Review Article

A review on the nutraceuticals of Parkinson's disease

Cassidy Vella[1], Renald Blundell[1,2*]

[1] Department of Physiology and Biochemistry, Faculty of Medicine and Surgery, University of Malta, Imsida MSD2080, Malta
[2] Centre for Molecular Medicine and Biobanking, University of Malta, MSD2080 Msida, Malta

* Correspondence to: Renald Blundell, renaldblundell@gmail.com

Abstract: Parkinson's disease is a neurological condition that progresses over time and causes both motor and non-motor symptoms. Both patients and healthcare professionals must deal with the numerous challenges of this disease. In recent years, there has been a growing interest in the potential therapeutic effects of nutraceuticals—natural chemicals with alleged health benefits—in the treatment of Parkinson's disease (PD). Parkinson's disease is influenced by a variety of factors, including aging, genetics and exposure to certain environmental toxins. Additionally, neuroinflammation, oxidative stress, mitochondrial dysfunction and protein aggregation play pivotal roles in the development of PD. The review integrated results from a variety of studies investigating the effects of different nutraceuticals, from preclinical models to clinical trials. This review focused on several key nutritional elements and dietary modifications that have a beneficial effect on a number of the pathogenic pathways, such as mitochondrial dysfunction and the antioxidant pathway, which are associated with the onset and progression of Parkinson's Disease. Hereby, we aim to explore the current body of research on nutraceutical interventions for Parkinson's disease, with a focus on their neuroprotective and symptomatic alleviation properties. Although numerous studies have been conducted on various nutraceuticals in relation to Parkinson's disease, currently there is no definitive evidence of their specific benefits in this condition. It is therefore strongly recommended that further studies and additional research be conducted in this area to gain a clearer understanding of the potential therapeutic effects.

Keywords: Parkinson's disease, Nutraceuticals, Mitochondrial dysfunction, Oxidative stress, Coenzyme Q, Caffeine, Creatinine

1. Introduction

Parkinson's disease is a heterogeneous neurodegenerative disorder [1]. Aging is the greatest risk factor, but environmental variables and genetics may also have an impact on the onset of the disease [2]. About 1% to 2% of people worldwide are affected by this neurological disorder [1].

Parkinson's disease includes motor, cognitive (non-motor) and social symptoms. Motor symptoms such as stiffness, tremors and bradykinesia, are easily identifiable due to their distinctive nature [3]. Cognitive symptoms are increasingly recognized and contribute to behavioural and communication problems that interfere with social

interaction [4]. Tremors, dyskinesia, bradykinesia, motor fluctuations, postural instability, abnormalities of gait, and poor turning ability are some of the motor symptoms [5]. Non-motor symptoms may precede diagnosis by up to ten years, including lethargy, sleep problems, constipation, memory issues and mood swings [6].

Parkinson's also manifests non-motor symptoms such as constipation, autonomic dysfunction, orthostatic hypotension, sleep issues, and neuropsychiatric symptoms [7]. Additionally, the social symptoms of Parkinson's disease, which affect emotional expression, speech, and perception, are less recognized but crucial. These symptoms contribute to negative outcomes like stigma, social isolation and reduced quality of life [4] .

Two pathological signs of Parkinson's disease are the presence of Lewy bodies in the midbrain and a loss of dopaminergic neurons in the substantia nigra. Protein clusters known as Lewy bodies include the protein α-synuclein along with other proteins [2]. Around 80% of dopaminergic neurons die before symptoms manifest [8]. The functions of the cell are disrupted by protein deposits, which ultimately lead to the death of the cell. Protein aggregation and the remnants of lysosomes and autophagosomes can all be seen in the neurons of PD patients [2]. In addition to dopamine depletion, Parkinson's disease is linked to degeneration of cholinergic neurons in the pedunculopontine nucleus, which could explain the typical symptoms such as postural instability, dysphagia and sleep disturbance in these patients [8]. The main factors contributing to the extremely complex aetiology of PD include oxidative stress, protein aggregate formation, calcium metabolism disorders, mitochondrial damage, gene mutations and ineffective autophagy [9]. Iron build-up, chronic inflammation and oxidative stress interact to cause abnormal pathogenetic signalling [10].

Currently, there is no known cure for Parkinson's disease, although some promising therapies are being investigated for their ability to delay or halt disease progression in light of recent discoveries on the genetic mechanisms underlying neuronal death [11]. The use of dopamine replacement treatment for this disease is associated with drug-induced dyskinesia and diminished effects after prolonged dosing. Therefore, it is crucial to develop new medicines with higher efficacy and a safer profile. Nutraceuticals are currently being used as a reasonably safer and cost-effective therapeutic option for diseases of aging, including PD [8]. Several herbal and natural remedies have been clinically evaluated for their use in PD to determine whether they can be used as an independent or adjunctive therapies to treat the disease [12].

1.1 Epigenetics of Parkinson's disease

Although the precise etiology of PD is still unknown, it is believed that environmental and genetic factors contribute to the development of disease [13]. Over the past two decades, a number of epidemiological studies have demonstrated a positive correlation between traumatic brain injury and a number of environmental factors [13]. Chronic exposure to several pesticides and herbicides, including rotenone and paraquet, have also been found to cause signs of the disease. Parkinson's symptoms were rapidly triggered by exposure to 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) [8].

Epigenetics generally refers to the study of any non-genetic effects that are persistent and transmissible and can affect gene expression or cellular phenotype without altering the DNA sequence. These mutations can alter the expression of genes, leading to changes in various cellular phenotypes. These modifications include chromatin remodelling, post-translational modifications of histones, DNA methylation, and short and long non-coding RNAs [14].

More than 20 monogenic variants of PD have been identified due to improvements in genetic techniques and demography studies. In addition, more than 100 loci have been found to constitute the risk factors of this illness's [15]. The onset of PD has been associated with several disease-related genetic variants, including SNCA, LRRK2 and VPS35 for autosomal-dominant variants and Parkin (PARK-2), PINK1 (PARK6), DJ-1 (PARK7) and ATP13A2 (PARK9) for autosomal-recessive forms [13]. Although PD is a basic core feature of Lewy bodies, genetic variation in the α-synuclein gene (SNCA) plays a significant role in the prevalence of the disease. In addition, a heterozygous missense mutation in the gene for the serine protease requiring high temperature (HtrA2/Omi) has been observed in sporadic forms of this disease [8].

The two preventive behaviours that have been demonstrated to be most strongly linked to a lower risk of PD are cigarettes smoking and coffee drinking. Higher level of serum urate, taking ibuprofen and exercise are some other observed connections. This inverse link is difficult to understand, but some have proposed that the biological mechanism underlying PD is a cautious mentality (avoidance tendency) that predisposes some people to quit smoking defensively [15].

DNA methylation, histone modifications and the regulation of non-coding RNA, play pivotal roles in modulating gene expression patterns associated with the onset and progression of PD. Furthermore, the impact of environmental factors, aging and genetic predispositions on epigenetic regulation in PD, also sheds light on the complex interplay between genetic and environmental influences.

1.2 Heavy metals

Metal ions are necessary for the effective operation of a number of physiological processes as well as for the maintenance of health [16]. Dopaminergic neuronal degeneration is triggered by exposure to toxic metals

that can enter the brain and cross the blood-brain barrier, such as selenium (Se), arsenic (As), lead (Pb), cadmium (cd), copper (Cu), iron (Fe), manganese (Mn), zinc (Zn), aluminium (Al), cadmium (cd), and mercury (Hg). The accumulation of heavy metal in the brain causes dopaminergic neuronal damage by inducing oxidative stress, mitochondrial dysfunction and mitochondrial dysfunction. There is evidence that heavy metals, which naturally present in small amounts in the human body, may accumulate and impair transmission in the basal ganglia through free radicals formation [17].

Manganese exposure has been reported to change histone modifications in the dopaminergic system. Its deleterious effects accumulate and cause oxidative stress and neuroinflammation in the brain [18]. Mercury, especially inorganic mercury, acts as a potent neurotoxin that impairs cognitive function, increases free radicals, causes mitochondrial damage and lowers glutathione levels [16]. Iron is a cofactor for the enzyme tyrosine hydroxylase, which limits the production of neurotransmitters and is required for dopamine deficiency in PD, and this enzyme is responsible for the toxicity of nigra in this disease [17].

Zinc deficiency can lead to cognitive decline with individual's age. Zinc reduces oxidative stress, which activates antioxidant mechanisms that promote neuronal growth in the brain. In vitro research, it has shown that Zn^{2+} ions from Park2 bind directly to peptide segments in the PD gene Park9, causing the protein to unfold [17].

Patients with this disease have lower levels of copper in their substantia nigra. The regulation of protein degradation pathways was supported by the interaction between copper and alpha-synuclein. Copper stimulates production while inhibiting clearance to promote the accumulation of alpha-synuclein by reducing its transit and promoting its accumulation [19]. Cadmium, a hazardous heavy metal, induces oxidative stress and contributes to the gradual decline of dopaminergic neurons [17]. The third most common element in nature is aluminium. By activating monoamine oxidase B, which breaks down dopamine and causes symptoms similar to Parkinson's disease, aluminium promotes the development of alpha-synuclein fibrils [20].

Arsenic is a metalloid and it induces apoptosis in the brain neurons, which in turn produces neurotoxicity. By increasing reactive oxygen species (ROS), superoxide dismutase activity and lipid peroxides while reducing glutathione levels in the brain, arsenic causes oxidative stress and DNA damage [17]. It was discovered that the use of insecticides containing arsenic (As) increased the likelihood of developing PD [21].

Selenium is a valuable micronutrient mineral. When selenium levels are low or high, selenoproteins are downregulated, and oxidative stress and mitochondrial dysfunction are promoted. By lowering glutathione levels, the altered selenium levels lead to the degeneration of cholinergic neurons [17].

2. Nutraceuticals

Nutraceuticals are naturally sourced substances that have been shown to be clinically useful in the management of a certain disease. These foods or their derivatives have been supported by reasonable scientific evidence [1]. Several dietary supplements for Parkinson's disease have been discovered to enable to protect neurons in animal models. When compared to commercially available treatments, these can be considered as exotic therapeutic options [8].

The following categories broadly generalize the mechanisms in which nutraceuticals work :
• Free radical scavenging and ROS
• Reduction of inflammation
• Chelation of iron
• Mitochondrial homeostasis
• Prevention of apoptosis
• Alteration of cell signaling pathways [1]

In Table 1, those nutraceuticals that most common and extensively studied to date were chosen in relation to providing benefits for PD.

Table 1. Nutraceutical supplements that therapeutically address the pathophysiology of Parkinson's disease

Nutraceuticals	Compound	Mechanism of action	References
Vitamin B complex	Supplement	Increase synaptic plasticity while decrease the mortality of dopamine-producing neurons. Has no impact on the blood homocysteine level.	[8]
Vitamin C and E	Antioxidant Supplement	Vitamin C: cytosolic free radical scavenger Vitamin E: Major lipid-soluble antioxidant that acts as a ROS scavenger to protect the integrity of cellular membranes against oxidative stress	[22] [8] [23]
Vitamin D	Supplement	Increases the levels of GDNF. Control the amounts of dopamine. Increases the levels of glutathione. Increases in circulating neutrophils. Ca^{2+}-binding protein synthesis. Prevents inducible nitric oxide synthase from being made.	[24]

Coenzyme Q10	Fat soluble Vitamin	Oil soluble CoQ10: -Dopaminergic neurons are preserved in the striatum and SNpc, and α-synuclein clumps are cleared away. Decreased levels of inflammatory cytokines Ubisol-Q10: Decrease oxidative stress. Maintain ATP production. Stabilize the mitochondrial membrane. Prevent the death of dopaminergic neurons. Activate pro-survival astrocytes, and alleviate motor dysfunction.	[25]
Creatine	Organic nitrogenous acid	Phosphocreatine, a source of energy for the brain and skeletal muscles, is phosphorylated by the enzyme creatine kinase. In order for synaptic activity and skeletal muscle function to occur. ATP levels must be maintained, and phosphocreatine plays an important role in this procedure.	[23]
Fish Oil	Polyunsaturated fatty acids	Via lowering microglial activity and neuroinflammation while preserving the ability of astrocytes to produce neurotrophins. Essential basal ganglia dopaminergic neuron modulators Effects of antidepressants via an increase in serotonergic neurotransmission	[26] [3]
Mucunapruriens	Natural sources of L-Dopa	The powder from mucuna seeds has CoQ10 and NADH, which are neuroprotective compounds that can defend neurons from 6-OHDA toxicity by inhibiting the activity of mitochondrial complex I. NADH can also upregulate tyrosine hydrolase and raise dopamine levels. Blocking pAkt and NF-B can help reduce neurotoxicity.	[27] [28]
EGCG in green tea	Compounds containing polyphenols	Antidoxant chelation of iron; Free radical scavenger; Regulation of PKC; Change in ROS-NO pathway; Activation of AMPK.	[10] [28]
Curcuminoids in curry	Polyphenolic flavonoid	Antioxidant Increases the glutathione level Anti-inflammatory (reduces LPS-induced synthesis of pro-inflammatory chemicals and prevents LPS-induced changes in the morphology of microglia)	[3] [29]
Resveratrol	Plants like grapes, peanuts, berries, and pines contain phytoalexin.	LPS-induced reduction of IL1-a, TNF- and inhibition of NADPH oxidase. Alter the in vitro concentrations of BAX and Bcl-2 SIRT1 stimulation in SK-N-BE cells. Free radical scavenger	[29] [30]
Quercetin	Natural flavonoid included in foods such as apples, broccoli, and onions	Activities that fight cancer, inflammation and free radicals	[31]
Ginkobiloba extract	Ginkobiloba leaves are rich in terpenoids and flavonoids	Antioxidant Anti-inflammatory Anti-apoptotic	[32]

As shown in Table 2, there are other nutraceuticals associated with PD, however these are less common or newly discovered thus there has not as much significant research conducted to confirm their benefits for disease treatment.

Antioxidant therapy may be used to treat PD. A few antioxidants that have been investigated in clinical studies include desferrioxamine, melatonin, pioglitazone, vitamin E, creatine and coenzyme Q10. However, none of these antioxidants has shown a strong evidence that they can reduce neurodegeneration. Due to the stagnant rate of neurodegeneration, the lack of biomarkers for the premotor stage of PD, and the inability of the current drugs to cross the blood-brain barrier, it may be difficult to conduct clinical research [23].

Table 2. Less common nutraceutical supplements that therapeutically address the pathophysiology of Parkinson's disease

Nutraceuticals	Structure	Role	References
Baicalein	Flavone	Decreases inflammation, encourages autophagy, suppresses apoptosis and prevents α-Syn fibrillation.	[1]
Oxyresveratrol	Stilbenoid	Reduces the synthesis of reactive oxygen species. Improves motor performance and prevents dopaminergic neuron aging in animal models.	[33]
Ginsenoside	Saponin	Reduces glutamate-induced excitotoxicity, inhibits the death of dopaminergic cells, and enhances synaptic transmission in the nigrostriatal nucleus.	[1]
Genistein	Isoflavone	The degeneration of dopaminergic neurons is exacerbated by oxidative stress and inflammation, which can be reduced by substances with antioxidant and anti-inflammatory characteristics. Suppresses the action of the monoamine oxidase B enzyme.	[34]
Nordihydroguaiaretic acid	Lignan	Inhibits the action of the enzyme protein kinase C (PKC), which is essential for controlling cellular activities like gene expression, cell division, and growth. PKC inhibition may have neuroprotective effects.	[35]
Caffeine	Xanthine Alkaloid	Neuroprotection is against the degradation of dopaminergic neurons. Modulation of α-Syn is degraded by coffee with increased autophagy.	[36]
Eucalyptus Oil	Essential Oil	There is limited research on the specific function.	[37]
Vincamine	Alkaloid	Has various modes of action, including chelating, antioxidant and vasodilator effects.	[1]
Vinpocetine	Synthetic derivative	Eliminates the limitations of CoQ10, particularly the restricted dispersion to mitochondria due to the substance's hydrophobic nature.	[1]
Mito Q	Coenzyme Q10 analogue	Restricts both glial-mediated inflammation and oxidative damage.	[1]
Mito-apocynin	Modified apocynin	Restricts both glial-mediated inflammation and oxidative damage.	[1]
Fulvic acid	Organic acid	By specifically focusing on cyclooxygenase-2 expression suppression in human monocytes, fulvic acid can combat inflammation triggered by homocysteine. It also has antioxidant, anti-inflammatory and immunomodulatory.	[38]
Spirulina	Blue-green algae	Prevents and/or accelerates the course of neurodegenerative illnesses by acting on glial cell activation and having good anti-inflammatory and antioxidant effects.	[39]
Chlorella	Green Algae	Not well understood, however some studies suggest that it may have neuroprotective qualities.	[39]

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2.1 Clinical trials

2.1.1 Caffeine

A case-control study was carried out on 566 patients at averaged 67 years old. Examining the correlation between coffee drinking and the risk of PD was the main goal of study. A semi-quantitative questionnaire was used to investigate the caffeine intake of each participant during their initial appointments. Participants were asked about their typical 12-month consumption of caffeinated and decaffeinated coffee, tea and soft drinks in standard amounts. The following estimated caffeine content was used to calculate average daily caffeine consumption: 46 mg per 12-ounce can of caffeinated soda, 137 mg per 8-ounce cup of coffee, and 47 mg per 8-ounce cup of tea. Regardless of gender, caffeine intake was associated with a lower likelihood of the onset of idiopathic PD [41]. A complete phase 3 clinical study was conducted involving 121 participants aged 45 to 70 years. The aim of the study was to investigate the effects of caffeine (200 mg) on people with idiopathic PD. The results of this study showed that although caffeine slightly reduced fatigue, it did not enhance motor parkinsonism. In long-term caffeine users, there was a slight increase in dyskinesia and a decrease in cognitive ratings [42].

Caffeine blocks adenosine A2A receptors, which explains part of its CNS actions. Caffeine and more selective A2A antagonists such as istradefylline have protective effects in models of PD. Levodopa, the precursor of dopamine that crosses the blood-brain barrier, has been administered to patients with advanced PD in combination with the adenosine receptor antagonist istradefylline. Clinical trials demonstrated that co-administration of istradefylline reduced these movement fluctuations. As levodopa is metabolized to 3-O-methyldopa in glial cells, the methyl group is depleted, which means that the methylation potential in the brain decreases with increasing levodopa dosage. Impaired methylation leads to the overexpression of adenosine receptors. The increased availability of adenosine receptors diminishes the effectiveness of istradefylline. Consequently, clinical trials with patients receiving higher doses of levodopa have shown less favorable results compared to studies involving individuals receiving lower levodopa dosages. Orally administered istradefylline has been approved in Japan and in the US [43].

2.1.2 Coenzyme Q

A randomized, parallel-group, placebo-controlled, double-blind, dosage-ranging experiment was conducted over a 16-month period in 80 participants with early-stage PD who did not require treatment for their condition. Up to 1200 mg/day of coenzyme Q10 was safe and well tolerated. Those who received coenzyme Q10 were less impaired than those who received a placebo, and the benefit was greatest in those who received the highest dose. Coenzyme Q10 seems to reduce steady functional decline in PD patients, but these findings need to be verified in a larger trial [23].

In contrast, a phase III clinical study was carried out at 67 locations in North America as also carried out with regards to Coenzyme Q. The study included individuals with a PD diagnosis within the past five years who were 30 years of age or older. Inclusion criteria were based on participants' PD symptoms, including bradykinesia, stiffness, and a rest tremor, as well as a modified Hoehn and Yahr stage of 2.5 or below and their expectation that no dopaminergic medication would be required within the next three months. The trial employed a randomized design with participants assigned to receive placebo, 1200 mg/d of CoQ10, or 2400 mg/d of CoQ10, with all participants also receiving 1200 IU/d of vitamin E. CoQ10 was shown to be safe and well-tolerated in the population under investigation. However, the study was stopped due to a predetermined futility criterion. In contrast to placebo, neither CoQ10 therapy group showed any clinical benefit. The research highlighted the significance of conducting thorough investigations to ascertain the effectiveness of potential treatments for neurodegenerative diseases [44].

2.1.3 Creatine

A randomized, double-blind, phase II futility clinical trial was carried out to investigate the effects of creatine and minocycline on the progression of early PD in relation to a predetermined futility threshold. This clinical trial included patients who had been diagnosed with PD within 5 years, and were not taking any medication to treat their symptoms. Subjects were administered randomly with Minocycline 200 mg/day, a matching placebo, or creatine 10 g/day. These patients were followed up after one year and creatine was found to be beneficial for preventing the progression of the disease [23].

However, another clinical trial, aimed to assess whether creatine monohydrate, a potential therapeutic candidate, was more effective than a placebo in slowing the long-term clinical decline of individuals with Parkinson's disease. In this multicentre, 1:1 randomised, placebo-controlled, double-blind, parallel-group study, 1741 men and women with early-stage PD who had previously taken dopaminergic medication participated in the effectiveness trial. Recruitment took place at 45 research locations in the US and Canada, and participants were monitored for

a minimum of five years and a maximum of eight years. Throughout the study period, participants were randomised to receive either a placebo or 10g of creatine monohydrate per day. Based on an interim analysis of patients enrolled at least five years before the analysis date, the experiment was deemed futile and terminated early. According the results, to sum up, there was no discernible difference in clinical outcomes between the creatine and placebo groups. There was also no discernible difference in adverse occurrences between the two groups. Long-term use of creatine monohydrate (at least 5 years) did not show improvement in clinical outcomes compared to a placebo in people with early stage PD under treatment. Therefore, these results do not lend credence to the use of creatine monohydrate as a therapeutic intervention for PD patients [45].

3. Nutraceutical impact on Parkinson's disease pathogenic mechanism

In order to slow the progression and lessen the impact of this disease, we investigated the potential function of nutraceuticals that target the underlying neurodegenerative processes of PD. By reducing numerous pathogenic processes such as neuroinflammation, oxidative stress, mitochondrial dysfunction and apoptosis, natural substances may be able to treat this disease [1].

3.1 Targeting mitochondrial dysfunction and oxidative stress

In neurodegenerative disorders, mitochondrial dysfunction and uncontrolled oxidative stress impede cellular energy metabolism, which has an impact on brain functions. According to research, dopamine, iron, calcium, mitochondria and neuroinflammation may all play a role in excessive oxidative stress and neurodegeneration. In order to minimize the radicals, a variety of antioxidants are upregulated by antioxidant reactions. However, since this disease lacks the necessary endogenous antioxidants, uncontrolled ROS generation may result in large amounts of harmful, non-physiological ROS [23]. The specific mechanism causing mitochondrial failure is unknown, although it has been hypothesized that dopaminergic neurons from PD patients have a damaged respiratory chain and altered mitochondrial DNA.

For neurotransmitter release and neuronal depolarization, mitochondria in neurons regulate ATP generation as well as Ca2+ storage to protect cells. Research has shown that α -Syn plays a role in maintaining mitochondrial morphology as well as improving ATP synthase efficiency. Nevertheless, α-Syn aggregates may impair mitochondrial bioenergetic function and boost the production of reactive oxygen species, which may cause an unbalanced oxidative state and neuronal death in rat primary neurons [1].

3.1.1 Calcium

ROS production increase due to the need for ATP-dependent pumps in the mitochondria to control intracellular Ca2+ [23]. In membranes, SYN can increase the activity of SERCA and cause the formation of Ca2+ permeable holes, which may be a factor in the Ca2+-induced aggregation and damage of SYN. Increased cytosolic [Ca2+] may potentially contribute to the spread of SYN disease since it increases SYN release. Additionally, ER-mitochondrial Ca2+ transport at MAMs is another way in which SYN influences Ca2+ homeostasis. Ca2+ signalling may also make neurons more vulnerable by increasing the formation of superoxide and other harmful ROS in the mitochondria [46].

3.1.2 Iron

Mice exposed to iron show Parkinson's symptoms, increased MPTP susceptibility and neuronal death in the SN and DA depletion in the striatum. The striatum of rats has more iron hydroxyl radicals after stereotaxic iron injection into their SN. Administration of an iron chelator to mice lowers the brain's iron concentration and exhibits a neuroprotective effect against MPTP- or iron-induced neurotoxicity. The research findings imply that elevated iron concentrations in the SN cause oxidative stress, which culminates in neurodegeneration in PD [23].

3.1.3 Mitochondrial dysfunction

The main places where ROS are produced are the mitochondria. O2- is generated in the mitochondria by electron leakage in complex I and III. Excessive ROS generation results from mitochondrial dysfunction. Mitophagy, fusion/fission, and mitochondrial biogenesis are all affected by mitochondrial dysfunction in PD. The first example of the connection between mitochondrial dysfunction and Parkinson's is MPTP-induced parkinsonism in drug users [23].

3.1.4 Neuroinflammation

DAergic neurodegeneration is exacerbated by neuroinflammation. Activation of microglia and pronounced proinflammatory cytokine production are both part of this inflammatory cascade. Active microglia release several cytokines that cause inflammation. Proinflammatory biomarkers including IL-1, IL-6, IL-10, TNF-, RANTES and hsCRP can be used to track changes in CSF or blood and aid in the early detection of PD [47].

3.1.5 Nutraceuticals targeting mitochondrial dysfunction and oxidative stress

Various nutraceuticals target mitochondrial dysfunction and oxidative stress including:

- Coenzyme Q10
- Resveratrol
- Lycopene
- Fish oil
- EGCG in green tea
- Ginsenoside
- Vincamine
- Vinpocetine
- MitoQ
- Mito-apocynin

3.1.5.1 Coenzyme Q10

In order to slow the progression of the disease, alternative therapy including fish oil and coenzyme Q10 (CoQ10) have been proposed [1]. CoQ10 is a 10-unit polyisoprenoid lipid tail linked to the nuclear benzoquinone molecule [48]. Involved in ATP production and as an important element of the electron transport chain, CoQ10 guards against the neurotoxicity of MPTP. It also prevents electrons from moving from complex 1 to other complexes [1].

3.1.5.2 Resveratrol

Resveratrol, a polyphenolic molecule abundant in red wine and grapes, has recently attracted interest due to its anti-inflammatory and antioxidant effects on brain disorders [49]. The presence of a C–C double bond results in cis and trans configurations that can be converted into one another under certain circumstances [50]. Previous research has shown that resveratrol can prevent the brain damage related to PD. The bioavailability of resveratrol is extremely low, which severely restricts its effectiveness [49]. According to an in vitro study, resveratrol acts via the protein kinase B (AKT)/glycogen synthase kinase-3 pathway to prevent mitochondrial dysfunction and mortality in nigrostriatal cells [1].

3.1.5.3 Lycopene

Lycopene is an acyclic lipid-soluble carotenoid found mainly in tomatoes, red fruits and vegetables. Eight isoprene units, consisting only of carbon and hydrogen, are linked to form the tetraterpene known as lycopene. It has antioxidant properties that make it show neuroprotective effects. Lycopene inhibits the formation of N-Bcl-xL. Preventing the accumulation of N-Bcl-xL may be a key mechanism for lycopene-mediated neuroprotection, as N-Bcl-xL disrupts energy metabolism and results in neuronal death [51].

3.1.5.4 Omega-3-polyunsaturated fatty acids

Omega-3-polyunsaturated fatty acids (-3 PUFA) have several beneficial effects on various neurological illnesses, including Parkinson's disease. A fatty acid consists of many double bonds, the first of which forms between the third and fourth carbon atoms at the chain's terminal. These contain anti-inflammatory properties and could help reduce inflammation in the brain that is involved in PD. Studies have shown that taking omega-3 supplements may help with the motor symptoms of PD [52]. Treatment with docosahexaenoic acid enhanced antioxidant defence, reduced the death of dopaminergic neurons, and increased motor performance in mice challenged with MPTP. A randomized, double-blind clinical investigation supported the positive effects of omega-3: inflammatory and oxidative biomarkers decreased in PD patients who took omega-3 and vitamin E for 12 weeks, and the metabolic impairment associated with PD was limited [1].

3.1.5.5 Epigallocatechin-3-gallate

As a primary polyphenol in green tea, epigallocatechin-3-gallate (EGCG) is known to be beneficial for those who have PD since it is well known for its properties of being anti-inflammatory, antioxidant and neuroprotective. According to an in vitro study, EGCG and its metabolites can pass through the blood-brain barrier and cause neuritogenesis in the brain parenchyma [52]. The preventive effect of EGCG against dangerous DA metabolites is contributed by its catechol-like structure. It is well-recognized to be an effective iron ion chelator and radical scavenger. In addition, in mice exposed to MPTP, EGCG increased striatal DA levels, decreased neurotoxicity and enhanced motor coordination [1].

3.1.5.6 Ginsenoside

It has been demonstrated that ginsenoside Rg3 isolated from Panax ginseng C.A. Meyer, has neuroprotective properties. A tetracyclic triterpenoid saponin is ginsenoside Rg3. Previous research has shown that the pharmacological properties of ginsenoside Rg3 include antioxidant, anti-aging, anti-cancer, cardiovascular protection, immune system improvement, and anti-inflammation actions. Ginsenoside Rg3 improved cell survival of SH-SY5Y cells exposed to oxygen-glucose deprivation while also prevented apoptosis. In mice with PD caused by rotenone, ginsenoside Rg3 also enhanced motor performance. The neuroprotective benefits of ginsenoside Rg3 are at least partially attributed to its anti-oxidative properties by controlling the regulatory subunit of glutathione cysteine ligase and modulatory subunit expression [52].

3.1.5.7 Vincamine

Vinca minor's leaves contain vincamine, a monoterpenoid indole alkaloid [53]. According to the research findings, Parkinson's disease-related traits can be suppressed by vincamine in PD models using human cell and Drosophila. Moreover, it reduced OS-induced mortality in human cells defective in DJ-1 by lowering apoptosis, OS levels and raising mitochondrial viability. In addition, it has

been shown that vincamine can exert at least partially its advantageous effects by inhibiting voltage-gated Na+ channels. As a result, it is proposed that vincamine is an effective treatment for the condition and that these channels represent a potentially useful target in the search for new medications for PD [54].

3.1.5.8 Vinpocetine

A synthetic ethyl ester of apovincamine is vinpocetine. Vinpocetine is a semi-synthetic derivative made from the alkaloid vincamine. It can treat a variety of cognitive and memory issues and has anti-inflammatory, analgesic and antioxidant properties. The medication is used to treat memory loss since it has neuroprotective properties. As a blood vessel-dilating medication, vinpocetine increases cerebral blood flow. Vinpocetine promotes the selective inhibition of calcium calmodulin-dependent CGMP-PDE1, which may increase intracellular CGMP levels in vascular smooth muscle and lower cerebrovascular resistance while increasing cerebral blood flow. Neuroprotection is also a result of this property. According to a recent study, vinpocetine possesses antioxidant activity, an antihyperglycaemic effect and a reduction in the generation of reactive free radical [55].

3.1.5.9 Mito Q and mito-apocynin

Tetraphenylphosphonium, a lipophilic cation, and quinone, an antioxidant, are linked together to form the compound known as mitoQ [56]. Due to its high membrane potential across the inner mitochondrial membrane and its concentration on mitochondria, the matrix surface of the inner membrane takes up all the deposited MitoQ, where complex II reduces it to the functional antioxidant ubiquinol. MitoQ neutralizes peroxyl radicals and protects against lipid peroxidation in the mitochondria. MitoQ showed protective effects in cellular and animal models of oxidative stress-related diseases. MitoQ significantly reduced the amount of 6-OHDA-induced mitochondrial fragmentation in a cellular PD model [57].

The effect of mito-apocynin, a recently manufactured derivative of the antioxidant component apocynin, was investigated. It decreases oxidative damage, glia-mediated inflammation and nigrostriatal neurodegeneration in rats exposed to MPTP by targeting mitochondria [1].

3.2 Targeting protein misfolding and aggregation, as well as the endoplasmic reticulum stress pathway

The primary site of protein synthesis and degradation is the endoplasmic reticulum (ER). The disruption of ER homeostasis by genetic mutations, irritating environmental factors and other factors results in the accumulation of misfolded proteins, which leads to ER stress that activates autophagy and inflammasomes.

Unfolded protein response is a complex signalling system that controls translation and transcription in response to the requirement for improved capacity of protein folding. It is primarily responsible for the regulation of UPR activation, ER homeostasis, ER dysfunction, and ER stress. The UPR controls cellular adaptation in response to stress by increasing the ER's capacity for protein-folding and concurrently lowering the synthetic load [58]. Since neurons are limited in their ability to remove damaged organelles or protein clusters leading to cell death and apoptosis, they are more susceptible to neurodegeneration [1].

3.2.1 Nutraceuticals targeting ER stress in Parkinson's disease

• Palmitoylethanolamide
• Vitamin A
• B-carotene
• Coenzyme Q
• Crocin
• EGCG
• Baicalein
• Rosmarinic Acid
• Resveratrol
• Gallic Acid
• Ginsenosides
• Salidroside

3.2.1.1 Palmitoylethanolamide

It has been discovered that the endogenous fatty acid amide palmitoylethanolamide (PEA) has anti-inflammatory, analgesic and neuroprotective effects [1]. It contains the saturating agent oleoylethanolamide as well as the endogenous cannabinoid receptor ligand anandamide [59]. Palmitoylethanolamide, a PPAR ligand, reduces ER stress in the striatum of mice administered 6-OHDA by decreasing BiP expression and activating the PERK-eIF2 pathway. Overall, PEA shows promise as a possible therapeutic agent for reducing ER stress in a variety of neurological illnesses, including PD, even though the evidence is still scarce. To completely comprehend its potential advantages and mechanisms of action in this situation, more research is necessary [1].

3.2.1.2 Vitamin A, CoQ10 and carotene

For their scavenger function, vitamins have been employed in PD patients with moderate success. Nevertheless, hydrophobic antioxidants with antifibrillogenic properties include CoQ10, vitamin A and carotene. Vitamin A in particular prevents the intracellular deposition of α-Syn in living cells [1]. The unsaturated isoprenoid chain structure serves as a defining feature of vitamin A [1, 60].

3.2.1.3 Crocin

A natural carotenoid molecule called crocin has been shown to offer medicinal potentials for treating neurological illness. Crocin is the diester formed chemically when the disaccharide gentiobiose and the dicarboxylic acid crocetin are combined. Via a variety of signaling channels, crocin directly inhibits inflammation, apoptosis and antioxidant activity. It was also discovered that crocin increased dopamine levels in the brain in an experimental model. With little side effects, it has been shown that this substance is a viable choice for treating neurodegenerative illnesses [61]. After MPP+ treatment, this carotenoid compound can reduce the expressions of CHOP and the binding immunoglobulin protein (BiP) / Grp78 as well as the activation of the pro-apoptotic component caspase-12 in PC12 cells [1].

3.2.1.4 EGCG

The proper folding of α-Syn monomers into stable oligomers by EGCG, which also reduces oxidative stress, occurs in a concentration-dependent manner. Moreover, it can alter the structure of mature -Syn fibrils without breaking them down into smaller and non-toxic ones. Recently, α-Syn fibrillation has been inhibited and dopaminergic neurons have been protected by EGCG and certain α-Syn proteolytic peptide sequences [1].

3.2.1.5 Baicalein

Baicalein is considered a lipophilic flavonoid [62]. It is a major bioactive flavone that exhibits neuroprotective properties in many animal models of PD. Baicalein can treat PD through multiple mechanisms, such as regulating neurotransmitters, modifying enzyme activities, acting as an antioxidant and anti-inflammatory, inhibiting protein aggregation, reversing mitochondrial dysfunction, and preventing apoptosis and autophagy [63]. By limiting the development of α-Syn oligomers, baicalein suppresses α-Syn fibrillation and shields SH-SY5Y and HeLa cells against neurotoxicity [1]. These first results showed that baicalein may have neuroprotective benefits in animal models through various signalling pathways [63].

3.2.1.6 Rosmarinic acid

A polyphenol called rosmarinic acid is mainly found in the Lamiaceae plant family. Significant antinociceptive, neuroprotective and neurodegenerative properties are exhibited by rosmarinic acid [64]. It was proven that rosmarinic acid upregulated HO-1 and inhibited the expression of -synuclein to provide defence against iron-induced -synuclein aggregation [52].

3.2.1.7 Resveratrol

In PC12 cells that express α-Syn, the natural phytoestrogen resveratrol enhances autophagic degradation of α-Syn via activation of the AMP-activated protein kinase signalling channel mammalian silent information regulator 1. Stimulation of autophagy and apoptotic pathways is a key tactic for therapeutically targeting α -Syn [1]. In conclusion, resveratrol extends the lifespan of MPTP-treated D. melanogaster and protects PC12 cells from rotenone oxidative damage. It also prevents the aggregation of -synuclein in mice suffering from PD. This action is largely mediated by activating the Akt1/SIR signalling pathway [52].

3.2.1.8 Gallic acid

The phenolic acid gallic acid with the molecular formula $C_6H_2(OH)_3COOHA$, is a naturally occurring substance with antioxidant effects [65]. This molecule is abundant in green tea and pineapples, among other foods. Gallic acid offers adequate defence against the oxidative damage caused by reactive species, which are frequently present in pathological conditions [66]. In vitro, gallic acid breaks down the preformed -Syn fibrils [1].

3.2.1.9 Ginsenosides

The active ginseng components known as Rg1, Rg3, and Rb1 have actions that are comparable to gallic acid. Rb1, a potent inhibitor of α-Syn fibrillation, destroys generated fibrils and inhibits α-Syn polymerization in vitro [1]. G-Rg1 has been shown to shield dopaminergic neurons against the toxicity of glutamate, MPTP and rotenone during in vivo investigations [67]. Ginsenoside Rg3 improved cell survival in SH-SY5Y cells exposed to oxygen-glucose deprivation while also preventing apoptosis [68].

3.2.1.10 Salidroside

A phenylpropanoid glycoside monomer called salidroside (SAL) is extracted from rhodiola [69]. Salidroside reduced the aggregation of α-Syn and simultaneously increased dephosphorylation at position Ser129, an enzyme activity that is solely responsible for the formation of Lewy bodies [1].

Overall, these findings indicate that nutraceuticals targeting ER stress may have possibilities as a plan for PD treatment. However, more investigations are required to thoroughly evaluate the security and efficacy of these compounds in PD-affected persons.

4. Nutraceuticals and mitochondrial homeostasis

Nutraceuticals involved in mitochondrial regulation can be used to treat PD symptoms, since abnormal mitochondrial homeostasis is typically implicated in the pathophysiology of the disease. It is crucial that coenzyme Q10 has the ability to accept and transfer electrons to

mitochondrial complex 1. Also useful in the control of mitochondrial complex 1 are curcuminoids from the macuna plant and turmeric. Another important participant in the brain is phosphocreatine, a high-energy phosphate that is responsible for ATP recycling and the maintenance of mitochondrial homeostasis [8].

Interestingly, creatine therapy seems to be able to reverse parkinsonian phenotypes in both human and animal models. In particular, dietary supplements containing creatine have been reported to elevate mood, lower the dosages needed for dopamine (DA) replacement therapy, and reduce the loss of dopaminergic neurons in the SNpc of mice treated with MPTP. Despite the controversy surrounding CoQ10, it seems that nutraceutical therapy usually targets mitochondrial homeostasis as a target mechanism [3].

The green tea catechin EGCG, which can cross the blood-brain barrier, may have neuroprotective effects through a variety of pathways, including the maintenance of mitochondrial homeostasis, metal chelation-mediated antioxidant activity, and free radical scavenging. The potential of calcium-calmodulin dependent kinase was controlled by EGCG, leading to the activation of AMPK and neuroprotection [8].

5. AMPK activation and neuroprotection

In addition to being related to chronic inflammatory diseases, AMPK is a highly conserved serine/threonine protein kinase that controls energy metabolism. Recent research has suggested that the development of PD may be influenced by faulty AMPK signalling [70].

Several research have shown that AMPK activation can enhance mitochondrial activity, increase cellular energy production and prevent the degeneration of dopaminergic neurons. Moreover, studies have shown that activated AMPK might promote autophagy, a cellular process that helps to remove the damaged proteins and organelles, which may further support neuroprotection in PD [71].

A possible therapy strategy for PD may involve targeting AMPK, according to a new research. For instance, AMPK-activating medications such as metformin and resveratrol have demonstrated encouraging outcomes in preclinical research and human clinical trials. Metformin stimulated AMPK kinase, potentially by increasing autophagy and mitochondrial ROS clearance, to provide neuroprotection to animals with PD. A mouse model of PD caused by MPTP was used in a study to examine the protective effects on mitochondrial dysfunction and apoptosis brought on by activating AMPK/GSK-3/PP2A pathway in PD (MPTP) [71].

Natural ingredients found in nutraceuticals can alter the AMPK pathway and lessen the pathophysiology that underlies neurodegeneration. Through regulating mitochondrial function, AMPK activated by ECGC could significantly improve the PD phenotypes that were generated in drosophila flies. When pharmacologically treated with AMPK activation induced by ECGC, the regulation of mitochondrial biogenesis would occur and the same results were observed in drosophila LRRK2 mutant flies. Resveratrol, which is found in the peel of grapes and berries, reduced the pathology of PD in human fibroblasts with parkin mutations by strongly activating AMPK and oxidative phosphorylation, enhancing mitochondrial biogenesis, and activating the autophagy cascade [8].

A Taiwanese cohort research on 800,000 individuals recently found that metformin-inclusive sulfonylurea therapy dramatically reduced the incidence of PD in those with type 2 diabetes, suggesting the neuroprotective effects of AMPK activation [3]. Based on the aforementioned studies, a relationship between mitochondrial regulation and apoptosis-mediated neuroprotection in PD was establish for the first time, presumably via the AMPK/GSK-3/PP2A pathway [71].

Nutraceuticals targeting AMPK pathways in PD include luteolin, EGCG, quercetin, genistein, caffeic acid, magnolol and resveratrol [8].

Conclusion

In conclusion, this thorough literature review highlights how the field of nutraceuticals is changing as it relates to PD. The integration of research results from multiple investigations indicates a complex potential for nutraceutical therapies concerning neuroprotection and symptom alleviation. The proven neuroprotective properties, which include anti-inflammatory effects, antioxidant processes, and regulation of neurotrophic factors, offer a viable option to complement conventional treatment modalities. There is compelling evidence that a variety of dietary supplements can be used in conjunction with other therapies to prevent and treat PD. The innovative, integrated therapeutic strategy of nutraceuticals has created a new situation for the treatment of this multifactorial, complex disease.

As shown in Figure 1, numerous nutraceuticals discussed in this review have been demonstrated to be both therapeutic and preventative for PD. Additionally, it has been shown that green tea-derived catechin EGCG, potentially via improving mitochondrial homeostasis, may improve the pathological outcomes of PD. Experts agree that we are still at the beginning, despite some encouraging results, there are still several unsolved mechanistic questions about the role of nutraceuticals in neuroprotection for PD.

In the future, it will be crucial for researchers, medical experts and the pharmaceutical sector to work together to bridge knowledge gaps, validate encouraging results, and establish evidence-based guidelines. Nutraceuticals have a great deal of potential to improve patients' quality of life and possibly even change the course of this complicated neurodegenerative disease when incorporated into the comprehensive treatment paradigm for PD. Even though these nutraceuticals are appealing and beneficial, nutraceuticals cannot treat PD. There is

not enough experimental data to support the creation of pharmaceuticals that are effective from nutraceuticals. It goes without saying that well-planned, placebo-controlled studies in humans are necessary to validate experimental results. The pharmacokinetics and pharmacodynamics of these nutraceuticals, the precise therapeutic target and the appropriate intake dosage are among the numerous unanswered questions that impede their use in a clinical setting. To encourage the introduction of more nutraceuticals into therapeutic use, high-quality studies are required.
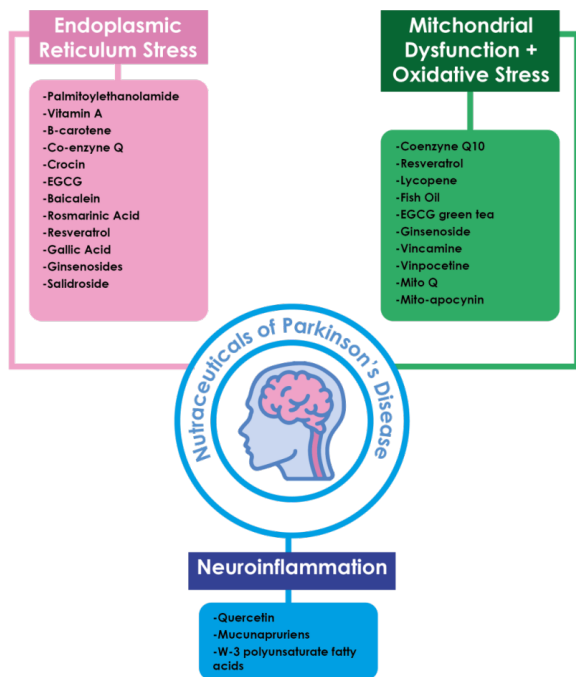

Figure 1. A summary of the nutraceuticals mentioned in this review

Many Parkinson's disease patients express a preference for natural or alternative approaches to managing their symptoms. These people are frequently drawn to nutraceuticals since they are made from natural sources such as plants or herbs and may be used as a supplementary or complementary therapy to conventional medications. For patients with PD, nutraceuticals may have additional health benefits beyond those of prescription medications. This perception may stem from the belief that natural supplements are less likely to have adverse side effects compared to prescription medications. By making dietary and lifestyle choices that incorporate these supplements, they may feel more actively engaged in the management of their disease.

Despite the perceived benefits, patients may have concerns about the safety and efficacy of nutraceuticals. They may worry about possible interactions with their existing medications or the lack of rigorous scientific evidence supporting the use of certain supplements for PD. Cost can be an important factor for patients considering nutraceuticals, as these supplements are often not covered by health insurance. Patients may weigh the perceived benefits against the financial burden of purchasing these products on a regular basis.

Despite numerous encouraging findings regarding the neuroprotective roles of nutraceuticals in PD, we acknowledge that there are still significant gaps in understanding the underlying mechanisms. However, it is crucial to recognize that while uncertainties persist, the recognition of nutraceuticals as potential therapeutic agents presents myriad opportunities for investigating other natural compounds that have not yet been explored for their potential neuroprotective contributions in PD. As an illustration, ergothioneine (EGT), an amino acid that occurs naturally in mushrooms, emerges as a candidate with the ability to safeguard mitochondria against oxidative stress.

Author's contributions

Cassidy Vella conceived the idea, conducted the literature review and drafted the initial manuscript. Renald Blundell guided, critically reviewed and edited the manuscript, and offered valuable insights. Both authors contributed to the final approval of the version to be published.

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Conflict of interests

The authors declare no conflict of interest.

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