Parkinson's Disease and Nutritional Interventions

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ABSTRACT

Objective: Parkinson's Disease (PD) is the second most common neurodegenerative disease process in the world. PD is a progressive neurodegenerative disorder that falls under the category of hypokinetic movement disorders. This literature review underscores the growing interest and potential of nutritional interventions as complementary therapies in the management of PD.

Methods: A literature review was performed relevant to therapeutic applications of dietary interventions and nutritional supplementation for PD.

Results: The evidence gathered highlights the intricate relationship between diet, nutrient supplementation, and the pathophysiological mechanisms of PD.

Conclusion: Nutritional interventions for PD or parkinsonism symptoms may be beneficial. The review identifies a gap in the understanding of the long-term effects of therapeutic interventions and their interactions with standard PD medications. Future research should aim to fill these gaps, providing a more comprehensive understanding of how nutrition can be optimally used in PD management.

Keywords: Parkinson's Disease, Diet, Supplements, Nutraceuticals, Ketogenic Diet

INTRODUCTION

Parkinson's Disease is the second most common neurodegenerative disease process in the world. The process is characterized by alpha-synuclein misfolding affecting dopamine signaling of the direct pathway of the basal nuclei at the substantia nigra pars compacta. Symptoms experienced negatively impact patients cognitively, socially, emotionally, and physically. A literature review was performed relevant to the behavioral effects of PD and symptomatology. Nutritional interventions with evidence were analyzed and reviewed. Studies indicated that intestinal dysbiosis, the Western diet, inadequacies in omega3 fatty acids, vitamin D, vitamin B6, environmental toxin exposure, elevated homocysteine, and previous traumatic brain injury are linked to symptomatology associated with PD. Dietary and nutraceutical support may improve symptoms associated with this condition.

Parkinson's disease (PD) is a progressive neurodegenerative disorder that falls under the category of hypokinetic movement disorders. It is clinically manifested by cardinal features such as a resting tremor, muscular rigidity, bradykinesia (slowed movement), and postural instability, often accompanied by a characteristic shuffling gait. While there are various hypokinetic conditions, including Progressive Supranuclear Palsy (PSP), Corticobasal Degeneration (CBD), Multiple Systems Atrophy (MSA), and Lewy Body Dementia (LBD), idiopathic Parkinson's disease emerges as the most prevalent form. Notably, PD is the second-most diagnosed neurodegenerative condition, trailing only Alzheimer's Disease in frequency.[1]

Epidemiologically speaking, the overall prevalence of hypokinetic movement disorders is not precisely determined; however, Parkinson's disease specifically is estimated to affect about 0.3% of the population in industrialized nations—a figure that increases to 1% among those aged 60 and older.[2] There is evidence to suggest ethnic disparities in the prevalence of PD, with higher rates observed in Caucasian populations compared to African or Asian groups. Nevertheless, this data is potentially skewed by factors such as diagnostic accuracy and variability in response rates. Additionally, some studies indicate a higher susceptibility in males, potentially due to the neuroprotective effects of estrogen, though the evidence is not conclusive. The incidence of Parkinson's disease is reported at 8-18 cases per 100,000 person-years, with a significant rise after the age of sixty.[2]

It is crucial to acknowledge the variability in reported prevalence and incidence of PD, which is largely dependent on the methodologies used in the studies and the case-finding strategies employed. Liberal diagnostic criteria can inflate reported figures, while the mode of study—whether in-person assessments or record-based investigations—also influences the reported rates, with in-person approaches generally revealing higher prevalence (by 24% to 42%) and incidence (by 39% to 53%) rates.[1]

The etiology of Parkinson's Disease (PD) lies in its classification as a proteopathy, characterized by the aberrant aggregation of misfolded proteins. More specifically, PD is an alpha-synucleinopathy, which denotes the accumulation of alpha-synuclein protein within certain neural structures. The aggregation predominantly occurs within the basal ganglia, a subcortical brain region integral to motor control. The basal ganglia comprise several interconnected nuclei, including the substantia nigra (pars compacta and reticulata) and the

neostriatum (encompassing the globus pallidus internus and externus, caudate nucleus, and putamen). Within this network, the direct and indirect pathways orchestrate movement, with dopaminergic synapses featuring D1 and D2 receptors being essential for signaling. Parkinsonian syndromes like PD, PSP, CBD, MSA, and LBD result from impaired signaling in the direct pathway, while the indirect pathway's dysfunction leads to hyperkinetic disorders.

PD specifically involves the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc), impacting both pathways due to alpha-synuclein accumulation and subsequent Lewy body formation, though it is primarily characterized as a disorder of the direct pathway. This interruption in dopaminergic signaling is the genesis of the motor deficits typical of PD.

In terms of risk factors, PD is influenced by both genetic and environmental components. A significant non-genetic contributor is exposure to environmental toxins, such as those encountered in certain occupations. Notably, the 1983 discovery that MPTP (4-phenyl-1,2,3,6-tetrahydropyridine) selectively targets and damages dopaminergic neurons in the SNpc highlighted the vulnerability of this region to environmental agents. Various herbicides and pesticides, notably Paraquat and Rotenone, have been implicated in striatal dopamine depletion. Additionally, heavy metal accumulation may foster PD pathogenesis by promoting alpha-synuclein aggregation in the SNpc.

Interestingly, lifestyle factors such as smoking, alcohol intake, and caffeine consumption have been inversely correlated with PD incidence, suggesting a protective mechanism that will be explored further in the context of nutritional interventions. Elevated homocysteine levels have also been identified as a potential risk factor.

Common to many of these risk factors is the induction of systemic inflammation, which subsequently impairs mitochondrial function through ATP synthase inhibition. This inflammation triggers a cascade characterized by heightened cytokine activity in the brain and cerebrospinal fluid, which has been documented in individuals with PD. Post-mortem examinations often reveal activated microglia within the brains of PD patients, indicative of an inflammatory response or possibly autoimmune reactions, as these cells attempt to clear the pathogenic protein accumulations. Additionally, various genetic factors contribute to both the causation and susceptibility of the disease.

Diagnosis of Parkinson’s Disease (PD) is inherently challenging, as definitive confirmation is traditionally achieved post-mortem via neuropathological examination. Despite advancements in clinical assessments, such as the Unified Parkinson’s Disease Rating Scale (UPDRS), there remains an absence of a singular conclusive diagnostic test for PD during a patient's life. Clinicians currently rely on the manifestation of cardinal motor symptoms—resting tremor, bradykinesia, rigidity, and postural instability—to substantiate a clinical diagnosis.

Additional prodromal features, such as anosmia, may herald the onset of motor symptoms, often decades in advance, and are becoming increasingly recognized in the early identification of PD. Certain signs are more specifically suggestive of PD, including the

classic 'pill-rolling' tremor and the distinctive rigidity patterns described as 'cogwheel' or 'lead-pipe'. Oculomotor abnormalities, such as impaired vertical saccades and compromised optokinetic reflexes, along with a stooped posture known as camptocormia, contribute to the clinical picture. Non-motor symptoms, including facial hypomimia, constipation, micrographia, and hypophonia, also inform the clinical diagnosis.

When a comprehensive clinical evaluation yields a pattern of these findings, a provisional diagnosis of PD is typically established. However, the inherent complexity of PD symptomatology underscores the necessity for high precision and caution in clinical judgment.

This review article aims to synthesize the existing body of literature on nutritional interventions for PD, reflecting the growing interest in dietary measures as potential modifiers of neurodegenerative processes. Recent research has begun to unravel the intricate relationships between nutrition, systemic health, and neurodegeneration, offering insights into how dietary practices and targeted nutrient administration may influence the course of PD. There is an emerging emphasis on the gut-brain axis, particularly the role of the intestinal microbiome, in modulating PD pathology. By exploring these associations, this review seeks to elucidate nutritional strategies that could potentially contribute to the management, and conceivably the prevention, of PD.

METHODS

In conducting this comprehensive review, we systematically searched electronic databases for scholarly articles addressing the intersection of Parkinson's Disease (PD) and nutritional interventions. We utilized PubMed, Google Scholar, and CINAHL as the primary repositories for sourcing the literature. Our search strategy employed a combination of terms tailored to each database to optimize relevance and specificity: 'Parkinson's Disease' paired with 'nutritional supplements' for PubMed, 'Parkinson's Disease' with 'nutraceuticals' for Google Scholar, and 'Parkinson's Disease' in conjunction with 'Ketogenic Diet' for CINAHL.

The inclusion criteria were confined to studies published in the English language, thereby streamlining the scope of our review. We selectively extracted studies that primarily examined the therapeutic applications of nutrition in PD or explored nutrition-related systemic alterations amenable to dietary interventions, excluding those that primarily focused on the pathogenic underpinnings of the disease. This selection criterion significantly narrowed the field of relevant research, as literature on PD pathophysiology substantially outweighs that on therapeutic nutritional strategies.

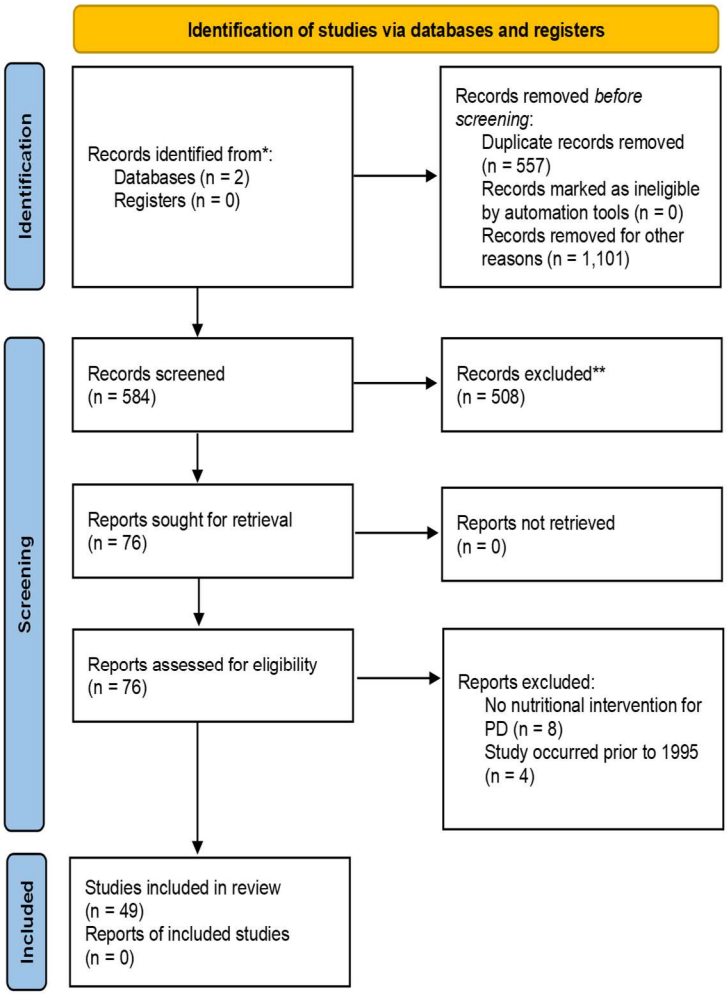
From the chosen studies, we extracted content that explicitly or implicitly related to therapeutic nutritional strategies or interventions in the context of PD or broader neurodegenerative processes. Our synthesis of the data involved a qualitative analysis of the proposed nutritional interventions for PD and related neurodegenerative conditions.

We applied filters to include a range of robust study designs: clinical trials, meta-analyses, randomized controlled trials (RCTs), and systematic reviews. In our review, we

encompassed cohort studies, epidemiological research, RCTs, meta-analyses, and systematic reviews that were published with full texts available from 1995 through 2022. Any studies that did not directly pertain to Parkinson's Disease were meticulously excluded to maintain a clear focus on the review's objectives.

RESULTS

A database search for this review resulted in 2242 abstracts. After accounting for duplicates and abstracts that did not meet inclusion criteria, 584 papers remained. Based on the title and abstract provided, 76 papers were considered relevant. After a full text review, 63 papers were included in this review. Included studies were papers involving nutraceutical and dietary interventions for treating Parkinson's Disease, as well as etiology reviews and population studies discussing current perspectives on Parkinson's Disease treatment.



DISCUSSION

Neuronal Resting Membrane Potential: Mitochondrial Requirements and Interventional Considerations

Within the realm of neurophysiology, the integrity of neuronal resting membrane potential is paramount for proper neural function and is intricately linked to mitochondrial health. The fundamental determinants for the maintenance of a stable resting membrane potential encompass a constellation of requirements: adequate oxygen supply, glucose, neuronal stimulation, and a robust mechanism for mitochondrial uncoupling during oxidative stress conditions. Collectively, these factors facilitate an enhanced synthesis of adenosine triphosphate (ATP), bolstering neuronal resilience and sustaining the activity of the sodium-potassium ATPase, a critical ion pump that regulates intracellular sodium levels.

A critical analysis reveals that impediments to these vital components can stem from various physiological dysfunctions. Compromised blood flow and anemic conditions can attenuate oxygen delivery to neurons. Dysglycemia—a hallmark of metabolic disorders—can disrupt glucose availability, while inadequate physical or cognitive activity can result in suboptimal neuronal stimulation. Moreover, inflammatory processes, autoimmune reactions, and the bioaccumulation of environmental toxins may inhibit the essential process of mitochondrial uncoupling, a protective mechanism against oxidative stress.

Such disruptions can precipitate a cascade of detrimental effects including a significant reduction in ATP generation. This deficit in energy production undermines neuronal stamina, precipitating a precipitous onset of fatigue. Additionally, it impedes the sodium-potassium pump's function, leading to an aberrant accumulation of intracellular sodium. Addressing these underlying conditions is paramount in restoring and maintaining the delicate equilibrium required for optimal neuronal function.

Nutritional Interventions in Neurodegenerative Disorders: Insights and Evidence

Nutritional strategies present a multifaceted and increasingly recognized approach for therapeutic intervention in the spectrum of neurodegenerative diseases, with PD being a prime candidate for such interventions. The complexity of PD, characterized by the progressive degeneration of dopaminergic neurons and the presence of alpha-synuclein aggregates,[1] necessitates a comprehensive approach that includes, but is not limited to, dietary modifications, targeted nutraceutical supplementation, and a potential reevaluation of gastrointestinal health. Dietary patterns, such as the ketogenic diet and caloric restriction, have been posited to exert neuroprotective effects, potentially through the modulation of energy metabolism and the enhancement of mitochondrial function.[3] Concurrently, specific nutrients such as omega-3 fatty acids, Coenzyme Q10, and various B vitamins have been implicated in mitigating oxidative stress and supporting mitochondrial biogenesis, suggesting a synergistic role in stalling or possibly reversing the pathophysiological processes of PD.[24,32,60] Collectively, these nutritional interventions embody a promising therapeutic adjunct, offering a non-pharmacological arsenal against the debilitating progression of neurodegenerative disorders.

Dietary Interventions in PD: Ketogenic Diet and Intermittent Fasting

This review synthesizes current research on dietary interventions that hold promise for modifying the disease process and providing symptomatic relief. Among these, the ketogenic diet (KD) and intermittent fasting (IF) have garnered attention. Uncontrolled clinical trials and animal studies suggest that such diets could confer both symptomatic and disease-modifying benefits across a spectrum of neurodegenerative diseases, such as Alzheimer's and Parkinson's, and even in conditions like traumatic brain injury and stroke.[3] The mechanisms posited include the stimulation of mitophagy and mitochondrial biogenesis during dietary restriction, which could act as a quality control mechanism, enhancing mitochondrial turnover.[4]

Intermittent Fasting

IF in particular has shown promise in mouse models where it has been demonstrated that fasting every other day increases the levels of brain-derived neurotrophic factor and glial-derived neurotrophic factor in the nigrostriatal pathway and attenuates MPTP-induced dopaminergic neuronal loss and astroglial activation in the substantia nigra and the striatum.[5] Dysfunction in mitochondria, excessive oxidative stress, and the targeted demise of specific neurons are recognized as underlying factors in the development of PD. This complex pathology gives rise to symptoms that encompass difficulties with motor function, mood disorders such as depression and anxiety, and cognitive deficits.[6,7,8] Studies have indicated that a Fasting Mimicking Diet (FMD) has been shown to modify gut microbiota composition, reestablish astrocyte and microglia equilibrium in the substantia nigra via metabolic signaling, and reduce inflammatory reactions in these PD models.[9] Additionally, research involving an animal model that simulates early-onset autonomic dysfunction in PD found that Alternate-day Fasting (ADF) enhanced cardiac autonomic regulation, ameliorated elevated resting heart rates, and rectified impaired cardiovascular reactivity, which were correlated with a decrease in parasympathetic function and a buildup of alpha-synuclein within the brainstem.[10]

Ketogenic Diet

In a preliminary investigation by VanItallie et al.[11] with a small cohort (n = 7), the impact of a KD on individuals with Parkinson's Disease (PD) was explored. Out of seven participants, five successfully adhered to the diet regimen, each exhibiting enhanced scores on the Unified Parkinson's Disease Rating Scale (UPDRS), including motor function improvements. Notably, the most compliant three participants achieved a mean serum β-hydroxybutyrate (β-HB) level of 6.6 mmol/L, indicating substantial ketosis. A subsequent, more extensive study by Phillips et al.[12] in 2018 involved 47 PD patients in a randomized setup to compare a modified ketogenic diet to a low-fat diet over eight weeks. The average serum β-HB in the ketogenic diet group reached 1.15 mmol/L. Notably, this group experienced a 41% improvement in the UPDRS I scores, which assess non-motor aspects of daily living, in stark contrast to the 11% improvement observed in the control group. This improvement was particularly evident in symptoms such as fatigue, daytime sleepiness, pain, urinary problems, and cognitive impairments. Further, a pilot trial by Krikorian et al.[13] assessed the KD's effects in 14 participants with mild cognitive impairment (MCI)

secondary to PD. The KD group showed an average increase in serum β-HB to 0.31 mmol/L and significant memory enhancements compared to the control diet group, although no notable changes in motor symptoms were detected.

In a recent study, Norwitz et al.[14] conducted a double-blind, placebo-controlled, crossover trial involving 14 individuals with PD, to evaluate the impact of an acute ketone ester supplementation against a carbohydrate placebo equivalent on exercise endurance. The ketone supplement significantly increased the mean β-hydroxybutyrate (β-HB) levels to 3.5 mmol/L within a half-hour of ingestion. This increase correlated with a notable 24% enhancement in the participants' capacity for endurance exercise relative to the carbohydrate placebo. These findings indicate that ketone ester intake may positively affect motor capabilities in PD.

Further investigation is warranted to clarify how ketogenic methods may ameliorate the motor symptoms associated with PD, given the varying levels of ketosis induced by different protocols. Preliminary evidence suggests that stronger ketone-producing agents and higher resultant β-HB concentrations may be required to exert a considerable impact on motor symptoms. Additionally, it is conceivable that a comprehensive treatment strategy, incorporating therapeutic ketosis as one facet, might be necessary to fully address the multifaceted nature of PD's pathophysiology.[15] According to the American Academy of Neurology (AAN) standards, the current body of research yields a "C" rating (potentially effective) for addressing non-motor symptoms and a "U" rating (evidence insufficient or conflicting) for motor symptoms in PD. Nonetheless, with optimistic initial results and numerous ongoing studies, these recommendations could potentially change in the near future.

A particular focus has been on the intersection between PD and metabolic disorders such as Type 2 Diabetes Mellitus. Research indicates shared pathophysiological mechanisms, chiefly perturbations in glucose metabolism, which may exacerbate PD.[16] Insulin and Insulin-like Growth Factor-1 (IGF-1) signaling pathways, involved in PD, highlight the potential exacerbating role of metabolic abnormalities and peripheral inflammation in the progression of nigrostriatal dopaminergic system degeneration.[16] This insight also suggests that targeting peripheral inflammation with dietary strategies like the KD could yield therapeutic benefits.

Gut Dysbiosis

Furthermore, the gut-brain axis has emerged as a significant area of interest in understanding PD etiopathogenesis. The gut microbiota’s role is increasingly acknowledged, where dysbiosis and small intestinal bacterial overgrowth could trigger systemic inflammation, potentially initiating pathogenic processes such as alpha-synuclein misfolding.[17] Early Lewy body pathology affecting the enteric nervous system and the dorsal motor nucleus of the vagus provides insights into the gastrointestinal dysmotility observed in PD, implicating both central and peripheral pathogenetic mechanisms.[18,19]

Experimental evidence underscores that various forms of alpha-synuclein can propagate from the gut to the brain, with microtubule-associated transport being implicated in the

neuronal translocation of aggregated alpha-synuclein.[20] The discovery of abnormal intestinal permeability in PD subjects and its correlation with intestinal alpha-synuclein accumulation — a PD hallmark — further accentuates the relevance of the gut in the disease process.[21] This body of evidence substantiates the rationale for supporting gut health to potentially mitigate alpha-synuclein misfolding and its consequences.

In summary, the current literature indicates a potential role for nutritional interventions influencing systemic inflammation and gut health in the therapeutic landscape of PD and related neurodegenerative disorders.

Nasal Dysbiosis

Impairment of the sense of smell is an early non-motor indication of PD, manifesting long before the clinical diagnosis, and it can have a detrimental impact on the life quality of individuals with PD. It has been suggested that alterations in the microbial populations in the deep nasal passages, in close proximity to the olfactory bulb, may initiate a neuroinflammatory process in the olfactory bulb, which could contribute to the depletion of dopamine typically seen in PD. Recent research has demonstrated that PD patients can possess notable differences in the prevalence of certain microorganisms, including a higher presence of potentially harmful species like *Moraxella catarrhalis*.[22] Notably, significant associations have been found between the presence of *M. catarrhalis* and more pronounced motor symptoms in those with PD. This research points to the possibility that certain pathogens can be identified in the olfactory bulb and that specific alterations in the microbial community of PD patients may stem from environmental factors uniquely associated with living with the disease. This opens the door to novel treatment avenues such as the potential for intranasal probiotic therapy.

Methylation and Hyperhomocysteinemia

Within the context of PD, hyperhomocysteinemia has garnered interest due to its potential contributory role in neurodegenerative processes. Recent studies suggest that deviations in homocysteine metabolism could influence the pathophysiological landscape of PD.[23] Notably, elevated homocysteine levels have been observed in PD patients, a phenomenon predominantly attributed to the methylated degradation of L-Dopa, a cornerstone in PD management.[23] The relationship between L-Dopa treatment and increased homocysteine concentrations has been substantiated through meta-analytical evidence.

Methylcobalamin, L-5-Methyltetrahydrofolate, and Pyridoxine

Vitamins, particularly of the B complex, have been recognized for their role in modulating homocysteine levels and serving as methyl donors, which may support neurological health in PD. Data indicates that PD patients often exhibit lower levels of vitamin B12 and comparable folate levels relative to control subjects.[24] Additionally, high dietary intake of vitamin B6 has been inversely associated with PD risk.[24] This seems to be due to the fact that chronic administration of levodopa is frequently associated with the development of peripheral neuropathy. Research indicates that the cumulative exposure to levodopa, coupled with insufficiencies in B-complex vitamins such as B6, B9, and B12, as well as genetic

predispositions, are significant contributors to the onset of neuropathy. This condition is further characterized by increased levels of methylmalonic acid (MMA) and homocysteine. The spectrum of neuropathic manifestations ranges from acute presentations, resembling Guillain–Barré syndrome, to more subacute and chronic forms.[25] Particularly at risk are patients subjected to daily doses of levodopa exceeding 2,000 mg or those whose dosage is escalated swiftly, such as during the commencement of Levodopa-Carbidopa Intestinal Gel (LCIG) therapy.[26] Elevated homocysteine levels combined with diminished pyridoxine are primarily implicated in the development of this adverse effect.

Thiamine and PD

Notably, serum thiamine levels have been found to be significantly lower in PD patients, with supplementation yielding promising clinical outcomes.[27] Thiamine has been shown to play a beneficial role in PD by promoting dopamine release and alleviating symptoms related to the condition. Advances in genetic research have shed light on specific proteins that serve as links between thiamine and PD pathogenesis. Moreover, thiamine impacts PD through both genomic and nongenomic pathways. Several elements implicated in PD and influenced by thiamine include the DJ-1 gene, excitatory amino acid transporters, the α-ketoglutarate dehydrogenase complex, coenzyme Q10, lipoamide dehydrogenase, genes located on chromosome 7, transcription factor p53, components of the renin–angiotensin system, heme oxygenase-1, and poly(ADP-ribose) polymerase-1.[28]

Additionally, gastrointestinal issues are prevalent among PD patients, potentially interfering with treatment efficacy.[29] Delays in gastric emptying are commonly observed in those with PD.[30] Furthermore, a reduction in passive absorption through the enterocyte brush border has been noted in PD patients, complicating the efficient uptake of therapeutics and nutrients.[31]

Cell Membranes

In the evolving landscape of PD therapeutics, the potential role of fatty acid supplementation has garnered considerable interest. Omega-3 polyunsaturated fatty acids (PUFAs), particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are increasingly recognized for their neuroprotective properties. Mechanistically, these PUFAs are thought to modulate neuroinflammation, a key component of PD pathophysiology, by influencing the inflammatory cytokine milieu and enhancing the resolution of neuroinflammatory responses. Furthermore, DHA and EPA are integral to maintaining neuronal membrane fluidity and integrity, which could be crucial in countering the dopaminergic neuronal loss characteristic of PD. Additionally, the role of monounsaturated fatty acids (MUFAs) such as oleic acid, typically abundant in the Mediterranean diet, is being explored for its potential anti-inflammatory and antioxidant effects. Emerging evidence suggests a beneficial impact on mitochondrial dysfunction and oxidative stress, both of which are pivotal in the progression of PD. However, the optimal dosages, formulations, and specific fatty acid profiles for maximal therapeutic benefit in PD remain to be conclusively determined, necessitating further robust clinical trials to elucidate these aspects. Nonetheless, the incorporation of specific fatty acids into the dietary regimen of PD patients could represent a promising adjunct to current pharmacological interventions, potentially mitigating disease progression

and improving quality of life.

DHA

In the realm of nutraceutical interventions, the impact of DHA on brain function presents a compelling avenue for research. Animal studies have demonstrated that oral DHA administration can modulate brain DHA levels, suggesting potential modifications in brain functionality relevant to disorders such as Alzheimer's and PD.[32] Further, brain levels of essential n-3 PUFAs, which are reliant on dietary sources, have been shown to influence elements critical to dopaminergic synapses. For instance, a deficiency in n-3 PUFAs in rats leads to decreased expression of brain-derived neurotrophic factor (BDNF) through a p38 MAPK-dependent pathway.[33] Considering the observed reduction of BDNF in PD post-mortem analyses, n-3 PUFA supplementation could represent a viable strategy to enhance BDNF production in the cerebral context.

EPA

Phospholipids enriched with Eicosapentaenoic acid (EPA-PL), commonly found in marine sources, have garnered attention for their potential neuroprotective effects. While the combined impact of EPA and DHA on PD has been documented, the specific influence of EPA alone remains less clear. Recent research has focused on EPA-PL derived from the sea cucumber (*Cucumaria frondosa*) and compared its effects against commercially available EPA in ethyl ester form (EPA-EE) in a mouse model of PD induced by the neurotoxin MPTP.[34] The results indicate that dietary supplementation with EPA-PL, rather than EPA-EE, significantly ameliorated behavioral deficits induced by MPTP. Further investigations have revealed that EPA-PL effectively mitigated oxidative stress and apoptotic processes triggered by MPTP, contributing to the preservation of dopaminergic neurons. This neuroprotection was mediated through the mitochondrial pathway and the mitogen-activated protein kinase pathway. Thia serves to demonstrate that EPA-PL can positively impact the symptoms and pathological progression of PD induced by MPTP, offering valuable insights for future preventive and therapeutic strategies against neurodegenerative disorders.

DGLA

Interestingly, recent research has found plasma levels of α-linolenic acid (ALA), linoleic acid (LA), and arachidonic acid (AA) to be reduced in the PD patients.[35] There was no substantial link between the dietary intake of PUFAs and their plasma levels in the PD cohort. Notably, in the PD patients, plasma levels of ALA and LA showed an inverse association with motor symptom severity, whereas docosahexaenoic acid and AA levels exhibited a positive correlation with non-motor symptoms, factoring in age and sex adjustments. This suggests a potential for supplemental Dihomo-y-linolenic acid supplementation to be administered in PD patients as direct precursor to arachidonic acid. Although, other research has shown DGLA to contribute to cellular ferroptosis.[36] While this has been a novel discovery for the targeting of senescent[37] and cancerous cells, research also suggests that externally sourced DGLA predominantly induces neurodegenerative effects in dopaminergic neurons via ferroptosis through its metabolite formed by cytochrome P450-epoxide hydrolase (CYP-EH), known as dihydroxyeicosadienoic acid (DHED) and is

actually pronounced in PD patients due to their potential for iron accumulation.[38]

The role of AA in Parkinson's Disease PD is a topic of ongoing debate. There is research suggesting that metabolites of AA, known as epoxyeicosatrienoic acids (EETs), might be beneficial in treating PD.[39] These compounds are found throughout the brain and are known for their anti-inflammatory and antioxidant properties. The same research team found that EETs could boost antioxidant enzyme levels and reduce oxidative stress and inflammation in a fruit fly model of PD. However, there's another side to this story. In PD, α-synuclein plays a critical role. Normally, in healthy neurons, this protein exists in the less harmful, a-helical form. There is data showing that AA can encourage α-synuclein to assemble a-helically, suggesting that AA might reduce neuronal damage in PD.[40]

Yet, the situation is more complex. AA interacts with a protein called fatty acid-binding protein 3 (FABP3), known to be an early marker of dementia and PD and prevalent in dopaminergic neurons.[41] When AA binds to FABP3, it seems to promote the harmful aggregation of α-synuclein in certain cell types. Supporting this, a study by Julien et al. in 2006 found higher levels of AA in the brains of PD patients upon postmortem examination.[42] Furthermore, a 2019 meta-analysis concluded that diets high in cholesterol and AA could increase the risk of developing PD.[43]

In summary, both AA and precursor dietary DGLA have contradictory evidence regarding their role in PD.

Neuroprotection and Neuroinflammation

Flavonoids

Flavonoids, a substantial family of phenolic compounds derived from plants, are commonly found in various plant-based foods and drinks. Structurally, these compounds are characterized by a 15-carbon framework that comprises two benzene rings, labeled A and B, linked through a heterocyclic pyrone ring known as the C ring. They are categorized into six primary subgroups - flavones, flavonols, flavanones, flavanols, isoflavones, and anthocyanins. This classification is based on the specific attachment point of the B ring to the C ring, alongside the level of oxidation and the pattern of substitution that occurs on the C ring.[44] Numerous research studies have indicated that flavonoids, despite having limited bioavailability, offer a variety of health advantages, including the potential to lower the risk of PD. These benefits are attributed to the biological activities of flavonoids, such as their antioxidant, anti-inflammatory, anti-apoptotic, and lipid-reducing properties.[45]

Apigenin

Apigenin (AGN), a non-mutagenic flavone present in many fruits and vegetables, demonstrates a range of biological activities. These include its ability to prevent cell death (anti-apoptotic), reduce inflammation (anti-inflammatory), and neutralize free radicals. Recent research demonstrate data which indicate that AGN confers neuroprotection against dopaminergic neuronal degradation in the nigrostriatum in a rotenone-induced mouse model of PD,[46] wherein it mitigated mitochondrial dysfunction, a-synuclein accumulation and

motor deficits.

Quercetin

Quercetin is a flavonoid known for its neuroprotective and antioxidant effects and has been shown in rotenone-induced a mouse model of PD to significantly mitigate behavioral impairment while simultaneously augmenting autophagy and ameliorating endoplasmic reticulum stress-induced apoptosis.[46]

Luteolin

Luteolin, a polyphenolic compound found in foods like celery, green peppers, perilla leaves, and chamomile tea, has been recognized for its anti-mutagenic, anti-tumorigenic, antioxidant, and anti-inflammatory properties and recent research has demonstrated that luteolin not only reduces oxidative stress, but also delays the loss of climbing ability of PD model flies that express human alpha synuclein in their brains.[47]

Rutin

Rutin is a flavonoid that is found abundantly in many plants, such as Eucalyptus, passionflower, buckwheat, tea, and apple that may prevent neuroinflammation. It is thought to be antioxidant and a free radical scavenger. Rutin is hydrolyzed in the gastrointestinal tract to release another flavonoid, quercetin, which is ultimately responsible for many of the primary actions of rutin. It has been demonstrated previously to protect dopaminergic neurons from oxidative stress in an animal model of PD.[48]

Catechin/Epigallocatechin and Proanthocyanidin

Tea ranks among the top beverages consumed globally. The three main varieties, green, black, and oolong tea, all originate from the *Camellia sinensis* (L.) O. Kuntze plant. Of these, green tea has received the most attention in research for its potential health benefits, including its impact on conditions like cancer, obesity, diabetes, as well as inflammatory and neurodegenerative diseases. Green tea contains flavonoids known as green tea catechins (GTC)s.

In a study involving over 129,000 people, researchers found a link between eating flavonoid-rich foods and a lower chance of developing PD. Specifically, they noticed that those who consumed more epicatechin (EC) and proanthocyanidin dimers, both found in certain foods, seemed to have a reduced risk of PD.[49] The researchers suggest that EC might help by activating a specific protein that supports brain cell health and learning processes, and by reducing the activity of a certain enzyme. Similarly, proanthocyanidins could help by increasing dopamine levels in the brain, slowing down another enzyme's activity, and protecting against certain types of brain cell damage. This study suggests that compounds found in tea, particularly catechin derivatives, might contribute to its potential benefits in preventing PD.

Naringenin

Naringenin is a major citrus flavonoid that is widely distributed in oranges, grapes, and tomatoes that has a bioactive effect on human health. It has several anti-inflammatory properties and has been demonstrated to decrease a-synuclein expression and neuroinflammation in MPTP-induced PD model in mice.[50]

Turmeric

There's growing evidence that problems with mitochondria and oxidative damage may contribute to the development of PD. This idea has gained support from animal studies, where the use of a specific inhibitor that targets part of the cell's energy production system closely reproduced the biochemical and tissue characteristics seen in PD. Various compounds have been identified that could potentially improve cellular energy processes and offer antioxidant benefits. One such compound is turmeric (*Curcuma longa* L.), a widely used medicinal plant in traditional practices like Ayurveda, Unani, and Siddha. It's commonly used as a home remedy for various ailments. Data from as far back as 2011 suggests that regular dietary intake of turmeric may boost the brain's antioxidant capacity and shield it from oxidative and nitrosative stress, thereby helping to prevent neurodegenerative damage.[51] Current research highlight the need for a deeper examination of turmeric and its constituents that may influence neuronal health and guard against neurotoxic effects.[52] These insights could aid in refining dietary habits and creating therapies with minimal side effects for in vivo applications.

Resveratrol

Resveratrol is a polyphenol most often recognized for its presence in red wine. A 2021 review encompassing 18 studies assessed the protective efficacy of resveratrol in animal models of PD. These studies were meticulously selected from three different databases. The findings from the analysis demonstrate that resveratrol exhibits significant neuroprotective properties across various PD models, as determined through quantitative methods.[53]

Silymarin

Silymarin, composed of flavonolignans like silybin, isosilybin, and silychristin, along with minor quantities of flavonoids (like taxifolin), fatty acids, and other polyphenolic substances, is derived from the dried fruit of the *Silybum marianum* plant. Historically, it has been used in clinical settings for its liver-protecting properties. Its potential for neuroprotection has been explored in different models of neurological conditions, including Alzheimer’s disease, PD, and cerebral ischemia. A review conducted in 2018 looking at in vitro and in vivo studies of silymarin’s anti-parkinsonian effects concluded that silymarin was a beneficial therapeutic choice in the treatment of PD due to its mitigation of dopaminergic neuron apoptosis in the substantia nigra, but also discusses silymarin’s poor bioavailability.[54]

Baicalein

For many years, mitochondrial dysfunction has been associated with the development of PD. Recently, it's been discovered that issues with mitochondrial biogenesis (mitobiogenesis) are frequently observed in PD cases. Baicalein, a primary active component found in *Scutellaria baicalensis Georgi*, has shown neuroprotective properties in various PD experimental models. Recent research findings demonstrate that baicalein alleviates behavioral issues and loss of dopaminergic neurons caused by rotenone in a rat model.[55] Additionally, baicalein was effective in restoring mitochondrial health and improving mitobiogenesis measured via mitochondrial density in the rotenone-induced parkinsonian rats.

Ginkgo Biloba

Ginkgo is one of the oldest living tree species and extracts of this tree have been used to treat memory problems and are thought to serve as natural cholinesterase inhibitors. The neuroprotective effects of EGb 761, a type of Ginkgo extract, particularly against MPTP-induced neurotoxicity, have been associated with the modulation of dopamine-related gene expression and transcription factors like Nurr1, essential for the preservation of dopaminergic neuron functionality.[56]

Tobacco and Caffeine

Prevailing epidemiological data suggests an intriguing inverse association between the incidence of PD and the consumption of tobacco and caffeine.[57] Two prevailing hypotheses exist to explain this phenomenon: the first posits that individuals predisposed to PD may inherently exhibit an aversion to substances like coffee and nicotine; the second suggests that these substances might exert a neuroprotective effect. Beyond these hypotheses, it has been suggested that the consumption of coffee and cigarettes may influence gut microbiota composition in a manner that reduces intestinal inflammation. This alteration could potentially attenuate the misfolding of alpha-synuclein, a protein implicated in PD pathology.[57]

Magnesium

Magnesium intake has demonstrated neuroprotective properties in models of neurotoxicant-induced PD as well.[58] Numerous investigations have demonstrated a decrease in magnesium (Mg) levels in individuals with PD. Experimentation has shown that in rats aged one year, which were fed a diet with Mg levels reduced to one-fifth of the normal intake over several generations, there was a pronounced loss of dopaminergic neurons specifically in the substantia nigra. Research has uncovered a notable and impactful role of Mg in safeguarding against damage to neurites and neurons.[58]

Glutathione

Glutathione is the human organism’s master antioxidant. While an exhaustive exploration of all the ways glutathione is neuroprotective exceeds the scope of this paper, it is noteworthy to mention the observed correlation between depleted glutathione levels and PD.[59]

Considering glutathione's role in cellular antioxidant defense mechanisms, its fortification in clinical settings warrants consideration as a therapeutic adjunct in PD management.

Mitochondrial Support Coenzyme Q10, Carnitine, Riboflavin, Niacin, Alpha-Lipoic Acid, and Magnesium, methylene blue

Various hypotheses have been proposed regarding the underlying causes of PD, with mitochondrial dysfunction being a key factor in both its sporadic and hereditary variants. This dysfunction is characterized by a range of issues including bioenergetic flaws, mutations in mitochondrial DNA, mutations in nuclear DNA genes associated with mitochondria, and alterations in mitochondrial dynamics, such as fusion or fission processes. Additionally, changes in mitochondrial size and shape, modifications in trafficking or transport mechanisms, impaired mitochondrial movement, transcriptional dysregulation, and the presence of mutated mitochondrial-associated proteins are also implicated in the pathogenesis of PD. There are various nutritional interventions that have been studied to treat these dysfunctions.

Coenzyme Q10 and Riboflavin

Coenzyme Q10 (CoQ10) has garnered significant interest as a nutritional intervention in PD due to its role in mitochondrial function and antioxidant properties. In PD, mitochondrial dysfunction is a well-documented phenomenon, and CoQ10, a key component in the mitochondrial electron transport chain, could potentially counteract this dysfunction. Earlier research delved into the neuroprotective mechanisms of CoQ10. Researchers found that combining CoQ10 with riboflavin significantly improved mitochondrial function and had a protective effect against neurodegeneration in PD models.[60] This highlights the potential of CoQ10 not just as a standalone treatment, but in combination with other vitamins.

Acetyl-L-Carnitine and A-Lipoic Acid

Acetyl-L-carnitine (ALC) and alpha-lipoic acid (ALA) are two compounds that have been explored as potential treatment strategies for PD due to their roles in cellular metabolism and antioxidant protection. Research in this area is focused on how these compounds might mitigate the mitochondrial dysfunction and oxidative stress often associated with PD. Research conducted in 2013 suggests that these compounds could protect dopaminergic neurons and improve mitochondrial function and emphasizes the importance of mitochondrial health in PD and proposes ALC and ALA as potential agents to counteract mitochondrial-related neurodegeneration.[61]

Niacin

Niacin, also known as Vitamin B3, has been explored in the context of treating PD due to its potential role in cellular metabolism and neuroprotection. Research in this area primarily focuses on how niacin might influence the health and function of neurons, particularly in the brain regions affected by PD. One significant angle of investigation is niacin's ability to activate specific receptors in the brain, known as PPAR receptors. These receptors play a crucial role in managing oxidative stress and inflammation, both of which are prominent

features in the pathogenesis of PD. By stimulating these receptors, niacin could potentially offer neuroprotective effects, reducing the damage to dopaminergic neurons, which are critically affected in PD.[62] Moreover, niacin is known to be involved in energy metabolism, a vital aspect considering the mitochondrial dysfunction observed in PD. Enhancing mitochondrial function and energy production in brain cells might be another way through which niacin contributes to neuroprotection in PD.

Iron

Iron supplementation is generally contraindicated in PD treatment due to several reasons. Iron can exacerbate oxidative stress, a key factor in PD pathogenesis. The involvement of iron in Fenton reactions leads to the production of harmful hydroxyl radicals. Additionally, the substantia nigra naturally has high iron levels. In PD, there's an abnormal iron accumulation in this area, which can worsen dopaminergic neuron degeneration.[63] Iron is also thought to promote the aggregation of alpha-synuclein. This protein forms Lewy bodies, characteristic of PD.[63]

CONCLUSION

In conclusion, this literature review underscores the growing interest and potential of nutritional interventions as complementary therapies in the management of PD. The evidence gathered from various studies highlights the intricate relationship between diet, nutrient supplementation, and the pathophysiological mechanisms of PD.

However, it's also evident from the review that the field is still in its nascent stages. While preliminary studies are promising, there is a need for more extensive, well-designed clinical trials to establish the efficacy, safety, and appropriate dosages of these nutritional interventions. It is also crucial to recognize the individual variability in response to these interventions, highlighting the need for personalized dietary plans for PD patients.

Moreover, the review identifies a gap in the understanding of the long-term effects of these interventions and their interactions with standard PD medications. Future research should aim to fill these gaps, providing a more comprehensive understanding of how nutrition can be optimally used in PD management.

In essence, this review points towards a hopeful direction where nutrition interventions may be beneficial for those with PD or managing parkinsonism symptoms. However, it also calls for cautious optimism and a balanced approach, integrating scientific evidence with clinical prudence to harness the full potential of nutritional interventions in PD.

LIMITATIONS

There were limitations for this review. Due to the large number of preliminary studies this review is limited by a lack of more extensive, larger scale, and well-designed clinical trials to establish the efficacy, safety, and appropriate dosages of these nutritional interventions for PD. The research highlighted variability between individuals in response to dietary and nutritional interventions for PD. Future research is needed to identify the potential benefits

of nutritional interventions with limited research identified in this review.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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