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To Assess the Effectiveness of Caffeine Consumption as a Potential Therapeutic Intervention for Parkinson's Disease: A Systematic Review

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Abstract:

The second most prevalent neurodegenerative disease, Parkinson's disease (PD), requires new approaches because there are currently no disease-modifying therapies. This systematic review evaluates the therapeutic potential of caffeine consumption for PD, focusing on the alleviation of motor and cognitive symptoms as well as potential neuroprotective mechanisms. Utilizing PubMed and Google Scholar, initially, 12,187 articles (2015-2025) were screened, with five clinical trials meeting the inclusion criteria (full-text, English, human or animal studies). Results indicated mixed outcomes: higher cognitive performance in low-demand activities [1] and improved motor function (e.g., lower UPDRS-III scores [2] were associated with low-dose caffeine (<400 mg/day). Inhibition of adenosine A2A and MAO-B receptors was linked to neuroprotective benefits, including reduced alpha-synuclein toxicity and neuroinflammation [3, 4]. However, conflicting studies reported negligible benefits [5] or dose-dependent risks [6]. Small sample sizes, methodological variability, and reliance on animal models were among the limitations that raised concerns regarding reliability. Caffeine shows potential in reducing Parkinson's disease symptoms by blocking A2A receptors and influencing oxidative pathways, but inconsistent findings highlight the necessity for large-scale human trials and standardised dosage recommendations. Caffeine's potential as an adjuvant therapy is highlighted by these findings, although caution is advised because individual variations and safety implications are still unknown. Further research is essential to establish the optimal therapeutic strategies and long-term success in the management of Parkinson's disease.

Keywords: caffeine, Parkinson's disease, systematic review, effectiveness, motor, cognitive, neuroprotective effects, therapeutic

1. Introduction

After Alzheimer's disease (AD), Parkinson's disease (PD) is the second most widespread neurodegenerative disease [7]. The number of patients with Parkinson's disease increased to almost 6 million between 1990 and 2015. This number is projected to nearly double, reaching about 12 million by 2040, primarily due to the aging population[8]. However, the precise diagnosis criteria for Parkinson's disease remain unclear and are still under investigation. It has traditionally been defined as the loss of dopaminergic neurons in the substantia nigra and by motor characteristics of Parkinsonism associated with Lewy bodies [9]. Symptoms of Parkinson's disease vary widely and include clinically significant non-motor features. Some examples, such as rapid eye movement, sleep disorder, and dysautonomia, are non-motor symptoms that often appear at the premotor stage [10]. Even though several therapeutic methods can relieve the symptoms of Parkinson's disease, there is still no clear evidence that any drug or treatment has a disease-modifying effect [11].

Caffeine is a natural stimulant found in coffee, tea, certain medications, and other beverages. It is the metabolite derived from purine nucleotides, composed of 2-5% of the dry weight of tea and 1-2% of the dry weight of coffee [12, 13]. It is widely consumed by people in daily life for its ability to elevate mood, increase alertness, and stimulate the release of catecholamines, all of which have positive behavioral consequences. It has been discovered that caffeine could act as an antioxidant and exert anti-inflammatory effects in the brain [12]. Furthermore, caffeine offers neuroprotection by regulating neuroinflammation, excitotoxicity, and mitochondrial function. In previous studies, caffeine has been found to provide protection in animal models of PD, primarily mediated by the adenosine A2A receptor (A2AR) in the brain. This supports the potential of caffeine intervention in Parkinson's disease, as one suggested cause of Parkinson's disease involves astrocyte-induced neuroinflammation, which caffeine could modulate [14].

This systematic review focuses on the fields of Neurology and Pharmacology. It further aims to explore the potential therapeutic effect of caffeine as a treatment for Parkinson's disease, specifically focusing on how caffeine could benefit the motor and cognitive aspects of PD.

2. Literature review

2.1 Symptom of Parkinson's disease

Three main motor symptoms are tremors, rigidity, and bradykinesia. Other symptoms also include alterations in gait and balance, eye movement control, speech and swallowing, and bladder control [15]. Furthermore, non-motor symptoms include cognitive decline, sleep disturbances, and depression, as well as dementia, hyposmia, and gastrointestinal alteration [16]. Moreover, the total symptoms of PD can be divided into early-stage PD and late-stage PD. The symptoms in early-stage Parkinson's disease, non-motor symptoms, take precedence over milder motor symptoms. Motor complications are limited to basic issues such as dyskinesia, wearing off, and axial symptoms, while numerous non-motor symptoms occur, including autonomic dysfunction, neuropsychiatric symptoms, sleep disturbances, and olfactory dysfunction. In the late stage PD, the symptoms increase their severity and may significantly influence daily activities. For instance, patients may experience severe bradykinesia, pronounced muscle rigidity, severe speech impairment, and cognitive decline [17].

2.2 Molecular Histopathology of Parkinson's disease

Although the exact cause of Parkinson's disease remains unclear, the most likely explanation for the pathological feature up to this point is the buildup of filamentous cytoplasmic inclusion bodies. These inclusions are mainly composed of misfolded alpha-synuclein, which aggregates into toxic oligomers and fibrils that accumulate into Lewy bodies and Lewy neurites (LN). In addition, the primary pathology of PD is the loss of dopaminergic neurons in the substantia nigra [16].

2.2.1 Lewy body

Lewy bodies (LB) are abnormal accumulations of proteins in the brain, strongly associated with dementia, including Lewy body dementia (LBD) or Parkinson's disease dementia (PDD). They are considered the origin of all the motor and some cognitive symptoms of Parkinson's disease. It had been discovered that certain neurotransmitters, such as dopamine and acetylcholine, are depleted in the brain due to the LBD. It can be deduced that PD and LDB have many shared pathological features that they are both alpha-synucleinopathies and the depletion of neurotransmitters. This implies that individuals with Parkinson's disease will possibly develop Lewy body dementia [17].

2.2.2 Alpha-synuclein

Alpha-synuclein is a highly charged small protein that is found primarily inside the brain and is abundant at the presynaptic terminals of neurons. It is thought to play a role in regulating neurotransmitter release (such as dopamine), maintaining vesicular trafficking, and facilitating neuronal communication [18]. The accumulation of alpha-synu-

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clein can lead to several pathological consequences. The first consequence may be neuronal dysfunction and death by impairing neuronal activity, causing them to malfunction and eventually die. Second, it can lead to disruption of cellular processes, including mitochondrial function, autophagy (the cell's waste disposal system), and synaptic transmission. Furthermore, another result could be neuroinflammation, the accumulation has the ability to trigger microglia (the brain's immune cells), which in turn can cause an inflammatory reaction [19]. This process is thought to be a critical contributor to the pathogenesis of PD.

2.2.3 Substantia Nigra (SN)

It is traditionally regarded as the main source of input into the circuitry of the basal ganglia and as essential to these processes. Therefore, if the substantia nigra is damaged then many neurological diseases may be induced such as Parkinson's disease, Huntington's disease, etc. [20].

2.2.4 Adenosine 2A receptor(A2A receptors)

The adenosine A2A receptors are essential for several physiological functions, such as immune system modulation, angiogenesis, and sleep regulation. These receptors are located mainly in the striatum, where they regulate the indirect pathway of the basal ganglia. This implies that A2A receptors may contribute to cognitive symptoms, such as sleep disturbances, and it induce the motor symptoms of PD by overactivity, which normally functions to inhibit movements. In PD, the loss of dopamine disrupts this balance, leading to overactive indirect pathways and motor symptoms. Moreover, depletion of dopamine can enhance A2A receptor activity and trigger neuroinflammation [21].

2.3 Current Therapeutic Strategies

2.3.1 Motor Symptoms Therapies

The primary pharmacological approaches for managing motor symptoms in PD involve the use of monoamine oxidase B (MAO-B) inhibitors, dopamine agonists (DA), and levodopa (LD).

2.3.2 MAO-B Inhibitors

The MAO-B inhibitors are a class of drugs primarily used in the treatment of Parkinson's disease, with selegiline and rasagiline being two of the most widely studied examples. MAO-B is a type of enzyme that is responsible for breaking down dopamine, and selegiline acts as an irreversible MAO-B inhibitor. This means that it can block the MAO-B enzyme to prevent dopamine breakdown and help retain more dopamine in the brain. Furthermore, when used in combination with selegiline and levodopa, selegiline could reduce levodopa requirements and, therefore, obtain fewer adverse effects. The DATATOP trial of selegiline had shown a result of delayed levodopa need by about 9 months, which indicates its effectiveness in the treatment of PD. However, long-term studies have yielded less promising results, with some reporting reduced motor complications but inconclusive evidence regarding neuroprotection. Rasagiline is another type of MAO-B inhibitor, with its effect is similar to selegiline, as it also inhibits the breakdown of dopamine. Unlike selegiline, however, rasagiline is thought to provide neuroprotective effects, shielding neurons from harmful processes such as oxidative stress and apoptosis, and thereby potentially slowing disease progression. The PRESTO/LARGO trials demonstrated the consequences of reduced "OFF" time in advanced PD [22].

2.3.3 Dopamine Agonists (DA)

Dopamine agonists are mainly classified into two types: ergoline dopamine agonists (derived from ergot alkaloids, compounds from a fungus) and non-ergoline dopamine agonists. Non-ergoline dopamine agonists, such as pramipexole, ropinirole, and rotigotine, are preferred over ergoline-derived dopamine agonists like bromocriptine, cabergoline, and pergolide due to their lower risk of fibrotic side effects. Ergoline-derived dopamine agonists have been associated with pulmonary, retroperitoneal, and pericardial fibrotic reactions [23]. The dopamine agonists (DA) function by mimicking the actions of neurotransmitters such as dopamine. They bind to and activate postsynaptic receptors (dopamine receptors) in the brain, specifically the D2 and D3 receptors, thereby helping to alleviate the symptoms of dopamine deficiency. Moreover, a previous trial evaluated the efficacy of three non-ergoline dopamine agonists, pramipexole, ropinirole, and rotigotine. Pramipexole has high selectivity for D3 receptors, with antioxidant and anti-apoptotic properties. Oxidative stress of PD is caused by the loss of dopamine-producing neurons in the brain, and antioxidants can neutralise the free radicals (unstable molecules that can damage cells) which cause oxidative stress. Furthermore, in PD, the extra apoptosis contributes to the excessive apoptosis of dopamine neurons, where the proteasome and autophagosome are involved in clearing them. The anti-apoptotic property helps inhibit this process. The second result is that it reduces "Off" time for PD, which leads to a more consistent symptom control. The "Off" Time in Parkinson's disease refers to a period of time when the drugs lose their efficacy, and the controlled symptoms re-emerge. The last result shown is that it improves the UPDRS score [24].

2.3.4 Levodopa (LD)

Levodopa [14], also called L-dopa and chemically known as L-3,4-dihydroxyphenylalanine, is a naturally occurring amino acid that the brain can convert into dopamine, thereby replacing the depleted dopamine in PD. Unlike dopamine, Levodopa has the ability to cross the blood-brain barrier and convert to dopamine within the brain by the enzyme aromatic L-amino acid decarboxylase (AADC) [25]. Furthermore, it is commonly provided together with carbidopa to prevent the conversion of levodopa into dopamine before it crosses the blood-brain barrier [26]. Therefore, levodopa is recognised as irreplaceable due to its consistent control of symptoms (especially motor impairments) and its role as a precursor to dopamine. This is exemplified in the prior randomized, double-blind, placebo-controlled trial involving 361 patients with early PD. The outcome was examined using the UPDRS Scores, and the results showed that levodopa significantly reduced the worsening of PD symptoms compared to placebo. Furthermore, during the washout period, some patients have a prolonged benefit effect up to two weeks. This implies that Levodopa is highly effective in treating PD. However, high doses of levodopa can cause adverse effects, including dyskinesia, nausea, and hypertonia. Moreover, the data also illustrate that the dopamine-transporter density diminished more in levodopa-treated patients than in placebo-treated patients, which may indicate a pharmacologic effect on the dopamine transporter or a possible toxic effect on dopamine neurons [27]. The dopamine-transporter (DAT) is a protein located on the membranes of dopaminergic neurons. DAT density reflects the integrity and number of dopamine-producing neurones (European Journal of Pharmacology, 1997). The neuropsychiatric symptoms of PD include depression, psychosis, and cognitive decline. Depression is a symptom in PD related to the neurodegeneration in dopaminergic, serotonergic, and noradrenergic pathways. It is treated by SSRIs (citalopram), SNRIs (venlafaxine), or activating antidepressants (bupropion). The optimal approach is to use selective serotonin reuptake inhibitors (SSRIs), which increase serotonin levels and have the fewest adverse effects. Serotonin (5-hydroxytryptamine (5-HT)) is a monoamine neurotransmitter that carries messages between nerve cells in the brain and throughout the body. It can influence sleep, mood, digestion, and other functions[26].

2.3.5 Adenosine A2A Receptor antagonist

In a 2003 study on the effect of adenosine receptor antagonists in PD patients treated with levodopa, optimal doses of levodopa showed no additional effect. However, at lower doses of levodopa, KW-6002 increased the antiparkinsonian effect by 36%. Furthermore, several PD symptoms, including resting tremor, improved, and KW-6002 also prolonged the efficacy of levodopa treatment by 47 minutes [28].

2.4 Caffeine

Caffeine (1,3,7-trimethylxanthine) is a psychostimulant purine-like alkaloid found naturally in coffee, tea, cacao beans, and more than 60 plant species. As one of the most widely consumed psychostimulants in the world (by approximately 80% of the population), caffeine has been extensively studied for its potential effects on various diseases. Furthermore, ongoing research continues to explore its specific mechanisms and therapeutic potential in greater detail. It has been discovered that a healthy adult can take in ≤ 400 mg per day. If an individual consumes excessive caffeine, this can lead to serious effects, including significant toxicity and even lethality (the potential to cause death). Caffeine is a largely dose-dependent substance; intake of ≥400 mg (500mg) can cause increased tension, nervousness, anxiety, excitement, irritability, nausea, paresthesia, tremor, perspiration, palpitations, restlessness, and possibly dizziness. Although individual responses vary (this also depends on individual metabolism). No more than 3 mg/kg per day is considered appropriate for children and teenagers, and it seems to be safe for pregnant women to consume up to 300 mg per day. Furthermore, the clinical features of caffeine intoxication have been reported to include symptoms such as cardiovascular symptoms, gastrointestinal symptoms, psychological/neurological symptoms, metabolic symptoms, musculoskeletal symptoms, pulmonary symptoms, tinnitus, dizziness, diuresis, and death [29]. In healthy adults, caffeine has a half-life of 3 to 7 hours and is metabolized in the liver [30].

2.4.1 Metabolism of Caffeine

2.4.1 .1 Neuroinflammation& Oxidative stress

As mentioned above, neuroinflammation is induced through the aggregation of alpha-synuclein. In this complex process, all CNS cells, including neuronal cells and microglia, coordinate their immediate local inflammatory responses. This process leads to the recruitment of immune cells throughout the body, including T cells, B cells, and macrophages [31]. Neuroinflammation is frequently advantageous for effectively managing external stresses. However, dysregulation of immune signaling due to chronic immune responses associated with aging or immune senescence may contribute to neurodegenerative pathogenesis [32]. Additionally, LPS (lipopolysaccharide) is another factor that contributes to neuroinflammation and oxidative stress. It elevates ROS levels, which can result in the overexpression of inflammatory genes [33].
A study in 2019 conducted in adult mice demonstrates that

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caffeine has a beneficial effect in lowering neuroinflammation and oxidative stress in the brain. The study primarily focused on two signaling pathways in the brain: the Nrf2 pathway and the TLR4/NF-κB pathway. Caffeine's benefits were associated with activation of the Nrf2 pathway, which is essential for upregulating antioxidant enzymes. It has also been shown to inhibit the activation of the TLR4/NF-κB pathway, which triggers inflammatory responses [34].

2.5 Research Gap

There are a considerable number of studies on caffeine and its therapeutic potential for Parkinson's disease and other conditions. However, the findings of much research are conflicting. Some studies report beneficial effects, while others report negative outcomes. Interestingly, caffeine has been shown to have a neuroprotective effect in all animal models of Parkinson's disease, but results from human studies have been conflicting. Some studies report improvements in cognitive symptoms, although certain adverse effects were observed. Furthermore, there are limited data on the effects of caffeine on cognitive symptoms of PD compared to motor symptoms, highlighting research gaps that have yet to be explored. Caffeine has been shown to be dose-dependent, and its optimal dose has not yet been established.

3. Methodology

3.1 Search strategy

This study employs a systematic review methodology to explore the therapeutic intervention of caffeine in Parkinson's disease. This review focuses on the studies published between 2015 and 2025; initially, 12187 papers were identified. The reason for selecting this 10-year period is that it captures the most recent advancements in understanding caffeine's role in Parkinson's disease. This ensures that the included studies are based on up-to-date and relevant evidence, which can deliver more reliable results. This time frame can also help ensure that the clinical trials and most recent discoveries are incorporated to avoid misuse of previous investigations that have been overturned.

3.2 Databases and Keywords

This dissertation utilizes two primary databases, which are PubMed and Google Scholar, with the first 10 pages of Google Scholar being examined. The reason that PubMed was chosen because it is a reputable and renowned biomedical database for the specialized literature in the biomedical field, offering a wide range of choices in some specific fields. Google Scholar was also selected because it offers a considerable amount of resources and can provide additional insights that are not always available in other databases. The keywords used for filtering the literature in PubMed and Google Scholar are ((((Parkinsons) OR (Parkinson's)) OR (Parkinsonism)) OR (Neurodegenerative)) AND (caffeine)) AND ((efficacy)) OR (effectiveness)).

3.3 Study Selection Criteria

The inclusion criteria involve the literatures being in full text, in English, and in the form of clinical trials. Only studies available in full text were included to ensure a thorough analysis of the data. Moreover, clinical trials were included because they provide the highest level of evidence for evaluation, are highly reliable, and help minimize bias.

The exclusion criteria were studies published in languages other than English, studies not available in full text, and reviews, meta-analyses, or other types of literature, in order to maintain a focus on experimental evidence.

3.4 Study Selection Process

The study selection process involved several stages to ensure the inclusion of relevant and high-quality studies. The inclusion and exclusion criteria were first applied using the search functions in the PubMed and Google Scholar databases. This step filtered out studies that did not meet the basic criteria, such as non-English studies or those not available in full text. After the initial screening, the remaining studies were comprehensively examined to determine whether the information was relevant to this systematic review. Both direct and indirect literature related to caffeine and Parkinson's disease were included. Moreover, some studies were identified through the reference lists of other reviews relevant to caffeine and PD. This proved highly valuable and allowed the inclusion of additional studies not retrieved through the initial database search.

3.5 Data Extraction

The data extraction process involved reviewing each individual paper and categorizing them based on their study type, their design such as "randomized controlled trial", participant characteristics, and their experimental intervention such as the administration of "100 mg caffeine (single dose)" or other doses. Moreover, their comparator group was identified, with most studies using a placebo group, which also includes the duration of each experiment. Finally, the results of each study were summarised individually to provide a clear overview of the findings.

Table 1 below shows the categorization of all the findings.

3.6 Ethical considerations

All studies included in this review must follow the ethical guidelines for clinical research. This ensures that the findings are based on ethically conducted studies.

4. Result

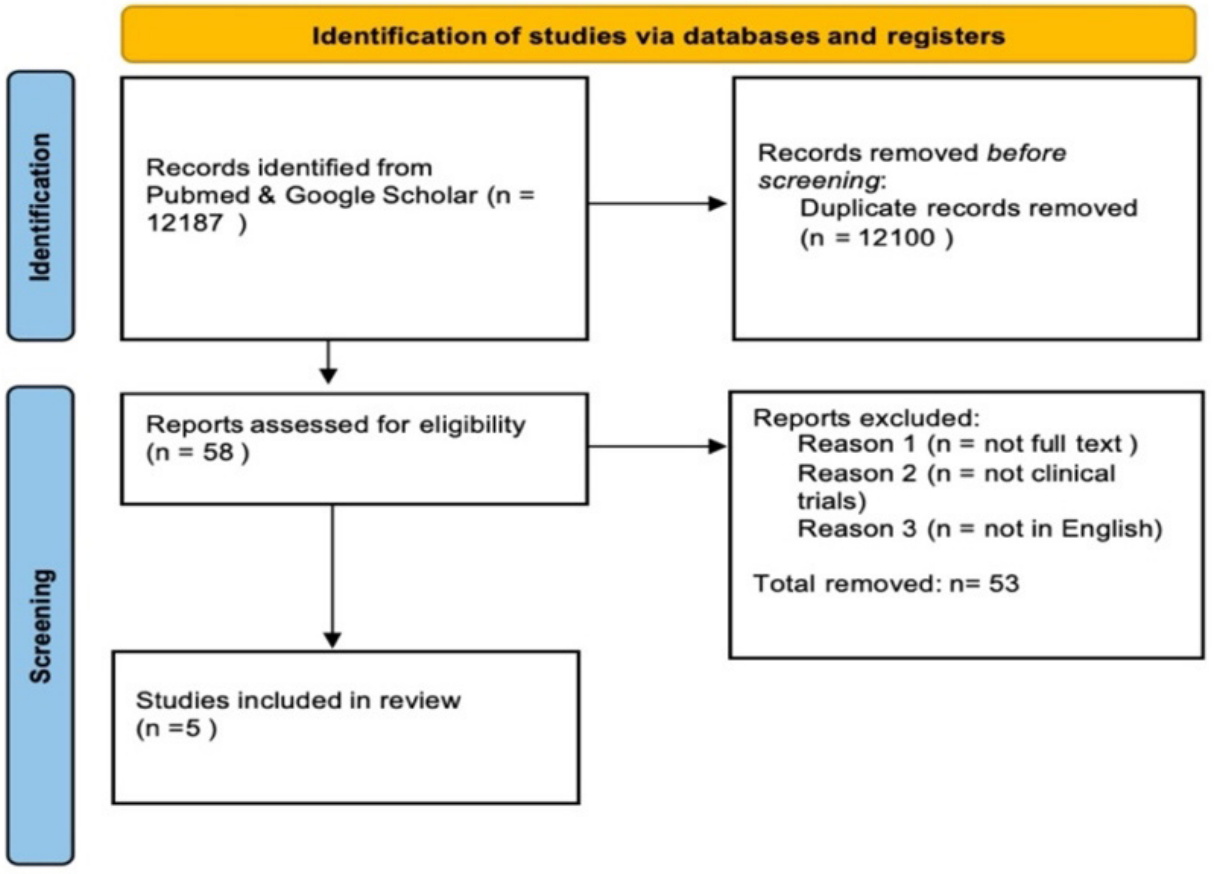

Figure 1 Flow diagram

4.1 Identification Process

Initially, 12,187 papers were identified from both PubMed and Google Scholar. After removing duplicates, the total number of selected papers was 12,100. Among these papers, 58 were assessed for eligibility and were published between 2015 and 2025, which also matched the relevant search terms. Out of the 58 papers, five were identified as clinical trials that were available in full text and written in English, while 53 papers were excluded.

4.2 Included studies

There were five papers selected in total; the details are shown in Table 1. The overall findings from the systematic review suggest that caffeine has some beneficial potential effects on PD. What stands out in this table is that both Hamdan[2] and Sharma[1] observed motor and task improvements in PD patients after caffeine consumption. Additionally, Machado [3] and Boulaamane [4] reported evidence of caffeine's neuroprotective effects. Overall, the findings suggest that caffeine or its derivatives have potential benefits for Parkinson's disease.

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Table 1 Result Table- illustrating all the chosen studies

Study/Year	Design	Participants	Experimental Intervention	Comparator Group	Duration	Key Results
Ferreira et al. (2016)	Multiple n-of-1 trials	4 PD patients with daytime somnolence	Regular espresso coffee (100 mg/cup, 2–4 cups/day)	Decaffeinated coffee (2 mg/cup)	10 weeks (3 crossovers per patient)	Espresso coffee reduced somnolence in 2/4 patients; inconclusive in others. No serious adverse events.
Hamdan et al. (2024)	Double-blind RCT	27 PD patients (15 intervention, 12 control)	Caffeine adjuvant (100 mg/day)	Placebo (50 mg amylum/day)	3 weeks	80% of caffeine group vs. 16.7% of placebo showed motor improvement (UPDRS-III reduction >4 points; p=0.004). Mild adverse events in
Sharma et al. (2022)	Single-blind crossover RCT	24 PD patients and 44 healthy older adults	100 mg caffeine (single dose)	Decaffeinated coffee (placebo)	Acute (testing 60 min post-dose)	Improved dual-task accuracy (p=0.037) but impaired single-task accuracy (p=0.044). No significant difference between PD and
Machado et al. (2020)	Preclinical study (in vivo)	Adult male CF1 mice (60 days old)	Caffeine (0.3 g/L and 1.0 g/L in drinking water)	SHAM-operated mice (without caffeine)	7 weeks (2 weeks pre-surgery, 5 weeks post-surgery)	Caffeine prevented OB-induced hyperactivity, memory impairment, and neurodegeneration. It also rescued self-care and motivational behavior. Caffeine increased A1R in the striatum and
Boulaamane et al. (2022)	Computational study (silico study)	Natural product-like caffeine derivatives from the COCONUT database	Virtual screening of caffeine derivatives for MAO-B inhibition and A2AR antagonism	Safinamide (reference MAO-B inhibitor) and istradefylline (reference A2AR antagonist)	not mentioned	Two caffeine-containing natural products (CNP0202316 and CNP0365210) showed high binding affinity for MAO-B and A2AR. This suggests they are potential candidates for further development as

4.3 Motor & Cognitive Improvements

The study by Hamdan [2] was a double-blind randomized controlled trial involving 27 patients. The results were assessed using the UPDRS III score, which showed a reduction of greater than 4 points following the intervention. Four of the 15 participants in the treatment group reported adverse effects; however, these diminished over time during the intervention. Consequently, approximately 80% of patients who received caffeine therapy demonstrated motor improvement.

In a similar study conducted in 2022, Sharma [1] examined the effects of caffeine consumption on task performance under varying levels of task demand. Caffeine was found to improve performance on low-demand tasks, such as simple reaction time, choice reaction time, and the Stroop test. In the Stroop test, caffeine only restored motor response speed in PD patients to baseline levels, without producing significant task improvement. In contrast, caffeine resulted in impaired performance or no significant effect on high-demand tasks, such as the rapid serial visual presentation paradigm and dual-task paradigms. Overall, Sharma discovered that caffeine improved the accuracy of response selection in both consistent and inconsistent conditions. Both studies noted that low doses of caffeine may be most effective. Moreover, Hamdan [2] reported that doses below 400 mg were generally associated with positive effects, while doses above 400 mg were linked to undesirable outcomes.

Additionally, Machado's [3] mouse study provided evidence of the cognitive improvements that caffeine can induce. The result of this study showed improvements in self-care, motivation, and depressive-like behaviours in the mice. Interestingly, only small doses of caffeine were effective, whereas high doses did not produce this effect.

4.4 Neuroprotective Effects

Boulaamane[4] conducted a computational study, applying models of natural caffeine derivatives and identifying their

dual inhibitory potential against MAO-B and Adenosine 2A receptors(A2AR). As mentioned in the literature review, MAO-B is an enzyme that breaks down dopamine, while A2AR is involved in regulating immune responses in the brain; overactivation of A2AR can lead to neuroinflammation. Notably, compounds such as CNP0202316 and CNP0365210 were identified as having high affinity for MAO-B, binding through hydrogen bonds and hydrophobic interactions. They also interacted with A2AR via hydrogen bonding, showing similar properties to istradefylline, an A2AR antagonist. Furthermore, they demonstrated blood-brain barrier permeability. These findings demonstrate that caffeine can inhibit MAO-B and A2AR, thereby providing neuroprotection by preventing dopamine breakdown and reducing neuroinflammation.

On the other hand, Machado [3] carried out a study on a mouse model of agitated depression induced by olfactory bulbectomy (OB). Administration of caffeine in drinking water prevented the psychomotor agitation induced by OB after 51 days of treatment. In contrast, mice in the control group without caffeine exhibited significant psychomotor agitation. Furthermore, it also prevented hyperactivity and memory impairment. Additionally, caffeine was shown to attenuate neuronal damage in brain regions affected by OB, including the hippocampus and striatum.

5 Discussion

5.1 Motor & Cognitive Improvements

The overall findings from the systematic review suggest that caffeine can lead to both motor and cognitive improvements in patients with Parkinson's disease. Supporting evidence comes from the study by Hamdan [2], in which 27 patients showed a reduction in the UPDRS III score of greater than 4 points, indicating significant motor improvement. Furthermore, Sharma [1] reported improved performance in the Stroop test and enhanced accuracy of response selection across all tasks. These results are consistent with previous findings, which have found that caffeine also has protective effects on motor symptoms. A previous therapeutic approach for PD involves adenosine A2A receptor antagonists. The A2A receptors are highly expressed in the striatum and regulate the indirect pathway of the basal ganglia (mainly for motor control). Dopamine can antagonize A2A receptors; however, in PD, dopamine deficiency leads to hyperactivity of these receptors. Caffeine is also an antagonist of the A2A receptor, so it could inhibit its activity and result in the improvement of motor symptoms. Additionally, other studies have provided evidence supporting cognitive benefits of caffeine in PD. The most striking evidence is that the A2A receptors are also distributed in other regions of the brain and regulate the sleep cycle, memory, and many cognitive functions. Similar to their role in motor symptoms, overactivation of A2A receptors in these regions can lead to cognitive impairments, including memory deficits and sleep disturbances [22].

This finding contrasts with a study by Ascherio [6], which investigated the relationship between caffeine consumption and the risk of Parkinson's disease (PD). The study found that women who consumed both high doses of caffeine and hormones had an increased risk of PD. Additionally, among women using hormone therapy, the risk of PD was fourfold higher compared to women who did not consume coffee. These findings suggest that high doses of caffeine may increase the risk of PD, or at least may not reduce it, which is inconsistent with the results reported in this systematic review. Furthermore, a study by Checkoway [35], which examined the relationship between PD, smoking, and caffeine, reported that caffeine had minimal effect on PD and provided no significant protection after adjusting for smoking. Additionally, Postuma [5] found no motor improvements, indicating that caffeine did not benefit the motor symptoms of PD.

5.2 Neuroprotective Effects

The previous findings also imply caffeine has neuroprotective effects in Parkinson's disease (PD). As shown in Table 1, Boulaamane [4] and Machado [3] conducted studies demonstrating the neuroprotective effects of caffeine in PD. Boulaamane's study demonstrated that natural caffeine derivatives have the potential to act as antagonists of MAO-B and adenosine A2A (A2A) receptors. Additionally, the study by Machado[3] use a mouse model of agitated depression induced by olfactory bulbectomy (OB). Removing the olfactory bulbs in rodents is known to cause behavioural and neurochemical changes similar to depression and neurodegeneration. The results showed that caffeine repaired neuronal damage in the brains of OB mice. These results have neuroprotective effects on Parkinson's disease. Consistent with these findings, previous studies have shown that caffeine possesses anti-inflammatory and antioxidant properties, which may inhibit neuroinflammation in the brain. One of PD's main symptoms is neuroinflammation induced in the brain by the aggregation of alpha-synuclein. Furthermore, caffeine has also been found to inhibit the A2A receptors, along with the stimulation of antioxidant enzymes that reduce inflammatory responses.

However, this result is shown to be inconsistent with other studies. Previous studies examining the relationship between caffeine and PD have highlighted that, although

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caffeine can be protective, its effects may vary depending on genetic factors. Genetic variations may influence the efficacy of caffeine's neuroprotective effects. Furthermore, Postuma [5] reported findings that contradict the present results. Specifically, caffeine did not significantly reduce insomnia and had no effect on sleep quality, depression, or cognitive function.

5.3 Cautions

These data must be interpreted with caution, as the studies were conducted using different methodologies and at different times, which may introduce uncertainties or biases. For example, Machado [2] used an animal model, and the results may not directly translate to human studies.

5.4 Limitations

The limitations of this study include several factors, such as selection bias and variability among the included studies. Table 1 shows that each study employed a different trial design. This can cause differences in results and methodology, which consequently result in some bias when analyzing and making direct comparisons of results. Furthermore, the interventions varied across studies; some administered 100 mg of caffeine per day or provided caffeine in drinking water, while others used coffee (200–400 mg) instead of pure caffeine, which may introduce additional uncertainties. Another factor that is noticeable in the chosen readings is the duration of each experiment varies from 3 weeks to 10 weeks. One unique experiment among all is the preclinical study carried out by Machado in 2020. The participants in this study were adult CF1 mice, making it the only animal study among the selected readings, which may limit the generalizability of the findings to humans. Participant numbers may also influence the reliability of the results. From Table 1, we can conclude that the number of participants is limited; Ferreira[36] had only 4 participants, and Hamdan[2] only included 27 patients, which is a relatively small amount and could cause more uncertainty for their results. The risk of bias table demonstrates the comprehensive analysis of risk in each study (Table 2).

Table 2 Risk of Bias table

Study/Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting
Ferreira et al. (2016)	Unclear	Unclear	Unclear	Unclear	Low	Unclear randomization and blinding, no serious adverse events
Hamdan et al. (2024)	Low	Low	Low	Low	Low	Double-blind RCT, proper randomization, and blinding
Sharma et al. (2022)	Low	Low	Low	Low	Low	Single-blind, crossover RCT with randomization and blinding
Machado et al. (2020)	Low	Low	Low	Low	Low	Preclinical study, randomization and blinding not fully detailed
Boulaamane et al. (2022)	Unclear	Unclear	Unclear	Unclear	Unclear	Computational study, no experimental data, simulation model

Apart from the selected studies, limited access to publications is another factor that may introduce bias. During the screening process, many papers were excluded because of limited access.This may partly explain why only a small number of studies were ultimately included. Additionally, some limitations arise from the exclusion criteria. For example, studies not published in English were excluded, introducing potential language bias. Moreover, the review only included clinical trials, which may cause study type restriction. Furthermore, only screening the first 10 pages of Google Scholar and filtering in PubMed may had led to some neglection of relevant studies.

6 Conclusion

Overall, caffeine shows a great potential in improving motor and cognitive symptoms of Parkinson's disease, but these findings are not consistent. The evidence summarized in Table 1 illustrates the neuroprotective effects of caffeine and its ability to improve PD symptoms(motor and cognitive). Unfortunately, there are inevitable limitations that need to be considered for this systematic review. Primarily, the heterogeneity of the studies is one of the main factors; the studies vary from computational studies to RCTs. Furthermore, in each clinical study, there are variations in doses and methodology. The type of model—animal or human—also significantly influences the observed outcomes. Despite these promising findings, questions remain, and additional research is needed to better understand the relationship between caffeine and PD. The optimal caffeine dose remains uncertain, as which one is the most effective combination with treatments of caffeine acting as an adjuvant therapy(e.g., Levodopa). Moreover, individual variability in caffeine responses may influence effective dosing, highlighting the need for personalized treatment approaches. Future research should explore tailored caffeine interventions for PD patients.

Additionally, the results remain inconsistent, and some adverse effects are still observed following caffeine consumption, highlighting the need for further research into its potential effects on Parkinson's disease. It is crucial for the future development aiming at PD due to the aging population mentioned before; the cases of PD will significantly rise to be a noteworthy disease, so a considerable amount of studies targeting Parkinson's disease are essential. Despite increasing the number of studies carried out, the need to apply large-scale, long-term human studies could validate the efficacy of the results remains.

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