Review Article

Foods with Potential Prooxidant and Antioxidant Effects Involved in Parkinson's Disease

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Oxidative stress plays a fundamental role in the pathogenesis of Parkinson's disease (PD). Oxidative stress appears to be responsible for the gradual dysfunction that manifests via numerous cellular pathways throughout PD progression. This review will describe the prooxidant effect of excessive consumption of processed food. Processed meat can affect health due to its high sodium content, advanced lipid oxidation end-products, cholesterol, and free fatty acids. During cooking, lipids can react with proteins to form advanced end-products of lipid oxidation. Excessive consumption of different types of carbohydrates is a risk factor for PD. The antioxidant effects of some foods in the regular diet provide an inconclusive interpretation of the environment's mechanisms with the modulation of oxidation stress-induced PD. Some antioxidant molecules are known whose primary mechanism is the neuroprotective effect. The melatonin mechanism consists of neutralizing reactive oxygen species (ROS) and inducing antioxidant enzyme's expression and activity. N-acetylcysteine protects against the development of PD by restoring levels of brain glutathione. The balanced administration of vitamin B3, ascorbic acid, vitamin D and the intake of caffeine every day seem beneficial for brain health in PD. Excessive chocolate intake could have adverse effects in PD patients. The findings reported to date do not provide clear benefits for a possible efficient therapeutic intervention by consuming the nutrients that are consumed regularly.

1. Introduction

Parkinson's disease (PD) is the second most common chronic progressive neurodegenerative disorder. PD is characterized by the selective loss of dopaminergic neurons of the substantia nigra (SN) pars compacta, which conditions deficiency of dopamine secretion in the basal ganglia of the midbrain with the ability to produce classic motor symptoms: bradykinesia, tremor, rigidity, posterior postural instability, gait disturbances, smell, memory, and dementia [1]. PD involves genetic, environmental, and toxicological factors [2, 3]. PD is associated with oxide-reduction processes through excessive production of reactive oxygen spices (ROS) [4]. The hallmark of PD is the appearance of insoluble inclusions in neurons called Lewy bodies. Lewy bodies mainly consist of α-synuclein deposition [5]. α-Synuclein is a 140 kDa protein encoded via the SNCA gene. α-Synuclein

plays an essential role in the pathogenesis of PD. Duplication, triplication, and point mutations in the N-terminal region (A30P, A53T, and E46K) are linked to familial PD [6]. A recent study suggests that α-synuclein monomers and tetramers are the physiological forms, while oligomers and fibrils are the pathogenic forms [7]. Abnormal accumulation of soluble α-synuclein monomers may lead to the formation of oligomers and fibrils as a key pathogenic event in the early stages of PD [8]. The first clinical signs and symptoms of PD appear after the loss of 50-70% of SN [9, 10]. Based on PD's progressive nature, oxidation might be responsible for gradual dysfunction as a continuous process that manifests itself through many cellular pathways throughout the disease. ROS are normally produced in the cell during the mitochondrial electron transfer chain or by redox reactions [11].

ROS are necessary components for cellular homeostasis. However, when ROS are produced in excess, they induce

transcription errors that cause dysfunction in the expression of different proteins, including C-terminal α-synuclein, parkin, and ubiquitin hydrolase which are directly related to PD [12]. A recent study reported the propensity of oligomers to cause ROS production and significant reduction in the presence of metal chelators such as deferoxamine. This evidence indicates that α-synuclein oligomers produce superoxide (O_2) radicals that bind to transition metal ions such as copper and iron [13]. α-Synuclein toxicity may contribute to elevated cellular oxidative stress. Oxidative stress may trigger α-synuclein toxicity [9]. In PD, α-synuclein oligomers cause the impairment of proteasomes and lysosomes' degradation activity, increasing protein accumulation and aggregation. The accumulation of α-synuclein is associated with a decrease of dopamine release [14]. The mitochondrial respiratory chain can produce oxidative stress by generating ROS and reactive nitrogen species (RNS). Excessive production of ROS and RNS can damage the cell, especially the mitochondrial system. Oxidative stress can trigger apoptosis signaling in nerve cells (Figure 1) [15].

In this review article, we will briefly discuss the role of lipoperoxidation, oxidative damage, DNA repair, mitochondria, endogenous antioxidants, and the anti- and prooxidant effects of some natural foods for daily consumption and some food alternatives with antioxidant potential in PD. These dietary alternatives at low or increased levels can have beneficial or detrimental effects to increase or decrease the signs and symptoms of PD.

1.1. Lipoperoxidation in Parkinson's Disease.
Oxidative stress induces toxicity in the cell by the oxidation of lipids. Lipid oxidation leads to the accumulation of intracellular aggregates, mitochondrial dysfunction, excitotoxicity, and apoptosis. Oxidative damage is a common phenomenon in neurodegenerative diseases. However, it is unclear whether oxidative stress is a cause or a consequence. The formation of modified lipids via oxidation can produce postmitotic cellular dysfunction, and the dysfunction is capable of leading to necrosis or apoptosis of neurons. Lipoperoxidation of polyunsaturated fatty acids (PUFAs) in cell membranes initiates the cumulative deterioration of cell membrane functions by causing decreased fluidity, reduced electrochemical potential, and increased permeability of the cell membrane [16]. Postmortem studies have shown that the effect of chronic oxidative stress is lipoperoxidation of PUFAs in the SN cell membranes [11]. Malondialdehyde (MDA) and glycosylation end-product levels increase in PD, resulting in impaired oxidation of glucose. The increase of MDA and glycation end-products leads to irreversible oxidation of proteins in the SN and the cerebral cortex. The SN has a high risk of aggressive oxidative attacks via lipoperoxides. It has been previously reported that the distribution of transition metals in the brain showed remarkable regional differences [17]. 4-Hydroxy-2-nonenal is a lipid peroxidation product capable of preventing the fibrillar formation of α-synuclein by promoting the formation of secondary β-sheets and toxic soluble oligomers in a dose-dependent manner. Therefore, oxidative stress can also influence α-synuclein toxicity and mediate the pathogenesis of PD [18]. In the

postmortem brains of PD patients, increased carbonylated proteins and TBAR markers have been detected [19]. Lipoperoxidation markers were increased in plasma and cerebrospinal fluid (CSF) in PD patients compared to controls without the disease [20].

1.2. Oxidative DNA Damage in Parkinson's Disease.
PD is characterized by defects in the ability to repair acute or chronic oxidative damage to neurons [21]. The 8-hydroxy-$2'$-deoxyguanosine (8-OHdG) marker is an indicator of nucleic acid oxidation; in particular, it is a marker of oxidative damage to nuclear and mitochondrial DNA. In patients with PD, the marker has been found to increase in the CSF coupled with increased levels of oxidized coenzyme Q10 [22]. Oxidative DNA damage leads to genomic instability and cellular dysfunction. More than 100 oxidative modifications to DNA are identified; many of these are mutagenic, while others interrupt replication or transcription, leading to cancer or cell death in PD [23]. Oxidative damage can arise from external sources, such as chemical agents and ionizing radiation. However, most of the oxidative damage is caused by ROS produced through normal cellular respiration and metabolism [24]. Oxidative damage to DNA in the brain is particularly frequent since it is produced by endogenous metabolic activity. The continuous electrochemical transmission between brain cells requires a large amount of energy. Brain tissue maintains a high basal metabolic rate to meet high energy demands, resulting in brain cells that produce high levels of ROS [25]. The oxidative stress imbalance amplifies the level of damage within brain cells, increasing the demand for DNA repair activity, requiring additional energy, and creating a perpetual state of oxidative stress. Differentiated postmitotic brain cells lack a robust DNA repair and detection machinery associated with replication [26]. However, brain cells have highly efficient base excision repair (BER) mechanisms to cope with the high oxidative stress involved in neurodegenerative disorders. Emerging research suggests that specific BER pathway deficiencies perpetuate neuronal dysfunction [5, 22]. Injuries that occur in DNA include base modifications, abasic sites, and single- and double-strand breaks of DNA. The injuries that occur are mostly repaired via BER [27]. The first step of BER is the recognition and removal of damaged DNA bases. DNA base modifications are recognized first and removed by glycosylase enzymes. Abasic sites are removed by apurinic enzymes/apyrimidinic endonucleases [28]. DNA glycosylases are the first DNA repair enzymes recruited for oxidative damage [29]. Eleven glycosylases are known in humans [30]. The three central glycosylases that recognize oxidative damage are 8-oxoguanin DNA glycosylase (OGG1), endonuclease III, and endonuclease VIII [29]. OGG1 shows specificity for lesions caused by the oxidative damage marker to DNA 8-oxoguanin. The mutY homolog (MYH) can cleave a mismatched adenine throughout the 8-oxoguanin injury to suppress mutagenicity [31]. In the brain, the most abundant oxidative lesions produced by the 8-oxoguanin and formamidopyrimidine (FAPY G) markers are derived from the oxidation and reduction of 8-hydroxyguanine injuries [32].
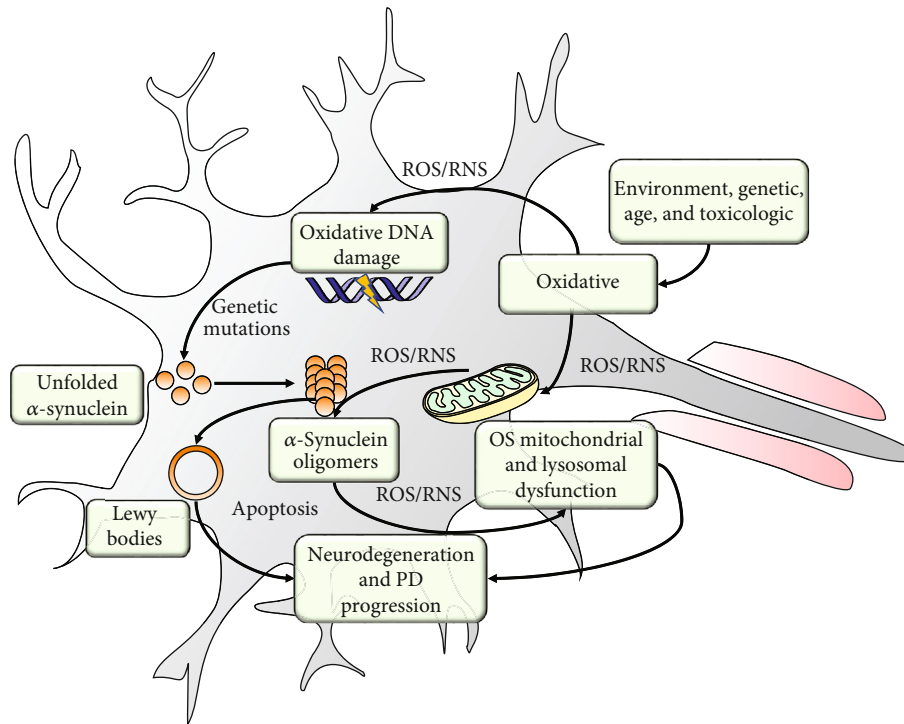
Figure 1: Schematic representation of the oxidative stress mechanism in the development of Parkinson's disease in dopaminergic neurons. Oxidative stress from aging or exogenous sources causes damage to vulnerable cellular structures such as mitochondria and DNA. α-Synuclein gene mutations can promote the formation of α-synuclein oligomers and Lewis bodies. Oxidative stress causes mitochondrial dysfunction that converts the mitochondria into a source of ROS/RNS. ROS/RNS increases α-synuclein aggregate formation, and these, in turn, damage mitochondrial function. Both mitochondrial dysfunction and Lewis bodies lead to a loss of dopaminergic neurons and thus neurodegeneration

1.3. Mitochondria in Parkinson's Disease. Mitochondria are organelles that produce ATP (chemical energy) and play a critical role in energy metabolism, the redox state, and Ca^{2+} homeostasis. Therefore, mitochondria are crucial to cell survival. Intracellular Ca^{2+} stimulates the electron transport chain in the mitochondria producing ATP and ROS as sub-products. The endoplasmic reticulum is a quality control organelle that organizes protein synthesis, folding, and transport. Crosstalk between the endoplasmic reticulum and mitochondria increases with oxidative stress and mitochondrial stress, which can cause endoplasmic reticulum dysfunction. Research in the postmortem brain tissue has previously reported impaired mitochondrial function and elevated oxidative stress caused by α-synuclein aggregates, autooxidation, and degradation of dopamine in the SN [33]. Chronic oxidative stress is characterized by altered levels of iron and antioxidant defenses (enzyme superoxide dismutase (SOD) and glutathione (GSH)) in brain cells in PD [34]. Antioxidant enzymes, SOD, and GSH prevent ROS levels from rising [35]. When antioxidant defenses fail to regulate ROS levels, there is an increase in OS capable of producing harmful effects [36]. Random oxidation of macromolecules within the cell can damage cell structures and even cause cell death [37]. OS increases the possibility of spontaneous cellular mutations. The appearance of mutations conditions the vulnerability of cells to dysfunction [38].

1.4. Prooxidant Foods. Prooxidant foods are compounds that promote oxidative stress by increasing ROS generation or by decreasing antioxidant systems [39]. Diet can participate in OS production processes depending on the quantity or quality of micro- or macronutrients [40]. Some characteristics and mechanisms of different types of prooxidant foods that have the ability to favor the clinical manifestations of PD are described below (Figure 2).

1.5. Processed Meat Containing Oxidized Proteins in Parkinson's Disease. Meat products are the primary source of protein, amino acids, vitamins (niacin, vitamin B6, and vitamin B12), and minerals such as iron and zinc [41]. However, meat also contains products that, in excess, can be harmful to human health such as sodium, advanced glycation end-products, cholesterol, and free fatty acids [42, 43]. Currently, most meat products undergo processing stages that involve modification of their structure, changes in aggregation, or fragmentation that can cause protein oxidation [44]. Protein carbonylation determination is a useful marker to measure oxidative damage in different foods with high protein content [45]. Carbonylation is common in some processed foods, such as fermented sausages, dry-cured loins, chicken thigh meat, and pork or beef patties [46]. These products accumulate oxidized molecules during their process, and when ingested, they come into contact with the intestinal mucosa, internal organs, and the bloodstream after
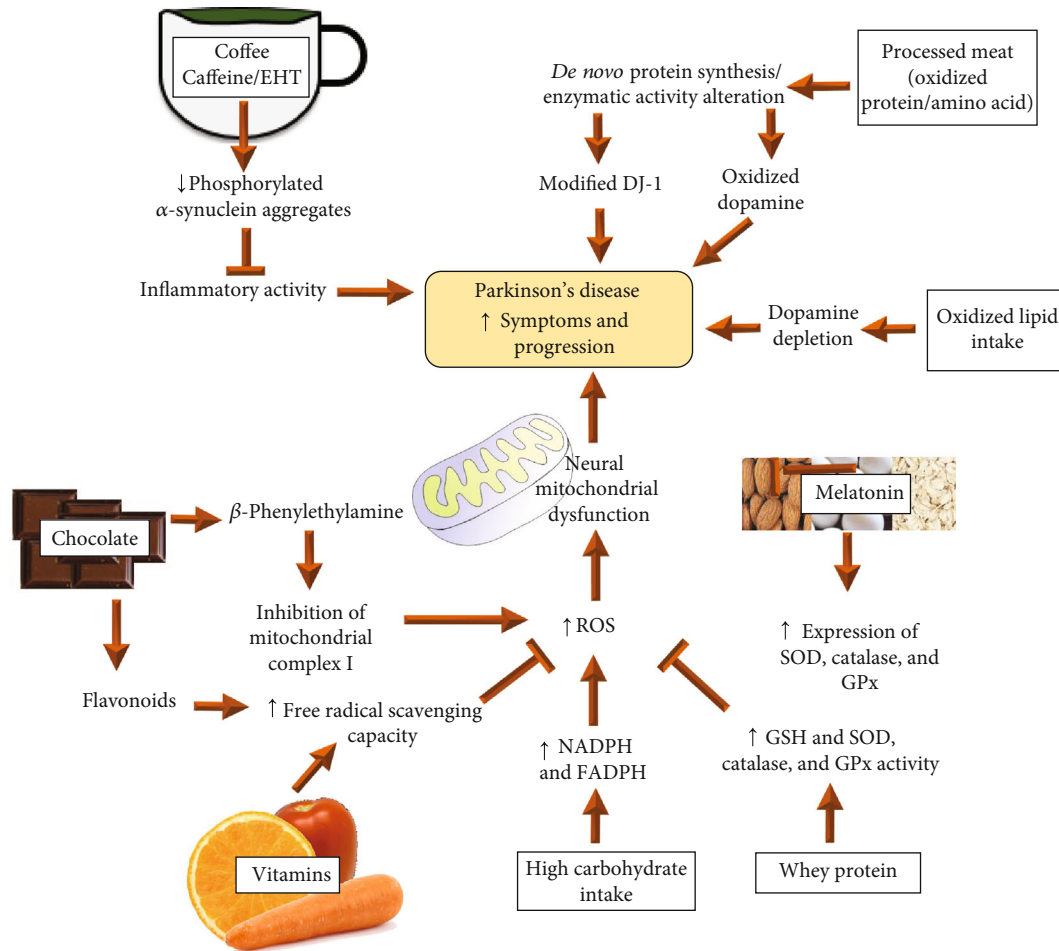
FIGURE 2: Proposed mechanism of food with pro- and antioxidant properties in the development of PD. Description of how the excessive intake of oxidized proteins and lipids causes the synthesis of oxidized molecules that worsens the symptoms of PD. A diet rich in carbohydrates can increase oxidative stress and cause oxidative neuronal damage. Food products can help to neutralize mediators of PD progression.

intestinal absorption [47]. Various studies have reported that oxidative protein modifications can accumulate in the body and damage specific tissues. For example, protein carbonyls correlated with the severity of damage in inflammatory bowel disease [48], and oxidized thyroxines are associated with dysfunction of insulin secretion [49]. Besides, the proteolytic damage of tissue releases 2-aminoadipic acid, which is a risk marker for diabetes mellitus (DM) [50]. Intake of products with these structural modifications is also associated with aging and age-related diseases like PD [51–53]. There are different pathological mechanisms in which the intake of peptides or modified amino acids in PD is involved. One mechanism depends on the incorporation of oxidized amino acids into *de novo* protein synthesis, resulting in enzyme dysfunction with the ability to cause cellular damage [54]. One of the examples is the oxidative modification of the DJ-1 protein. The DJ-1 protein, which contains 189 amino acids, has been linked to PD because the loss of its functions causes disease with parkinsonian characteristics [55]. The oxidative modifications in a single amino acid of the DJ-1 protein are sufficient to favor PD development. Oxidative modifications of dopamine have been linked to PD [56].

Oxidized dopamine accumulates in the dopaminergic neurons of patients with sporadic or genetic PD, resulting in mitochondrial and lysosomal dysfunction [57].

1.6. Oxidized Lipids in Parkinson's Disease. Lipids are a necessary part of nutrition, providing large amounts of energy and essential fatty acids and promoting food acceptance [58]. Lipids provide important quality characteristics to meat products such as flavor and juiciness [59]. Lipids are highly prone to oxidation and represent the leading nonmicrobial cause of decomposition of meat products [60, 61]. During the oxidation of lipids in food, nutrient quality is lost due to the decrease of some macro- and micronutrients such as PUFAs, tocopherols, and amino acids or proteins that react with oxidized lipids [62]. Oxidized cholesterol products can be found in beef, *mortadella*, and anchovies [63–65]. Lipid oxysterols and hydroperoxides can be found in butter, corn oil, or olive oil [66, 67]. During food processing or cooking, lipids can react with proteins to form advanced lipid oxidation end-products (ALE) [68]. The health effects of ALEs in food are controversial. Some authors describe that oxidized fats can activate the inflammatory response and damage

organs such as the intestine, liver, and kidney [69, 70]. Baynes reported that enzyme systems can neutralize oxidized fats during metabolism and that harmful metabolic processes can occur in people with compromised cellular functions [71]. The effect of the high-fat diet on PD is not entirely clear. Mouse studies showed that high-fat diets could increase dopamine depletion in the nervous system and promote the progression of PD [72, 73]. Human studies associate the consumption of animal fat with an increased risk of developing PD [74, 75]. However, results were not replicated in other more extensive recent studies [76–78]. The contradictory findings may be due to different types of fat used in the diet that are not always described. Some studies indicate that high cholesterol or a keto diet may lower the risk of developing PD or improve the motor and nonmotor symptoms of the disease [79]. Also, the consumption of PUFAs contributes to the neuroprotective anti-inflammatory capacity [80–82].

1.7. The Effect of a Diet Rich in Carbohydrates in Parkinson's Disease. Eating a diet rich in carbohydrates can promote cellular signaling of inflammatory effects [83]. High carbohydrate consumption increases the glycemic index. A high glycemic index is associated with cancer risk and comorbidities due to overweight or obesity [84, 85]. In the Asian population, high consumption of rice or total carbohydrates is positively related to type 2 DM [86, 87]. Additionally, consuming refined carbohydrates, such as fructose-rich syrups, may lead to metabolic problems such as DM, obesity, and cardiovascular disease [88, 89]. High caloric intake can induce oxidative stress by increasing the substrates of mitochondrial respiration [90]. The high level of glucose metabolism increases NADPH and FADPH, which are capable of increasing O_2 production [91]. High glucose concentrations increase the activity of the thioredoxin-interacting protein that favors the generation of ROS [92]. The increased consumption of fructose products plays an important role as a trigger for oxidative stress. Animal studies showed that increased fructose in the diet causes metabolic and endocrine changes that affect different organs and tissues [93, 94]. Some retrospective studies report risk factors for developing PD due to high carbohydrate intake, but the effects of high carbohydrate intake on PD are still inconclusive. Consumption of dairy products is a risk factor in men, but not in women [74]. It has been previously reported that carbohydrates, monosaccharides, refined sugar, lactose, and other carbohydrate-rich foods such as bread and cereals are risk factors for PD [95]. However, cohort studies have not confirmed that total carbohydrate intake is associated with the risk of developing PD [76]. Diet with a high glycemic index or high carbohydrate intake found in a case-control study reduces the risk of PD [96]. A diet rich in carbohydrates could link DM to the risk of developing PD [97, 98]. PD and DM share common pathogenic mechanisms involving mitochondrial dysfunction, inflammation, and metabolic disturbances [99]. There is evidence between the association of DM with PD risk by increasing postural instability and difficulty walking [100]. However, further confirmatory studies are still needed [101, 102].

1.8. Parkinson's Disease Management Alternatives. Due to the increase in life expectancy and generational change, PD has become a common health problem and care of a PD patient has become a treatment challenge. PD is a costly disease for health services characterized by the accelerated appearance of clinical manifestations. PD becomes devastating for patients and their families. In the field of neurodegenerative diseases, the existing therapies only limit the activity of the disease. Alternative treatments need to be evaluated for both their beneficial and harmful properties (Table 1). A combination of therapies is recommended, which could condition the real delay in the evolution of PD as a possibility to improve the symptomatology of the disease or improve the quality of life of patients [103].

1.9. Antioxidants in Parkinson's Disease. Cells have developed antioxidant defense systems to protect themselves against their destructive products. The antioxidant defense system consists of enzymes that involve BER, SOD, glutathione peroxidase (GPx), peroxiredoxins, and GSH [26]. Due to the brain's high metabolic rate, there may be a decreased ratio of antioxidant to prooxidant enzymes [104]. The SN's antioxidant defenses are relatively low compared to other regions of the central nervous system (CNS). Low levels of GSH are produced during the early stages of PD. Extravesicular dopamine and its breakdown products can act as GSH depleting agents [105]. N-acetylcysteine (NAC) shows antioxidant properties by restoring cellular GSH and participating in important endogenous antioxidant systems. In experimental studies, NAC has been reported to protect against the development of PD [106]. The antioxidant characteristics of GSH have been demonstrated in oxidative stress models, including models that use buthionine-sulfoximine to deplete GSH. GSH depletion increases oxidative stress in all cells and mitochondrial fractions. Most of the antioxidant functions of GSH are exerted as a cofactor of the GPx enzyme family [107]. The GPx family forms a group of selenium-containing enzymes with the ability to reduce toxic peroxides [108]. Under neurotoxicity conditions, the overexpression of the antioxidant enzyme GPx can decrease the number of neurons lost [109]. An immunocytochemical study of GPx1 expression showed that dopaminergic neurons in SN express low levels of the enzyme. In contrast, in other regions not affected by PD, they express high levels of the enzyme [110]. GPx is an enzyme involved in the elimination of peroxides in the brain. The enzymatic activity of GPx reduces the probability that the hydroxyl radical (OH) will be produced by transition metals [44]. One of the major cellular defense systems for oxidative attacks is the antioxidant enzyme SOD. Three types of SOD have been identified in mammalian cells: copper-zinc SOD (Cu/ZnSOD or SOD1), manganese SOD (MnSOD or SOD2), and extracellular SOD (ECSOD or SOD3). SOD1 is a 32 kDa homodimer of a 153-residue polypeptide with one copper and one zinc-binding site per subunit [111]. Specifically, each monomer possesses a β-barrel motif and two functionally important large loops, called zinc and electrostatic loops that coat the metal-binding region. SOD1 catalyzes the reaction of the O_2^- anion in molecular oxygen (O_2) and hydrogen peroxide

Table 1: Antioxidant and prooxidant properties of nutrients used in Parkinson's disease.

Nutrient	Antioxidant/benefit effects in PD	Prooxidant/side effects in PD
Melatonin	Increases the expression of GPx, SOD, and catalase [134] Improves sleep disturbances in PD patients [139, 140]	Melatonin can promote ROS production at a concentration of 10-1000 μM [143]
Vitamins	The low singular form of vitamin B (10 mM) can induce differentiation of embryonic stem neuron cells [153] Vitamin C has antioxidant properties and it is well distributed in the brain [155] Vitamin D protects dopaminergic neurons [159]	The high singular form of vitamin B3 (>20 mM) can induce cytotoxicity and cell death [153] Vitamin C can induce OS in the presence of free transition metals and H_2O_2 [156]
Whey protein supplements	20 g/day increases GSH in PD patients but does not improve the severity of disease [176]	High protein intake decreases the absorption of levodopa and increases the symptoms of PD [177]
Chocolate	Chocolate rich in flavonoids has free radical scavenging capacity and neuroprotective effects [180] No improvement was found in motor function after administration of 200 g of cocoa chocolate in PD patients [188]	Cocoa chocolate contains β-phenylethylamine which can promote $^-$OH formation and psychomotor dysfunction [192]
Berberine	Administration of 50 mg/kg prevents loss of dopaminergic neurons and improves motor balance and coordination in a rat PD model [219]	Long-term administration of berberine increases loss of dopaminergic neuronal mass in vitro and in vivo [220] Berberine along with chronic L-DOPA administration causes degeneration of dopaminergic cells in the substantia nigra in a rat model of PD [221]
Curcumin	Decreases ROS and the neurodegenerative severity and improves locomotor symptoms in Drosophila PD model [226]	
Quercetin	Administration of quercetin and piperine decreases the neurotoxicity in rat PD model [230]	
Coffee	Components in coffee have antioxidant, anti-inflammatory, and neuroprotective effects [204, 206]	

GSH: glutathione; GPx: glutathione peroxidase; SOD: superoxide dismutase; PD: Parkinson's disease; ROS: reactive oxygen species.

(H_2O_2) in a bonded copper ion [112]. The intracellular concentration of SOD1 is high (between 10 and 100 μM) [113]. SOD1 represents 1% of the total protein content in the CNS. SOD1 is located in the cytoplasm, nucleus, lysosomes, peroxisomes, and intermitochondrial membrane spaces of eukaryotic cells [114]. Reports suggest that SOD1 is a crucial antioxidant enzyme whose mutations are a significant target of oxidative damage to brains with PD [115, 116]. SOD1 and mitochondrial SOD2 are among the most abundant antioxidant proteins in the brain and are fundamental in protecting neurons from oxidative stress. SOD enzymes eliminate toxic O_2^- converting it catalytically into oxygen and H_2O_2. Some studies suggest that abnormalities in SOD1 or SOD2 may contribute to the development of PD [117].

1.10. Melatonin in Parkinson's Disease. Melatonin is a natural hormone mainly secreted by the pineal gland that regulates different physiological functions. Melatonin is also synthesized by other organisms, such as bacteria, invertebrate animals, and plants [118]. The consumption of foods rich in melatonin such as pineapple, orange, and banana, can increase the antioxidant capacity of the organism [119]. Melatonin has also been identified in vegetables, meats, and sprouts [120, 121]. Meng et al. evaluated that eggs, fish, nuts,

cereals, and some seeds are the foods with the highest melatonin content [122]. Melatonin is known for its antioxidant properties and anti-inflammatory and cardiovascular effects. Melatonin has properties that inhibit tumor proliferation in the autoimmune system and provide a neuroprotective effect [123–127]. The main interest in the investigation of the effects of melatonin on PD arises from the relationship between the decrease in the activity of the pineal gland and melatonin in these patients [128]. MT1 and MT2 melatonin receptors are also decreased in PD [129]. Melatonin neutralizes ROS and induces the expression and activity of antioxidant enzymes [130, 131]. In mice, the effect of melatonin counteracts the progression of dopamine by increasing the activity of the mitochondrial complex I by decreasing the levels of lipoperoxides and nitrites in the cytosol and mitochondria of brain cells [132]. Other studies have shown antiapoptotic, neuroprotective, and antidepressant activity in mouse models with PD [133–135]. Other studies have shown that melatonin treatment can help improve sleep disorder and increase neuroprotection in PD patients [136, 137]. However, the consumption of melatonin has not been able to improve the motor symptoms of PD [138]. Some studies reported that melatonin could promote ROS generation. *In vitro* studies showed that melatonin has prooxidant effects

mainly at lipids and proteins [139]. However, high concentrations of melatonin (10-1000 μM) are reported to promote ROS production by inducing cytotoxicity and apoptosis in human leukemia cells [140]. Similar effects were found in an Alzheimer's disease model culture, where melatonin concentrations of 1 mM increased oxidative stress markers, while concentrations < 0.1 mM reduced oxidative damage [141]. The prooxidant mechanisms of melatonin have not been fully described. Leukocyte studies show that melatonin has little interaction affinity for calmodulin and that this phenomenon seems to favor ROS production [142]. The benefits and risks of melatonin supplementation in PD patients require more clinical evidence to support the previously described findings.

1.11. Vitamins in Parkinson's Disease. Complementary to the usual pharmacological therapy for PD, it is suggested to add some other natural compounds as adjuvants. Vitamins are natural bioactive products with antioxidant properties [135]. Vitamins are necessary to maintain normal body functions; since essential vitamins cannot be synthesized endogenously by the body, they must be obtained through the diet. Vitamin deficiency is common in the elderly. Vitamins A, D, E, and K are fat-soluble. Fat-soluble vitamins bind primarily to nuclear receptors and affect the expression of specific genes [143]. Vitamins B and C are soluble in water and are cofactor constituents that affect enzyme activity [144]. The antioxidant properties of vitamins and their biological functions to regulate gene expression may be beneficial for the treatment of PD. Recent clinical evidence indicates that adequate supplementation of different vitamins can reduce PD incidence and improve the clinical symptoms of patients. Vitamin supplementation may be a beneficial adjuvant treatment for PD [145]. The members of the vitamin B family which are soluble in water include thiamine (vitamin B1), riboflavin (vitamin B2), niacin (vitamin B3), pantothenic acid (vitamin B5), pyridoxine (vitamin B6), biotin (vitamin B7), folic acid (vitamin B9), and cobalamin (vitamin B12) [146]. B vitamins play an important role as enzyme cofactors in multiple biochemical pathways in all tissues, such as regulating metabolism, improving the immune system and nervous system function, and promoting growth and cell division. Recently, the association between vitamin B and PD is receiving increasing attention [147]. Fukushima suggests that excess vitamin B3 (nicotinamide) is related to PD development [148]. Excess nicotinamide can induce the overproduction of 1-methyl nicotinamide (MNA) in PD patients [149]. Griffin et al. found that the singular form of nicotinamide (10 mM) has a significant effect in inducing the differentiation of embryonic stem cells in neurons. However, high singular forms (>20 mM) of nicotinamide cause cytotoxicity and cell death [150].

Vitamin C (ascorbic acid) is an essential water-soluble vitamin that is widely distributed in various tissues. Vitamin C is abundant in vegetables, fresh fruits, and animal livers. Vitamin C contains two molecular subforms in the body. The reduced form of vitamin C is ascorbic acid and the oxidized form of dehydroascorbic acid. Vitamin C is essential for the nervous system's physiological function and antioxidant function by inhibiting oxidative stress, reducing lipoperoxidation, and eliminating free radicals [151]. Vitamin C has the potential for the treatment of PD because it is mainly distributed in areas rich in neurons [152]. Vitamin C deficiency can cause scurvy. However, ascorbic acid exhibits prooxidant properties in the presence of free transition metals because it reduces ferric ions to ferrous ions in a Fenton-type reaction. Ascorbic acid in the presence of H_2O_2 stimulates the formation of OH radicals [153]. Therefore, the final prooxidant or antioxidant effect depends on the relationship between ascorbic acid concentration and the available ferrions [38]. At sufficiently high levels, ascorbic acid reduces and destroys the radicals formed [154]. Postmortem studies have shown that vitamin D receptors are present in dopaminergic neurons in the human SN. Vitamin D administration has been suggested to protect dopaminergic neurons, and its deficiency is associated with increased motor severity, postural instability, worsening verbal fluency, and memory [155, 156]. In early PD, patients have been reported to have significantly lower serum 25-(OH)-D concentrations than controls of the same age, which may have implications for bone health and fracture risk. Sleeman et al. reported a small significant association between vitamin D status at baseline and worsening PD motor function at 36-month follow-up [157]. 25-Hydroxyvitamin-D deficiency and reduced exposure to sunlight are significantly associated with an increased risk of PD. However, vitamin D supplementation does not produce significant benefits to improve motor function in PD patients [158].

1.12. Whey Protein Supplementation in Parkinson's Disease. In addition to the protein obtained from food, there is also whey protein (WP) supplements used to treat some metabolic disorders [159]. WP is a soluble by-product obtained from the separation of casein during cheesemaking [160]. WP is mainly rich in globulins, albumin, and amino acids [161, 162]. Some studies have shown that specific WP preparations can reduce proinflammatory cytokine levels (TNF-α, IL-6) and work as a hepatoprotective agent in hepatitis and liver fibrosis in rat models [163]. Other studies evaluated the antioxidant effect of (WP) supplementation on oxidative stress [164]. Rat studies reported that WP supplementation increases the antioxidant enzyme activity of catalase, SOD, and GPx and reduces the effect of TBAR [165]. Falim et al. evaluated the effect of WP supplementation on oxidative stress in subjects with overweight/obesity and DM. The authors found no significant effect on oxidative stress markers (TBAR, AOPP, and 8-OHdG) [166]. Reyes et al. and Katz et al. demonstrated that supplementation of the amino acid NAC contributes to raising GSH levels in mice and patients with PD [167, 168]. PD patients are generally malnourished and have decreased muscle strength. In these patients, the use of WP may be recommended [169–171], although there is little clinical evidence in this regard. Tosukhowong et al. conducted a double-blind, placebo-controlled clinical trial of 38 patients with PD, and they also conducted a six-month follow-up to assess WP's clinical effects. The authors found that 20 g/day increased the levels of reduced GSH and decreased homocysteine levels. These

results did not impact the severity of PD measured according to the unified PD classification scale (UPDRS) [172]. Clinical studies involving a larger number of patients with long-term follow-up are required to establish the possible beneficial effects of WP supplementation in PD patients. WP supplementation must be monitored because high protein intake decreases the therapeutic effects of levodopa, increasing the symptoms of PD [173].

1.13. Chocolate in Parkinson's Disease. Chocolate is produced from the cocoa bean of the *Theobroma cacao* tree. Polyphenols, especially flavonoids, are the main components of health interest in cocoa and its derivatives [174]. Currently, research on the potential health benefits of consuming PD cocoa is attractive due to their high content of antioxidant polyphenols [175]. The antioxidant capacity of flavonoids has been previously reported due to their free radical scavenging capacity, chelation of transition metal ions, and the mediation of some cell signaling cascades [176]. *In vitro* studies have shown the beneficial antioxidant effects of cocoa [177, 178]. However, these effects are not always extrapolated to *in vivo* studies [179]. It is difficult to establish the recommended amount of chocolate intake to obtain any specific health benefit because the bioavailability characteristics and polyphenol contents are different in each type of chocolate [180]. Dark chocolate, unlike white or milk chocolate, has been used in studies to evaluate its health effects due to its high flavonoid content close to 50% [181]. Dark chocolate shows potential benefits in DM [182], cancer [183], cardiovascular disease [184], and neuroprotective effects [185]. The study on the effects of chocolate in PD patients could be of great importance because the intake of chocolate and other sweets is frequent. A study reported that PD patients consume more chocolate (100 g weekly) than a control group without the disease. PD patients increase chocolate intake by 22% during the disease [186]. A single-dose crossover study evaluated the immediate effect of 200 g of cocoa chocolate on motor function in PD patients. Contrary to expectations, no significant differences in motor function were found in this study at 1-3 h after the ingestion of cocoa chocolate compared to cocoa-free chocolate [187]. An important factor to consider in addition to the flavonoid content is that cocoa contains β-phenylethylamine, traces of a type of amine with neurotransmitter activity [188, 189]. Studies suggest that the distribution of β-phenylethylamine in the brain reaches its maximum concentration in dopaminergic regions [190]. Studies in mice show that β-phenylethylamine causes inhibition of mitochondrial complex I favoring the generation of OH and psychomotor dysfunction [191]. Furthermore, the intake of β-phenylethylamine in mice causes alterations of akinesia, catalepsy, and other motor disorders found in PD [192, 193]. Due to this, it has been reported that long-term intake of cocoa chocolate can promote neurodegeneration and dopamine complications due to its content of β-phenylethylamine [194]. There is still insufficient clinical evidence to support the benefits of the chocolate diet in PD patients. It is necessary to know the singular form and composition of cocoa-derived products that can help improve PD symptoms safely.

1.14. Coffee in Parkinson's Disease. Normally, soluble α-synuclein in PD is intrinsically disordered. This protein erroneously folds and forms distinctive amyloid fibrils in neuropathological inclusions. Initial oligomerization and eventual fibrillation are believed to be critical steps leading to neuronal dysfunction and death [195]. Postmortem brain studies show that α-synuclein in aggregates is hyperphosphorylated in serine 129, and antibodies to phospho-Ser129-α-synuclein (p-α-syn) are useful in detecting these inclusions [196]. The phosphorylation of α-synuclein in serine 129 accelerates its oligomerization and fibrillation *in vitro*. Consequently, this posttranslational modification is of pathogenic and therapeutic interest in α-synucleinopathies [197]. Dephosphorylation of the protein is carried out by a specific isoform of protein phosphatase 2A (PP2A). Serine/threonine phosphatase is the primary brain enzyme consisting of a structural A subunit, a catalytic C subunit, and one of the multiple regulatory B subunits that determine substrate specificity [198]. Carboxyl PP2A methylation is regulated by different PP2A-specific leucine carboxyl methyltransferase 1 (LCMT-1) and a PP2A-specific methylesterase (PME-1). The levels of these methylation regulatory enzymes are disturbed in the brains in PD, with low regulation of LCMT-1 and high regulation of PME-1, associated with reduced relative levels of methylated PP2A (methyl-PP2A), which is the enzymatically more active form [199]. In addition to the antioxidant effects present in the components of coffee [200], caffeine has shown protective effects on altered α-synuclein activity in PD [201]. In 2013, the treatment of transgenic mice with PD was reported; these mice were administered eicosanoyl-5-hydroxytryptamide (EHT), an inhibitor of PME-1 methyl esterase activity present in many types of coffee. The authors found increased brain methylation and PP2A phosphatase activity with reduced accumulation of phosphorylated α-synuclein aggregates with improved neuronal integrity and suppression of the neuroinflammatory response [202]. The study results suggest that EHT and caffeine have synergistic effects in protecting the brain against α-synuclein-mediated toxicity by maintaining active PP2A [203]. Decaffeinated coffee has even been found to have a protective effect in PD models in *Drosophila* [204]. Caffeine is one of the widely consumed purines (phytochemicals) that can contribute beneficial effects to the brain. Among the purines, caffeine is the most studied, theobromine and theophylline have been studied less, and other methylxanthines have been mostly unexplored. While caffeine's neurological effects are well established, it is unknown whether this purine alone is responsible for the beneficial effects of coffee consumption on cognition and resistance to neurodegenerative disorders. Emerging evidence suggests that other classes of phytochemicals present in large quantities in coffee may improve neuroplasticity and protect neurons against dysfunction and degeneration. Among the many nonpurine phytochemicals in coffee, flavonoids such as epicatechins have been shown to promote synaptic plasticity [205]. Growing evidence indicates that regular coffee consumption results in better cognitive performance during stressful conditions [206]. Acute caffeine intake improves performance on memory tasks [207]. A 150 mg dose of

caffeine was previously reported to improve cognitive performance for at least 10 h, and caffeine is recommended in military rations [208]. Extensive longitudinal clinical studies have established an inverse relationship between coffee consumption and decreased memory during aging [209].

1.15. Other Phytochemicals in Parkinson's Disease. Interest in scientific research on the properties of natural antioxidants in chronic degenerative diseases has been steadily increasing over the past two decades [210]. Medicinal plants are the source of a wide variety of bioactive components with antioxidant and anti-inflammatory properties that can be useful as neuroprotective agents [211]. The neuroprotective molecular mechanisms of plant extracts include the elimination of toxins, antioxidant activity, and antiapoptotic effects [212, 213]. Berberine is one of the active components of different Chinese medicinal herbs, including *Hydrastis canadensis*, *Coptis chinensis*, *Berberis aquifolium*, and *Berberis vulgaris* [214]. Berberine has been used as a natural remedy to treat diarrhea, stomatitis [215], hepatitis [216], and hypoglycemic effect [217]. Studies have shown that berberine also has neuroprotective effects by regulating neurotrophin levels [218, 219]. Experimental PD models report that berberine prevents the loss of dopaminergic neurons and enhances motor balance and coordination with maximum effect at 50 mg/kg [220]. However, the long-term treatment with berberine has been associated with decreased dopamine levels and increased degeneration of dopaminergic neuronal cells and its loss in experimental models of PD in rats [221, 222].

Curcumin is a compound derived from the *Curcuma longa* plant that has been extensively researched for its antioxidant and anti-inflammatory properties [223]. *In vitro* studies report that the antioxidant properties of curcumin contribute to its neuroprotective effects [224]. Cognitive deficiencies have improved after the administration of curcumin due to increased levels of the brain-derived neurotrophic factor [225]. Curcumin also has beneficial effects on PD by destabilizing the α-synuclein protein [226]. A study in the *Drosophila* model of PD has shown that the administration of curcumin decreases ROS and neurodegenerative severity and improves motor skills [227].

Another bioactive molecule of natural products is quercetin. Quercetin is one of the main flavonoids widely distributed in apples, berries, onions, tea, tomatoes, and other plant products [228]. The antioxidant and anti-inflammatory properties of quercetin administration have been demonstrated in rat models [229, 230]. The administration of quercetin and piperine (a natural alkaloid) has potent neuroprotective effects against neurotoxicity in rat PD models [231].

2. Conclusions

PD is a common neurodegenerative disorder. PD incidence generally increases with age. Potential risk factors in developing PD include environmental toxins, drugs, pesticides, brain microtrauma, focal cerebrovascular damage, and genomic defects. Previous studies suggest that the intake of certain products may be associated with an increased risk of PD.

Many foods for daily consumption have benefits because of their content of amino acids, vitamins, minerals, and micronutrients. However, increased use of some prooxidant foods may increase the risk of developing or increasing PD symptoms. Processed meat is characterized by high sodium content, advanced glycation end-products, cholesterol, and free fatty acids. The overconsumption of meat conditions a prooxidant effect. The alteration or fragmentation of the structure of meat products can cause oxidation of proteins by carbonylation. On the other hand, fruits and vegetables stand out for their antioxidant effect due to their amounts of vitamins and minerals. The evidence about the beneficial effect of coffee intake and the health risk by consuming large amounts of chocolate in PD patients is noteworthy. Short-term, medium-term, and long-term follow-up clinical studies are required to establish the useful quantities of the food substances, alone or in combination, to determine the bioavailability and nutritional content of each type of food in PD.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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