Current Understanding on the Beneficial Role of Nutrition in Parkinson's Disease –An Overview

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Abstract

Various nutritional components belonging to different classes of natural dietary origin display modulatory (protective) properties against age-related neurodegenerative disorders (NDD) such as Parkinson's disease (PD) and Alzheimer's disease. These compounds termed as nutraceuticals which have been shown to act at various biochemical and metabolic levels and exhibit different degree of neuroprotective properties. Present review aims to summarize the current status on the modulatory impact of some of the major nutritional compounds on the pathophysiology of PD, the second most common NDD in humans. Primarily, we have examined the data demonstrated in animal models and postulated through epidemiological studies on the compounds/molecules/life style factors which reduce the risk associated with PD and probable mechanism/s through which they elicit neuroprotection. Further we also included some of the conflicting information about the compounds which may enhance the risk associated with PD. Additionally, emphasis is also given about the new approaches to understand the impact of nutrition on the epigenome in relation to the development of NDD with a short note on emerging ideas relating to nutritional genomics.

Abbreviations: NDD-Neurodegenerative disease; PD-parkinsons disease; L-Dopa-Levodopamine; PUFA-Polyunsaturared fatty acids; 6-OHDA-6-hydroxydopamine; MPTP-1-methyl-4-phenyl-1,2,3,6-tetra hydropyridine; ROT-Rotenone; PQ-Paraquat; DHA-Docosahexaenoic acid; EPA-eicosapentaenoic acid

Introduction

The World Health Organization (WHO) has estimated that the proportion of elderly people (over 60 years) will increase from 11% to 22% during the next 40 years throughout the world. With respect to this, the morbidity and mortality rates of age-related diseases such as neurodegenerative diseases (NDD) will increase. Thus it is imperative to identify means of prevention, delay of onset, and management of symptoms in these neurodegenerative disorders. Parkinson's disease (PD) is the second most common neurodegenerative movement disorder, afflicting 1–2% of the population above the age of 60 years. The pathological hallmarks of PD include selective loss of dopaminergic neurons in the substantia nigra and the presence of Lewy bodies in surviving dopamine neurons [1]. Lewy bodies are cytoplasmic inclusions composed mainly of alpha-synuclein, which are believed to disrupt the brain's normal functioning in PD. Although, it is well known that environmental exposures and individual genetic susceptibility may determine the onset of PD symptoms, the precise cellular and molecular mechanism(s) responsible for the neurodegeneration processes remain elusive. The majority (95%) of PD cases appear to be sporadic, likely to be caused by a combination of genetic and environmental risk factors, the most apparent being increasing age [2].

Genetic susceptibility and environmental factors that mediate mitochondrial dysfunction, inflammation [3], abrogation of the autosomal-lysomal autophagy system and endoplasmic reticulum stress play a vital role in disease development. Currently the involvement of oxidative stress, mitochondrial dysfunction, and abnormal protein aggregation are well appreciated in the pathogenesis of several NDD [4]. Currently there is no cure for PD. Motor symptoms of the disease are most often treated using levo-dopa and dopamine agonists. As the disease progresses, more neurons are lost, the drugs become less effective and some patients develop disabling dyskinesia.

Currently, the treatment for PD subjects is primarily symptomatic involving either replenishment of striatal dopamine levels or preventing its post synaptic degradation. While levodopa (L- dopa) is the standard treatment , its chronic usage results in adverse effects such as dyskinesia, motor fluctuations and other non-motor complications [5,6]. Hence other approaches such as use of Dopamine agonists, inhibitors of mono-amino oxidase-B and Catechol-O-methyl transferase, and anti-glutamatergic have been attempted. However, several limitations have been documented with the use of these drugs such as: a) the effects are temporary; b) the drugs fail to slow down the progression of disease and c) chronic usage causes adverse effects. Hence there is a paradigm shift in the existing pharmacotherapy for PD with new approaches such as usage of natural products and nutraceutical formulations as adjuvants.

With the growing limitations in the treatment of PD, alternate approaches are being explored to supplement and complement the current treatments. One of the most important is the nutritional approach. Although food is classically perceived as a means to provide energy and building material to the body, its ability to prevent and protect against diseases is starting to be recognized. For the past two decades, several lines of evidence suggest that nutrition may play a

vital role in the development and progression of PD. Accordingly, attenuation of oxidative damage by natural constituents has been considered as an attractive complementary proposition to delay or prevent the development/progression of several NDD including PD. Epidemiological and biochemical studies have recently identified promising components in certain food groups that may elicit neuroprotection in PD [7]. Interestingly, few recent studies have also indicated an increasing risk of malnutrition among PD patients and that malnourished patients remain under-recognized by health professionals. In fact, a recent study revealed that approximately 30% of patients with mild to moderate PD are at risk of malnutrition [8] clearly emphasizing the importance of nutrition in managing PD.

However, it should be noted that our understanding of the impact of nutrients on PD patients is in its infancy. Evidence gathered by epidemiological studies have significantly contributed towards a better understanding related to the various factors which are neuroprotective as well as those which may increase the risk associated with the disease progression [9], which provides an idea to look into the linkage between nutrition and reducing the burden of PD.

In this review, we have attempted to present an overview of the current status of knowledge related to the various nutritional factors and their putative mechanisms by which they are known to offer neuroprotection in PD. Further, the factors which may be increase the risk of the disease process have also been dealt with briefly.

Models employed

To obtain basic understanding on the pathophysiology and progression of the PD, several *in vitro* cell and animal models have been developed by researchers in the field. Thus far, however, all of these experimental models continue to be categorized into two main categories: toxic and genetic (and sometimes, both approaches are combined). More importantly, none of the currently available models precisely phenocopy PD, mainly because they lack some specific neuropathological and/or behavioral feature of PD. A number of pharmacological and toxic agents including reserpine, haloperidol, and inflammogens like lipopolysaccharide have been used over the years to model PD [10].

The most widely used are still the classical neurotoxins viz., 6-hydroxydopamine (6-OHDA) in rats and 1-methyl-4-phenyl-1,2,3,6-tetra hydropyridine (MPTP) in mice and monkeys. Further, Rotenone (ROT) and Paraquat (PQ) have also been employed in both rodent and invertebrate models such as Drosophila and Caenorhabditis elegans. These models have also found extensive application in evaluating the neuroprotective potential of various dietary components, nutritional supplements and phytochemicals. Further a variety of cell lines have also been employed to obtain basic understand on the underlying mechanisms as well as to identify specific molecular targets with various phytochemicals, spice bioactives and nutraceutical molecules.

Neuroprotective Nutrients

Vitamins

Epidemiological studies have suggested that high intake of fruits, vegetables and fish was inversely associated with PD risk [11]. Most fruits and vegetables are rich sources of antioxidants, including vitamins A, B (riboflavin), C and E, which are present in low levels in some PD patients. Accordingly, it is suggested that health benefits associated with the intake of phytochemicals present in fruits and vegetables leads to decreased functional decline associated with aging and may slow the progression of PD.

Neuroproective effects of Vitamins: Vitamin A and Carotenoids: Data on the role for vitamin A in PD development is rather limited. Carotenoids (α and β-carotene) are precursors of vitamin A in humans. Carotenoids possess antioxidant properties and act as a reducing agent by protecting lipids through oxidation interference and free radical entrapment. Previously, vitamin A and β-carotene were shown to inhibit alpha-synuclein fibril formation and destabilize formed fibrils in dose-dependent manner *in vitro* [12]. Although several human studies failed to identify a link with vitamin A and PD [13], one study reported a protective effect of β-carotene in PD in a Japanese population [14]. In mice, pretreatment with β-carotene partially protected against MPTP-induced neurotoxicity [15,16], but not in primates.Lycopene, another carotenoid compound, reduces oxidative stress and cognitive decline in a rotenone-induced rodent model of PD [17]. Egg yolks, organ meats, and milk are rich sources of vitamin A, while carotenoid rich diet includes carrots, sweet potatoes, and peaches, as well as other fruits and vegetables.

1. Vitamin B: Homocysteine is a metabolite of methionine that is essential for the DNA synthesis and has been shown to exert adverse effects of mitochondrial functions. Vitamins B6, B9,and B12 indirectly regulate level of homocysteine [18]. Folate-deficient diets result in increases in homocysteine. MPTP-induced motor activity impairment and loss of nigral dopaminergic neurons were significantly exacerbated in folate-deficient mice. In animal models, vitamin B deficiency appears to exacerbate neurotoxicants induced motor deficits and pathology. Epidemiological studies presented variable findings. Higher intake of vitamins B6, B9, and B12, but not B2, was associated with lower risk of PD in a German population [19]. Riboflavin supplementation with 8-hour intervals for 6 months gave rise to promising improvements in motor activity of patients. Vitamin B complexes are found in meat, fish, cereal, dairy products, and some vegetables (eg. potato) and fruits (eg. banana).

2. Vitamin C: Several studies have suggested that there is no clear association between vitamin C and human PD. Humans consuming a diet rich in vitamin C showed a 40% reduction of PD risk [19]. Interestingly, high doses of vitamin C and E given to early stage PD patients, demonstrated a decrease in disease progression. However, subsequent studies found no significant association between intake of dietary vitamin C or vitamin C supplements and risk of PD [13]. Vitamin C was found to increase dopamine synthesis in human neuroblastoma cell line [20]. Although vitamin C is the most potent antioxidant among other vitamins, exogenous administration may not affect disease development due to limited access to the brain.

3. Vitamin D: While a protective role of vitamin D against PD is not well established, there are number of laboratory studies suggesting that exogenous administration may be protective. MPP+ toxicity in primary mesencephalic dopaminergic neurons was decreased by low doses of vitamin D (1–100 nM) *in vitro*. Pretreatment of rats with calcitrol prior to 6-hydroxydopamine (6-OHDA) administration attenuated neuronal toxicity *in vivo* [21]. Interestingly, significantly lower bone mass index and vitamin D deficiency have been reported in PD patients.

Although Vitamin D deficiency is prevalent among PD patients, it is not certain whether it is cause or an effect. Dysregulation in calcium homeostasis is known to accelerate SNpc dopaminergic neuron loss [22]. Supplementation with vitamin D is shown to be beneficial in

slowing disease progression in animal and cell culture models of PD, [23]. A recent study showed that vitamin D3 supplements stabilized motor symptoms among PD patients [24]. However, it is not clear if a reduction in vitamin D due to nutritional deficiency causes an increase in PD and/or if UV radiation or exposure to sunlight plays a role.

4. Vitamin E: Vitamin E is found at high levels in vegetable oils, nuts, and whole-grain products. It has strong antioxidant capacity. Pretreatment of neurons with vitamin E alleviated MPTP-induced dopaminergic neuron toxicity *in vitro* [25]. Serum levels of vitamin E in PD patients were significantly lower than controls. Vitamin E provided significant protection against DA neurons in the SNpc [26] and reduced DA loss. The potential benefits seen are explained to be linked to its chain-breaking capabilities in biological membranes, preventing induced oxidative damage by trapping reactive oxyradicals. Interestingly, a meta-analysis showed a protective effect against PD in humans with both moderate and high intake of vitamin E, the effect being more significant in men [13]. Data for a protective or preventative role of vitamin E appears to be stronger than other vitamins. Although low dietary Vitamin E levels could potentially increase risk, data on supplementation in patients already diagnosed with PD has failed to show a disease modifying effect.

Polyphenols

Polyphenol flavonoids are found ubiquitously in a wide range of fruits and vegetables such as apple skin, celery, oranges, onion, mango, apples, and buckwheat, as well as food and beverages derived from plants including olive oil, black/green tea, and red wine. Over the last two decades, a significant amount of data pertaining to the antioxidant effects of different types of flavonoids has been documented. Studies to validate neuroprotective effects of flavonoids has been performed in neurotoxin-induced models with either pre- or post-treatment with flavonoid compounds. Majority of the published literature suggest that flavonoids can exert neuroprotective effects in pathological conditions, that is, in the presence of prooxidants or neurotoxins but not under normal physiological conditions. These findings clearly explain the antioxidant nature of flavonoids in arresting free radical-induced oxidative damage, which is known to be central to many degenerating diseases including PD.

Tea: Earlier regular tea drinking was reported to reduce the risk for PD and protect against PD in Chinese patients [27]. A large prospective study also showed a reduced risk of PD incidence among subjects who habitually drank three or more cups of tea per day and a recent retrospective study reported a delayed onset of motor symptoms in Israeli PD patients [28].

Evidence in animal models: Both black and green tea was shown to exert neuroprotective effects in animal models of PD [29]. Polyphenols in green and black tea extracts provide highly potent antioxidant-radical scavenging activities in brain mitochondria. In addition, polyphenols in tea reduce the occurrence of disease and provide neuroprotection in cell culture and animal models [30]. The polyphenol theaflavin (TF) present in black tea, possess a wide variety of pharmacological properties including antioxidative, antiapoptotic, and anti-inflammatory effects [31]. TF-mediated neuroprotection against MPTP-induced dopaminergic neuro-degeneneration in rodents was evidenced by increased expression of nigral TH, DAT and reduced expression of apoptotic markers [32].

The polyphenol epigallocatechin-3-gallate (EGCG) in green tea shows promise in neuroprotection. Oral pretreatment with EGCG prevented dopaminergic neuron loss in MPTP-treated mice and reduced neuronal cell death and induced nitric oxide synthase (NOS) expression in an MPTP mouse model of PD [33]. EGCG inhibits nitric oxideand tumor necrosis factor-α secretion from LPS-activated microglia in dopaminergic mesencephalic cells. EGCG's mechanisms of action include iron-chelation, scavenging of oxygen and nitrogen radical species, activation of protein kinase C signaling pathway and expression of pro-survival genes [34].

Phytochemicals – plant extracts

Some of the major polyphenols studied in the context of PD in rodent models are presented in Table 1 and the potential mechanisms by which neuroprotection is known to occur is also explained in Table 2.

Polyphenol	Toxin	Model	Reference
Baicalein	MPTP	Mice	[88]
Naringenin	6-OHDA	Mice	[89]
	6-OHDA	Rats	[90]
Puerarin	MPTP	Mice	[91]
Quercetin	6-OHDA	Rats	[92]
Theaflavin	MPTP	Mice	[93]
Curcumin	6-OHDA	Rats	[94]

Table 1: Some of the polyphenols shown to be neuroprotective in rodent PD models* (*Various neuroprotective effects have been explained in the Table 2).

Some of the plant extracts and pure compounds which have been demonstrated to be neuroprotective in Drosophila models of PD are presented in Table 3.

1. *Mucuna pruriens:* A well-known medicinal plant, whose seed preparations are in contemporary use for PD in India [35]. Phytochemical analysis has revealed the presence of saponins, tannins, anthraquinones, terpenoids, flavonoids, and glycosides. The seeds also contain carbohydrates, proteins, lipids, minerals, fiber, lecithin and sterols. L-dopa the dopamine precursor accounts for nearly 7-10%.

2. *Bacopa monneri* (BM) and *Centella asiatica* (CA): Numerous evidences have clearly demonstrated that Brahmi (BM and CA) display all the capabilities necessary to impart neuroprotection, improve memory and learning abilities. Various attributes such as metal ion chelation, upregulation of antioxidative enzymes, and scavenging of free radicals are believed to be responsible for the neuroprotective effects of BM [36]. Dietary feeding of BM powder to Drosophila was demonstrated to markedly attenuate rotenone induced oxidative stress owing to its antioxidative nature and its ability to modulate the activities of antioxidant defenses such as reduced GSH and antioxidant defenses. Further, BM extract also showed prophylactic neuroprotective action against paraquat toxicity in Drosophila and rotenone in mice model [37].

Potential mechanisms by which polyphenols bring about neuroprotection
Antioxidative properties of polyphenols: Diminish the formation of ROS; inducing an increase in the expression levels of Nrf2 protein levels: Activation of Keap1/Nrf2/ARE pathway; Restoration of levels of striatal tyrosine hydroxylase (TH), a key enzyme in DA synthesis; increase in the Levels of DA/ its metabolites resulting in amelioration of Behavioral phenotype in parallel to improved oxidative status.
Upregulation of endogenous antioxidants (enzymic/non-enzymic): Upregualtion of GSH system; elevation of GSH synthesis, Y-glutamylcysteine synthetase (g-GCS), the enzyme that synthesizes GSH; increased levels of GPx enzyme; Increased expression of Catalase, SOD (cytosol/mitochondria) and thioredoxin reducatase.
Enhancement of detoxification enzymes: Induction of GST enzyme increased expression of SIR T 1; Activation of MAPK pathways (Involved in cell survival and apoptosis); Inhibition of phosphorylation of JNK and extracellular signal-regulated kinase (ERK) and Increased Phosphoryaltion of Akt.
Anti inflammatory pathways: Diminish the expression or transcription of pro-inflammatory cytokines (IL -1β; IL-6; TNF- α); Reduction in the levels of other pro-inflammatory agents cyclooxygenase-2 (COX-2), nitric oxide synthase (iNOS), and markers of astrogliosis or microgliosis (glial fibrillary acidic protein (GFAP).
Fibril destabilizing properties: inhibition and initiation and/growth of a-synuclein fibrils *in vitro/in vivo*; clearance of aggregates and oligomers mediated by autophagic pathways.
Restoration of Mitochondrial Homeostasis: Recovery of Mitochondrial membrane potential; Enhancement in the activity levels of citrate synthase and ETC enzymes (complex I and II) and expression levels of complex IV and V (ATP synthase).

Table 2: Potential mechanisms by which polyphenols bring about neuroprotection.

3. *Withania somnifera* (Aswagandha): Withania somnifera root extracts and withanolides have been shown to stimulate growth of new dendrites in human neuroblastoma cells [38,39]. The protective efficacy of WS root extracts, against oxidative stress and degeneration of hippocampal cells *in vivo* under stress conditions have been reported [40]. Recent studies have demonstrated the neuroprotective effect of WS extract in rotenone models in both Drosophila and mice models [41].

4. Pepper: The bioactive compound of pepper is the alkaloid, piperine, and the biological role in CNS has attracted attention. Although the neuroprotective effects of piperine in PD models is not directly demonstrated, it is shown to enhance the bioavailability of curcumin in animal and humans [42]. Several formulations are patented which contain the dried seed pepper for their use in NDD.

Phytochemical/ compound - Neurotoxin	Behavioral phenotype and features	Reference
Melatonin/ Rotenone	Rescues loss of dopaminergic neurons and severe locomotor dysfunctions	[95]
Bacopa monneri-Rotenone	lower incidence of mortality; improved locomotor phenotype; attenuates oxidative stress/ mitochondrial dysfunctions and restores DA levels	[96]
Creatine-Rotenone	Rescues locomotor phenotype; restored the GSH levels, nitric oxide levels, activity of Mn-SOD and dopamine depletion.	[37]
Sealginella-Rotenone	Reduces lethality; improves phenotype; restores antioxidant defenses; GSH levels; attenuates mitochondrial impairments; restores cholinergic function and DA levels in head region	[97]
Vallerina offinalis-Rotenone	Better locomotor performance; increase mRNA levels of antioxidant enzymes-SOD, catalase and Th enzymes; elevated thiol levels	[98]
Gallic acid-PQ	Improved locomotor performance; prolonged lifespan; protected DA ergic neurons,	[99]

Curcumin	Significant delay in the loss of locomotor activity reduction in the oxidative stress and apoptosis, and increase in life span	[100]
Withania somnifera extract/ROT	Rescues lethality/ phenotype; restores antioxidant defenses; attenuates mitochondrial impairments; restores DA	[41]
Curcumin/PQ	Rescues mobility defects in young flies and transition phase; Replenishes DA levels only in health span	[101]
Tomato seed extract-Rotenone	attenuated oxidative stress, mitochondrial dysfunctions, protein carbonyls content, restored the cholinergic function/ DA levels.	[39]
Saffron extract/ crocin-Rotenone	Rescues locomotor phenotype; restores GSH levels/ antioxidant defenses; attenuates; mitochondrial impairments; restores DA	[102]

Table 3: List of Phytochemcials/extracts evaluated in *Drosophila* model of parkinsonism.

5. Genistein: Existing evidence in animal models suggests that genistein, the primary isoflavone protein present in soybean is neuroprotective. Genestin was demonstrated to be neuroprotective in ovariectomised rats administered with 6-OHDA, suggesting that it may be useful in post-menopasual women. Further, pretreatment with geniestein was shown to improve spatial learning and memory, restore tyrosine hydroxylase and DA transporter, in the mid brain of in MPTP administered rats [43]. It restored the levels of DA and its metabolites in the striatum. However, no clinical evidence exists in PD subjects.

Bio Flavonoids and Flavones: Flavonoids are the secondary plant metabolites which form the largest class of plant polyphenols which are classified based on the number of phenolic rings and the structural elements that link these rings. Flavonoids are known to protect against oxidative damage either by complexing with iron or copper or by direct detoxification due to their inherent structural characteristics which enhance their antioxidant potential.

Quercetin: Quercetin is a planate derived flavonoid and foods rich in quercetin include black and green tea, apple, onion, red grapes, citrus fruits and some variety of honey. Owing to its antioxidant and other neuropharmacological actions, quercetin has been demonstrated to be neuroprotective in several cell and animal models of PD [6].

Omega-3 polyunsaturated fatty acids (PUFAs)

In general, PUFA appear to be neuroprotective against several NDD [44]. Both DHA and EPA have shown protective effects. DHA is an essential factor in brain growth and development and possess anti-inflammatory potential owing to its ability to inhibit cyclooxygenase-2. DHA protects neurons against cytotoxicity, inhibits nitrogen oxide (NO) production, and calcium (Ca^{2+}) influx. DHA enhances the activities of antioxidant enzymes such as glutathione peroxidase and glutathione reductase and diminishes apoptosis in dopaminergic cells [45] in the brains of mice post-MPTP treatment. Short-term administration of DHA markedly reduced levodopa-induced dyskinesias in parkinsonian primates and caused significant reduction in parkinsonian behaviors and elevated dopamine (DA) levels in 6-OHDA rodents [46]. The precursor to DHA, eicosapentaenoic acid (EPA) is also neuroprotective in experimental models of PD.

In animal models of PD recent studies have demonstrated that Fish oil prophylaxis offers significant protection against rotenone-induced oxidative stress and mitochondrial dysfunctions in brain predominantly due to its ability to enhance the GSH levels, antioxidant status, and decreased protein oxidation Further, quercetin-enriched Fish oil offered higher degree of neuroprotection in the rat PD model [47].

Suggested mechanisms: The protective effects of DHA in neurons against oxidative stress, inflammation, disruption of the cytoskeleton, and activation of apoptotic signaling pathways are known to be mediated by a metabolic derivative -neuroprotectin D1 [48]. Studies show that DHA may protect the brain by increasing glutathione reductase activity resulting in decreased accumulation of oxidized proteins, lipid peroxide and ROS levels [49]. Further, DHA also inactivates caspase activation signaling pathways [50], inhibits hyperphosphorylation of tau protein [51] and regulates the PI3K/Akt cascade.

Clinical studies: Excepting for one study which showed that supplementation with omega-3 PUFA reduced depression in PD patients [52], there are no studies describing the neuroprotective effects of PUFA in PD patients. Hence more systematic research is warranted to establish their beneficial effects among PD patients.

Common Beverages

Coffee – caffeine

Common sources of caffeine are coffee, tea (especially black tea), soft and energy drinks, and chocolate. Caffeine is known to be a CNS stimulant and an adenosine receptor antagonist. A body of epidemiological data clearly demonstrate the health promoting benefits of caffeinated beverages [53]. Further, a clear inverse association between PD and coffee has been reported.

Evidence from animal studies: Both acute and chronic administration of caffeine among rats significantly diminished the effect of MPTP [54], 6-OHDA induced striatal DA loss and motor dysfunctions [55].

Similarly, administration of caffeine to maneb- and paraquat-treated rodents was shown to reduce the number of degenerating dopaminergic neurons, microglial cells, nitrite content and normalize the expression of IL-1β, p38MAPK, NF-kB, and TK [56]. Further, Caffeine partially restored DA metabolites in rats following 6-OHDA lesions [55] and provided significant neuroprotection in MPTP models

of PD. Interestingly, with caffeine intake, neuroprotection was evidenced even after the onset of neurodegeneration in rats [57].

Suggested mechanisms: In SH-SY5Y cells, caffeine was shown to be cytoprotective through activation of the PI3K/Akt signaling pathway [58]. Accordingly, the ability of caffeine to down-regulate NO production, neuroinflammation, and microglial activation through these pathways are speculated to contribute to neuroprotection [56]. Recent evidence indicate that caffeine reduces dopaminergic toxicity and slows disease progression through the antagonism of adenosine vA2A receptors [57]. Hence, currently, clinical studies are underway to evaluate several lA2A receptor antagonists for symptomatic relief and slowing of disease progression [59]. Estrogen is shown to significantly modulate the neuroprotective potential of caffeine and epidemiological studies have consistently demonstrated a greater improvement in male than female PD patients [60].

Nutrients for Which Conflicting Data Exists

Data on the major nutrients such as carbohydrates, fat and meat in relation to PD are briefly outlined below.

Carbohydrates (CH)

Carbohydrates are suggested to increase DA production in the brain by allowing easier passage of the DA precursor, tyrosine, through the blood-brain barrier into cerebrospinal fluid [61]. Interestingly, CH with high glycemic index is shown to decrease the risk of PD by an insulin-induced increase in brain DA [62]. Epidemiological studies about CH consumption and PD are rather inconclusive.

It is generally well accepted that high CH diets are associated with an increased risk of type 2 diabetes (T2DM). While several epidemiological studies indicate T2DM is associated with an increased risk of PD [63], the evidence is rather conflictive [64]. However, T2DM is associated with more severe motor symptoms in PD [65]. Since CH are a vital part of people's diets and its high consumption may increase risk for T2DM several researchers in the field strongly opine that generation of data on the amount and type of dietary CH consumed would be very highly beneficial to understand its relationship to the risk of PD in humans.

Fat

Data on the relationship between dietary fat and PD is also inconsistent. While few epidemiological studies found a higher risk of PD among individuals with greater intake of total animal fat [19,56], several studies showed no significant relationship [66,67]. These inconsistencies were attributed to the specific type of fat in the diet which is not always specified.

In animal studies and clinical trials, a ketogenic diet, which is high in fat, was shown to provide symptomatic and beneficial disease-modifying activity in PD. In a clinical trial, five PD patients consuming low protein (8%) diet and given a hyperketonemia diet showed improvement [68] and it was speculated that the improvement could have been a result of higher bioavailability of L-dopa caused by low protein diet.

Meat

Although evidence from prospective studies is limited [69], meat consumption is suggested to be associated with higher incidence of PD.

In the case of red meat, a positive association between red meat consumption and PD was explained by the heme content that may act as a toxin when not digested properly. Hemin increases intracellular iron concentrations and generation of hydroxyl radicals, contributing to iron deposits and mitochondrial damage. It is suggested that iron intake from dietary nutrients may be related to risk for PD [67], although evidence for this association is conflictive.

Specific Diets – Mediterrenean Diet, Ketogenic Diet

A recent clinical trial compared the impact of a healthy high carbohydrate (50% of daily calories) diet including fruits and vegetables to a low carbohydrate diet (≤ 20 g per day) in PD. Previously, a small feasibility study found that a ketogenic diet consisting of high fat and very low carbohydrate intake improved motor symptoms in PD patients [68]. Another promising diet for neurodegenerative diseases is the Mediterranean diet, characterized by the high intake of vegetables, legumes, fruits, grains, monounsaturated fatty acids, fish, low to moderate consumption of dairy products, meat and poultry and moderate consumption of red wine. Higher adherence to a Mediterranean diet has been associated with a reduced risk of cognitive decline and essential tremor [70], conditions associated with neurodegeneration. Furthermore, adherence to a Mediterranean diet may be associated with a reduced risk of PD, whereas low adherence is associated with an earlier age of onset [71].

Dairy Products

Till date no reliable epidemiological link exists between dairy products and PD. Limitation of milk consumption is not therefore recommended, just as smoking or coffee drinking cannot be recommended in order to prevent PD. It is generally agreed upon that foods that supply calcium and high-quality protein should not be limited in view of the high prevalence of osteoporosis and hip fracture among PD patients [72]. Because of their high nutritional qualities, consumption of milk and dairy products is also encouraged in PD to the same degree as in the general population. There are few reports which suggest that consumption of dairy products and milk possibly increase the risk of PD although the specific component of milk or the underlying mechanism has not yet been determined.

Other Potential Risk Factors: Evidence from Epidemiology

Pesticides and PD

As mentioned earlier, currently, it is assumed that there is a significant non-genetic contribution in the development of PD. It seems that the disease results from a combination and accumulation of environmental exposures, and complex gene-environment interactions sustained by the slow and progressive development during aging [1]. There is mounting evidence that long-term/low dose pesticide exposure is potentially neurotoxic and increases risk of PD [73]. Experiments concerning the environmental etiology of PD are more frequent and several animal models have been proposed [74]. Both Paraquat (PQ) and Maneb(MB) exposure has been largely associated with PD, while other pesticides such as rotenone, dieldrin and diquat have also been shown to reproduce some features of PD in animal models. However, no single compound, including the non-pesticide MPTP, is able to reproduce all the hallmarks of human PD [75]. Owing to the complexity of the effects of pesticide/s exposures on human health, the current available data do not support a good correlation between actual pesticide exposure and development of PD.

Metabolic disorder – diabetes and PD

An increased risk in the prevalence of neurological disease is reported among patients suffering with the metabolic syndrome. Specifically, patients with diabetes mellitus often develop neurodegenerative diseases such as PD and Alzheimer's disease [76]. Recent findings suggest that the metabolic syndrome may increase particularly when the metabolic syndrome develops in midlife [77]. Although clinically, PD and diabetes are dissimilar, existing evidence suggest both share remarkably similar dysregulated pathways. In view of these recent findings, an intriguing hypothesis has emerged that suggests that mitochondrial dysfunction, endoplasmic reticulum stress, inflammation, and alterations in metabolism may lead to insulin resistance and, ultimately, to diabetes and/or neuro-degeneration.

PD and diabetes share genetic susceptibilities that put individuals at risk for both diseases. For example, single nucleotide polymorphisms in akt, which encodes the kinase AKT that regulates cell survival and metabolism, increase an individual's risk for PD and diabetes [78]. In addition, the protein DJ-1, which is encoded by the PD-related park 7 gene, is reduced in pancreatic islets of patients with T2DM [79].

Interestingly, a genome-wide transcriptome profiling study identified common dysregulated pathways that link PD, diabetes, and inflammation [80]. Hence it is opined that research focusing on the shared mechanistic pathways between PD and diabetes in future could provide new targets for therapeutics for both chronic diseases.

Alcohol

Our current understanding regarding the association between alcohol consumption and the risk of PD is limited. While a recent study suggests that low to moderate beer consumption may be associated with a lower PD risk, higher liquor consumption is suggested to increase the risk [81]. Although one case control study suggested an inverse association between total alcohol consumption and PD majority of studies do not support an any association [82]. Interestingly, specific components found in red wine including resveratrol and quercetin, are known to elicit neuroprotection in cell and animal models of PD [83]. Epidemiological studies do not support an association between red wine consumption and PD despite the evidence from *in vitro* and animal studies is quite promising.

Epigenetics, Nutrigenomics

PD is believed to be caused by the combination of gene mutations, environmental toxins and mitochondrial dysfunction. Epigenetics refers to alterations in gene expression or function without changes in DNA sequence [84], which mainly includes DNA methylation, post-modifications of histone, and non-coding RNAs. This process can be influenced by lifestyle, environmental factors and modifying genes, resulting in expression but also play a vital role in development, regeneration, and in human diseases such as NDD [85].

Epigenetic modification acts as mediator between environmental exposure and genes, contributing to PD-related neurodegeneration. Abnormal DNA methylation of specific genes or histone acetylation may be a potential clinical biomarker useful in the diagnosis of the disease. The most widely studied epigenetic modification is DNA methylation. Currently, several kinds of epigenetic-based drugs are

investigated as potential treatment strategies, including methylating cytosine bases and HDAC inhibitors [86].

Nutrition-gene interactions are known to play a critical role in dysfunction and disease [87]. Individual differences in genes such as single nucleotide polymorphisms, mutations and copy number variants significantly modify the effects of nutrition on gene expression. A person's epigenome is as important as their genome and it reflects the interaction of the person's genome with their environment. Since at present our understanding about how individual nutrients affect the epigenome generally remains unknown, this area of nutrition research has tremendous application potential.

Summary and Concluding Remarks

Globally, with the prevalence of PD projected to increase concurrently with an aging population, identifying potential protective nutritional factors is certainly an urgent need and is likely to be valuable. Since current therapeutic approach to PD is of a symptomatic type, use of L-DOPA, is still considered the gold standard, aims to attenuate PD motor symptoms by replacing the deficient neurotransmitter, DA. Unfortunately, till to- day, no treatment has been found that could slow down the progression of the disease or that could prevent DAergic neuronal cell death. Since the pathophysiology of PD is quite complex and several mechanisms are demonstrated to be involved in the DAergic neuronal death, experimental therapeutic approaches should also target multiple pathways. Accordingly, nutritional compounds (prophylactic or interventional paradigms) may be employed as a therapeutic approach to either prevent or delay a number of NDDs including PD. In the recent past, there has been considerable scientific evidence supporting the potential application and benefit of dietary/nutritional substances in this regard. Interestingly, several large studies of human populations have identified dietary components as impacting the risk of developing PD. Many of the compounds briefly discussed here exert therapeutic effects by limiting pathologic progression associated with common metabolic, oxidative, and inflammatory processes. However, there is a need to conduct comprehensive well designed clinical studies to properly delineate their utility as a therapeutic intervention. For the most consistently occurring variables, prospective studies with robust and detailed measures of dietary intake would help to clarify dietary risk factors for PD. In summary, the potential of dietary substances (nutraceuticals) to confer therapeutic effects to PD still needs to be critically explored and warrants continued basic research.

Conflict of Interest

Authors declare no conflict of interest.

Acknowledgements

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