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Optimization of Parkinson's disease therapy with plant extracts and nutrition's evolving roles

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disease characterized by death of dopaminergic neurons in the substantia nigra pars compacta (SNpc). Death of dopaminergic cells in the SNpc leads to manifestations of motor dysfunction and non-motor symptoms of PD. The progression of PD symptoms severely affects the quality of life of patients and poses socio-economic problems to families and society at large. The clinical and neuropathological characteristics of PD are triggered by multiple factors such as oxidative stress, neuroinflammation, mitochondrial dysfunction, and protein aggregation. Notwithstanding the advancements in pharmacological therapy in PD management, there is burgeoning interest in alternative and complementary approaches, essentially nutrition and plant extracts strategies. This review gives widespread analysis of the role of nutrition and plant extracts in the management of PD. Studies that investigated the effects of various dietary compounds and plant extract on PD symptoms and progression were reviewed from existing literatures. Nutraceuticals, including vitamins and phytochemicals such as *Mucuna pruriens* have shown potential neuroprotective functions in preclinical and clinical studies. Indeed, these strategies ameliorate mitochondrial dysfunction, oxidative stress, and neuroinflammation, all which are implicated in the pathogenesis of PD. The neuroprotective mechanisms of nutrition and plant extracts in PD, with emphasis on their capacity to target multiple pathways implicated in PD are discussed. Additionally, challenges and limitations related with translating preclinical findings into clinical practice including standardization of dosing regimens, bioavailability, and inter-individual variability are discussed. Largely, this review elucidates on the role of nutrition and plant extracts as adjunctive therapy in PD management.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disease that affects the ageing population due to the degeneration or death of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and accumulation of intracellular protiens known as Lewy bodies (Massano and Bhatia, 2012; Miller and O'Callaghan, 2015). The pathological hallmark of PD which is the death of dopaminergic neurons alongside dysregulation of neurotransmitters (particularly dopamine, acetylcholine, and glutamate) causes disruption of delicate neuronal signaling axis, resulting into motor dysfunction, which includes postural instability, resting tremor, bradykinesia, and rigidity (Mao et al., 2021). Asides the motor symptoms, PD is also characterized by non-motor manifestations such as anosmia, anxiety, depression, insomnia, orthostatic hypertension, and gastrointestinal symptoms (dyspepsia, constipation, faecal incontinence, and abdominal pain which often precedes motor symptoms)

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(Huang et al., 2021; Abolarin et al., 2022). Neuroinflammation, impaired protein degradation mechanisms, mitochondrial dysfunction, and oxidative stress further aggravate the neuronal damage, eventually climaxing the clinical symptoms of PD.

About 6.1 million people worldwide were diagnosed with PD in 2016, a value that was 2.4 times higher than in 1990 (Ou et al., 2021). In 2018, approximately seven to ten million PD patients were diagnosed worldwide and this population is expected to double by the year 2030 (Huang et al., 2021). The increased prevalence of PD might be attributed to enhanced techniques used for the detection and diagnosis of PD, improved awareness of PD, increased ageing population, and probably increased life expectancy. While a combination of genetic predisposition (genetic mutations of SNCA, LRRK2, PARKIN, and PINK1 genes), environmental factors (such as pesticides and metals exposure), and age-related alterations contribute immensely to PD pathogenesis, the exact etiology remains elusive (Helley et al., 2017). The diagnosis of PD relies basically on clinical assessment, involving the presence of cardinal manifestations, exclusion of secondary causes of PD, and response to dopaminergic treatments (Marsili et al., 2018). Neuroimaging approach, such as dopamine transporter (DAT) imaging and structural MRI, assist in checking the diagnosis and evaluating PD progression. (Porter et al., 2020). Both PD patients and healthcare providers are posed with significant challenges associated with PD. Many individuals continue to experience progressive disability and diminished quality of life notwithstanding the advancements in pharmacological therapies of PD management (Armstrong and Okun, 2020). In light of these challenges, PD management now encompasses the utilization of complementary and alternative approaches.

Currently, there is a burgeoning interest in the applications of nutrition and plant extracts as therapeutic approaches for supporting PD patients. These strategies leverage on the potential anti-inflammatory, neuroprotective, and antioxidant properties of nutrition and plant extracts to mitigate neuronal damage and enhance dopaminergic function beyond conventional therapies. Strong evidence have emerged from many studies, which suggest that certain dietary elements and phytochemicals possess neuroprotective functions and may influence PD progression through numerous mechanisms. This review aims to critically evaluate the existing literature and explore the potential beneficial effects of nutrition and/or plant extracts applications in the management of PD, shedding light on their underlying mechanisms of action against PD. It is crucial to understand the impact of nutrition and plant extracts as this forms the bedrock of advancing our body of knowledge concerning the disease pathogenesis and identifying novel treatment strategies. This review gives insight into the potential benefits of these strategies for the treatment of PD by synthesing existing evidence and explicating their underlying mechanisms.

2. Pathophysiology of Parkinson's disease

The pathological description of PD has to do with the death, loss, or degeneration of dopaminergic neurons (dopamine-producing neurons) within the SNpc and the formation of cytoplasmic inclusions which is made up of abnormal, aggregating a-synuclein (aSyn) proteins otherwise known as Lewy bodies (the major pathological hallmark of PD) in the dopaminergic neurons (Chetty et al., 2021; Hass et al., 2021). aSyn oligomers are not only deposited in the SNpc but also in the brainstem (Hass et al., 2021), olfactory bulb (Chen et al., 2021), and gastrointestinal tract, a phenomenon supporting the role of the gut-brain network with bidirectional crosstalk between the central and enteric nervous system through the vagus nerve (Chetty et al., 2021). The pathologic alterations may precede the obvious manifestations of PD by two decades or more (Hilton et al., 2014), making early diagnosis and management problematic. The preferential death or loss of dopaminergic neurons leads to motor dysfunction and non-motor symptoms. Lewy Bodies, or abnormal intracellular masses, contain different types of proteins with alpha-synuclein and ubiquitin inclusive which distorts the homeostasis of neuronal activities (Beitz, 2014; Pang et al., 2019; Ren et al., 2012).

Many publications have suggested the role of environmental stress and ageing itself in the pathogenesis and the promotion of PD neuropathology. Most importantly, overexposure to environmental toxins (e.g. pesticides) (Pang et al., 2019), drug abuse, and the stress of the ageing process favour a long-term low-level inflammation and oxidative stress in the brain. This inflammatory process in the due course results in the generation of cellular senescence in the brain neurons (Ceccatelli et al., 2013; Chinta et al., 2013). From the pathological point of view, the brain's SNpc and the pontine locus coeruleus (LC) which contains norepinephrine (NE)-synthesizing neurons are affected by abnormalities of PD including depigmentation, neuronal loss, and gliosis. By the time motor or non-motor symptoms of PD begin to manifest, about 60–70% of dopaminergic neurons in the SNpc would have been lost (Brini and Ottolini, 2013; Postuma et al., 2010).

Alpha-synuclein is an important component of the Lewy Body which can become abnormal and self-aggregate. This aggregated, insoluble alpha-synuclein is a major cytoplasmic inclusion that is the hallmark of PD (Chetty et al., 2021; Huang et al., 2021). Apart from protein misfolding and aggregation, there is also impairment of the proteasome system that is required for the breakdown of abnormal proteins like ubiquitin. Other impaired processes play a vital role in the pathogenesis and progression of PD, for instance, mitochondrial dyshomeostasis, oxidative stress,and neuroinflammation results in neuronal death and degeneration (Beitz, 2014).

Another remarkable characteristic of the vulnerable SNpc neurons is an increased concentration of iron and the metabolism of iron. Iron is required for many physiological processes in the peripheral nervous system and central nervous system, including transportation of oxygen, generation of ATP, synthesis of neurotransmitters and axon myelination (Rouault, 2013). The concentration of iron has been reported to be high during healthy aging in various regions of the brain, including SNpc (Zecca et al., 2001; Zecca et al., 2004). Notably, the accumulation of iron in the SNpc of PD patients is remarkably amplified and seems to correlate with disease severity in the (Genoud et al., 2017; Ghassaban et al., 2019). Indeed, excess iron induces cell death though neuroinflammation and oxidative stress due to its catalytic function in the synthesis pd hydroxyl radicals and non-enzymatic oxidation of cytosolic dopamine to form dopamine-o-quinones (DAQs) and other toxic dopamine derivatives, highly reactive species which complex with proteins, resulting to insoluble complexes that become sequestered in the neuromelanin pigment (Ferrari et al., 2017; Segura-Aguilar et al., 2014). Hence, dyshomeostasis in in the levels of iron in the SNpc may also play a leading role in the dopaminergic neurodegeneration. Furthermore, this pathological process is considered to be self-propagating, as is has been demonstrated that specific quinones (i.e. aminochrome) have capacity to transform the expression of proteins involved in iron homeostasis, such as, increasing the iron transporter divalent metal transporter 1 (DMT1 or SLC11A2) and reducing the iron exporter ferroportin (FPN) (Aguirre et al., 2012). In effect, this causes enhancement of iron accumulation and possibly subsequent dopamine oxidation.

3. Risk factors/diagnosis

Based on epidemiological studies, ageing is the most potent risk factor for the development of PD having approximately 50–60 years as the average age of onset (Ascherio and Schwarzschild, 2016; Collier et al., 2011). Apart from ageing, two other risk factors have been identified to be important in the pathogenesis of PD: family history (a genetic link) and pesticide exposure (Ascherio and Schwarzschild, 2016; Beitz, 2014; Collier et al., 2011). High intake of dairy products, family history, and traumatic brain injury have also been implicated in the development of PD and its progression, whereas, a reduced risk has been documented in relation to smoking, caffeine intake, increased serum concentrations of urate, increased physical activity, and use of ibuprofen

and other common medications (Ascherio and Schwarzschild, 2016). Wu and colleagues identified SMPD1 p.L302P mutation as a novel risk factor for the development of PD. Although this is rare on a population level, delineating this mutation as a potent risk factor for PD would go a long way in explaining PD pathogenesis and the role of lysosomal pathways in the development of PD (Wu et al., 2014).

Clinical diagnosis of PD is based on the presence or the manifestations of the motor symptoms of PD: bradykinesia, resting tremor, and postural instability (Gazewood et al., 2013). An important fact to note in the diagnosis of PD is that differential diagnosis can be challenging given that the classic PD motor symptoms can be present or noticed in

other neurodegenerative diseases (Gazewood et al., 2013). Non-parkinsonian tremors such as essential tremor, and diseases with parkinsonian properties such as progressive supranuclear palsy, vascular parkinsonism, and drug-induced parkinsonism are commonly misdiagnosed as PD. Importanlyly, features associated with bradykinesia, such as a shuffling gait, micrographia, and difficulties performing motor tasks such as rising from a chair, turning in bed, or opening jar increase the chanc of PD. It is therefore expedient that careful history is taken alongside astute physical evaluation. (Gazewood et al., 2013; Marté and Tolosa, 2013).

4. Nutraceuticals and plant extracts as alternative therapeutics in managing Parkinson's dosease

Pharmacological therapy approach reamins the major backbone in the treatment of PD (Pang et al., 2019). Even though, pharmacological approach for the treatment of PD has substantially increased in the array of options, it is usually coupled with some undesirable effects (Chao et al., 2012; Wang et al., 2017). In effect, nutraceuticals and plant extract approaches may provide health and medical benefits, either for prevention or treatment of PD or for symptomatic relief, yet with posiible side effects.

Nutraceuticals stems for two words, 'nutrition' and 'pharmaceuticals,'. It refers to the application of foods or food products that reasonable clinical evidence proposes may provide medicinal and health benefits including neuroprotection (Wang et al., 2017). Products in this category may be classified as dietary supplements, specific diets, herbal products, or processed foods such as cereals, soups, and beverages. Food or dietary supplements exist in the form of extracts or concentrates and are usually found in various forms, including tablets, capsules, liquids, and powders. Vitamins, minerals, herbs, or isolated bioactive compounds are only a few examples of dietary supplements in the products (Chao et al., 2012).

It is a well-accepted phenomenon that neuroprotection inhibits neurons from subscribing to the damages caused by different insults (Chaturvedi *et al.,* 2006). Nutraceuticals and plant extracts may therefore provide neuroprotection through a wide spectrum of proposed mechanisms, such as scavenging of free radicals and reactive oxygen species, chelation of iron, modulation of the cell-signalling network, and prevention of or modulation of inflammation (Aruoma et al., 2003). In the following section, the neuroprotective functions of some selected vitamins and some selected medicinal plants are reviewed and discussed.

5. Role of nutritional-derived antioxidants and their mechanism in attenuation of Parkinson's disease

5.1. Role of vitamin E therapy in management of Parkinson's disease

Vitamin E is a fat soluble-compound that exists in different formulations, such as tocopherols and tocotrienols. Vitamin E is potent free radicals scavenger that protects cells against oxidative stress. Application of Vitamin E in the management of PD has aroused interest due to its capacity to neutralize reactive oxygen species (ROS) while extenuating oxidative stress and slowing down the progression of PD (Roghani and Behzadi, 2001).

Many preclinical evidence-based researches supporting the role of Vitamin E have been reported. For instance, Karunanithi et al. (2011) reported that α-tocopherol provided neuroprotective effect on PD models by attenuating dopaminergic neuronal loss and reducing oxidative damage in animal models of PD. Also, Sharma and Nehru, (2013) reported the beneficial effects of vitamin E in rotenone-induced PD model by significantly decreasing lipid peroxidation and improving associated biochemical parameters, such as SOD and GSH. The researchers observed a significant improvement in the motor function of PD animals upon administration of vitamin E. Cytoprotective effective of tocotrienol was demonstrated on *in Vitro* and *in Vivo* models of PD. In this study, Matsura, (2019) observed that tocotrienol exerts its cytoprotection through a novel mechanism which includes membrane ERβ/PI3K/Akt signaling via caveola formation as well as its antioxidant activity. An analogue of vitamin E, Trolox was recently reported by Atiq et al. (2023) to inhibit activated astrocytes (GFAP) and microglia (Iba-1), also reduces phosphorylated nuclear factor-κB, (p-NF-κB) and tumor necrosis factor-alpha (TNF-α) in the PD mouse brain. Just recently, vitamin E administration was reported to offer neuroprotective function on manganese-induced neurodegeneration in the nigrostriatal system. In this study, Song et al. (2024) observed that vitamin E protected dopaminergic cells against manganese-induced neurotoxicity by upregulating cholinergic receptor muscarinic 1 (CHRM1) and potassium voltage-gated channel subfamily J member 4 (KCNJ4) mRNA stimulated in the SN.

A clinical and experimental evidence reports on the use of Vitamin E shows and inverse relationship between Vitamin E intake and the risk of developing PD, buttressing its potential neuroprotective function (Schirinzi et al., 2019). In this study, authors provided a mechanistic explanation on how vitamin E slows down the risk of PD development. Authors tested the effects of vitamin E and some other alimentary antioxidants in vitro through the application of PTEN-induced kinase 1 knockout (PINK1−/−) mouse model of PD. They observed that at corticostraital synapses, the PINK1−/− mice displayed a regular pattern of synaptic plasticity alterations, involving the loss of long-term potentiation (LTP) and long-term depression (LTD), in the absence of obvious neurodegeneration. Interestingly, chronic administration of vitamin E fully restored synaptic plasticity of corticostraital tract in the PINK1−/− mice. The results is suggestive of a definite neuroprotective effect of vitamin E which might specifically compensate PINK1 haploinsufficiency and mitochondrial impairment, reverting some key steps of the pathogenic process. Even though, there are myriad preclinical evidence supporting the promising role of Vitamin E in PD management, clinical trials investigating the efficacy of Vitamin E supplementation in PD management are still limited. Worthy of note that variability in Vitamin E formulations and dosage regimen, heterogeneity of PD, and methodological variations among clinical trials is huge challenge in the interpretation and of vitamin E therapy and efficacy. Furthermore, the lipid solubility of Vitamin E, its ability to penetrate the blood brain barrier with ease, and bioavailability of Vitamin E formulations requires consideration for enhanced therapeutic results.

5.2. Role of ß-carotene therapy in management of Parkinson's disease

Beta-carotene (BT) exists as a natural occurring antioxidant found in many vegetables and fruits. BT is known for its potent neuroprotective functions (Collins et al., 2022).

Neuroprotective functions of BT have been demonstrated in 6-hydroxydopamine (6-OHDA) rat models of PD (.Jamali *et al.,* 2020). BT provides its antioxidant function by inhibiting oxidative damage to cells and scavenging free radicals. Furthermore, BT has been demonstrated to mitigate neuroinflammation by reducing microglial activation and modulation of inflammatory mediators. These mechanisms contribute to the protection of dopaminergic neurons and mitigation of motor abnormalities associated with PD. Chaves et al. (2023) reported

that beta carotene-rich nanoparticles were able to ameliorate motor deficit, improve memory, increase cell survival survival in Drosophila melanogaster, and restored oxidative stess factors (CAT, SOD, ROS and TBARS), dopamin concentration, and AChE activity in rotenone mdoel of Parkinson's disease. This report is in conformity with Perry et al. (1985), who revealed in a MPTP-mouse model of Parkinson's disease that pretreatent of mice with high doses of BT inhibted the loss of GSH induced by MPTP and partially inhibited dopaminergic nigrostraital neurons from damage. Nevertheless, another group of researhers reported that large oral doses of BT did not protect MPTP-induced neurotoxicity in marmosets (Perry et al., 1987).

In the same vein, epidemiological data have given evidence of an inverse association between dietary consumption of BT contained food and risk of PD development. A meta-analysis by Niu et al., (2023) revealed that there was significant reduction in the development of PD with higher dietary consumption of BT, suggestive of a possible protective action against PD pathogenesis. Int eh clinical studies, the relatiosnhip between serum BT levels and the risk of PD developmet is currently cofnlicting. Some reaserchers opined that serum BT concetrations are considerably low in PD patients, while others surgest that ther was no significant alterations in the serum levels of BT between PD patients and control groups (Molina-Arjona et al., 1999; JV et al., 2001; Kim et al., 2017).

Neuroprotective capacity of BT alongside vitamins C and E in was investigated in PD patients. In this study, two population-based cohorts (38,937 women and 45,837 men) were used. It was discovered that during a mean 14.9-year follow-up period, 1,329 PD cases were identified. Dietary consumption of BT was connected to a lower risk of PD (hazard ratio: 0.86; 95% confidence interval: 0.78–0.95; P_{trend} <0.01 for women and hazard ratio: 0.91; 95% confidence interval: 0.84–0.99; P_{trend} =0.05 for men). An inverse relationship between dietary vitamin E and PD risk was found in women (hazard ratio: 0.87; 95% confidence interval: 0.79–0.96; P_{trend} = 0.02). Dietary consumption of vitamin C was inversely correlated to PD risk in women at borderline significance (hazard ratio: 0.91; 95% confidence interval: 0.83–1.00; P_{trend} =0.04) (Yang et al., 2017). In another study, where 249 patients within 6 years of onset of PD were examined. The control was 368 inpatients and outpatients without a neurodegenerative disorder. Data collected from the validated self-administered diet history questionnaire revealed that an increase in the consumption of vitamin E and ß-carotene was considerably associated with a decreased risk of PD (Miyake et al., 2011).

5.3. Role of vitamin C therapy in management of Parkinson's disease

Vitamin C is potent antioxidant that naturally occurs in various fruits and vegetables. There is currently and increasing interest in the study of neuroprotective properties of vitamin C against PD. Vitamin C is a powerful scavenger of free radicals, thereby protecting neuronal cells from damage of oxidative stress (Proteggente et al., 2002). Asides this, vitamin C has been reported to offer neuroprotection by enhancing mitochondrial function and promoting the production of neurotransmitter, specifically dopamine which is implicated in PD (Kocot et al., 2017). Furthermore, vitamin C provides a potent anti-inflammatory actions through modulation of immune reactions and preventing the production of pro-inflammatory cytokines (De Nuccio et al., 2021a, 2021b). Through mitigation of neuroinflammation, vitamin C may help in attenuation of neurodegeneration and promote motor function in related to PD. Vitamin C acts by reducing oxidative damage of dopaminergic neurons in the SNpc in progressive PD. Vitamin C acts as a major *in vitro* and in vivo free radical scavenger in the cytosol. Vitamins C and E act in a synergistic way whereby vitamin C can oxidise Vitamin E to improve its antioxidant functions (Barichella et al., 2013). Additionally, vitamin C helps in improving the efficacy of L-DOPA. In pharmacokinetic research, Vitamin C was found to increase the absorption of L-DOPA in elderly patients with PD (Nikolova et al., 2019). Sirajo et al. (2019) concluded in haloperidol wister rat model of Parkinson's disease that administration of vitamin C ameliorated motor deficit in the Parkinsonian rats but did not influence regeneration of already lost neurons in the nigrostraital and corticostraital networks.

In an open label trial, PD patients in the early stage were administered high doses of Vitamin C and E. It was discovered that patients who were administered Vitamins recorded a 2.5- to 3-year delay in receiving L-dopa treatment relative to those who did not receive vitamins. Treatment was deferred from 40 months to 72 ± 6.5 months for those PD patients that took the vitamins before 54 years of age, and from 24 months to 63 ± 3.9 months for those who took the vitamins after 54 years of age (Chao et al., 2012; Fahn, 1991). Notwithstanding the placebo effect that might be acting here, the delay of onset of parkinsonism was extraordinarily noted. Another report from animal study, by De Nuccio et al. (2021a, 2021b) showed that administration of Vitamin C provided neuroprotection in MPTP-induced mouse model of PD by protecting and alleviating MPTP-induced loss of tyrosine hydroxylase (TH)-positive dopaminergic neuronal cells in the substantia nigra, behavioural abnormalities, and inflammatory processes in the PD mice.

5.4. Role of vitamin D therapy in management of Parkinson's disease

The deficiency of Vitamin D has been reported to play a key role in the pathogenesis and progression of PD (Chao et al., 2012; Deluca et al., 2013; Wrzosek et al., 2013). The efficacy of Vitamin D was revealed in the 6-OHDA-induced and MPP+-induced neurotoxicity by improving the motor functions in the PD rodents (Hsiao et al., 2020; Lima et al., 2018). It was observed that treatment of PD mice with vitamin D3 attenuated motor function deficits by upregulating the expression of tyrosine hydroxylase enzyme (a rate-determining enzyme in the synthesis of dopamine), dopamine transporter (DAT), and brain-derived neurotrophic factor (BDNF) in PD mice (Bayo-olugbami et al., 2020). Furthermore, Vitamin D knockout mice were shown to display symptoms of motor dysfunction (Fullard and Duda, 2020; Kalueff et al., 2004; Wang et al., 2015). The levels of vitamin-D-binding protein have been suggested as one of the important biomarkers of PD (Chao et al., 2012). The argument has always been whether vitamin D deficiency or inadequacy in serum predicts the risk of PD and that is it a result of reduced physical activity and sunlight exposure, rather than just factors that cause PD progression. Knekt and colleagues conducted research based on the Mini-Finland Health Survey from 1978 to 1980. They showed PD occurrence follow-up through the end of 2007. During the 29-year follow-up period, 50 incident PD cases were reported. Individuals with the highest serum vitamin D levels showed a significant reduction in the risk of PD (Knekt et al., 2010; Trojsi et al., 2020). In 2002, serum concentrations of vitamin D were also examined, and results revealed that individuals with increased serum concentrations of Vitamin D had a remarkably lower risk of developing PD (Ding et al., 2013). This information asserts that serum vitamin D concentration is a predictive indicator of PD risk. Moreover, SNpc contains high concentrations of Vitamin D receptors and 1a-hydroxylase, (Cui et al., 2013; Deluca et al., 2013; Knekt et al., 2010) the enzyme that is responsible for the physiological action of Vitamin D. This implies that Vitamin D may be involved in many signaling axis, and several mechanisms may be responsible for the neuroprotective roles of vitamin D. For instance, in animal studies, vitamin D was found cause upregulation of glial cell line-derived neurotrophic factor levels (Wang et al., 2017). Glial cell line-derived neurotrophic factor is an antiparkinsonian in animal and in vitro studies (Gonzalez-Aparicio et al., 2010; Wang et al., 2015). It can influence the development of dopaminergic axons in the striatal neurons in an area-specific manner and can even preserve SNpc neurons from 6-OHDA toxicity (Kordower and Bjorklund, 2013). In addition, vitamin D has been shown to increase glutathione concentrations, control calcium homeostasis, exert anti-apoptotic and immunomodulatory actions, decrease nitric oxide synthase, and regulate dopamine levels in rat (Cass et al., 2006; Farghali et al., 2020).

Table 1
Effectiveness of Bm extract on motor and non-motor functions modulation in environmental toxins-induced Parkinson's disease animal models and cell lines.

PLANT	PLANT EXTRACT	PD MODEL	MAJOR RESULTS	AUTHOR
Bacopa monnieri	Standardized Bm extract (200 mg/kg body weight/day; 3 weeks) and PQ (10 mg/kg, i.p. three times a week; 3 weeks)	Paraquat-Induced PD mice model	Bm extract supplementation significantly restored exploratory behaviours, gait dysfunction (stride length and mismatch of paw placement), and motor impairment (rotarod test). Bm extract also inhibited the reduction in dopamine concentration and upturned cholinergic activity in SNpc, striatum, and cerebellum. Moreover, a PQ-induced decrease in the succinate dehydrogenase (SDH) activity and energy charge (MTT reduction in the mitochondria was restored with Bm supplementation.	(Krishna and Hosamani, 2019)
	Bm Ethanolic extract co-treated with the MPTP-induced PD mouse model	MPTP-induced PD mouse model	Bm Ethanolic extract restored motor deficit (Rotarod, Grip Strength, and Foot Printing test). In addition, it caused a marked improvement in Catalase, LPO, Nitrite, SOD, GR, GPx parameters. Levels of Dopamine, DOPAC, and HVA were enhanced significantly. It further restored the TH immunoreactive cells in the SNpc of MPTP-treated mice.	(Singh et al., 2017)
	Whole plant Bm extract (48 mg/kg bw);	MPTP-induced PD mouse model	Bm considerably decreased the elevated oxidative stress markers (MDA, SOD, LPO) in Parkinsonian mice. It showed a marked restoration in locomotor activity and grip strength test. Furthermore, Bm markedly improved TH activity, caspase 3 and expression of a neurogenic gene in SNcp of MPTP-treated mice	(Singh *et al.,* 2016)
	Standardized Bm extract (prophylaxis oral 200 mg/kg bw/day for 4 weeks); PQ neurotoxicity in	Paraquat-Induced neurotoxicity in prepubertal mice	Oral administration of Bm for 4 weeks led to significantly decreased levels of oxidative markers such as reactive oxygen species (ROS), malondialdehyde (MDA), and hydroperoxides (HP) in SNcp. It also attenuated mitochondrial dysfunction and restored the activities of cholinergic enzymes along with the restoration of striatal DA levels among the PQ-treated mice	(Hosamani *et al.,* 2016)
	Bm extract	Rotenone-induced (i.p. 1.0 mg/ kg b.w./day) cytotoxicity in dopaminergic N27 cell lines and mice mode	Bm exhibited cytoprotective action as shown by the reduction of rotenone-induced oxidative stress and cell death in dopaminergic cells. Bm offset rotenone-induced oxidative impairment (normalized malondialdehyde, ROS levels, and hydroperoxide) and restoration of depleted GSH levels) in mice brains.	(Shinomol et al., 2012)
	Standard Bm extract 0.1% in the diet	PQ (20 mM) PD model in Drosophila	Bm supplementation reduced acute PQ-induced neurotoxicity in Drosophila by decreasing mortality and enhancing climbing capacity. Bm acts by boosting redox equilibrium, and mitochondria activity and reducing the level of apoptosis. The mechanisms of action were linked to the enhancement of active JNK and cleaved Caspase-3 activity with transcriptional stabilization of oxidative stress and apoptosis (jnk, caspase-3, damb and nrf-2) associated genes.	(Srivastav et al. 2018)
	Bm extract	PD genetic model (phosphatase and tensin-induced putative kinase 1-PINK1 Drosophila mutant	Bm extract enhanced the climbing behaviours	(Jansen et al. 2014)
	Bm extract supplemented diet at concentrations of 0.25, 0.50 and 1.0. µl/ml for 24 days	Alpha-synuclein transgenic Drosophila PD model	Bm extract improved the climbing behaviours. Decreased oxidative stress (lipid peroxidation and protein carbonyl content) and apoptosis in a dose-dependent brain of PD model flies.	(Siddique et al. 2014)
	Standardized Bm extract (prophylactic 0.1% for 7d);	PQ-model in Drosophila	Bm extract inhibited the oxidative stress induced by PQ and Restored the actions of the electron transport chain (ETC) complex enzymes. It also Improved enzymatic and non-enzymatic antioxidant defence mechanisms	(Hosamani, 2010)
	Standardized Bm extract in a diet for 7 d	Rotenone PD model in Drosophila	Bm extract provided protection against rotenone (500 mM)-induced mortality and prevented dopamine depletion. Administration of Bm gave a better performance in a negative geotaxis test.	(Hosamani, 2009)
	Bm-stabilized platinum nanoparticle	MPTP model (225 mg/kg bwt. i.p. injection) in zebrafish	BmE-PtNPs pretreatment upturned toxic effects of MPTP through the upregulation of dopamine and its metabolites. It also increased GSH and activities of GPx, catalase, SOD and complex I, with decreased MDA levels. BmE-PtNPs improved locomotor behaviour.	(Nellore et al. 2013)

6. Application of medicinal plant extracts and their mechanism in attenuation of Parkinson's disease

6.1. Roles Mucuna pruriens extracts in models of Parkinson's disease

The Mucuna pruriens (Mp) plant is known as Cowhage or velvet bean or Cowitch in English, known in Nigeria's local languages as Werepe/Yerepe in the Yoruba language, Agbala or Agboloko in the Igbo language, and Karara in Hausa language (Majekodunmi et al., 2011). It is known for its notorious spiky hairs on the mature bean pods that cause severe irritation (intense itching) to the skin (Chinnamadasamy and Veerabahu, 2011). It is grown in almost all parts of Nigeria, India, and other parts of the tropics including Central and South America (Avoseh et al., 2020; Majekodunmi et al., 2011). Mp has been used as a nerve tonic for nervous system diseases including Parkinson's disease (Arulkumar and Sabesan, 2010). Its therapeutic action against PD is attributed to the concentrations of L-DOPA in its seeds, stem, and leaf (Arulkumar and Sabesan, 2010). Different toxin-induced models of PD like MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), Rotenone, Paraquat, 6-hydroxydopamine (6-OHDA) have been used to demonstrate the anti-parkinsonian effect of Mp. Lieu and colleagues observed that Mp alleviates the behavioural abnormalities in MPTP-induced neurotoxicity in the primate model of PD (Chinta et al., 2013; Lieu et al., 2010). Still, an electrophysiological study reveals a better performance of Mp at an equivalent dose with conventional L-DOPA probably through a unique mechanism (other bioactive components) (Lieu et al., 2012). Yadav and colleagues showed the neuroprotective capacity of the aqueous extract of Mp seeds against Paraquat (PQ)-induced neurotoxicity in a PD mouse model through the reduction of oxidative stress and consequential improvement of motor coordination. They also observed an upregulation in the expression of tyrosine hydroxylase (TH) in the SNpc and striatum of the brain together with normal expression concentrations of inducible nitric oxide synthase (iNOS) and glial fibrillary acidic protein (GFAP) in PD mice (Yadav et al., 2014).

The high concentrations of L-DOPA in the seeds make it to be widely utilized as an anti-PD agent (Pulikkalpura et al., 2015). Besides the high concentration of L-DOPA in the Mp, it also contains other important bioactive components such as Ursolic acid (UA) and Betulinic acid (BA) which also exhibit a related neuroprotective activity against PD through their anti-oxidative and anti-inflammatory properties (Nand et al., 2020). Researchers have faced huge problems trying to figure out the best treatment option for PD. Unfortunately, most of the available medications so far for PD only provide symptomatic relief to the patients and cause severe side effects much later in their lives. For instance, long-term use of L-DOPA induces dyskinesia (Armstrong and Okun, 2020; Gazewood et al., 2013). On the contrary, Mp has been documented with beneficial properties with extremely minimal side effects (Nand et al., 2020). Mp has more neuroprotective capacity compared to the conventional L-DOPA. Most importantly, the anti-Parkinsonian effect was seen in the water extract of Mp in the hemiparkinsonian rat model of PD (Lieu et al., 2010). Some human studies on the effects of Mp against PD have also been documented. For instance, Manyam et al. (2004) reported the long-term efficacy and safety of Mp in 60 PD subjects for a period of 52 weeks. The researchers reported a sustained improvement in quality of life and motor coordination while no adverse effects were stated. Katzenschlager et al. (2004) made a comparison between the safety and efficacy of gold standard anti-PD drug, levodopa/carbidopa with Mp extract among 60 PD patients. The results revealed that Mp showed a significant improvement in motor function in similar version to the standard drug, yet with a very quick onset of action and longer duration of action. Furthermore, Cilia et al. (2017) carried out a randomized, double-blind, crossover study that compared the efficacy of MP with the levodopa/carbidopa therapy in 20 PD subjects. They reported that Mp treatment resulted into similar improvements in motor symptoms and quality of life relative to the standard therapy, yet with fewer dyskinesias. These studies opine that Mp could offer beneficial effects that are well –tolerated relative the known anti-PD drugs, levodopa/carbidopa. Mp is currently an identified potential source of food because it is rich in crude protein, essential fatty acids, and starch, alongside essential amino acids. *In vitro* experiments have shown that cotyledon powder of Mp considerably improved the mitochondrial complex-I activity, while the monoamine oxidase activity remains unaltered. They have successfully shown that the neurorestorative capacity of Mp cotyledon powder was due to enhanced complex-I–action together with the presence of NADH and coenzyme Q-10 in Parkinsonian rats (Longhi et al., 2011; Nand et al., 2020). Apart from Mp, four important medicinal antiparkinsonian plants shall be discussed in this review: Bacopa monnieri, Withania somnifera, Centella asiatica, and Sida cordifolia.

6.2. Roles of Bacopa monnieri extracts in models of Parkinson's disease

Bacopa monnieri (Bm) is one of the well-known medicinal plants recognized as a memory booster and belongs to the Scrophulariaceae family (Singh et al., 2020). It is a creeping semi-succulent plant that is mainly found in marshy wetlands in the Indian subcontinent, Asia, Australia, the subtropical United State, and tropical Africa (Hosamani, 2020). The therapeutic potentials of both Bm and Bacopa floribunda have been reported in Ayurvedic medicine and Nigeria for the treatment of many neurodegenerative diseases (Oyeleke et al., 2022; Oyeleke and Owoyele, 2022) most importantly anxiety, depression, and memory deficit (Babawale et al., 2016). The neuroprotective function of Bm is essentially through the regulation of neuroinflammation. Neuroinflammation plays a central role in the pathogenesis and progression of PD. Reports have shown that administration of Bm suppressed the level of proinflammatory cytokines (TNF-α, IL-1β, IL-6, and MIP-1b), decreased the levels of alpha-synuclein, and reduced reactive oxygen species (ROS) generation in the rotenone-induced neurotoxicity of an animal model of PD (Hosamani, 2020; Singh et al., 2020). Singh and colleagues reported that pre-administration of Bm revealed better results compared to co-and post-treatment in mice model of PD, a result similar to the activities offered by the conventional L-DOPA treatment in the hippocampus, substantia nigra, and striatum region in PD mice (Singh et al., 2020). In MPTP induced mouse model of PD, Bm showed a significantly improved motor function in Rotarod, Grip Strength, and Foot printing tests and showed its neuroprotective function by a significant improvement in the levels of Catalase, LPO, Nitrite, SOD, GR, GPx. Again, the downregulation of TH immunoreactive cells observed in MPTP group was considerably restored with the administration of Bm. Bm also facilitated its neuroprotective function through the creation of an anti-apoptotic environment as indicated via the reduction of Bax and caspase-3 (apoptotic properties) and upregulation of Bcl2 (anti--apoptotic protein). They also observed a decrease in GFAP immunostaining and expression of inducible nitric oxide synthase (iNOS) in the substantia nigra region (Singh et al., 2021, 2017). Some of the notable studies on Bm are listed in Table 1.

The recognized mechanisms of action of Bm extract in the modulation of PD show that the neuroprotective capacity of Bm is essentially through modulation of antioxidant parameters, removal of free radicals, balancing of redox homeostasis, restoration of mitochondria functions, modulation of inflammatory pathways, and inhibition of pro-apoptotic parameters. All these as evidenced by neurotoxins such as rotenone, paraquat, and MPTP which readily cross the BBB possibly by the dopamine transporter.

6.3. Roles of Withania somnifera extracts in models of Parkinson's disease

Withania somnifera (Ws) is one of the nutritive Nigerian medicinal plants (called Karamanta in the Hausa language) having an important role in the treatment of various diseases stress, anxiety, arthritis, and

Table 2
Roles of *Centella asiatica* extracts in models of Parkinson's disease.

PLANT	PLANT EXTRACT	PD MODEL	MAJOR RESULTS	AUTHOR
Centella asiatica	CA extract at 0.25, 0.50, and 1.0 μL/ml mixed with the diet for 24 days feeding	Transgenic *Drosophila* model flies expressing normal human alpha-synuclein (h-αS) in the neurons	Exposure of CA extract to PD model flies led to considerable delay in loss of climbing function and activity pattern. It also reduced oxidative stress in the brain of PD flies	(Siddique et al. 2014)
	Asiatic acid (AA), a pentacyclic triterpene obtained from CA/ 5 weeks	1-methyl 4-phenyl 1, 2, 3, 6-tetrahydropyridine hydrochloride/probenecid (MPTP/p)-induced neurotoxicity in PD mice model	AA attenuated MPTP/p-induced motor dysfunction, dopamine depletion, and reduced expressions of neurotrophic factors (NTFs) and tyrosine kinase receptors (TrKB). AA inhibited the MPTP/p-induced phosphorylation of MAPK/P38 related proteins such as JNK and ERK AA potentiated the phosphorylation of PI3K, Akt, GSK-3β, and mTOR	(Nataraj et al. 2017)
	Standardized extract of CA ECa233 (10, 30 and 100 mg/kg) for 20 days.	rotenone-induced parkinsonism rats	CA treatment led to improved motor function, a higher number and intensity of dopaminergic neurons in the SNcp and striatum and protected mitochondrial complex I inhibition, decreased MDA levels. It also increased SOD and catalase expression	(Teerapattarakan et al. 2018)
	Methanolic extract of CA (2.5, 5.0 and 10.0 μg/ml) /28 days.	Rotenone-exposed zebrafish.	CA caused a reduction in oxidative stress and caused a considerable decrease in the mortality rate of zebrafish. CA caused an increase in dopamine level	(Khotimah et al. 2015)
	Aqueous CA extract (10 mg/kg for 21 days)	1-methyl-4-phenyl-1,2,3,6 - tetrahydropyridine (MPTP) - induced neurotoxicity in aged Sprague-Dawley rats	Administration of CAA extract decreased lipid hydroperoxides and protein-carbonyl-content and markedly increased total antioxidants and antioxidant enzyme levels (GPx, SOD, and CAT) in corpus striatum and hippocampus.	(Haleagrahara and Ponnusamy, 2010)

other disorders related to the central nervous system (CNS) such as PD (Afewerky et al., 2021; Ahmad et al., 2005). In Lagos state of Nigeria, Ws is commonly used for the treatment of amenorrhoea and aphrodisiac purposes (Afewerky et al., 2021). Prakash and his colleagues studied the effects of Ws on dopamine and its metabolites in the SNpc region of PD mice. It was discovered that there was a reduction in the concentration of dopamine and its metabolites in the PD mice brain relative to the control. However, treatment with Ws for 9 weeks caused a significant improvement in the concentration of dopamine and its metabolites (DOPAC and HVA). This is upholding the claim that Ws can elevate catecholamine levels and fight against PD-like disorders. (Prakash et al., 2014, 2013). The protective activity of Ws is also accomplished through restoration of mitochondrial and endothelial function, extenuation of apoptosis, reduction of inflammation, and oxidative stress mechanisms (Ahmad et al., 2005; Dar and MuzamilAhmad, 2020). Ethanolic extract of Ws has been shown to considerably reduce oxidative stress profile alongside the improvement of motor function in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced Parkinson-like symptoms in Balb/c mice (Bhatnagar et al., 2017; Prakash et al., 2013) and 6-Hydroxydopamine mice (6OHD) PD models (Ahmad et al., 2005; Sankar et al., 2007)

Furthermore, a study evaluated the neuroprotective action of KSM-66, Ws root extract, on 6-hydroxydopamine (6-OHDA)-induced toxicity in the human neuroblastoma SH-SY5Y cell line, alongside the associated oxidative reaction protein expression and redox regulation activity with a focus on S-glutathionylation. In this study, SH-SY5Y cells were treated with 6-OHDA before or followed by treatment with the KSM-66 extract. Using KSM-66 dosages from 0.25 to 1 mg/ml before and after treatment of the cells with 6-OHDA. It was shown that there was an increase in the viability of SH-SY5Y cells. Remarkably, the extract considerably improved glutathione peroxidase activity and thioltransferase activity upon pre- or post-6-OHDA treatment. KSM-66 also modulated oxidative reaction proteins: peroxiredoxin-I, VGF, and vimentin proteins upon 6-OHDA pre/post-administration. Moreover, the extract controlled redox regulation via S- glutathionylation. Pretreatment of SH-SY5Y cells with KSM-66 reduced protein-glutathionylation levels in the cells treated with 6-OHDA. The rescue of mitochondria with 0.5 mg/ml KSM-66 extract revealed an increase in ATP levels (Wongtrakul et al., 2021). The neuroprotective activity of Ws may be attributed to its bioactive chemical compounds that include alkaloids (isopelletierine, anaferine, cuseohygrine, anahygrine, etc.) (Singh et al., 2010; Wongtrakul et al., 2021) making it to be a potential antiparkinsonian entity.

6.4. Roles of Centella asiatica extracts in models of Parkinson's disease

Centella asiatica (CA), also known as Gotu kola, has garnered attention because of its medicinal use, traced with a rich history of traditional applications. CA is currently known for its potential neuroprotective properties (Rao et al., 2008; Mohandas Rao et al., 2012). Many bioactive compounds such as, asiatic acid, asiaticoside, and triterpenoids are contained in CA. Conceivably, these bioactive components are known for their antioxidant, anti-inflammatory, and neurotrophic properties (Xu ChangLiang et al., 2012; Mairuae et al., 2019). Essentially, these compounds exert their effects through modulation of molecular pathways concerned with pathogenesis of PD, including mitochondrial dysfunction, neuroinflammation, and oxidative stress (Haleagrahara and Ponnusamy, 2010; Xu ChangLiang et al., 2012). Furthermore, CA has been shown to promote synaptic plasticity, neurogenesis, neuronal survival, and function in disease rodent brain regions and networks (Omar et al., 2011; Gray et al., 2016; Sbrini et al., 2020; Boondam et al., 2021).

Some preclinical studies have demonstrated the neuroprotective functions of CA in animal models of PD. For instance, Teerapattarakan et al. (2018) revealed that CA extracts mitigated dopaminergic neuronal loss and improved motor function through the protection of protection of mitochondrial complex I activity and enhancement of antioxidant enzyme expression in rotenone-induced motor deficits. Khotimah et al. (2015) also reported the capacity of CA to increase motility and dopamine concentration by minimizing alpha-synuclein aggregation and expression in zebrafish model of Parkinson's disease.

Although, CA provides a promising therapeutic approach through its neuroprotective and cognitive-enhancing properties in PD management, further research including larger randomized controlled trials is required in order to validate the CA ability to ability to mitigate neuronal damage and improve motor function observed in animal models of PD. This would provide the premise to elucidate the optimal dosing regimen and long-term safety profile of CA in the management of PD. Table 2 is a summary of the roles of *Centella asiatica that* have been documented to be essential in the management of PD.

Table 3
Roles of *Sida cordifolia* extracts in models of Parkinson's disease.

PLANT	PLANT EXTRACT	PD MODEL	MAJOR RESULTS	AUTHOR
Sida cordifolia	Standardized SC extract (50, 100, 250 mg/kg; p.o.) for 35 days SC supplemented diet	Rotenone-induced oxidative stress model of PD Drosophila melanogaster Parkinson's Disease Model	Treatment with SC attenuated rotenone-induced oxidative damage and increase catecholamines level in the midbrain. It also improved motor function SC supplementation showed no significant alteration in the climbing ability of fruit fly (Drosophila melanogaster) PD model based on loss of function of phosphatase and tensin-induced putative kinase 1 (PINK1)	(Khurana and Gajbhiye, 2013) (Jansen et al., 2014)

6.5. Roles of Sida cordifolia extracts in models of Parkinson's disease

Sida cordifolia (Sc) is an important medicinal plant that belongs to the family of Malvaceae. The bioactive components of Sc includes phytosterols, mucin, gelatin,vasicinone, vasicine and vasicinol, asparagin, ephedrine, hypaphorine, potassium nitrate (Pattar and Jayaraj, 2012). Sc is known for its in vitro and ex vivo antioxidant function (Auddy et al., 2003a, 2003b). Antiperoxidative and antiinflammatory effects of Sc has been reported in quinolinic acid induced neurotoxicity Swathy et al. (2010). Interestingly, Sc was reported in 1985 in the ancient Ayurvedic literature to mitigate some nervous disorders such as hemiplegia and facial paralysis (Rastogi. and Malhotra, 1985). Navneet-Khurana and Gajbhiye (2013) investigated the effects of Sida cordifolia (AESC), and its different fractions; hexane (HFSC), chloroform (CFSC) and aqueous (AFSC) in rotenone-induced rat model of PD. They reported that Sc ameliorated PD symptoms by protecting against biochemical, neurochemical, histopathological and behavioral alterations. Currently, data on clinical studies about the therapeutic effects of Sc in PD are scarce. Nevertheless, Traditional application and anecdotal documentations suggest that Sc supplementation may offer symptomatic relief and better the quality of life in PD patients. Hence, further, clinical studies are required to corroborate these reports and expatiate the optimal dose regimen and long term safety profile of Sc in PD management. Table 3 is a summary of the roles of ***Sida cordifolia*** that have been documented to be essential in the management of PD.

7. Challenges and limitations

Numerous preclinical studies are available on the application of nutrition and phytochemicals in the management of PD. Translating these findings into clinical practice faces significant challenges and limitations, essentially with respect to standardization of dosing regimens, bioavailability, and inter-individual variability. It is putative that preclinical studies employ the use of animal models to evaluate the potency and efficacy of nutriceuticals and phytochemicals. However, defining appropriate doses for human trials is a complex due to the fact that in animal studies, there are interspecies variations in metabolism and reaction to drugs. Even though, dose regimen standardization is crucial for certifying consistency and comparability of results across clinical trials, identification of optimal doses for PD management would involve wide-ranging dose reaction studies in humans. Of course, this can pose financial burden on the researchers on account of resource-intensive and time consuming factors.

With respect to bioavailability, plant extracts and nutriceuticals derived from natural sources are often poor in bioavailability and they possess less therapeutic efficacy. For instance, factors such as chemical structures, formulation, and interactions with other dietary components often affect bioavailability of these compounds. Worthy of note is that, bioavailability can be improved via formulation approaches or co-administration with substances that enhance absorption and in turn enhance therapeutic action. Essentially, a comprehensive pharmacokinetic studies in humans is required in other to optimize bioavailability which in effect improve understanding of absorption, distribution, metabolism, and excretion (ADME) profiles of the compounds.

Inter-individual variability is another challenge with respect to application of nutriceuticals and phytochemicals in the clinical practice. Sex, gut microbiota composition, diet, age, genetic factors and disease pathology influence variability in response to treatment. Notwithstanding, personalized medicine strategies, such as precision nutrition and pharmacogenomics may assist in the identification of biomarkers related to different response. Nevertheless, incorporating these strategies into clinical practice needs implementation and validation of biomarker-guided dosing strategies.

Collaboration among researchers, clinicians, pharmacologists, and nutritionists is required to address these challenges. Furthermore, large-scale clinical research are needed to affirm the safety, efficacy, and

optimal dose of plant extracts and nutraceuticals for the management of PD. in the same vein, progressions in the field of technologies for evaluating bioavailability and inter-individual variability can give insight into the mechanism and monitor the development of personalised treatment approaches for PD patients.

8. Conclusions

The association that exists between the application of nutrition and medicinal plants in the treatment or management of diseases is an age-long concept. There is Ayurvedic medicine in India and Chinese Traditional Herbal Medicine in China. It is also widely applied in other European and Asian and African countries. The general conception is that "medicine and diet share the same origins." Many reports have shown the role of a nutritious diet, medicinal plants, and an active lifestyle as a healthy ageing tactic for the prevention of most ageing-related disorders such as neurodegenerative diseases cancer, and cardiovascular disease. Not only should this concept be promoted as part of daily living to prevent disease, it should also be encouraged and applied in a clinical setting.

Oxidative stress, neuroinflammation, mitochondrial dysfunction, and protein aggregation pathways enhance synaptic dysfunction, affect neuronal survival, and modulate signaling pathways involved in cell survival and apoptosis. These factors culminate the pathogenesis of PD. Yet, various nutraceuticals and phytochemicals are known with antioxidant properties, anti-inflammatory properties, mitochondrial function and energy metabolism enhancing properties, and protein anti-aggregation properties. By targeting these pathways, application of nutrition and phytochemicals in PD have the potential to exert beneficial effects including neuroprotection, symptom management, and possibly disease modification.

Despite the aforementioned beneficial effects of nutrition and plant extracts for improving PD management, standardization, bioavailability, and clinical trial design of these therapies pose current challenges that need to be addressed. However, implementation of emerging opportunities, such as personalized medicine, combination therapies, and multimodal interventions may proffer better solutions for more effective and holistic strategies for the management of PD in the future. Furthermore, better innovations, collaboration, and future research are essential requirements to harness the full potential of nutrients and plant extracts in the menace of PD and improving the general quality of life of patients.

Conflicts of interest

The authors have no relevant or non-financial interests to disclose.

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CRediT authorship contribution statement

Patrick Oluwole Abolarin: Data curation, Methodology, Writing – original draft, Writing – review & editing. **Abdulbasit Amin:** Formal analysis, Methodology, Supervision, Writing – review & editing. **Bamidele Victor Owoyele:** Conceptualization, Formal analysis, Funding acquisition, Project administration, Writing – review & editing. **Abdulrazaq Abidemi Nafiu:** Conceptualization, Supervision, Writing – review & editing. **Olalekan Michael Ogendele:** Conceptualization, Supervision, Writing – review & editing.

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