffeine intake and cognitive decline in men. However, women with higher caffeine intake showed a smaller decline in visuospatial memory over four years compared to women with lower intake, with the protective effect of caffeine increasing with age [35]. A 2022 Mendelian randomization study, using data from the International Genomics of Alzheimer's Project (IGAP), reported a non-significant reduction in AD risk associated with genetically predicted high plasma caffeine levels [36]. In summary, numerous studies support the AD risk associated with genetically predicted high plasma caffeine levels beneficial role of caffeine in AD risk associated with genetically predicted high plasma caffeine levels AD.

AD is a neurodegenerative disease that predominantly affects the elderly, with pathological features, including β-amyloid (Aβ) deposition and neurofibrillary tangles formed by hyperphosphorylated Tau protein.

Research has demonstrated that cognitive impairment in AD patients is related to synaptic and axonal damage in the neocortex, basal forebrain, and limbic system [37]. This has also been confirmed in animal models, where intracerebroventricular injection of Aβ in mice induces cognitive impairment and neurotoxicity. Administration of caffeine or the selective $A_{2A}R$ antagonist SCH58261 both prevented Aβ-induced cognitive impairment [38]. Arendash's research demonstrated that, after long-term moderate caffeine consumption, the working memory of elderly APPsw mice with Alzheimer's disease significantly improved compared to the control group. Moreover, there was a marked reduction in Aβ deposition in the hippocampus and entorhinal cortex, accompanied by a decrease in soluble Aβ levels in the brain. Mechanistic studies have shown that caffeine's inhibitory effect on BACE1 involves the c-Raf/NF-κB pathway, and physiologically relevant concentrations of caffeine effectively reduce the levels of glycogen synthase kinase 3 in N2a neuroblastoma cells [39]. Giunta also confirmed that caffeine can prevent neuroblastoma cell death caused by the combined effects of Aβ and aluminum chloride ($AlCl_3$) through the non-selective blockade of A_1 and A_{2A} adenosine receptors [40]. The pathological hyperphosphorylation of Tau in Alzheimer's disease is crucial for cognitive decline. Laurent et al. found that long-term caffeine administration (0.3 g/L) could prevent the development of spatial memory deficits in THY-Tau22 AD mice [41]. The improvement in memory was associated with a reduction in hippocampal Tau phosphorylation and proteolytic fragments. Additionally, caffeine was observed to alleviate the upregulation of pro-inflammatory and oxidative stress markers (such as CD45, TLR2, CCL4, and TNF-α) in the hippocampus of AD mice.

Basic research suggests that oxidative stress may be a key factor in the pathogenesis of AD [42]. The brain contains a high concentration of polyunsaturated fatty acids, which are highly susceptible to attack by reactive oxygen species (ROS), leading to lipid peroxidation. Leite et al. investigated the effects of caffeine and SCH58261, a selective $A_{2A}R$ antagonist, on age-related memory impairment and oxidative stress in rats. The results showed that caffeine and SCH58261 treatment effectively reversed memory deficits associated with aging. Additionally, both treatments significantly reduced elevated levels of reactive oxygen and nitrogen species in the brains of aged rats. Furthermore, CAF and SCH58261 restored Na^+/K^+-ATPase activity, which was inhibited in the brains of aged rats [43]. Ullah et al. further highlighted the antioxidant-like properties of long-term caffeine consumption, demonstrating its protective effects against memory deficits, neuroinflammation, and neurodegeneration induced by D-galactose treatment. Potential mechanisms include: (1) Reversing oxidative stress by reducing 8-oxoguanine; (2) Reducing the phosphorylation of key stress response kinases, such as c-Jun N-terminal kinase (p-JNK); (3) Normalizing the levels of inflammatory mediators, such as cyclooxygenase-2 (COX-2), nitric oxide synthase-2 (NOS-2), tumor necrosis factor (TNF-α), and interleukin-1 (IL-1); (4) Preventing apoptosis and neurodegeneration (by reducing cytochrome C levels, lowering the Bax/Bcl2 ratio, and decreasing caspase-9, caspase-3, and PARP-1 levels); (5) Increasing the levels of presynaptic protein synaptophysin and postsynaptic density protein (PSD95) [44]. Prasanthi et al. also confirmed the protective effects of caffeine against oxidative stress and Alzheimer's-like conditions. They found that caffeine treatment could partially reverse sporadic AD induced by a high-cholesterol diet. Their study demonstrated that caffeine reduced ROS production, glutathione depletion, and Aβ synthesis, while increasing the concentration of adenosine A_1Rs in the hippocampus. In addition, increased cerebrospinal fluid (CSF) production is also considered a potential mechanism for caffeine's protective effects against AD. This study showed that long-term caffeine consumption increases CSF production and is associated with increased expression of Na^+/K^+-ATPase and improved cerebral blood flow [45]. This, in turn, promotes better clearance of Aβ.

In summary, caffeine exerts neuroprotective effects in AD mainly by inhibiting adenosine $A_{2A}R$, which helps reduce amyloid-beta (Aβ) accumulation and tau hyperphosphorylation. Additionally, it mitigates neuroinflammation and oxidative stress, thereby preserving synaptic plasticity and cognitive function. These mechanisms indicate that caffeine may have a potential role in delaying or preventing the progression of AD.

5. Caffeine and Parkinson's Disease (PD)

Since the 1970s, research on the relationship between PD risk and caffeine consumption has been continuous [46]. Studies have consistently shown a significant inverse relationship between caffeine intake and the risk of PD [47,48]. Studies have shown a linear relationship between tea and caffeine intake and overall PD risk, with the association being stronger in andropause than in postmenopausal women [49]. These findings suggest that caffeine consumption is associated with a lower risk of PD. The large 27-year prospective study using data on the incidence of PD from the Cancer Prevention Study II Nutrition Cohort (CPS II-Nutrition) also confirmed this association: after adjusting for age, smoking, and alcohol consumption, higher caffeine intake was associated with a reduced PD risk. Drinking decaffeinated coffee was not associated with the PD risk, and the protective effect was weakened in women using estrogen replacement therapy [50]. Another study, using data from the International PD Genomics

Consortium, did not find a significant association between caffeine and PD [36]. Altman et al. found that the maximum tolerated dose of caffeine in PD patients was 200–400 mg/day, with caffeine potentially providing benefits for certain motor and non-motor symptoms in PD patients [51]. Postuma et al. conducted a 6-week randomized controlled trial of caffeine in PD to evaluate its effects on daytime sleepiness, motor severity, and other non-motor functions. Caffeine was administered at a dose of 200 mg/day for 3 weeks, followed by 400 mg/day for another 3 weeks. Caffeine reduced the total score on the PD Rating Scale and improved the objective motor components [52]. However, these findings contrast with a recent randomized trial, which indicated that caffeine did not provide significant clinical improvement in motor performance in PD [53]. This suggests that the epidemiological link between caffeine and reduced PD risk may not be explained by symptom effects. More clinical data are needed to with caffeine potentially providing benefits for certain motor and non-motor symptoms in PD patients assess the potential motor benefits of caffeine in PD.

A key pathological mechanism of PD is the degeneration and loss of dopaminergic neurons in the nigrostriatal pathway in the brain, leading to dysregulation of dopamine in the control of extrapyramidal motor functions. This dysfunction results in motor abnormalities, a primary characteristic of the disease, with cognitive changes occurring in both early and late stages of the disease. In addition to the high density of dopamine receptors, the striatum also contains a large number of A_{2A}Rs. These A_{2A}Rs coexist with dopamine receptors in GABA/enkephalinergic neurons and are involved in the pathological processes of basal ganglia dysfunction. In recent years, adenosine A_{2A}Rs have emerged as a new target for treating both motor and non-motor symptoms of PD [54,55]. Animal models have also confirmed that caffeine can prevent PD by inhibiting adenosine A_{2A}Rs, with the mechanism possibly through the inhibition of dopaminergic neurotoxicity and neurodegeneration in the nigrostriatal pathway [56]. Caffeine pretreatment has been shown to reduce neuronal damage in the substantia nigra, improve motor function [57], decrease dopamine loss [58], and reduce microglial activation [59]. Sonsalla et al. recorded that oral caffeine reduced the loss of substantia nigra cells by 94% and 69% at one week and three weeks, respectively, after MPTP infusion, which models early and late stages of striatal dopamine reduction. They also observed reduced loss of nigrostriatal dopaminergic neurons in the rats. Long-term caffeine consumption not only elevates dopamine levels but also enhances hippocampal neuronal viability, increases tyrosine hydroxylase immunoreactivity in the striatum [59]. Xu et al. observed that the caffeine's neuroprotective effect on dopaminergic neurons is dose-dependent, with the maximum neuroprotective effect achieved at a daily dose of 10 mg/kg. Additionally, the effect was more pronounced in younger mice (10 weeks old) compared to older mice (6–9 months old) [58]. In addition, caffeine's metabolites, theophylline and paraxanthine, can also significantly reduce MPTP-induced dopamine reduction in mice, demonstrating neuroprotective effects [60]. It is generally believed that caffeine and its methylxanthine metabolites exert their effects by blocking adenosine A_{2A} receptors, inhibiting the activation of adenylate cyclase, thereby suppressing protein kinase A and reducing the release of excitatory glutamate in the CNS [61]. Recent neurochemical and immunohistochemical studies have shown that, in animal models of PD [59], long-term caffeine consumption reduces the number of histone deacetylase immunopositive cells, and lowers the levels of inflammatory cytokines [62]. The abnormal aggregation of α-synuclein and its interaction with neuroinflammation is a core pathological feature of PD. One research demonstrated that chronic caffeine treatment attenuated a cascade of pathological events leading to α-synucleinopathy, including pSer129α-Syn-rich aggregates, apoptotic neuronal cell death, microglia, and astroglia reactivation [63]. Whether caffeine can directly alleviate neuroinflammation caused by α-synuclein remains to be further explored. The A_{2A} KO completely prevented the loss of dopamine and dopaminergic neurons caused by the mutant α-synuclein transgene without altering levels of its expression. The adenosine A_{2A}R appears required for neurotoxicity in a mutant alpha-synuclein model of PD [64]. Together with prior studies, these findings indirectly support the neuroprotective potential of caffeine and more specific A_{2A} antagonists. Therefore, caffeine may reduce neuroinflammation through this possible mechanism.

In summary, caffeine has been shown to exert neuroprotective effects in Parkinson's disease primarily through the inhibition of adenosine A_{2A}R, which modulates dopaminergic signaling and reduces neuroinflammation. Additionally, caffeine can decrease microglial activation and oxidative stress, both of which contribute to neurodegeneration in PD. Some studies suggest that caffeine may also affect the degradation of alpha-synuclein, a key pathological protein in PD. Together, these mechanisms highlight caffeine's potential in preventing dopaminergic neuron loss and mitigating disease progression in PD.

6. Caffeine and Stroke

Until recently, coffee was still classified as a potential risk factor for cardiovascular disease [65], largely due to caffeine's ability to increase peripheral vascular resistance and raise blood pressure. However, some studies

suggest that moderate coffee consumption, equivalent to 2–3 cups per day, may improve metabolic syndrome and offer protective effects against cardiovascular disease [66]. Therefore, the relationship between caffeine and stroke has been controversial, with some studies indicating that caffeine is not associated with an increased risk of cardiovascular disease or mortality [67]. A meta-analysis by Ding et al. in 2014 evaluated the dose-response relationship between long-term coffee consumption and cardiovascular disease risk. This analysis found that moderate coffee consumption was inversely associated with cardiovascular disease risk, with the lowest risk observed at 3–5 cups per day. High coffee consumption did not appear to increase cardiovascular disease risk [68]. To further assess the relationship between caffeine and stroke, Lopez-Garcia evaluated coffee intake and stroke risk in women over 24 years of follow-up. The study found that long-term coffee consumption was not associated with an increased risk of stroke in women [69]. In animal experiments, the co-administration of low-dose ethanol and caffeine has been shown to protect against ischemic brain damage. Studies by Piriyawat on stroke patients using a combination of caffeine and ethanol also confirmed its neuroprotective effects [70]. A cross-sectional study based on data from the China National Health and Nutrition Examination Survey (NHANES) 2009–2014 examined the relationship between urinary caffeine and its metabolite levels and stroke risk. The results showed that higher urinary caffeine levels may be associated with a reduced risk of stroke, with 1-methylxanthine (1-MU) showing a particularly significant protective effect [71].

Ischemic brain disease can lead to neuronal cell death, with the specific mechanisms involving multiple factors. Glutamate-mediated excitotoxicity and calcium influx play important roles in the pathophysiology of cerebral ischemia. During ischemia, ATP depletion occurs, which is accompanied by the release of large amounts of endogenous adenosine. When brain injury approaches the threshold and lasts for a short duration, A_1R is triggered to initiate preconditioning, inhibiting excessive glutamate release and providing neuroprotection. Brain injury also upregulates $A_{2A}R$, possibly to promote adaptive changes, but this upregulation enhances the release of excitatory neurotransmitters, exacerbating brain damage. The use of $A_{2A}R$ antagonists can provide neuroprotection [72]. Sutherland et al. used magnetic resonance imaging (MRI) and histopathological examinations to study the effects of caffeine pretreatment on ischemic neuronal injury in rats. Chronic caffeine-treated rodents showed significantly less neuronal damage in sensitive brain areas, including the cerebral cortex, striatum, and hippocampus, compared to the control group. Although MRI scans provided evidence of accelerated damage in acutely caffeine-treated rats, quantitative analysis of the 72-h histopathological data showed no significant difference compared to the control group. Therefore, it is believed that the accelerated ischemic damage in acutely caffeine-treated rats may be due to the antagonistic effects on adenosine receptors, whereas the neuroprotective effects of chronic caffeine administration may result from the upregulation of adenosine receptors [73]. Rudolphi et al. administered oral caffeine (0.2% in drinking water) to Mongolian gerbils, and after four weeks, they observed upregulation of adenosine receptors along with a significant reduction in ischemic necrosis of pyramidal cells in the CA1 region of the hippocampus following bilateral carotid artery occlusion. This supports the neuroprotective role of caffeine during cerebral ischemia [74]. Similarly, Potter's study also supports caffeine as a neuroprotective agent for neonatal hypoxic-ischemic encephalopathy, showing improvements in cognitive behavior in the P6 HI rat model [75]. Evans examined the effect of injecting caffeine (70 mM) into the cortex 60 min before inducing a cerebral ischemia model in rats. The response to ischemia was evaluated by recording the reduction in somatosensory evoked potential (SSEP) amplitude and the recovery rate of SSEP during reperfusion. Results found that caffeine significantly reduced the ischemia-induced attenuation of SSEP [76].

In conclusion, Ischemic brain disease leads to neuronal death through mechanisms such as glutamate-mediated excitotoxicity and calcium influx, which are exacerbated by ATP depletion and excessive adenosine release. Caffeine's neuroprotective effects are mediated by antagonism of adenosine $A_{2A}R$, which helps reduce excitotoxic neurotransmitter release, while preconditioning via A_1R inhibits glutamate release and provides protection. Chronic caffeine treatment upregulates adenosine receptors, contributing to reduced neuronal damage in sensitive brain regions during ischemia, as shown in various animal studies.

7. Caffeine and Diabetes-Related Nerve Damage

A meta-analysis of multiple cohort studies concluded that habitual coffee consumption is significantly associated with a reduced risk of type 2 diabetes [77]. A review in 2024 also suggested that dietary alkaloid compounds, such as caffeine, can help regulate cognitive disorders in diabetic patients [32]. A cohort study from China, which included 553 community patients with type 2 diabetes, found that individuals with diabetes and hypoglycemia exhibited significant impairments in visuospatial and executive functions. Serum metabolomics analysis revealed that caffeine and its major downstream metabolites (theophylline and paraxanthine) were

significantly reduced in the diabetes-hypoglycemia group. These findings suggest that the combination of caffeine and its metabolites could serve as a reliable predictive biomarker for hypoglycemia (AUC = 0.88) [78].

Patients with type 2 diabetes frequently experience cognitive dysfunction, with mechanisms involving vascular dysfunction, glucotoxicity, hypoglycemic events, and disrupted brain insulin signaling. This dysfunction is particularly related to hippocampal atrophy, which affects learning and memory processes [79]. Duarte et al. found that the expression and density of adenosine receptors in the hippocampus of diabetic rats were altered [80]. Caffeine intake has been shown to prevent synaptic and astrocyte degeneration induced by streptozotocin, exhibiting potential neuroprotective effects [81]. Duarte et al. also developed a type 2 diabetes animal model to observe whether caffeine intake could prevent the behavioral, neurochemical, and morphological changes in the hippocampus caused by diabetes. Their findings revealed that, compared to wild-type mice, diabetic mice showed upregulation of $A_{2A}R$ expression, downregulation of A_1R expression, reduced spontaneous alternation in the Y-maze, decreased density of presynaptic markers (synaptophysin, SNAP25), increased glutamatergic activity (vesicular glutamate transporter), and astrocyte proliferation (GFAP immunoreactivity). Caffeine intake restored memory function and reversed the loss of presynaptic terminals and astrocyte pathology induced by diabetes. These findings suggest that caffeine intake can prevent synaptic dysfunction, astrocyte proliferation, and memory impairment in patients with type 2 diabetes [82].

In summary, caffeine consumption is associated with a reduced risk of type 2 diabetes and may help regulate cognitive dysfunction in diabetic patients. In diabetic animal models, caffeine intake has been shown to prevent synaptic and astrocyte degeneration, and restore memory function by modulating adenosine receptor expression (upregulating $A_{2A}R$ and downregulating A_1R), glutamatergic activity, and astrocyte proliferation. These findings suggest that caffeine may offer neuroprotective effects, preventing synaptic dysfunction, astrocyte proliferation, and memory impairment in patients with type 2 diabetes.

8. Caffeine and Depression

Tea, coffee, or caffeine may reduce the incidence of depression [83], and this has become a popular research topic in recent years [84–86]. One study found that long-term intake of low-dose caffeine (60 mg/day), in conjunction with antidepressant treatment, could reduce depression scores, improve cognitive ability, and have no adverse effect on sleep. These findings suggest the potential benefits of supplementing caffeine to reverse the progression of depression and enhance the effectiveness of antidepressant treatment in major depressive disorder [87]. Data from the UK Biobank, which included a total of 146,566 participants who completed a touchscreen questionnaire between 2006 and 2010, Found a J-shaped association between coffee consumption and depression and anxiety. The lowest risk of mental disorders was observed in individuals who drank 2–3 cups of coffee per day [88]. A meta-analysis included 12 studies with 23 datasets, covering a total of 346,913 individuals and 8146 cases of depression. found that those with higher coffee intake had a pooled relative risk (RR) of depression of 0.76 (95% CI: 0.64, 0.91) compared to individuals with lower coffee consumption. A dose-response analysis indicated a nonlinear J-shaped relationship between coffee consumption and the risk of depression, with the greatest protective effect observed at 400 mL/day [89]. Another study based on NHANES data from 2007 to 2018, which included 821 participants, found that consuming more than three cups of caffeinated coffee per day may reduce the risk of postpartum depression, especially in the 1 to 2 year postpartum period and among non-breastfeeding women [90]. However, some research has shown no significant association between the severity of depression, anxiety, and stress and daily caffeine consumption among university students, which contradicts the theory that high levels of caffeine intake are associated with increased levels of depression, stress, and anxiety [91]. One possible explanation could be the complexity of the relationship between caffeine consumption and mental health. Factors such as individual differences in caffeine metabolism, tolerance levels, lifestyle factors, genetic predispositions, and varying psychological and physiological responses to caffeine may influence the outcomes, making it difficult to establish a direct link between caffeine intake and mental health issues like depression, anxiety, and stress. Additionally, confounding variables such as diet, sleep patterns, and stress management practices may also play a role, potentially masking any significant effects of caffeine.

Some studies suggest the role of $A_{2A}R$ in central nervous system intervention in depression. Adult male rats overexpressing human $A_{2A}R$ under the control of the CaMKII promoter [Tg(CaMKII-h$A_{2A}R$)], exhibit depressive-like behaviors, hyperlocomotion, and altered exploratory activity [92]. A study suggests that the lateral septum (LS) plays a key role in the regulation of depression. Activation of $A_{2A}R$ in the LS increased the spiking frequency of $A_{2A}R$-positive neurons, which led to reduced activation of surrounding neurons. The bidirectional manipulation of LS-$A_{2A}R$ activity demonstrated that LS-$A_{2A}R$ s are both necessary and sufficient to trigger depressive phenotypes. Moreover, $A_{2A}R$ expression was upregulated in the LS in two male mouse models of stress-induced

depression, providing neurophysiological and circuit-based support for the antidepressant potential of $A_{2A}R$ antagonists and encouraging their clinical translation [93]. These studies suggest that caffeine may exert central intervention effects on depression through $A_{2A}R$. Chronic paradoxical sleep deprivation (PSD) can induce rat depression-like behaviors and lead to microbial changes in the gut microbiota. Both regular and decaffeinated coffee significantly improved these depression-like behaviors. Additionally, serum levels of interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) were reduced in both the coffee and decaffeinated coffee groups, while levels of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) were elevated. Gut microbiota analysis showed that the abundance of S24-7, Lachnospiraceae, Oscillospira, and Parabacteroides was significantly increased in PSD rats, while the abundance of Akkermansia and Klebsiella was significantly decreased. These findings suggest that caffeine may not be the only active substance in coffee responsible for regulating gut microbiota [94]. One study investigated the effects of caffeinated coffee on lipopolysaccharide (LPS)-induced depression-like behaviors and inflammatory biomarkers in rats. Caffeine downregulated the expression of p-AKT and NF-κB in the cortex of LPS-induced Sprague-Dawley rats [95]. The group treated with caffeine plus duloxetine showed the greatest reduction in immobility and an increase in norepinephrine, dopamine, and serotonin levels in the hippocampi, cerebral cortices, and the whole brain compared to their respective monotherapy-treated groups. These combination approaches may help in reducing the dose of duloxetine or bupropion, thereby minimizing the associated side effects [96].

In summary, caffeine can reduce the incidence of depression through various mechanisms, including enhancing the effects of antidepressants, improving cognitive function, and regulating mood-related neurotransmitters. Caffeine may also modulate inflammation by reducing IL-6, TNF-α, and NF-κB levels, as well as improving oxidative stress markers such as SOD and GSH-Px. Additionally, caffeine may help alleviate depression by influencing gut microbiota.

9. Conclusion and Prospective

In summary, caffeine, as a commonly used stimulant and food additive, exhibits a broad and complex range of pharmacological effects and is closely related to diseases such as AD, dementia, PD, stroke, and diabetes (Table 1). Its neuroprotective effects on various central nervous system diseases have been demonstrated, although further research is necessary to fully understand its long-term impact. There are potential limitations in clinical studies on caffeine. Since the human body can develop tolerance to caffeine, the long-term effects of caffeine still remain to be observed. Additionally, despite recent studies controlling for certain confounding factors, epidemiological research is often affected by other lifestyle factors. The estimation of caffeine intake is influenced by various factors (such as cup size, brewing methods, and additives). Genetic polymorphisms in caffeine metabolism means that caffeine intake may not fully represent circulating caffeine levels [97], which could be somewhat misleading. As research on caffeine continues to advance, there is hope for identifying new potential targets for the treatment of PD, AD, and ischemic-hypoxic brain diseases. However, excessive coffee consumption may be associated with certain unpleasant symptoms, such as anxiety, headaches, elevated blood pressure, nausea, and restlessness. While the effects of caffeine on human health remain a topic of debate, moderate caffeine intake could be considered a beneficial component of a healthy lifestyle for preventing nervous system diseases.

Table 1. Mechanisms of Caffeine in Neurological Diseases.

Disease	Caffeine Target Site	Affected Signaling Molecules	Specific Effects	Caffeine Content
Alzheimer's Disease (AD)	A_1R and $A_{2A}R$	β-amyloid (Aβ) [37,38,40], Tau protein [41], NF-κB [39], BACE1, ROS [43,45], PSD95 [44]	Reduces Aβ accumulation, inhibits Tau hyperphosphorylation, decreases neuroinflammation	200–400 mg per day, or about 2–3 cups of coffee
Parkinson's Disease (PD)	$A_{2A}R$	Dopamine [59,60], oxidative stress markers, excitatory glutamate [61], cytokines (e.g., TNF-α) [62]	Protects dopaminergic neurons, improves motor function, reduces neuroinflammation	300–400 mg per day, or about 3–4 cups of coff
Stroke	A_1R and $A_{2A}R$	cAMP, excitatory amino acids (e.g., glutamate) [72]	Protects against ischemic brain injury, reduces glutamate release, improves neuron survival	200–300 mg per day, or about 2–3 cups of coffee

Depression	$A_{2A}R$	IL-6,TNF-α [94], p-AKT and NF-Kb [95], Serotonin (5-HT), dopamine [96],	Increases neurotransmitter levels, reduces neuroinflammation, improves depression-like behavior	60–200 mg per day, or as low as 1–2 cups of coffee
Diabetes-Related Neuropathy	A_1R and $A_{2A}R$	Synaptophysin (SNAP25), glutamate [79], GFAP [82],	Restores memory function, prevents synaptic damage, reduces astrocyte proliferation	200–300 mg per day, or about 2–3 cups of coffee

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References

1. Drewnowski, A.; Rehm, C.D. Sources of Caffeine in Diets of US Children and Adults: Trends by Beverage Type and Purchase Location. *Nutrients* **2016**, *8*, 154. https://doi.org/10.3390/nu8030154.
2. van Dam, R.M.; Hu, F.B.; Willett, W.C. Coffee, Caffeine, and Health. *N. Engl. J. Med.* **2020**, *383*, 369–378. https://doi.org/10.1056/NEJMra1816604.
3. Marcus, C.L.; Meltzer, L.J.; Roberts, R.S.; Traylor, J.; Dix, J.; D'Ilario, J.; Asztalos, E.; Opie, G.; Doyle, L.W.; Biggs, S.N.; et al. Long-term effects of caffeine therapy for apnea of prematurity on sleep at school age. *Am. J. Respir. Crit. Care Med.* **2014**, *190*, 791–799. https://doi.org/10.1164/rccm.201406-1092OC.
4. Derry, C.J.; Derry, S.; Moore, R.A. Caffeine as an analgesic adjuvant for acute pain in adults. *Cochrane Database Syst. Rev.* **2014**, *2014*, CD009281. https://doi.org/10.1002/14651858.CD009281.pub3.
5. Gokcen, B.B.; Sanlier, N. Coffee consumption and disease correlations. *Crit. Rev. Food Sci. Nutr.* **2019**, *59*, 336–348. https://doi.org/10.1080/10408398.2017.1369391.
6. Oleaga, C.; Ciudad, C.J.; Noe, V.; Izquierdo-Pulido, M. Coffee polyphenols change the expression of STAT5B and ATF-2 modifying cyclin D1 levels in cancer cells. *Oxid. Med. Cell. Longev.* **2012**, *2012*, 390385. https://doi.org/10.1155/2012/390385.
7. Santos, R.M.; Lima, D.R. Coffee consumption, obesity and type 2 diabetes: A mini-review. *Eur. J. Nutr.* **2016**, *55*, 1345–1358. https://doi.org/10.1007/s00394-016-1206-0.
8. Homan, D.J.; Mobarhan, S. Coffee: Good, bad, or just fun? A critical review of coffee's effects on liver enzymes. *Nutr. Rev.* **2006**, *64*, 43–46. https://doi.org/10.1111/j.1753-4887.2006.tb00172.x.
9. Shan, L.; Zhao, N.; Wang, F.; Zhai, D.; Liu, J.; Lv, X. Caffeine in Hepatocellular Carcinoma: Cellular Assays, Animal Experiments, and Epidemiological Investigation. *J. Inflamm. Res.* **2024**, *17*, 1589–1605. https://doi.org/10.2147/jir.S424384.
10. Arendash, G.W.; Cao, C. Caffeine and coffee as therapeutics against Alzheimer's disease. *J. Alzheimers Dis.* **2010**, *20* (Suppl. S1), S117–S126. https://doi.org/10.3233/JAD-2010-091249.
11. Mirzaei, F.; Agbaria, L.; Bhatnagar, K.; Sirimanne, N.; Omar A'amar, N.; Jindal, V.; Gerald Thilagendra, A.; Tawfiq Raba, F. Coffee and Alzheimer's disease. *Prog. Brain Res.* **2024**, *289*, 21–55. https://doi.org/10.1016/bs.pbr.2024.06.002.
12. Trevitt, J.; Kawa, K.; Jalali, A.; Larsen, C. Differential effects of adenosine antagonists in two models of parkinsonian tremor. *Pharmacol. Biochem. Behav.* **2009**, *94*, 24–29. https://doi.org/10.1016/j.pbb.2009.07.001.
13. de Mendonca, A.; Cunha, R.A. Therapeutic opportunities for caffeine in Alzheimer's disease and other neurodegenerative disorders. *J. Alzheimers Dis.* **2010**, *20* (Suppl. S1), S1–S2. https://doi.org/10.3233/JAD-2010-01420.
14. Evans, J.; Richards, J.R.; Battisti, A.S. *Caffeine*; StatPearls: Treasure Island, FL, USA, 2024.
15. Bonati, M.; Latini, R.; Tognoni, G.; Young, J.F.; Garattini, S. Interspecies comparison of in vivo caffeine pharmacokinetics in man, monkey, rabbit, rat, and mouse. *Drug Metab. Rev.* **1984**, *15*, 1355–1383. https://doi.org/10.3109/03602538409029964.
16. Tanaka, H.; Nakazawa, K.; Arima, M.; Iwasaki, S. Caffeine and its dimethylxanthines and fetal cerebral development in rat. *Brain Dev.* **1984**, *6*, 355–361. https://doi.org/10.1016/s0387-7604(84)80111-4.
17. Rybak, M.E.; Pao, C.I.; Pfeiffer, C.M. Determination of urine caffeine and its metabolites by use of high-performance liquid chromatography-tandem mass spectrometry: Estimating dietary caffeine exposure and metabolic phenotyping in population studies. *Anal. Bioanal. Chem.* **2014**, *406*, 771–784. https://doi.org/10.1007/s00216-013-7506-9.

18. Guo, J.; Zhu, X.; Badawy, S.; Ihsan, A.; Liu, Z.; Xie, C.; Wang, X. Metabolism and Mechanism of Human Cytochrome P450 Enzyme 1A2. *Curr. Drug Metab.* **2021**, *22*, 40–49. https://doi.org/10.2174/1389200221999210101233135.
19. Abu-Hashem, A.A.; Hakami, O.; El-Shazly, M.; El-Nashar, H.A.; Yousif, M.N. Caffeine and Purine Derivatives: A Comprehensive Review on the Chemistry, Biosynthetic Pathways, Synthesis-Related Reactions, Biomedical Prospectives and Clinical Applications. *Chem. Biodivers.* **2024**, *21*, e202400050. https://doi.org/10.1002/cbdv.202400050.
20. Fredholm, B.B.; Battig, K.; Holmen, J.; Nehlig, A.; Zvartau, E.E. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacol. Rev.* **1999**, *51*, 83–133.
21. Ribeiro, J.; Sebastião, A. Caffeine and adenosine. *J. Alzheimer Dis.* **2010**, *20*, S3–S15. https://doi.org/10.3233/jad-2010-1379.
22. Burnstock, G. Purinergic Signalling: Therapeutic Developments. *Front. Pharmacol.* **2017**, *8*, 661. https://doi.org/10.3389/fphar.2017.00661.
23. Fredholm, B.B.; Chen, J.F.; Cunha, R.A.; Svenningsson, P.; Vaugeois, J.M. Adenosine and brain function. *Int. Rev. Neurobiol.* **2005**, *63*, 191–270. https://doi.org/10.1016/S0074-7742(05)63007-3.
24. Fredholm, B.B.; AP, I.J.; Jacobson, K.A.; Klotz, K.N.; Linden, J. International Union of Pharmacology. XXV. Nomenclature and classification of adenosine receptors. *Pharmacol. Rev.* **2001**, *53*, 527–552.
25. Karcz-Kubicha, M.; Antoniou, K.; Terasmaa, A.; Quarta, D.; Solinas, M.; Justinova, Z.; Pezzola, A.; Reggio, R.; Muller, C.E.; Fuxe, K.; et al. Involvement of adenosine A1 and A2A receptors in the motor effects of caffeine after its acute and chronic administration. *Neuropsychopharmacology* **2003**, *28*, 1281–1291. https://doi.org/10.1038/sj.npp.1300167.
26. Mohamed, R.A.; Agha, A.M.; Abdel-Rahman, A.A.; Nassar, N.N. Role of adenosine A2A receptor in cerebral ischemia reperfusion injury: Signaling to phosphorylated extracellular signal-regulated protein kinase (pERK1/2). *Neuroscience* **2016**, *314*, 145–159. https://doi.org/10.1016/j.neuroscience.2015.11.059.
27. Rombo, D.M.; Newton, K.; Nissen, W.; Badurek, S.; Horn, J.M.; Minichiello, L.; Jefferys, J.G.; Sebastiao, A.M.; Lamsa, K.P. Synaptic mechanisms of adenosine A2A receptor-mediated hyperexcitability in the hippocampus. *Hippocampus* **2015**, *25*, 566–580. https://doi.org/10.1002/hipo.22392.
28. Sitkovsky, M.V.; Lukashev, D.; Apasov, S.; Kojima, H.; Koshiba, M.; Caldwell, C.; Ohta, A.; Thiel, M. Physiological control of immune response and inflammatory tissue damage by hypoxia-inducible factors and adenosine A2A receptors. *Annu. Rev. Immunol.* **2004**, *22*, 657–682. https://doi.org/10.1146/annurev.immunol.22.012703.104731.
29. Hu, Q.; Ren, X.; Liu, Y.; Li, Z.; Zhang, L.; Chen, X.; He, C.; Chen, J.F. Aberrant adenosine A2A receptor signaling contributes to neurodegeneration and cognitive impairments in a mouse model of synucleinopathy. *Exp. Neurol.* **2016**, *283*, 213–223. https://doi.org/10.1016/j.expneurol.2016.05.040.
30. Li, P.; Rial, D.; Canas, P.M.; Yoo, J.H.; Li, W.; Zhou, X.; Wang, Y.; van Westen, G.J.; Payen, M.P.; Augusto, E.; et al. Optogenetic activation of intracellular adenosine A2A receptor signaling in the hippocampus is sufficient to trigger CREB phosphorylation and impair memory. *Mol. Psychiatry* **2015**, *20*, 1481. https://doi.org/10.1038/mp.2015.43.
31. Prasanthi, J.R.; Dasari, B.; Marwarha, G.; Larson, T.; Chen, X.; Geiger, J.D.; Ghribi, O. Caffeine protects against oxidative stress and Alzheimer's disease-like pathology in rabbit hippocampus induced by cholesterol-enriched diet. *Free Radic. Biol. Med.* **2010**, *49*, 1212–1220. https://doi.org/10.1016/j.freeradbiomed.2010.07.007.
32. Alkanad, M.; Hani, U.; Annegowda, H.V.; Ghazwani, M.; Haider, N.; Osmani, R.; Pandareesh, M.D.; Hamsalakshmi; Bhat, R. Bitter yet beneficial: The dual role of dietary alkaloids in managing diabetes and enhancing cognitive function. *BioFactors* **2024**, *50*, 634–673. https://doi.org/10.1002/biof.2034.
33. Maia, L.; de Mendonca, A. Does caffeine intake protect from Alzheimer's disease? *Eur. J. Neurol.* **2002**, *9*, 377–382. https://doi.org/10.1046/j.1468-1331.2002.00421.x.
34. Eskelinen, M.H.; Ngandu, T.; Tuomilehto, J.; Soininen, H.; Kivipelto, M. Midlife coffee and tea drinking and the risk of late-life dementia: A population-based CAIDE study. *J. Alzheimers Dis.* **2009**, *16*, 85–91. https://doi.org/10.3233/JAD-2009-0920.
35. Ritchie, K.; Carriere, I.; de Mendonca, A.; Portet, F.; Dartigues, J.F.; Rouaud, O.; Barberger-Gateau, P.; Ancelin, M.L. The neuroprotective effects of caffeine: A prospective population study (the Three City Study). *Neurology* **2007**, *69*, 536–545. https://doi.org/10.1212/01.wnl.0000266670.35219.0c.
36. Larsson, S.C.; Woolf, B.; Gill, D. Plasma Caffeine Levels and Risk of Alzheimer's Disease and Parkinson's Disease: Mendelian Randomization Study. *Nutrients* **2022**, *14*, 1697. https://doi.org/10.3390/nu14091697.
37. Bateman, R.J.; Aisen, P.S.; De Strooper, B.; Fox, N.C.; Lemere, C.A.; Ringman, J.M.; Salloway, S.; Sperling, R.A.; Windisch, M.; Xiong, C. Autosomal-dominant Alzheimer's disease: A review and proposal for the prevention of Alzheimer's disease. *Alzheimers Res. Ther.* **2011**, *3*, 1. https://doi.org/10.1186/alzrt59.
38. Dall'Igna, O.P.; Fett, P.; Gomes, M.W.; Souza, D.O.; Cunha, R.A.; Lara, D.R. Caffeine and adenosine A(2a) receptor antagonists prevent beta-amyloid (25–35)-induced cognitive deficits in mice. *Exp. Neurol.* **2007**, *203*, 241–245. https://doi.org/10.1016/j.expneurol.2006.08.008.
39. Arendash, G.W.; Mori, T.; Cao, C.; Mamcarz, M.; Runfeldt, M.; Dickson, A.; Rezai-Zadeh, K.; Tane, J.; Citron, B.A.;

Lin, X.; et al. Caffeine reverses cognitive impairment and decreases brain amyloid-beta levels in aged Alzheimer's disease mice. *J. Alzheimers Dis.* **2009**, *17*, 661–680. https://doi.org/10.3233/JAD-2009-1087.

40. Giunta, S.; Andriolo, V.; Castorina, A. Dual blockade of the A1 and A2A adenosine receptor prevents amyloid beta toxicity in neuroblastoma cells exposed to aluminum chloride. *Int. J. Biochem. Cell Biol.* **2014**, *54*, 122–136. https://doi.org/10.1016/j.biocel.2014.07.009.
41. Laurent, C.; Eddarkaoui, S.; Derisbourg, M.; Leboucher, A.; Demeyer, D.; Carrier, S.; Schneider, M.; Hamdane, M.; Muller, C.E.; Buee, L.; et al. Beneficial effects of caffeine in a transgenic model of Alzheimer's disease-like tau pathology. *Neurobiol. Aging* **2014**, *35*, 2079–2090. https://doi.org/10.1016/j.neurobiolaging.2014.03.027.
42. M Yelanchezian, Y.M.; Waldvogel, H.J.; Faull, R.L.; Kwakowsky, A. Neuroprotective Effect of Caffeine in Alzheimer's Disease. *Molecules* **2022**, *27*, 3737. https://doi.org/10.3390/molecules27123737.
43. Leite, M.R.; Wilhelm, E.A.; Jesse, C.R.; Brandao, R.; Nogueira, C.W. Protective effect of caffeine and a selective A2A receptor antagonist on impairment of memory and oxidative stress of aged rats. *Exp. Gerontol.* **2011**, *46*, 309–315. https://doi.org/10.1016/j.exger.2010.11.034.
44. Ullah, F.; Ali, T.; Ullah, N.; Kim, M.O. Caffeine prevents d-galactose-induced cognitive deficits, oxidative stress, neuroinflammation and neurodegeneration in the adult rat brain. *Neurochem. Int.* **2015**, *90*, 114–124. https://doi.org/10.1016/j.neuint.2015.07.001.
45. Wostyn, P.; Van Dam, D.; Audenaert, K.; De Deyn, P.P. Increased Cerebrospinal Fluid Production as a Possible Mechanism Underlying Caffeine's Protective Effect against Alzheimer's Disease. *Int. J. Alzheimers Dis.* **2011**, *2011*, 617420. https://doi.org/10.4061/2011/617420.
46. Ren, X.; Chen, J.F. Caffeine and Parkinson's Disease: Multiple Benefits and Emerging Mechanisms. *Front. Neurosci.* **2021**, *14*, 602697. https://doi.org/10.3389/fnins.2020.602697.
47. Suraj, R.; Bonnie, K. Parkinson's Disease: Risk Factor Modification and Prevention. *Semin. Neurol.* **2022**, *42*, 626–638. https://doi.org/10.1055/s-0042-1758780.
48. Heinz, R.; Ilona, C.; Jiri, K.; Stefan, L.; Christoph, S.; Juergen, W.; Ullrich, W. Life style and Parkinson's disease. *J. Neural Transm.* **2022**, *129*, 1235–1245. https://doi.org/10.1007/s00702-022-02509-1.
49. Qi, H.; Li, S. Dose-response meta-analysis on coffee, tea and caffeine consumption with risk of Parkinson's disease. *Geriatr. Gerontol. Int.* **2014**, *14*, 430–439. https://doi.org/10.1111/ggi.12123.
50. Palacios, N.; Gao, X.; McCullough, M.L.; Schwarzschild, M.A.; Shah, R.; Gapstur, S.; Ascherio, A. Caffeine and risk of Parkinson's disease in a large cohort of men and women. *Mov. Disord.* **2012**, *27*, 1276–1282. https://doi.org/10.1002/mds.25076.
51. Altman, R.D.; Lang, A.E.; Postuma, R.B. Caffeine in Parkinson's disease: A pilot open-label, dose-escalation study. *Mov. Disord.* **2011**, *26*, 2427–2431. https://doi.org/10.1002/mds.23873.
52. Postuma, R.B.; Lang, A.E.; Munhoz, R.P.; Charland, K.; Pelletier, A.; Moscovich, M.; Filla, L.; Zanatta, D.; Rios Romenets, S.; Altman, R.; et al. Caffeine for treatment of Parkinson disease: A randomized controlled trial. *Neurology* **2012**, *79*, 651–658. https://doi.org/10.1212/WNL.0b013e318263570d.
53. Postuma, R.B.; Anang, J.; Pelletier, A.; Joseph, L.; Moscovich, M.; Grimes, D.; Furtado, S.; Munhoz, R.P.; Appel-Cresswell, S.; Moro, A.; et al. Caffeine as symptomatic treatment for Parkinson disease (Cafe-PD): A randomized trial. *Neurology* **2017**, *89*, 1795–1803. https://doi.org/10.1212/WNL.0000000000004568.
54. Chen, J.F.; Schwarzschild, M.A. Do caffeine and more selective adenosine A(2A) receptor antagonists protect against dopaminergic neurodegeneration in Parkinson's disease? *Park. Relat. Disord.* **2020**, *80*, S45–S53. https://doi.org/10.1016/j.parkreldis.2020.10.024.
55. Heinz, R. Caffeine, Chocolate and Adenosine A2A Receptor Antagonists in the Treatment of Parkinson's Disease. *Fortschr. Neurol Psychiatr.* **2022**, *91*, 3632. https://doi.org/10.1055/a-1785-3632.
56. Xu, K.; Di Luca, D.G.; Orru, M.; Xu, Y.; Chen, J.F.; Schwarzschild, M.A. Neuroprotection by caffeine in the MPTP model of parkinson's disease and its dependence on adenosine A2A receptors. *Neuroscience* **2016**, *322*, 129–137. https://doi.org/10.1016/j.neuroscience.2016.02.035.
57. Bagga, P.; Chugani, A.N.; Patel, A.B. Neuroprotective effects of caffeine in MPTP model of Parkinson's disease: A (13)C NMR study. *Neurochem. Int.* **2016**, *92*, 25–34. https://doi.org/10.1016/j.neuint.2015.11.006.
58. Xu, K.; Xu, Y.; Brown-Jermyn, D.; Chen, J.F.; Ascherio, A.; Dluzen, D.E.; Schwarzschild, M.A. Estrogen prevents neuroprotection by caffeine in the mouse 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of Parkinson's disease. *J. Neurosci.* **2006**, *26*, 535–541. https://doi.org/10.1523/JNEUROSCI.3008-05.2006.
59. Sonsalla, P.K.; Wong, L.Y.; Harris, S.L.; Richardson, J.R.; Khobahy, I.; Li, W.; Gadad, B.S.; German, D.C. Delayed caffeine treatment prevents nigral dopamine neuron loss in a progressive rat model of Parkinson's disease. *Exp. Neurol.* **2012**, *234*, 482–487. https://doi.org/10.1016/j.expneurol.2012.01.022.
60. Xu, K.; Xu, Y.H.; Chen, J.F.; Schwarzschild, M.A. Neuroprotection by caffeine: Time course and role of its metabolites in the MPTP model of Parkinson's disease. *Neuroscience* **2010**, *167*, 475–481.

https://doi.org/10.1016/j.neuroscience.2010.02.020.

61. Xu, K.; Bastia, E.; Schwarzschild, M. Therapeutic potential of adenosine A(2A) receptor antagonists in Parkinson's disease. *Pharmacol. Ther.* **2005**, *105*, 267–310. https://doi.org/10.1016/j.pharmthera.2004.10.007.
62. Machado-Filho, J.A.; Correia, A.O.; Montenegro, A.B.; Nobre, M.E.; Cerqueira, G.S.; Neves, K.R.; Naffah-Mazzacoratti Mda, G.; Cavalheiro, E.A.; de Castro Brito, G.A.; de Barros Viana, G.S. Caffeine neuroprotective effects on 6-OHDA-lesioned rats are mediated by several factors, including pro-inflammatory cytokines and histone deacetylase inhibitions. *Behav. Brain Res.* **2014**, *264*, 116–125. https://doi.org/10.1016/j.bbr.2014.01.051.
63. Luan, Y.; Ren, X.; Zheng, W.; Zeng, Z.; Guo, Y.; Hou, Z.; Guo, W.; Chen, X.; Li, F.; Chen, J.F. Chronic Caffeine Treatment Protects Against α-Synucleinopathy by Reestablishing Autophagy Activity in the Mouse Striatum. *Front. Neurosci.* **2018**, *12*, 301. https://doi.org/10.3389/fnins.2018.00301.
64. Kachroo, A.; Schwarzschild, M. Adenosine A2A receptor gene disruption protects in an α-synuclein model of Parkinson's disease. *Ann. Neurol.* **2012**, *71*, 278–282. https://doi.org/10.1002/ana.22630.
65. Daphne, J.T.; Stavroula, J.T.; Andreas, Z.; Vasiliki, G.; Anna, G. Energy drinks enriched with caffeine and ischemic stroke. *J. Clin. Neurosci.* **2024**, *12*, 12–13. https://doi.org/10.1016/j.jocn.2023.12.016.
66. Chieng, D.; Kistler, P.M. Coffee and tea on cardiovascular disease (CVD) prevention. *Trends Cardiovasc. Med.* **2022**, *32*, 399–405.
67. Zhang, W.; Lopez-Garcia, E.; Li, T.Y.; Hu, F.B.; van Dam, R.M. Coffee consumption and risk of cardiovascular diseases and all-cause mortality among men with type 2 diabetes. *Diabetes Care* **2009**, *32*, 1043–1045. https://doi.org/10.2337/dc08-2251.
68. Ding, M.; Bhupathiraju, S.N.; Satija, A.; van Dam, R.M.; Hu, F.B. Long-term coffee consumption and risk of cardiovascular disease: A systematic review and a dose-response meta-analysis of prospective cohort studies. *Circulation* **2014**, *129*, 643–659. https://doi.org/10.1161/CIRCULATIONAHA.113.005925.
69. Lopez-Garcia, E.; Rodriguez-Artalejo, F.; Rexrode, K.M.; Logroscino, G.; Hu, F.B.; van Dam, R.M. Coffee consumption and risk of stroke in women. *Circulation* **2009**, *119*, 1116–1123. https://doi.org/10.1161/CIRCULATIONAHA.108.826164.
70. Piriyawat, P.; Labiche, L.; Burgin, W.; Aronowski, J.; Grotta, J. Pilot dose-escalation study of caffeine plus ethanol (caffeinol) in acute ischemic stroke. *Stroke* **2003**, *34*, 1242–1245. https://doi.org/10.1161/01.Str.0000067706.23777.04.
71. Jinming, F.; Yajun, Y.; Xiaoting, Z.; Wenhan, L.; Wuqin, M.; Wenhao, W.; Jinyan, G.; Bin, Z. Association between urinary caffeine and caffeine metabolites and stroke in American adults: A cross-sectional study from the NHANES, 2009–2014. *Sci. Rep.* **2023**, *13*, 11855. https://doi.org/10.1038/s41598-023-39126-1.
72. Gomes, C.V.; Kaster, M.P.; Tome, A.R.; Agostinho, P.M.; Cunha, R.A. Adenosine receptors and brain diseases: Neuroprotection and neurodegeneration. *Biochim. Biophys. Acta* **2011**, *1808*, 1380–1399. https://doi.org/10.1016/j.bbamem.2010.12.001.
73. Sutherland, G.R.; Peeling, J.; Lesiuk, H.J.; Brownstone, R.M.; Rydzy, M.; Saunders, J.K.; Geiger, J.D. The effects of caffeine on ischemic neuronal injury as determined by magnetic resonance imaging and histopathology. *Neuroscience* **1991**, *42*, 171–182. https://doi.org/10.1016/0306-4522(91)90157-j.
74. Rudolphi, K.A.; Keil, M.; Fastbom, J.; Fredholm, B.B. Ischaemic damage in gerbil hippocampus is reduced following upregulation of adenosine (A1) receptors by caffeine treatment. *Neurosci. Lett.* **1989**, *103*, 275–280. https://doi.org/10.1016/0304-3940(89)90112-2.
75. Potter, M.; Rosenkrantz, T.; Fitch, R.H. Behavioral and neuroanatomical outcomes in a rat model of preterm hypoxic-ischemic brain Injury: Effects of caffeine and hypothermia. *Int. J. Dev. Neurosci.* **2018**, *70*, 46–55. https://doi.org/10.1016/j.ijdevneu.2018.02.001.
76. Evans, S.M.; Pinto Pereira, L.M.; Addae, J.I. Neuroprotection by caffeine and pentoxifylline during experimental cerebral ischaemia. *West Indian Med. J.* **1999**, *48*, 23–25.
77. van Dam, R.M.; Hu, F.B. Coffee consumption and risk of type 2 diabetes: A systematic review. *JAMA* **2005**, *294*, 97–104. https://doi.org/10.1001/jama.294.1.97.
78. Wang, L.; Ke, S.; Wang, L.; Huang, L.; Qi, L.; Zhan, Z.; Wu, K.; Zhang, M.; Liu, X.; Liu, X.; et al. Altered Caffeine Metabolism Is Associated With Recurrent Hypoglycemia in Type 2 Diabetes Mellitus: A UPLC-MS-Based Untargeted Metabolomics Study. *Front. Endocrinol.* **2022**, *13*, 843556. https://doi.org/10.3389/fendo.2022.843556.
79. Gold, S.M.; Dziobek, I.; Sweat, V.; Tirsi, A.; Rogers, K.; Bruehl, H.; Tsui, W.; Richardson, S.; Javier, E.; Convit, A. Hippocampal damage and memory impairments as possible early brain complications of type 2 diabetes. *Diabetologia* **2007**, *50*, 711–719. https://doi.org/10.1007/s00125-007-0602-7.
80. Duarte, J.M.; Oliveira, C.R.; Ambrosio, A.F.; Cunha, R.A. Modification of adenosine A1 and A2A receptor density in the hippocampus of streptozotocin-induced diabetic rats. *Neurochem. Int.* **2006**, *48*, 144–150. https://doi.org/10.1016/j.neuint.2005.08.008.
81. Gaspar, J.M.; Baptista, F.I.; Galvao, J.; Castilho, A.F.; Cunha, R.A.; Ambrosio, A.F. Diabetes differentially affects the

content of exocytotic proteins in hippocampal and retinal nerve terminals. *Neuroscience* **2010**, *169*, 1589–1600. https://doi.org/10.1016/j.neuroscience.2010.06.021.

82. Duarte, J.M.; Agostinho, P.M.; Carvalho, R.A.; Cunha, R.A. Caffeine consumption prevents diabetes-induced memory impairment and synaptotoxicity in the hippocampus of NONcZNO10/LTJ mice. *PLoS ONE* **2012**, *7*, e21899. https://doi.org/10.1371/journal.pone.0021899.
83. Gian Carlo, T.; Maria, D.; Valentina, O.; Emanuela, D.U.; Seyed Hassan, S.; Ettore, N.; Seyed Fazel, N.; Seyed Mohammad, N. Coffee and Depression: A Short Review of Literature. *Curr. Pharm. Des.* **2015**, *21*, 5034–5040. https://doi.org/10.2174/1381612821666150825145112.
84. Park, R.J.; Moon, J.D. Coffee and depression in Korea: The fifth Korean National Health and Nutrition Examination Survey. *Eur. J. Clin. Nutr.* **2014**, *69*, 501–504. https://doi.org/10.1038/ejcn.2014.247.
85. Navarro, A.M.; Abasheva, D.; Martínez-González, M.Á.; Ruiz-Estigarribia, L.; Martín-Calvo, N.; Sánchez-Villegas, A.; Toledo, E. Coffee Consumption and the Risk of Depression in a Middle-Aged Cohort: The SUN Project. *Nutrients* **2018**, *10*, 1333. https://doi.org/10.3390/nu10091333.
86. Lucas, M.; Mirzaei, F.; Pan, A.; Okereke, O.I.; Willett, W.C.; O'Reilly, É.J.; Koenen, K.; Ascherio, A. Coffee, caffeine, and risk of depression among women. *Arch. Intern. Med.* **2011**, *171*, 1571–1578.
87. Liu, Q.S.; Deng, R.; Fan, Y.; Li, K.; Meng, F.; Li, X.; Liu, R. Low dose of caffeine enhances the efficacy of antidepressants in major depressive disorder and the underlying neural substrates. *Mol. Nutr. Food Res.* **2017**, *61*, 1600910. https://doi.org/10.1002/mnfr.201600910.
88. Min, J.; Cao, Z.; Cui, L.; Li, F.; Lu, Z.; Hou, Y.; Yang, H.; Wang, X.; Xu, C. The association between coffee consumption and risk of incident depression and anxiety: Exploring the benefits of moderate intake. *Psychiatry Res.* **2023**, *326*, 115307. https://doi.org/10.1016/j.psychres.2023.115307.
89. Giuseppe, G.; Agnieszka, M.; Sabrina, C.; Andzrej, P.; Fabio, G. Coffee, tea, caffeine and risk of depression: A systematic review and dose-response meta-analysis of observational studies. *Mol. Nutr. Food Res.* **2015**, *60*, 223-234. https://doi.org/10.1002/mnfr.201500620.
90. Wang, Y.; Wang, Z.; Gui, P.; Zhang, B.; Xie, Y. Coffee and caffeine intake and depression in postpartum women: A cross-sectional study from the National Health and Nutrition Examination Survey 2007–2018. *Front. Psychol.* **2023**, *14*, 1134522. https://doi.org/10.3389/fpsyg.2023.1134522.
91. Makki, N.M.; Alharbi, S.T.; Alharbi, A.M.; Alsharif, A.S.; Aljabri, A.M. Caffeine Consumption and Depression, Anxiety, and Stress Levels Among University Students in Medina: A Cross-Sectional Study. *Cureus* **2023**, *15*, 48018. https://doi.org/10.7759/cureus.48018.
92. Coelho, J.; Alves, P.; Canas, P.; Valadas, J.; Shmidt, T.; Batalha, V.; Ferreira, D.; Ribeiro, J.; Bader, M.; Cunha, R.; et al. Overexpression of Adenosine A2A Receptors in Rats: Effects on Depression, Locomotion, and Anxiety. *Front. Psychiatry* **2014**, *5*, 67. https://doi.org/10.3389/fpsyt.2014.00067.
93. El Yacoubi, M.; Costentin, J.; Vaugeois, J. Adenosine A2A receptors and depression. *Neurology* **2003**, *61*, S82–S87. https://doi.org/10.1212/01.wnl.0000095220.87550.f6.
94. Xinyi, G.; Shuyi, Z.; Weini, M.; Qixue, W.; Ying, L.; Chenyi, X.; Ying, X.; Ting, Z.; Li, Y.; Mingmei, Z. The Impact of Instant Coffee and Decaffeinated Coffee on the Gut Microbiota and Depression-Like Behaviors of Sleep-Deprived Rats. *Front. Microbiol.* **2022**, *13*, 778512. https://doi.org/10.3389/fmicb.2022.778512.
95. Ruicheng, Z.; Lei, Z.; Wenqi, D.; Jiao, T.; Long, Y.; Deqin, G.; Yanbo, C. Caffeine alleviate lipopolysaccharide-induced neuroinflammation and depression through regulating p-AKT and NF-κB. *Neurosci. Lett.* **2024**, *837*, 137923. https://doi.org/10.1016/j.neulet.2024.137923.
96. Pravin Popatrao, K.; Veeranjaneyulu, A. Augmentation of antidepressant effects of duloxetine and bupropion by caffeine in mice. *Pharmacol. Biochem. Behav.* **2014**, *124*, 238–244. https://doi.org/10.1016/j.pbb.2014.06.005.
97. Cornelis, M.; Byrne, E.; Esko, T.; Nalls, M.; Ganna, A.; Paynter, N.; Monda, K.; Amin, N.; Fischer, K.; Renstrom, F.; et al. Genome-wide meta-analysis identifies six novel loci associated with habitual coffee consumption. *Mol. Psychiatry* **2015**, *20*, 647–656. https://doi.org/10.1038/mp.2014.107.