Dietary Supplements in Parkinson’s Disease

Subjects: Neurosciences
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The use of food supplements or functional food has significantly increased in the past decades, especially to compensate both the modern lifestyle and the food shortages of the industrialized countries. Despite food supplements are habitually intended to correct nutritional deficiencies or to support specific physiological functions, they are often combined with common drug therapies to improve the patient’s health and/or mitigate the symptoms of many chronic diseases such as cardiovascular diseases, cystic fibrosis, cancer, liver and gastrointestinal diseases. In recent years, increased attentions are given to the patient’s diet, and the use of food supplements and functional food rich in vitamins and antioxidants plays a very important role in the treatment and prevention of neurodegenerative diseases such as Parkinson’s disease (PD). Natural compounds, phytochemicals, vitamins, and minerals can prevent, delay, or alleviate the clinical symptoms of PD in contrast to some of the main physiopathological mechanisms involved in the development of the disease, like oxidative stress, free radical formation, and neuroinflammation.

Keywords: Parkinson’s disease ; food supplements ; functional food ; antioxidants ; anti-inflammatory ; neuroprotection ; natural compounds

1. Introduction

The use of food supplements has significantly increased over the past decades, especially in the industrialized countries, with a trend that is expected to increase for the coming years [1]. The reasons for this growth can be ascribed primarily to the modern times, the industrialization process, and the food sources, which are now poorer in important nutrients. Moreover, the frenetic lifestyle that people tend to adopt, as well as the increase of life expectancy and the incidence in chronic diseases provide a constant attention to the intake of specific nutritional elements to compensate for food shortages.

In recent years, a positive outlook toward the medical nutrition market was assessed, estimating that the constant use of food supplements has led to the global dietary supplements market at $133.1 billion in 2016 and is projected to accelerate at CAGR (compound annual growth rate) of 9.6%, reaching $278.02 billion by 2024 [1]. Vitamins-based supplements are projected to account for 48% of the global share by the end of 2024. The European Food Safety Authority (EFSA) defines food supplements as a “*concentrated source of nutrients or other substances with a nutritional or physiological effect that are marketed in dose form. A wide range of nutrients and other ingredients might be present in food supplements, including, but not limited to, vitamins, minerals, amino acids, essential fatty acids, fiber and various plants and herbal extracts*” [2]. In this context, the role of food supplements is to compensate nutritional deficits through an appropriate consumption of specific components, thus supporting several biological processes. It is important to underline that these products are not medicines, since they cannot simulate any pharmacological activity and treat or prevent the onset of diseases [3]. Indeed, claims relating to food supplements are strictly regulated by EFSA, which only after a deep evaluation of scientific literature allows to indicate in which terms the vitamin or more in general the nutrient in question can exert beneficial nutritional effects [4].

Nevertheless, nutritional supplements are often combined with pharmacological therapies for many chronic diseases such as cardiovascular diseases, cystic fibrosis, cancer, human immunodeficiency virus and acquired immune deficiency syndrome, liver and gastrointestinal diseases, and nutritional status related diseases [5][6]. Moreover, nutrition also plays a very important role in the treatment and prevention of neurodegenerative diseases, especially in the older age groups [7]. Recently, it has been highlighted that the consumption of functional food and food supplements can contribute greatly in the management of age-related diseases such as Parkinson’s disease (PD) [8]. Indeed, natural compounds, phytochemicals, vitamins, minerals present in the food supplements or fruits, vegetables, and spices can prevent, delay, or alleviate the clinical symptoms of chronic neurodegenerative diseases, improving cognitive functions, learning, general brain status, and wellbeing [9].

2. Natural Compounds Useful in the Prevention and Management of PD

Scientific evidences have shown that numerous molecules and natural compounds are able to mitigate the symptoms of PD by counteracting the physiopathological mechanisms which dominate the disease, such as oxidative stress and neuroinflammation. Furthermore, some molecules have shown to possess neuroprotective and neuro-modulatory properties.

Table 1 displays the analyzed molecules, describing for each compound the beneficial effects demonstrated experimentally and the performed mechanism that support a positive incidence in the treatment of PD.

Table 1. Summary of the beneficial effects and the involved mechanisms for the examined compounds.

Molecule	Beneficial Effects	Mechanism	Ref.
oenzyme Q10	Antioxidant Neuroprotection	Coenzyme Q10, due to its 1,4-benzoquinone structure, is a powerful antioxidant acting as a free radical scavenger. Since it is also a redox component of the electron transport chain of mitochondria, it may exert neuroprotection through the modulation of mitochondrial activity in neuronal cells.	[10][11] [12][13] [14][15] [16]
Lipoic acid	Antioxidant Anti-inflammatory Neuroprotection	The dithiolane ring, with its oxidized and reduced forms, makes lipoic acid a potent antioxidant. As an anti-inflammatory agent, it inhibits NF-kappaB and inflammatory cytokines like TNF-α. Neuroprotection is given by enhancing the intracellular levels of cysteine, thus increasing the glutathione levels.	[17][18] [19][20]
N-acetyl-cysteine	Antioxidant Neuroprotection	The thiol group of *N*-acetyl-cysteine can act both as a direct antioxidant and as a glutathione precursor. It increases the mitochondrial complex I and IV activities and prevents reactive species of oxygen (ROS) accumulation in neuronal cells.	[21][22] [23][24] [25][26]
Vitamin E	Antioxidant	Vitamin E acts as a scavenger of several ROS by donating a hydrogen atom to free radicals, thus reducing their reactivity and toxicity.	[27][28] [29][30] [31][32]
Carvacrol	Antioxidant Anti-inflammatory Neuromodulation	Carvacrol induces the production of antioxidative enzymes and modulates oxidative stress. The anti-inflammatory effect is exerted by reducing the production of pro-inflammatory cytokines. Carvacrol is also able to inhibit the acetylcholinesterase activity, with positive effects on memory and cognitive performance in PD.	[33][34] [35]
Curcumin	Antioxidant Anti-inflammatory Neuroprotection	Curcumin is an excellent free radical scavenger thanks to the phenolic rings and diketone groups. It protects mitochondrial complex I from enzyme nitration and subsequent inhibition, reducing mitochondrial disfunction. Anti-inflammatory and neuroprotective actions are exerted by modulation of chemokines which mediate the inflammatory cascade.	[36][37] [38][39] [40][41] [42][43] [44]
Omega−3 fatty acids	Antioxidant Anti-inflammatory	Omega-3 fatty acids reduce ROS formation acting as free radical scavengers. They also decrease chemotaxis of neutrophils and monocytes, as well as the production of pro-inflammatory cytokines.	[45][46]
Whey protein	Antioxidant	Since whey protein is an excellent source of cysteine, it can increase the production of glutathione, thus reducing oxidative stress.	[47][48]
Vitamin D_3	Antioxidant Neuroprotection	Vitamin D_3 inhibits oxidative stress, reduces free radical formation, and decreases neurotoxicity by enhancing autophagy signaling pathways. Neuroprotection is exerted by reducing the endothelial dysfunction observed in patients with PD.	[49][50] [51][52] [53]
Creatine	Antioxidant Neuroprotection	Creatine is able to contrast free radicals and ROS acting as antioxidant. Moreover, it can stimulate mitochondrial activity through the production of phosphocreatine, thus modulating the production of ATP and the energy homeostasis in the brain.	[54][55] [56][57]
Melatonin	Antioxidant	Melatonin has interesting antioxidant properties, probably related to the indole group. The antioxidant activity is also performed by preventing the antioxidative catalysts lowering in neuronal cells.	[58][59] [60][61] [62]
Niacin (Vitamin B_3)	Antioxidant Neuroprotection	Niacin and its active form nicotinamide reduce oxidative stress. Neuroprotection is reached since they are involved in the biosynthesis of nicotinamide adenine dinucleotide (NAD), an essential cofactor for the ATP production at the mitochondrial complex I level.	[63][64] [65][66] [67][68]
Vitamin C	Antioxidant	Vitamin C is an excellent antioxidant, suitable in reducing ROS levels, lipid peroxidation, and oxidative stress. It is also useful in regenerating other antioxidants.	[69][70] [71][72]

Molecule	Beneficial Effects	Mechanism	Ref.
6-shogaol	**Antioxidant Anti-inflammatory Neuroprotection**	**The α,β-unsaturated ketone moiety makes 6-shogsol a good free radical scavenger. It possesses anti-inflammatory properties by reducing the production of prostaglandin E and pro-inflammatory cytokines such as TNF-α and interleukin-1β. Neuroprotection is assessed by inhibiting microglial activation.**	[73][74] [75]
β-carotene	**Antioxidant**	**β-carotene is an excellent free radical scavenger. The high number of conjugated double bonds in its structure confers to this compound's peculiar antioxidant properties.**	[76][77] [78][79]
Lycopene	**Antioxidant**	**Lycopene is an excellent free radical scavenger. The high number of conjugated double bonds in its structure confers to this compound's peculiar antioxidant properties.**	[80][81] [82][83] [84]
Flavonoids ***Quercetin Epigallocatechin-3-gallate Ginkgo Biloba extract***	**Antioxidant Anti-inflammatory Neuroprotection Neuromodulation**	**The antioxidant activity of flavonoids depends upon the arrangement of functional groups on the 15-carbon skeleton. Beside the free radical scavenger capacity, they regulate the overproduction of inflammatory cytokines, reducing pro-inflammatory mediators and conferring to neuroprotection. This last property is exerted also through the increment of striatal dopamine and the modulation of cell survival/cell cycle genes, which increase neuronal survivability.**	[85][86] [87][88] [89][90] [91][92] [93][94] [95]

2.1. Coenzyme Q10

Coenzyme Q10 (CoQ10, **Figure 1**), also known as ubiquinone, is a 1,4-benzoquinone that is ubiquitous in animals and most bacteria. Its natural sources are foods such as tuna or salmon, organ meats, and whole grains, but recently food supplements rich in CoQ10 have also become popular. CoQ10 is a component of the electron transport chain and participates in the aerobic cellular respiration, which generates energy in the form of ATP. This molecule acts not only as an important electron carrier in the electron transport chain, but also as a free-radical scavenging antioxidant [10]. In particular, several in vitro studies showed that CoQ10 has neuroprotective effects in multiple models of neuronal toxicity. It was also highlighted that oral supplementation of CoQ10 can reduce the loss of dopamine and dopaminergic axons in the striatum in 1-year-old mice treated with MPTP-induced mouse model of PD (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, MPTP) [11][12]. Nevertheless, the role of CoQ10 in the management of PD is controversial.

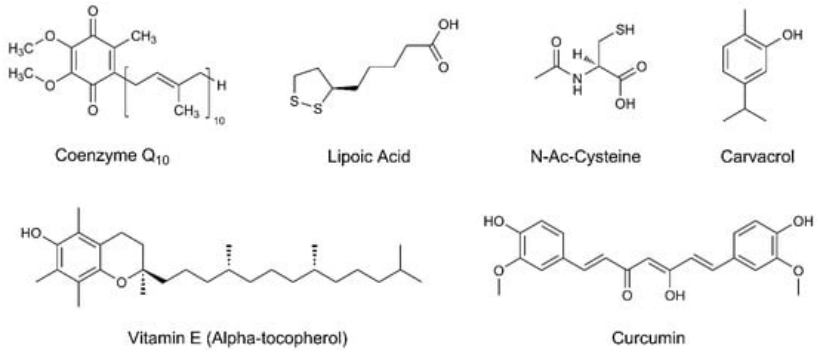

Figure 1. Chemical structures of the examined natural compounds.

Shults and collaborators in 2002 conducted a phase II trial, comparing placebo and three dosages of CoQ10 (300, 600, and 1200 mg/day) in a prospective, randomized, double-blind study with 20 subjects in each group [13]. The authors found that the high dosages of CoQ10 were safe and well tolerated, with a reduction of disability for patients treated with the coenzyme compared to placebo, inducing a slowdown of the progressive deterioration of function in PD.

Moreover, Muller et al. in 2003 performed a monocenter, parallel group, placebo-controlled, double-blind trial to determine the symptomatic response of daily oral application of 360 mg CoQ10 during 4 weeks of treatments [14]. Results suggested that an oral CoQ10 supplementation provides moderate beneficial effect in PD patients.

On the contrary, Storch et al. in 2007 performed a clinical study applying the same protocol and the same maximum dosage as of the Shults' study (1200 mg/day) but did not find any appreciable benefits in mid-stage PD after three months of treatment [15].

More recently, meta-analysis was done to highlight the qualitative and quantitative conclusions about the efficacy of CoQ10 for the treatment of PD [16]. Final results showed that CoQ10 was safe and well tolerated in PD patients but did not present evidence of clinical benefits. Additional trials are required to confirm the role of CoQ10 in slowing the progressive deterioration of function in PD.

2.2. Lipoic Acid

Lipoic acid (LA, **Figure 1**) is a compound naturally synthesized in the human body and also found in several foods. It has potential therapeutic value since it exhibits antioxidative and anti-inflammatory activity, as well as it inhibits free radical formation [17].

Zhang et al. in 2018 investigated not only the antioxidant and anti-inflammatory properties of LA in an in vivo mouse model of PD, but they also assessed the capacity of LA to reduce the dyskinesia side effects related to the L-DOPA administration [18]. The 6-OHDA-lesioned rats (6-hydroxydopamine, 6-OHDA) were treated with LA (31.5 mg/kg or 63 mg/kg) in combination with L-DOPA treatment, highlighting that LA reduces L-DOPA-induced dyskinesia in a dose-dependent manner without compromising the anti-PD effect of the drug. Moreover, LA reduced the level of malondialdehyde, a product of lipid peroxidation, and upregulated the glutatione (GSH) activity, a clear indication of the positive antioxidant effects. The authors concluded that LA can be recommended as a promising disease-modifying therapy when administered with L-DOPA.

Jalali-Nadoushan and Roghani investigated the effect of this compound (at doses of 50 and 100 mg/kg) in a 6-OHDA-induced mouse model of PD, highlighting that LA significantly attenuated rotations on behavioral testing in particular at a dose of 100 mg [19]. These results confirm that LA can partially afford neuroprotection against 6-OHDA neurotoxicity due to the attenuation of oxidative stress burden.

Li et al. tested the antioxidant and anti-inflammatory properties of LA on a lipopolysaccharide (LPS)-induced inflammatory PD model [20]. After the treatment with LPS, in order to induce the microglia activation, mice were treated with LA once a day at 100 mg/kg. Results showed important improvement in motor dysfunctions, a reduction in α-synuclein accumulation, and a reduction of the pro-inflammatory molecules activation, suggesting that LA may exert a significant neuroprotective, anti-neuroinflammatory, and anti-oxidative effect, thus becoming a promising agent for halting the progression of PD.

2.3. N-Acetyl-Cysteine

N-acetyl-cysteine (NAC, **Figure 1**) is an N-acetylated derivative of the sulphurated cysteine amino acid. The -SH group is able to actively contrast ROS, conferring antioxidant properties to the molecule [21]. At the same time, NAC and its analogues contribute to the physiological antioxidant activity by acting as a GSH precursor [22][23].

Potential protective properties of NAC in the management of PD were assessed in animal model studies, demonstrating a sensible reduction of oxidative damage by increasing mitochondrial complex I and IV activities and preventing ROS accumulation, leading in this way to the protection of dopamine-induced cell death [24].

Holmay et al. in 2013 investigated the potential antioxidant properties of NAC by measuring the level of GSH in patients with PD before and after its administration [25]. Results showed that after intravenous injection of NAC, there was a boost in antioxidant GSH levels in the brain and blood of PD patients, making possible the compensation of the hypothesized deficiency and lower GSH activity in PD.

Monti et al. in 2016 highlighted the potential protective properties of NAC in PD using an in vitro and in vivo model [26]. The first model revealed an increased dopaminergic neurons survival in cells treated with rotenone compared to placebo. The clinical study confirmed the protective effects previously observed with an increased dopamine transporter binding in the caudate and putamen in the PD group treated with NAC, and no measurable changes in the control group.

2.4. Vitamin E

Vitamin E is a group of eight fat soluble compounds that include four tocopherols and four tocotrienols; abundant in vegetable oils, whole-grain cereals, butter, and eggs. They are involved in several human biological functions, with the alpha-tocopherol (**Figure 1**) as the main form of vitamin E, preferentially absorbed and accumulated in human body. It acts as an antioxidant, scavenger of several ROS, including hydroxyl and peroxyl radicals, and it is able to inhibit lipid peroxidation [27]. Some clinical trials were carried out to better understand the potential neuroprotective properties of this molecule in the management of PD, but the results are controversial [28].

Fahn tried to administer a combination of ascorbate and vitamin E to patients with early PD in a first pilot open-labeled trial [29]. The primary end point of the trial was the progression of the disease until patients needed treatment with L-DOPA or a dopamine agonist compared to control, and results showed that patients who received the antioxidants combination extended the time when L-DOPA became necessary by 2.5 years, suggesting that the progression of PD may be slowed by the administration of vitamin C and E.

Zhang et al. documented the occurrence of PD within two large cohorts of men and women who completed detailed and validated semiquantitative food frequency questionnaires, highlighting that supplementation with antioxidant vitamins is not associated with the risk of PD, but it is significantly reduced among men and women with high intake of dietary vitamin E [30].

Nevertheless, in another clinical trial, Scheider and collaborators took into consideration the possible role of long-term dietary antioxidants intake in PD onset [31]. Results showed that vitamin E did not show evidence of benefits in either improving the clinical features of PD or delaying the functional decline.

A large clinical trial was conducted to examine the benefits of deprenyl (selegiline) and alpha-tocopherol in slowing the progression of PD (DATATOP study, Deprenyl and tocopherol antioxidative therapy of parkinsonism) [32]. The observation indicated that deprenyl delay the time of disability development, while alpha-tocopherol produced no benefits. Additional trials are still needed to confirm the role of vitamin E in slowing the progressive deterioration of function in PD.

2.5. Carvacrol

Carvacrol (**Figure 1**) is a phenolic monoterpene found in numerous aromatic plants including basil, rosemary, thyme, and oregano. The last possesses the highest percentage of carvacrol-enriched essential oil. Several studies investigated the properties of this monoterpene, highlighting the numerous pharmacological properties, including antibacterial, antifungal, anti-inflammatory, antioxidant, and neuro-modulatory action [33][34]. As a neuro-modulatory agent, the ability to also regulate the activity of dopaminergic neurons has made the use of carvacrol for the treatment of PD interesting.

Haddadi et al. experimentally assessed the effect of carvacrol in a mouse model of PD [35]. The animals were treated with 6-OHDA to induce the onset of the typical symptoms of PD, and subsequently different tests were carried out to determine the motor and cognitive abilities of the treated animals. In particular, the apomorphine-induced rotation test showed that treatment with carvacrol exerted no differences between the treated and the untreated group. Regarding the passive avoidance memory test, the treatment of mice with carvacrol at concentrations of 25 mg/kg showed clear improvements compared to the control group. Finally, the tail-flick test showed no difference between the carvacrol-treated group and the control. The authors concluded that carvacrol showed improved cognitive impairments without having effects on pain and motor symptoms.

2.6. Curcumin

Curcumin (diferuloylmethane, **Figure 1**), is a polyphenol extracted from the rhizome of *Curcuma longa*, a plant widely distributed in Asia. The powder, derived from the rhizome, is used as a spice and as a natural remedy in traditional oriental medicine. The properties that curcumin boasts include antioxidant, anti-inflammatory, and neuroprotective activities, which can have a positive impact on the treatment of PD [36].

Wang et al. carried out an analysis of the scientific literature, collecting 113 studies concerning curcumin and PD [37]. Among these, specific inclusion criteria led to assessing 13 studies as relevant in relationship to the effects that curcumin can exert in animal models of PD. In particular, the three major findings that the authors described are that curcumin can perform anti-inflammatory, antioxidant, and antiapoptotic action. The anti-inflammatory properties were highlighted in five studies, where curcumin attenuated the DNA damage caused by numerous metals and reduced the presence of pro-inflammatory cytokines [38][39][40][41][42]. The antioxidant properties presented in several studies, demonstrated the ability of curcumin to reduce in vivo the ROS levels, lipid peroxidation, and NO generation [38][42][43]. Finally, the antiapoptotic properties have been identified in two studies, where curcumin reduced the pro-apoptotic cellular proteins level, conferring neuroprotection to the brain tissues in the examined animal models of PD [39][44].

2.7. Omega-3 Fatty Acids

Omega-3 fatty acids have as main feature, a double bond, located three atoms far from the last methyl group, which is part of the backbone in their polyunsaturated structure (**Figure 2**). Omega-3 are present in certain foods such as cold-water fish (salmon) and fish oils, walnut, edible seeds and flaxseed oil, as well as dietary supplements in which fish oil is formulated as soft gel capsules. These types of fatty acids are important constituents of animal lipid metabolism, and they play an important role in the human diet and in human physiology, contributing to lower the levels of cholesterol and LDL (low-density lipoproteins) in the blood [45].

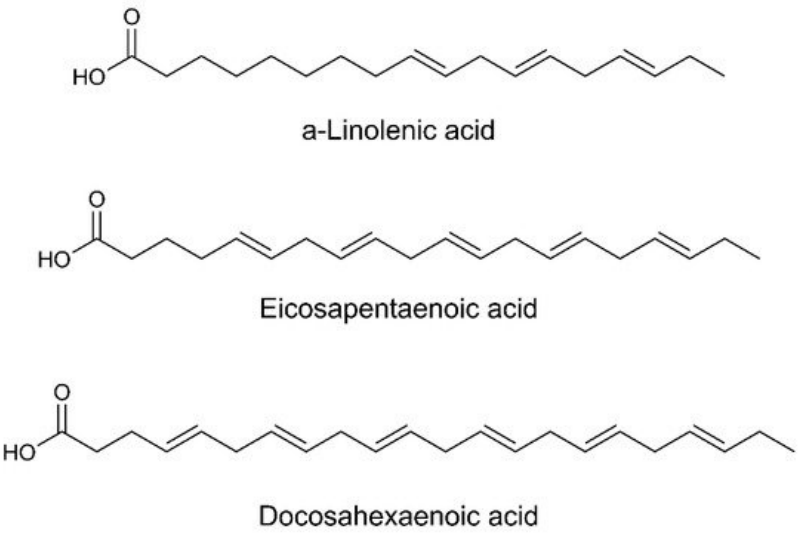

Figure 2. Chemical structures of the principal polyunsaturated fatty acids omega-3.

Beside these already known functions, Taghizadeh et al. evaluated the effects of omega-3 fatty acids and vitamin E co-supplementation on clinical signs and metabolic status in patient with PD, assessing a randomized clinical trial conduced in double-blind against a control group [46]. The treated group received omega-3 fatty acids (1000 mg) in combination with vitamin E (400 IU) for three months. Results showed that omega-3 fatty acids and vitamin E co-supplementation led to a significant improve in the selected rating scale used to assess the stage of PD. Furthermore, co-supplementation decreased high-sensitivity C-reactive protein and increased total antioxidant capacity compared with the placebo, demonstrating that omega-3 fatty acids and vitamin E co-supplementation in people with PD had favorable effects not only on the development of PD symptoms, but also in the management of ROS production and oxidative stress reduction.

2.8. Whey Protein

Protein obtained by whey are a mixture of different lactoglobulins, serum albumin, and immunoglobulins, and more importantly, it is an excellent dietary source of cysteine. Several studies highlighted the capacity of whey protein to increase GSH, suggesting that this complex mixture is capable of boosting GSH synthesis, thus reducing oxidative stress [47].

Tosukhowong et al. in 2016 conducted a placebo-controlled, double-blind study on PD patients to investigate the effects of whey protein supplementation on plasma GSH, plasma amino acids, and the unified Parkinson's disease rating scale modifications [48].

Results showed a significant increase in plasma concentration of reduced GSH, plasma branched chain amino acids (BCAA), and essential amino acids in the whey-supplemented group only. The rate of disease modification was not significantly ameliorated in either group, indicating that whey protein supplementation significantly increases plasma reduced glutathione in patients with PD with no significant changes in clinical outcomes.

2.9. Vitamin D_3

Vitamin D_3 (cholecalciferol, **Figure 3**) is endogenously produced when skin is exposed to the UV-B rays from the sun. Only a few foods such as cod liver oil, tuna, carp, salmon, fat cheeses, and mushrooms contain vitamin D_3. Thus, it can be ingested directly from food supplements. Between the liposoluble steroids belonging to the group of vitamin D, the vitamin D_3 is one of the most important since it is involved in different physiological processes, among them the most known is the calcium absorption and the bone growth regulation. Recently, several studies highlighted a possible implication in the muscular and endocrine apparatus, as well as in the central nervous system, with a positive attitude as neuroprotective agent in the management of PD [49].

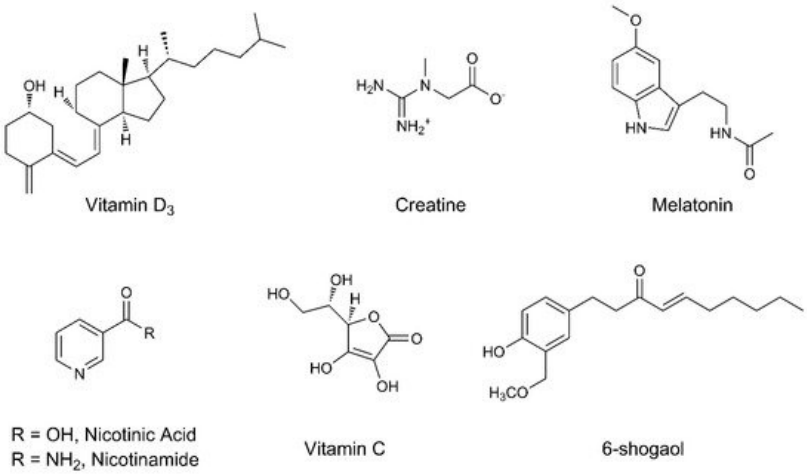

Figure 3. Chemical structures of the examined natural compounds.

Wang et al. studied the neuroprotective effects of vitamin D_3 against 6-OHDA-lesioned mice in vivo and in vitro [50]. Results showed that the pretreatment with vitamin D_3 for eight days significantly restored locomotor activity in the lesioned mice. Neurochemical analysis determined a protection from oxidative stress and reduction in depletion of DA neurons in mice treated with the vitamin compared to the control.

Jang et al. investigated the protective, autophagy-modulating effects of an active form of vitamin D_3 in an in vitro model of PD [51]. Result showed that the treatment with the vitamin reduced ROS levels and increased the levels of intracellular signaling proteins associated with cell survival.

Moreover, some clinical studies suggest that vitamin D_3 has a positive effect on PD.

The first evidence was described by Evat et al. in a study of 2008, in which the level of vitamin D_3, in 55% of patients with PD, was insufficient compared to 36% of a control population [52].

Knekt et al. carried out a cohort study on the Finnish population, collecting information regarding the onset of PD and measuring at the same time the levels of 25-hydroxy vitamin D, which is a serum indicator of the vitamin D_3 concentration in the body, from 1978–1980 until the end of 2007 [53]. The results showed that higher levels of vitamin D_3 are related to a lower risk of developing PD, giving an important indication of the potential neuroprotective activity of vitamin D_3 against this disease.

2.10. Creatine

Creatine is a nitrogenous guanidine molecule that occurs naturally in vertebrates and helps to supply energy to muscle and nerve cells (**Figure 3**). This molecule usually is used by athletes to increase maximum power and performance in high-intensity anaerobic repetitive work, but there are also evidences of antioxidant properties, mitochondrial dysfunction reduction, and neuroprotective properties in in vitro and in vivo models of PD [54].

Matthews et al. assessed the neuroprotective effect of creatine in a MPTP-induced mouse model of PD [55]. Results showed that oral supplementation with either creatine or cyclocreatine produced significant protection against MPTP-induced dopamine depletions in mice, with a decreased dopaminergic neurons degeneration.

Yang et al. examined whether a combination of CoQ10 with creatine can exert additive neuroprotective effects in a MPTP mouse model of PD [56]. After administration of MPTP, the treatment with the two antioxidant molecules significantly reduced lipid peroxidation and pathologic α- synuclein accumulation in the neurons of the MPTP-treated mice, producing additive neuroprotective effects.

Despite these positive results, Bender et al. conducted a two-year placebo-controlled randomized clinical trial on the effect of creatine in 60 patients with PD, highlighting that creatine improves patient mood and led to a smaller dose increase of dopaminergic therapy but had no effect on the disease modification [57]. Further clinical trial may clarify clinical benefits of creatine in the treatment of PD.

2.11. Melatonin

Melatonin is a hormone produced in the pineal gland (**Figure 3**), and it is involved in synchronizing the circadian rhythms including sleep–wake timing, blood pressure regulation, and seasonal reproduction. Moreover, several studies described

the capacity of melatonin to exert relevant antioxidant properties [58].

In particular, Antolin et al. described the capacity of melatonin to act as an antioxidant in a MPTP-induced mouse model of PD [59]. Results showed that melatonin can prevent neuronal cell death, contrasting the damage induced by chronic administration of MPTP, and preventing neuronal degeneration in the nigrostriatal pathway by counteracting induced oxidative and nitrative stress.

Dabbeni-Sala et al. demonstrated the neuroprotective action of melatonin in a 6-OHDA animal model of PD [60]. The authors observed the protective activity of melatonin in the treated-mice, with an increased activity of mitochondrial oxidative phosphorylation enzymes and a reduction of neuronal oxidative stress disorders.

Finally, two studies indicated that the administration of melatonin in mice was ineffective in protecting nigral dopaminergic neurons from MPTP-induced toxicity. Results for both studies indicated that the neuronal enzymatic levels and DA concentration were not different from melatonin-treated mice versus control [61][62].

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