

## Review Article

## Nutrition and Parkinson's Disease: What is the interplay?

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**ABSTRACT**

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease and affects about 1% of the population over the age of 60 years in industrialized countries. The aim of this review is to examine nutrition in PD. The Parkinson's disease (PD) patients has increased over the past few years to 8.5 million people in 2019. Early-stage symptoms of Parkinson's disease such as malnutrition and weight loss are eminently related to nutrition. Parkinson's disease (PD) is a progressive neurological disorder characterized by motor and non-motor features. The clinical characteristics of PD are associated to dopamine deficiency in the substantia nigra pars compacta. The causes of Parkinson's disease in terms of biochemical factors such as dopaminergic neuron loss and MPTP neurotoxins that cause neuronal death are addressed. Individuals with PD are at increased risk of malnutrition due to the increased metabolic demands and disease pathophysiology. Risk of malnutrition is further complicated by anosmia, swallowing difficulties, constipation, and drug-nutrient interactions. An emerging body of evidence suggests that the intestinal tract is affected early in the disease, creating therapeutic opportunities for early intervention. Dietary modification and nutritional supplementation may improve symptoms of constipation, depression, insomnia, dystonia, and help prevent cognitive dysfunction. Edible bird's nest which is high in neuroprotective chemicals shows good potential against Parkinson's disease. It is important to understand the interplay between PD, comorbidities and nutritional status. The positive impact of vigorous aerobics exercise for the Parkinson's disease patients' is also emphasized. The physical exercise will enhance PD patients' motor function and brain health. Increasing understanding of the relationship between nutrition and Parkinson's disease will lead to the future discovery of the disease's etiology. Further research may contribute to the development of interventional strategies to improve symptoms, augment care and, importantly, enhance the quality of life for patients living with this complex neurodegenerative disease. This review summarizes the state of the science related to nutrition and non-motor symptoms of PD.

**KEYWORDS:** Parkinson's Disease,  $\alpha$ -syn, Substantia nigra (SN), Nutrition, Levodopa



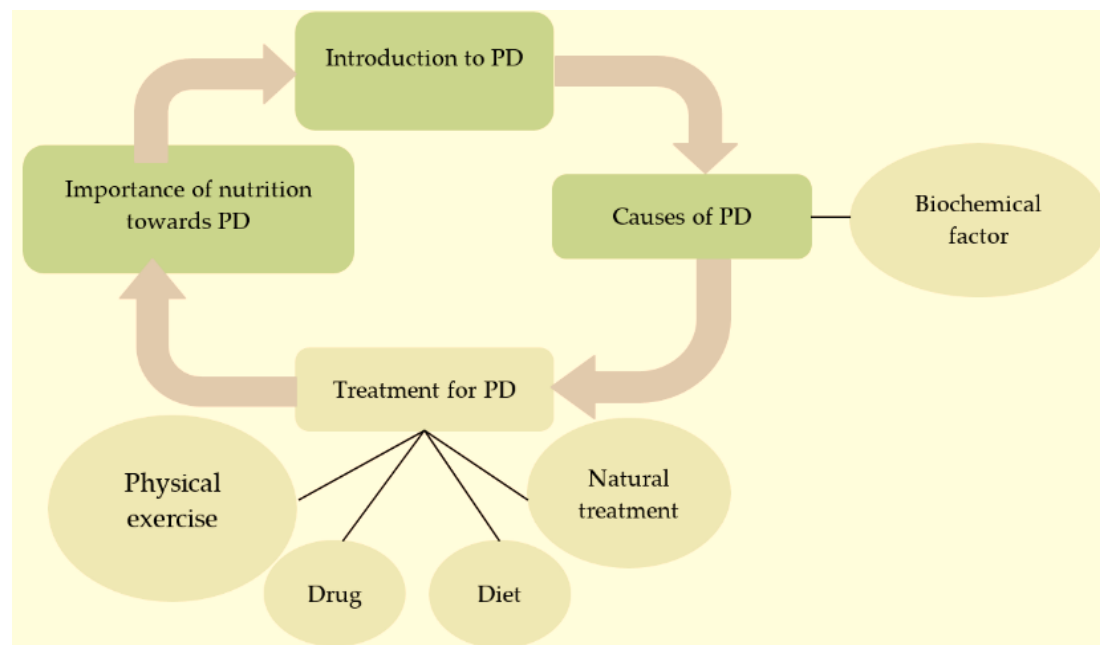
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## 1. Introduction

Parkinson's disease PD is the second most prevalent neurodegenerative disorder that is brought on by the degeneration of nerve cells occurring in the brain region that modulates movements [1]. While the prevalence of PD is expected to increase, no preventative or curative therapy for PD exists at this time. Although nutrition and diet represent modifiable risk factors for reducing chronic disease risk, research on the impact of single nutrients on PD has yielded mixed results [2]. According to Bexci & Subramani, there were between 15,000 and 20,000 PD patients in Malaysia in 2018, and they estimated that this number would only rise by 9.5% by 2020 [3]. There are various risk factors for developing PD, but the most significant one is age, as the risk of getting PD increases with accordingly to age [2]. Research found that most patients first develop the disease at the age of 60 and above [4]. Individuals can develop this illness at a younger age. PD is considered synucleinopathy as it was believed to be linked to aberrant Lewy body deposits of  $\alpha$ -syn is a protein, which is found in presynaptic terminal of the brain [2,5]. The abnormal overabundance of  $\alpha$ -syn is the responsible of the development of PD [5]. Although the physiological function of  $\alpha$ -syn is still unknown, many studies suggest that it may play a key role in managing the number of SNARE complexes, which impacts on neurotransmitter production [5]. Patients with Parkinson's disease are provided with symptomatic treatment, which aims to improve both motor and nonmotor signs and symptoms. Dopaminergic medications assist in ameliorating motor symptoms such as rigidity, bradykinesia, grip force, speech impairment, and tremor while nonmotor symptoms such as hyposmia, constipation, and depression are treated with non-dopamine therapy [2,4]. According to Ongun (2018), the research on how diet affects the quality of life (QoL) in PD patients reveals that individuals with poor nutritional status have been exhibited to have lower QoL, particularly the elderly. Parkinson's disease can cause a decline in mobility, which disturb the patient's nutrition intake, risk of malnutrition, which effect on their functional status and undermine their QoL [6]. Therefore, current study presents the relationship between nutrition and PD medicine and potential treatments to relieve some symptoms of the disease.



**Figure 1.** Flowchart of relationship between nutrition and PD and potential treatments

## 2. Pathophysiology of Parkinson's Disease

### 2.1. Biochemical factors

PD is caused by the loss of dopaminergic neurons in the substantia nigra (SN) of the brain. SN refers to the midbrain region where dopamine is produced, and it has an important role in the central nervous system as it controls movements, "cognitive executive functions and emotional limbic activity" [7]. It is mentioned that none of the PD models discovered in the recent genetic discoveries had presented the typical degeneration of dopaminergic neurons [8]. Meanwhile, in the previous study showed that neurotoxins have been the well-known substances that are responsible for selective neuronal death. A human parkinsonian neurotoxin known as 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP) previously reported [8]. MPTP an unexpected product from the synthesis of 1-methyl-4-phenyl-4-propionpiperidine (MPPP), which is an intravenous injection of a street drug by several drug addicts from Northern California in the early 1980s. From the PD model designed using the mitochondrial electron transport chain complex I inhibitor MPTP, the authors highlighted that the MPTP results in a serious Parkinsonian syndrome such as "tremor, rigidity, slowness of movement, postural instability, and freezing" in the tested mammals such as humans and monkeys. Based on the neuropathological data, it was observed that MPTP disturbs the nigrostriatal dopaminergic pathways similarly to PD. The authors specify that the MPTP destroys the dopaminergic neurons in the substantia nigra greater compared to the effect of PD. [8]. A study done by Burns and his collaborators stated that an extracellular neuromelanin accumulation and activated microglia were found in the substantia nigra based on the postmortem studies made towards three individuals and four monkeys who had survived after being exposed to MPTP for 3-16 years and 5-14 years respectively. These two substances are responsible for the degenerative process which occurs in the brain.

## 3. Treatments of Parkinson's Disease

### 3.1. Pharmacological treatment

Levodopa, dopamine agonists and anticholinergics are examples of conventional drugs used in treating PD. Levodopa's method of action includes gastrointestinal absorption and then a passage through the blood-brain barrier (BBB), followed by uptake by neurons, enzymatic conversion to dopamine by aromatic amino acid decarboxylase and synaptic release of dopamine [9]. Dopamine's concentrations drop as a result of the nigrostriatal pathway disruption, which also causes PD symptoms. As a result, the dopamine from exogenous levodopa will stimulate the central dopamine receptors, alleviating the signs of Parkinson's disease. Levodopa is typically used together with AADC inhibitors like benserazide and carbidopa or COMT inhibitors like tolcapone and entacapone since aromatic-L-amino-acid decarboxylase (AADC) and COMT are accountable for the peripheral levodopa's metabolism [9]. levodopa has a short half-life of between 36 and 96 minutes and will produce fluctuations in plasma levels, it must be injected several times per day. Levodopa therapy reduces bradykinesia and other common motor symptoms of PD(PD) [9]. On the other hand, long-term Levodopa therapy is linked to problems such as dyskinesia and motor fluctuations that significantly reduce quality of life. Most frequently, levodopa and carbidopa are combined to treat PD like symptoms that can occur after encephalitis (swelling of the brain), and nervous system damage from carbon monoxide or manganese poisoning. Ergot and non-ergot dopamine agonists are the two kinds of dopamine agonists that can be distinguished. Due to their direct action on dopamine receptors, which imitate the neurotransmitter, they have antiparkinsonian properties [9]. Examples of ergot dopamine agonists include bromocriptine, cabergoline, pergolide, and lisuride, whereas non-ergot dopamine agonists include ropinirole and pramipexole. Ergot dopamine agonists primarily affect D2-like dopamine receptors, which include D2, D3, and D4 [9]. On the other hand, pramipexole has a greater affinity for D3 receptors while ropinirole, a non-ergot dopamine agonist, is a powerful and selective agonist of the D2 dopamine receptors. According to one theory, the nigra striatum develops a lesion in PD patients [9]. Dopamine levels in the intranigral region decrease as a result. More cholinergic firing results from imbalances in the

dopaminergic and cholinergic brain systems [9]. The stimulation results in tremors and dyskinesia [9]. Therefore, the anticholinergic drug's mechanism is to prevent acetylcholine from activating the cholinergic receptors. They work to balance out the neurotransmitter imbalance in the nigrostriatal pathway. Anticholinergics specifically target the M4 receptor for blocking. The patient's tremor and dyskinesia disorders will gradually improve as a result [9].

### 3.2. Nutritional treatment

Parkinson's disease, which slows down the digestive system. Constipation is common symptom of PD that can cause your large intestine to become impacted. A diet high in fiber, including fresh fruits and vegetables, whole grains, vegetables, legumes, and whole-grain bread and cereals, will help you avoid constipation. Parkinson's disease medications have the potential to dehydrate you. Dehydration cannot only make you feel more exhausted over time, but it can also result in confusion, balance problems, weakness and kidney troubles. Throughout the day, make sure to consume lots of water and other liquids. Carbidopa-levodopa, the medication most frequently prescribed to treat Parkinson's disease, is taken up in the small intestine. If the patients take their prescription soon subsequent to consuming a meal that is rich in protein, as this includes the corresponding mechanism, that absorption may be interfered with. Eat foods that are high in proteins at different times of the day to assist this drug work as well as possible. Instead of high-protein eggs for breakfast, if you take your medication in the morning, go for oatmeal and reserve the rest of the day's protein consumption for dinner [10].

### 3.3. Natural products for PD

The natural food or product available in Malaysia that has neuroprotective effects is Edible bird's nest (EBN). Edible bird's nest (EBN) is "an animal-derived natural food product made of saliva secreted by swiftlets from the *Aerodramus* genus" [11]. According to recent research, EBN extracts may have neuroprotective effects against 6-OHDA-induced dopaminergic neuron degeneration, mainly through inhibiting apoptosis [11]. Therefore, EBN could be a good nutraceutical choice to guard against oxidative stress-related neurodegenerative diseases like Parkinson's disease. EBN was initially generated as water extract and crude extract that had been digested by pancreatin [11]. By subjecting SH-SY5Y cells to the neurotoxin 6-hydroxydopamine (6-OHDA), an in vitro PD model was created. Using the MTT assay, the extracts' cytotoxicity towards SH-SY5Y cells was evaluated. Afterward, microscopic morphological and nuclear analysis, a cell viability test and a ROS assay were carried out in order to determine if EBN extracts had any protective effects against 6-OHDA-induced cellular damage [11]. Later, Annexin V-propidium iodide flow cytometry was used to evaluate the apoptotic event [11]. Measurement of mitochondrial membrane potential (MMP) and quantification of caspase-3 were done to determine if the mechanism behind the neuroprotective effect of EBN was conciliated via a mitochondrial or caspase-dependent route [11]. The neuroprotective effects of EBN extracts have been effectively shown in a 6-OHDA-challenged SHSY5Y cell culture [11]. In particular, S1 increased cell viability and showed neuroprotective potential, while S2 reduced oxidative damage and blocked the activation of caspase-3. The two EBN extracts have been found to suppress programmed cell death [11]. To pinpoint and facilitate describing the characteristics of the bioactive components in EBN that are the source of the neuroprotective advantages, more research is required. This research implies that EBN may be useful for treating neurodegenerative illnesses such as Parkinson's disease when oxidative stress is a contributing factor.

### 3.4. The contribution of physical exercise towards PD

Exercise is an essential for Parkinson's disease (PD) patients. This is because one of the non-pharmacological methods for treating Parkinson's disease rehabilitation is through exercise, especially exercise that enhances balance and minimises the risk of falling, such as walking, running, strength training, whole-body vibration, and functional exercises. These activities have affected executive functioning, quality of life, and decreased motor symptoms [12]. Physical exercise is very important for

patients with PD will cause a positive benefit to their functional independence, motor test scores, and autonomy in daily life. A promising method is aerobic exercise (A) for maintaining or enhancing physical fitness), which can be defined as a rhythmic, continuous activity of the body's major muscles over an extended period. The most common association between aerobic exercise and Parkinson's disease (PD) is that it enhances overall fitness and assists with various motor functions. As a matter of fact, research shows that moderate to vigorous aerobic exercise is most beneficial for patients with Parkinson's disease [13]. Therefore, practicing aerobic exercise with PD patients might be done successfully to enhance their physical health [13]. By lowering oxidative stress and inflammation while maintaining calcium homeostasis, AE helps to maintain brain health [14]. Based on studies in rat models, the central nervous system (CNS) can undergo plasticity-related changes because of aerobic exercise, including neurogenesis, angiogenesis, synaptogenesis, and improved glucose utilization [15]. It was stated that forced running wheel exercise over four weeks improved motor function and altered regional brain activation in rats with intra-striatal benzodiazepine-induced parkinsonism [15]. The effects of continuous aerobic exercise on the functional connectivity of the motor circuits were also discussed. Additionally, after a four-week treadmill training programme, there was evidence of angiogenesis in the brains of chronic Parkinson'. Recently, it has been revealed that strength training is advantageous for patients with Parkinson's disease [16]. This is because strength training helps Parkinson's patients regain some of their physical abilities and may even enable them to compete physically with disease-free people. The term strength training is used to describe an exercise in which a muscle or a group of muscles are trained against an external force. Leg extensions, leg curls, leg presses, chest presses, and low-row machines are among the most effective exercises for using large muscular groups in a strength training plan. The major muscle groups like quadriceps, gluteus, hip abductors, hamstrings, gastrocnemius, soleus, and trunk muscles are the focus of most strength-training exercises. These can help with functional gait and balance.

#### 4. Nutrigenomics Perspective in PD

PD is a neurodegenerative condition that affects 1-2% of people over the age of 60. The substantia nigra pars compacta pigmented dopamine-containing neurons lost because of the neuropathological alterations, and Lewy bodies, intracytoplasmic eosinophilic inclusions, are present. The underlying cause of PD is yet unknown. However, a triad of independent risk variables has developed, including genetic predisposition, aging, and environmental exposures. Relieving symptoms is the accepted therapeutic approach to treating Parkinson's disease. Advanced pharmacological techniques only offer a temporary advantage. As a result, improved complementary therapies with fewer side effects have been created using suspected neuroprotective substances, preferably with a natural origin.

It has been suggested drinking coffee during last few decades a preventive effect against the risk of PD [17]. Although the health benefits of coffee have not yet been fully understood, its protective effect in PD gene expression modulation has drawn some attention. A mechanism of action for caffeine's protective effect in the onset of Parkinson's disease has been discovered through experimental investigations [17]. Low amounts of caffeine mostly inhibit adenosine A2A receptors, which are found alongside D2 dopaminergic receptors in the striatum, or the brain area responsible for controlling movement and locomotion and where dopaminergic neuron transmission is severely compromised in people with Parkinson's disease [17]. By stimulating D2 receptors in the striatum, the inhibition of A2A receptors improves motor impairments in models of Parkinson's disease [17]. Data from a number of preclinical investigations show to the positive effects of chronic A2A receptor antagonists (like caffeine) on the motor difficulties brought on by long-term L-DOPA administration as well as on PD motor impairment, indicating that they will be useful in the symptomatic treatment of PD [17]. Additionally, A2A antagonists, such as caffeine and D2 agonists, have neuroprotective qualities and can slow down the deterioration of dopaminergic cells in a variety of animal models [17].

## 5. The Importance of Nutrition Towards PD

In addition to protecting patients from malnutrition, nutrition is essential to treat Parkinson's disease. Malnutrition is most common in Parkinson's disease (PD) patients [18]. Malnutrition is reportedly a risk for 3 to 60% of PD patients, and the rate of it is estimated to be between 0 and 24%. Weight loss and famine result from an unbalanced energy, in which energy output exceeds energy inflow. Early-stage non-motor symptoms of PD have been connected to weight loss in patients because of reduced food intake, such as sensory dysfunctions (taste, smell), neuropsychiatric symptoms (depression, cognition), and gastrointestinal dysfunctions [18]. Multiple reasons of malnutrition. According to a recent study, the ketogenic diet is high in fat and low in carbohydrates. Its application has a fasting-like effect that induces ketosis in the body. PD patients with ketogenic diets to minimize food consumption which leads to malnutrition as a result of incorrect dietary management. In addition to this, the majority of PD patients also experience deficiencies in vitamin D, thiamin, zinc, and iron [19]. Neuropsychiatric symptoms such as sorrow, anxiety, dementia, confusion, and apathy in an elderly PD population correlate to decreased food intake and subsequent weight loss. Depression identified as a major predictor of nutritional status in PD patients [6]. Considering a wide spectrum of non-motor symptoms, both depression and anxiety were associated with a higher risk of malnutrition in PD [6].

## 6. Conclusion

Overall, PD is a neurodegenerative disorder associated with diminished nutrition status and quality of life. Since no preventative or curative therapy for PD exists currently, nutrition and diet represent modifiable risk factors for reducing disease risk. Depression and anxiety are common neuropsychiatric manifestations of Parkinson's disease. However, they are often under-recognized because the somatic symptoms of depression often overlap with the motor symptoms of Parkinson disease and there is low self-reporting. Clinicians need to be vigilant about early detection and treatment of anxiety and depression in the patients with Parkinson disease. The development of new therapeutic strategies, including diet, exercise, and counseling along with antidepressants provide a holistic approach to management. Parkinson's disease develops when the number of dopamine-producing cells in the substantia nigra of the brain decreases. Targeting the nutritional status is important for the well-being of PD patients. Pharmacological therapy such as Levodopa, dopamine agonists, and anticholinergics can reduce the effect of Parkinson's disease, with an emphasis on motor symptoms as well as potential adverse effects. Nutritional therapies for constipation and drug interference that focus on food and water control can also slow down motor-related symptoms of PD. Moreover, edible bird's nests have been proposed as a possible neuroprotective agent. Aerobic exercise and strength training were found to be useful in improving motor function. Therefore, good nutrition intake is crucial in order to treat Parkinson's disease. Nevertheless, more research is needed to examine the relationship and explore the impact of specific dietary patterns.

### Authors Contributions:

F.H., N.S., H.H., N.S., N.J. and W.M. contributed toward drafting, writing and revising the paper and agreed to be responsible for all the aspects of this work. All authors have read and agreed to the published version of the manuscript.

### Conflicts of Interest:

The authors declare that there are no competing interests in this work.

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