Parkinson's Disease: Possible Mechanisms for Nutritional Approaches

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ABSTRACT

Parkinson's disease (PD) is among the most common chronic neurodegenerative conditions, affecting 1% of those over 60 years of age, and involves motor and non-motor impairments. Alterations in normal physiology may become apparent years – in some cases, 10–20 years – before established diagnostic criteria are met. Thus, better clinical outcomes may result when practitioners utilize nutritional and supplement interventions that support reductions in neuroinflammation and neurodegeneration as early as possible. PD is a devastating, progressive neurodegenerative condition that has both hereditary and environmental components to its pathogenesis, and early identification of risk factors and onset is critical. The purpose of this review is to highlight various nutrition and supplement interventions that may positively affect disease onset and progression, and that warrant further research.

Keywords: Parkinson's disease: Parkinsonism; Neurodegeneration; PD nutrition; Lewy bodies, α-Synuclein; Striatal dopaminergic neurons

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INTRODUCTION

Parkinson's disease (PD) was initially referred to as "shaking palsy" by Dr. James Parkinson in 1817. It is among the most common chronic neurodegenerative conditions, affecting 1% of those over 60 years of age,[1] and involves motor and non-motor impairments. Manifestations of motor-related impairments include symptoms such as resting tremor, bradykinesia, and muscular rigidity. The pathogenesis of the motor-related symptoms of PD involves the loss of striatal dopaminergic neurons, which decreases the amount of dopamine released, while the pathogenesis of non-motor symptoms encompasses aberrations in adenosine and enkephalins, and the loss of neurons comprising the glutaminergic, cholinergic, serotonergic, and adrenergic systems.[2,3]

Furthermore, histological studies indicate that alpha-synuclein (α-Syn) aggregates in neuronal perikaryal and neuronal processes to form Lewy bodies and Lewy neurites, respectively.[4] Another pathophysiological change that is prominent and may play a role in the early identification of PD is mitochondrial dysfunction. Research indicates that the aggregation of α-Syn in the mitochondria of individuals with PD damages mitochondrial complex I, which leads to iron accumulation causing the production of reactive oxygen species (ROS) and subsequent oxidative stress.[5,6] Damage to mitochondrial complex IV (i.e. cytochrome c oxidase) also appears to be evident in individuals with PD.[7,8] Such mitochondrial damage decreases energy production in dopaminergic neurons and may increase the generation of ROS, causing oxidative stress that damages lipids, cell proteins, and DNA – ultimately, leading to neuronal cell death and neuroinflammation.[6,8,9]

Alterations in normal physiology may become apparent 10–20 years before established diagnostic criteria are met.[10] Some of these earlier alterations include motor function impairments (e.g. tremor, balance issues), autonomic dysregulation (e.g. constipation, hypotension, erectile dysfunction, dizziness), neuropsychiatric conditions (e.g. depression, anxiety), and other imbalances (e.g. fatigue, anosmia, sleep disturbances, handwriting changes, mood swings, dysphagia, drooling).[11] Of note, evidence reveals that degeneration from PD occurs first in the gastrointestinal system and then in the brain.[12] Thus, better clinical outcomes may result when practitioners identify early indications of PD with or without a diagnosis,[10,11] allowing for nutritional, supplement, and lifestyle interventions that support reductions in neuroinflammation and neurodegeneration. Some of these potential interventions are discussed in detail below.

POSSIBLE NUTRITIONAL INTERVENTIONS

WHOLE FOODS DIET

Studies suggest that a whole foods dietary pattern that focuses on a diverse array of vegetables, low-sugar fruits, healthy fat intake, quality proteins, and complex carbohydrates may positively influence mitochondrial and neuronal integrity and both motor and non-motor functions, while also potentially protecting against inflammation, oxidative stress, and neurodegeneration.[13] Additionally, certain herbs and spices may increase the neuroprotective benefits of such a diet.[14] A diet that provides anti-oxidants, fatty acids, and B vitamins (including folate) may facilitate lowering the risk of neurodegeneration, neuroinflammation, PD,[15,16] cognitive decline, and dementia.[17] Research also suggests that such potentially anti-inflammatory dietary components improve neutralization of excessive ROS and reactive nitrogen species (RNS) associated with cognitive and motor impairments in neurodegenerative diseases.[18,19]

Findings from a variety of epidemiological and nutrient-related studies guide tailoring the anti-inflammatory diet to best meet the needs of individuals with PD. Some of the nutrients and food groups that research suggests may positively affect neural pathways that support synaptic plasticity include omega-3 fatty acids, curcumin, flavonoids, B vitamins, vitamin D, vitamin E, choline, antioxidant combinations, and selenium.[20]

POTENTIALLY BENEFICIAL FOODS AND BIOACTIVE SUBSTANCES

ANTHOCYANINS

In a mouse model of PD, anthocyanins have demonstrated protective effects against bradykinesia and neuronal damage.[21] It is important to note that rodent data do not always translate to humans.

SELENIUM

A rat model of PD suggests that selenium helps counter oxidative stress and decreases DNA damage.[22]

NIGHTSHADES AND NICOTINE

Individuals with PD may benefit from consuming nightshade vegetables, including tomatoes, eggplant, peppers, and potatoes. The naturally occurring nicotine and other compounds in nightshade vegetables may reduce the risk of PD.[23] The purported mechanisms involve attenuating nigrostriatal damage, and reductions in dyskinesias resulting from L-DOPA, tremor, and rigidity have been observed.[24] Despite these promising findings, it should be noted that the research is inconclusive.[23]

NIACIN

Interestingly, individuals with PD often have low levels of niacin.[25] Studies have found that 250 mg of niacin minimizes abnormal sleep architecture by regulating peripheral immune cell niacin receptor 1 (NIACR1) expression.[26] Including niacin-rich foods may be another way to tailor a diet for PD.

GREEN TEA

Green tea, which is a rich source of polyphenols – especially epigallocatechin-3-gallate (EGCG) and theaflavins – confers neuroprotective and neuroregenerative effects. *In vitro* and animal studies have shown that the polyphenols in green tea regulate intracellular signaling pathways and prevent α-Syn accumulation, which protects against and delays PD onset. Such mechanisms broaden the polyphenols' anti-oxidant, anti-inflammatory, and transition metal chelating effects, removing a source of neuroinflammation.[27–30] Very high caffeine intake should be avoided with monoamine oxidase type B (MAO-B) inhibitors, as this combination may cause a hypertensive crisis.

RED WINE

Red wine, which is high in phenolic compounds (e.g. quercetin, myricetin, resveratrol, catechins, tannins, and anthocyanidins), has shown neuroprotective effects in both *in vitro* and *in vivo* PD models. These include anti-inflammatory, anti-oxidant, free-radical scavenging, metal chelating, and cell signaling pathway modulatory properties.[31] As alcohol use disorder may increase the risk of PD,[32] individuals who do not already drink red wine in moderation, or who have issues with alcohol should refrain from consuming this alcoholic beverage. Instead, these individuals would benefit from finding a comparable source of polyphenols. In addition, alcohol is contraindicated with dopamine agonists, catechol-*o*-methyl transferase (COMT) inhibitors, and some other PD-related medications.

CAFFEINE

Another particularly beneficial compound for individuals with PD is caffeine. Roshan *et al*.[33] suggest three to four cups of caffeinated coffee (about 200 mg) per day. Caffeine intake must be timed carefully, however, to avoid exacerbating sleep issues. It also may not be appropriate for slow caffeine metabolizers. Research suggests that caffeine acts as an adenosine (A2) receptor antagonist. Interestingly, the highest concentrations of this receptor type are found in the basal ganglia. A proposed mechanism of action for caffeine is that it inhibits astrocyte-related inflammatory processes in a manner that promotes excitation in the basal ganglia.[33] Furthermore, caffeine demonstrates an ability to maintain blood–brain barrier (BBB) integrity, which may otherwise be compromised in PD.[34] That said, Lee *et al*.[35] posit that coffee's neuroprotective effect is due to quercetin, not caffeine. Very high caffeine intake should be avoided with MAO-B inhibitors, as this combination may cause a hypertensive crisis.

PREBIOTIC FOODS

Individuals with PD exhibit dysbiotic gut microbiomes: notably a decrease in *Prevotella* that

correlates with motor-related symptoms,[36] and an increase in Enterobacteriaceae, which is associated with postural and gait abnormalities.[36,37] Eating foods rich in prebiotic carbohydrates such as Jerusalem artichokes, onions, garlic, leeks, dandelion greens, asparagus, chicory root, bananas, cocoa, and nuts will help increase the population of *Prevotella* in the gut, and support improved motor function.[38,39] Given that evidence suggests disruptions in the intestinal barrier and gut microbiome are involved in PD pathogenesis,[37,40] it is significant that many foods and bioactive substances mentioned in this paper help enhance immune function by preventing micronutrient deficiencies; reducing inflammation;[41,42] and supporting a healthy intestinal barrier[43] and gut microbiome.[44]

FOODS, FOOD GROUPS, AND SUBSTANCES TO ELIMINATE

Certain foods, food groups, and substances may contribute to or exacerbate PD symptoms. Eliminating them could prove to be an important component of an anti-inflammatory diet.

DAIRY

Dairy often contains pesticide residues,[45] which have been associated with PD and disease progression.[15,46,47] Moreover, dairy breaks down uric acid. As a neuroprotective anti-oxidant, uric acid minimizes oxidative damage by neutralizing ROS, RNS, and the damaging peroxynitrite molecule in the central nervous system (CNS).[15,46] Individuals with PD often have reduced levels of uric acid.[15] Eliminating dairy may prevent further break down of these already low levels.[46] Dairy may also contribute to insulin resistance and the development of "type III diabetes," an emerging condition associated with neurodegenerative diseases.[15]

Individuals with PD often have increased intestinal permeability, which may play a role in the development of this disease.[40,48] Dairy products such as cow's milk may cause hypersensitivity reactions in some individuals, which results in intestinal inflammation and increased intestinal permeability. Specifically, dairy protein may act as an antigen that initiates a Th1 immune response.[49] The resulting increase in tumor necrosis factor-alpha (TNF-α) degrades tight junctions in the intestinal epithelium, leading to increased intestinal permeability. Immunogenic lipopolysaccharide (LPS) can then enter systemic circulation, causing the chronic production of pro-inflammatory cytokines.[48,50] Pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, and TNF-α increase BBB permeability. The ROS characteristic of systemic inflammation can also increase BBB permeability. As a result, systemically circulating α-Syn can enter the CNS, trigger a neuroinflammatory response, and further expose the CNS to neurotoxic chemicals.[48,51]

TRANS FATTY ACIDS

Hydrogenated vegetable oils, which generate trans fatty acids,[52,53] are found in a variety of food items to prolong shelf life. They have been shown to impair the BBB, decrease glucose utilization in brain regions such as the hippocampus, and reduce cognitive function.[53]

HIGH-FRUCTOSE CORN SYRUP AND REFINED SUGAR

High-fructose corn syrup (HFCS) has been shown to contain the neurotoxin mercury.[54] Research also suggests that fructose disturbs gene networks responsible for neuronal and central metabolic modulatory processes. This provides insight into the potential epigenetic effects that link fructose consumption to metabolic and neurologic dysfunctions.[55] Both HFCS and refined sugar may contribute to the development of insulin resistance and diabetes,[56,57] conditions that are associated with an increased risk of developing PD.[58,59] Identifying food sources of HFCS is not always easy, but many foods contain them, making it important to read food labels.[60]

ARTIFICIAL SWEETENERS

While there is much debate about the safety profile of artificial sweeteners such as aspartame, sucralose, acesulfame-K, and saccharine,[61] evidence suggests that they and their accompanying metabolites may have neurotoxic effects.[62,63] It is also possible that artificial sweeteners alter neurotransmitter synthesis and release, as well as inducing oxidative stress.[64] In addition, studies have found that artificial sweeteners and sugar substitutes such as xylitol can increase Bifidobacteria in the

gut. People with PD often have higher levels of Bifidobacteria in the first place.[65,66] The relationship between artificial sweetener intake and neurodegenerative conditions is, however, inconsistent.[62,67]

Multiple supplements may complement a personalized diet for individuals with PD. Supplementation and dosages should always be considered in the context of an individual's diet, medications, and health condition. For the following supplements, the PD medications that were researched for potential contraindications include:

- Anti-Parkinson's agents: carbidopa, levodopa, Sinemet
- Dopamine agonists: Mirapex, Requip, Neupro, Apokyn
- MAO-B inhibitors: Eldepryl, Zelapar, Azilect, Xadago
- COMT inhibitors: Comtan
- Anticholinergics: Cogentin
- Other: amantadine

COENZYME Q10

Decreased mitochondrial coenzyme Q_{10} (CoQ_{10}) levels are frequently found in individuals with PD. In complexes I and II of mitochondria, CoQ_{10} accepts electrons.[68] However, studies administering 200–1200 mg of CoQ_{10} per day to individuals with PD demonstrate inconsistent results – some suggest higher dosages yield the best outcomes, while others found that comparable outcomes were found with lower dosages.[69–72] There are no known contraindications with the PD medications listed.

N-ACETYLCYSTEINE

Individuals with PD tend to exhibit decreased glutathione concentrations in the substantia nigra, where dopaminergic neurons are often lost.[73–75] *N*-acetylcysteine, the precursor to glutathione, can cross the BBB. This anti-oxidant supports endogenous glutathione production, including intraneuronal glutathione,[76] to protect against oxidative stress and mitochondrial damage. A daily dose of at least 600 mg is advised. An optimal oral dosage is currently undergoing research, with one phase 2 clinical trial (https://clinicaltrials.gov/ct2/show/NCT02212678) utilizing 6000 mg/day, and a completed phase 1/2 trial (https://clinicaltrials.gov/ct2/show/NCT01470027) demonstrating the benefit of 1800 mg and 3600 mg/day. There are no known contraindications with the PD medications listed.

VITAMIN B12

A deficiency of B12 is associated with movement disorders, including tremor and Parkinsonism due to the relationship between vitamin B12 deficiency and the rare neurological consequence of involuntary movements.[77,78] There are no known contraindications with the PD medications listed.

VITAMIN D

Vitamin D acts as a neuro-immunomodulator.[79] Findings from one study showed that low serum 25-hydroxyvitamin D levels are associated with an increased risk of developing PD. In this study, after adjusting for confounding variables, individuals who had a 50 nmol/l or higher serum 25-hydroxyvitamin D level had a risk of PD that was 65% lower than individuals who had levels below 25 nmol/l.[80] There are no known contraindications with the PD medications listed.

CURCUMIN

The antioxidant properties of curcumin may be particularly beneficial for individuals with PD as a component of an anti-inflammatory diet. *In vitro* experiments indicate that curcumin helps minimize reduced glutathione concentrations resulting from oxidative stress in dopaminergic cells .[81] In addition, an *in vitro* α-Syn model has also shown that curcumin decreases α-Syn aggregation.[82] A 400 mg daily dose could be beneficial, but bioavailability will vary based upon formulation and adjuvants. There are no known contraindications with the PD medications listed.

MUCUNA PRURIENS (COWAGE)

Ayurvedic medicine uses the seeds from the legume *M. pruriens*, a naturally occurring botanical source of levodopa, as a PD treatment. Studies suggest that the *M. pruriens* seeds and the traditional lab-created levodopa differ pharmacokinetically and that, unlike levodopa, the seeds from *M. pruriens* confer neuroprotective effects.[83] Of note, a finding that a HP-200 *M. pruriens* endocarp preparation improved Parkinsonism symptomatology but did not influence dopamine metabolism

to an appreciable extent, implies that other constituents in the botanical (i.e. not levodopa) may be responsible for the benefits of *M. pruriens* in individuals with PD.[84] Current research suggests both low and high doses demonstrate efficacy.[85] There are no known contraindications with the PD medications listed.

CONCLUSION

While PD is a devastating, progressive neurodegenerative condition that has both hereditary and environmental components to its pathogenesis, multiple nutrition and supplement interventions show promise for positively affecting disease onset and progression. To intervene as early as possible, clinicians should assess vitamin D status, vitamin B12 status, oxidative stress, inflammation, essential fatty acid status, insulin resistance, BBB integrity, intestinal integrity, and gut microbiome health.

Earlier identification of risk factors and PD onset (i.e. pre-motor PD), could result in better outcomes. Further research is warranted to determine whether personalized, PD-targeted anti-inflammatory and neuroprotective nutrition, and supplementation may protect against neurodegeneration and optimize the quality of life for individuals with this condition.

COMPETING INTERESTS

The authors declare they have no competing interests.

AUTHORS' CONTRIBUTIONS

CECC: Apprehended the general idea, wrote the first drafts and preliminary outline of the review, and participated in rewriting and redrafting. SJVL: Participated in rewriting and redrafting. Both authors read and approved the final manuscript.

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REFERENCES

1. Tysnes O-B, Storstein A. Epidemiology of Parkinson's disease. *J Neural Transm (Vienna)*. 2017;124(8):901–5. doi:10.1007/s00702-017-1686-y.

2. DeMaagd G, Philip A. Parkinson's disease and its management. *P T*. 2015;40(8):504–32.

3. Nazario LR, da Silva RS, Bonan CD. Targeting adenosine signaling in Parkinson's disease: from pharmacological to non-pharmacological approaches. *Front Neurosci*. 2017;11:658. doi:10.3389/fnins.2017.00658.

4. Dickson DW. Parkinson's disease and Parkinsonism: neuropathology. *Cold Spring Harb Perspect Med*. 2012;2(8):a009258. doi:10.1101/cshperspect.a009258.

5. Kushnareva Y, Murphy AN, Andreyev A. Complex I-mediated reactive oxygen species generation: modulation by cytochrome c and NAD(P)+ oxidation-reduction state. *Biochem J*. 2002;368(Pt 2):545–53. doi:10.1042/BJ20021121.

6. Park J-S, Davis RL, Sue CM. Mitochondrial dysfunction in Parkinson's disease: new mechanistic insights and therapeutic perspectives. *Curr Neurol Neurosci Rep*. 2018;18(5):21. doi:10.1007/s11910-018-0829-3.

7. Reeve AK, Grady JP, Cosgrave EM, *et al*. Mitochondrial dysfunction within the synapses of substantia nigra neurons in Parkinson's disease. *NPJ Parkinson's Dis*. 2018;4(1):9. doi:10.1038/s41531-018-0044-6.

8. Thomas B, Beal MF. Mitochondrial therapies for Parkinson's disease. *Mov Disord*. 2010;25 Suppl 1:S155–60. doi:10.1002/mds.22781.

9. Michel PP, Hirsch EC, Hunot S. Understanding dopaminergic cell death pathways in Parkinson disease. *Neuron*. 2016;90(4):675–91. doi:10.1016/j.neuron.2016.03.038.

10. Rees RN, Acharya AP, Schrag A, *et al*. An early diagnosis is not the same as a timely diagnosis of Parkinson's disease. *F1000Res*. 2018;7:1106. doi:10.12688/f1000research.14528.1.

11. Schrag A, Horsfall L, Walters K, et al. Prediagnostic presentations of Parkinson's disease in primary care:

a case-control study. *Lancet Neurol*. 2015;14(1):57–64. doi:10.1016/S1474-4422(14)70287-X.

12. Lebouvier T, Neunlist M, Bruley des Varannes S, *et al*. Colonic biopsies to assess the neuropathology of Parkinson's disease and its relationship with symptoms. *PLoS One*. 2010;5(9):e12728. doi:10.1371/journal.pone.0012728.

13. Joseph J, Cole G, Head E, Ingram D. Nutrition, brain aging, and neurodegeneration. *J Neurosci*. 2009;29(41):12795–801. doi:10.1523/JNEUROSCI.3520-09.2009.

14. Ferrari CKB. Functional foods, herbs and nutraceuticals: towards biochemical mechanisms of healthy aging. *Biogerontology*. 2004;5(5):275–89. doi:10.1007/s10522-004-2566-z.

15. Mischley LK, Lau RC, Bennett RD. Role of diet and nutritional supplements in Parkinson's disease progression. *Oxid Med Cell Longev*. 2017;2017:6405278. doi:10.1155/2017/6405278.

16. Seidl SE, Santiago JA, Bilyk H, Potashkin JA. The emerging role of nutrition in Parkinson's disease. *Front Aging Neurosci*. 2014;6:36. doi:10.3389/fnagi.2014.00036.

17. Smith PJ, Blumenthal JA. Dietary factors and cognitive decline. *J Prev Alzheimers Dis*. 2016;3(1):53–64. doi:10.14283/jpad.2015.71.

18. Farooqui T, Farooqui AA. Aging: an important factor for the pathogenesis of neurodegenerative diseases. *Mech Ageing Dev*. 2009;130(4):203–15. doi:10.1016/j.mad.2008.11.006.

19. Shen L. Associations between B vitamins and Parkinson's disease. *Nutrients*. 2015;7(9):7197–208. doi:10.3390/nu7095333.

20. Gómez-Pinilla F. Brain foods: the effects of nutrients on brain function. *Nat Rev Neurosci*. 2008;9(7):568–78. doi:10.1038/nrn2421.

21. Kim HG, Ju MS, Shim JS, *et al*. Mulberry fruit protects dopaminergic neurons in toxin-induced Parkinson's disease models. *Br J Nutr*. 2010;104(1):8–16. doi:10.1017/S0007114510000218.

22. Ellwanger JH, Molz P, Dallemole DR, *et al*. Selenium reduces bradykinesia and DNA damage in a rat model of Parkinson's disease. *Nutrition*. 2015;31(2):359–65. doi:10.1016/j.nut.2014.07.004.

23. Nielsen SS, Franklin GM, Longstreth WT, *et al*. Nicotine from edible solanaceae and risk of Parkinson disease. *Ann Neurol*. 2013;74(3):472–7. doi:10.1002/ana.23884.

24. Quik M, O'Leary K, Tanner CM. Nicotine and Parkinson's disease: implications for therapy. *Mov Disord*. 2008;23(12):1641–52. doi:10.1002/mds.21900.

25. Fricker RA, Green EL, Jenkins SI, *et al*. The influence of nicotinamide on health and disease in the central nervous system. *Int J Tryptophan Res*. 2018;11:1178646918776658. doi:10.1177/1178646918776658.

26. Kennedy DO. B vitamins and the brain: mechanisms, dose and efficacy – a review. *Nutrients*. 2016;8(2):68. doi:10.3390/nu8020068.

27. Caruana M, Vassallo N. Tea polyphenols in Parkinson's disease. *Adv Exp Med Biol*. 2015;863:117–37. doi:10.1007/978-3-319-18365-7_6.

28. Li F-J, Ji H-F, Shen L. A meta-analysis of tea drinking and risk of Parkinson's disease. *ScientificWorldJournal*. 2012;2012:923464. doi:10.1100/2012/923464.

29. Pan T, Jankovic J, Le W. Potential therapeutic properties of green tea polyphenols in Parkinson's disease. *Drugs Aging*. 2003;20(10):711–21.

30. Weinreb O, Mandel S, Amit T, Youdim MB. Neurological mechanisms of green tea polyphenols in Alzheimer's and Parkinson's diseases. *J Nutr Biochem*. 2004;15(9):506–16. doi:10.1016/j.jnutbio.2004.05.002.

31. Caruana M, Cauchi R, Vassallo N. Putative role of red wine polyphenols against brain pathology in Alzheimer's and Parkinson's disease. *Front Nutr*. 2016;3:31. doi:10.3389/fnut.2016.00031.

32. Eriksson A-K, Löfving S, Callaghan RC, Allebeck P. Alcohol use disorders and risk of Parkinson's disease: findings from a Swedish national cohort study 1972–2008. *BMC Neurol.* 2013;13(1):190. doi:10.1186/1471-2377-13-190.

33. Roshan MHK, Tambo A, Pace NP. Potential role of caffeine in the treatment of Parkinson's disease. *Open Neurol J*. 2016;10:42–58. doi:10.2174/1874205X01610010042.

34. Chen X, Ghribi O, Geiger JD. Caffeine protects against disruptions of the blood–brain barrier in animal models of Alzheimer's and Parkinson's diseases. *J Alzheimers Dis*. 2010;20 Suppl 1:S127–41. doi:10.3233/JAD-2010-1376.

35. Lee M, McGeer EG, McGeer PL. Quercetin, not caffeine, is a major neuroprotective component in coffee. *Neurobiol Aging*. 2016;46:113–23. doi:10.1016/j.neurobiolaging.2016.06.015.

36. Scheperjans F, Aho V, Pereira PAB, *et al*. Gut microbiota are related to Parkinson's disease and clinical phenotype. *Mov Disord*. 2015;30(3):350–8. doi:10.1002/mds.26069.

37. Minato T, Maeda T, Fujisawa Y, *et al*. Progression of Parkinson's disease is associated with gut dysbiosis: two-year follow-up study. *PLoS One*. 2017;12(11):e0187307. doi:10.1371/journal.pone.0187307.

38. Lamuel-Raventos RM, Onge M-PSt. Prebiotic nut compounds and human microbiota. *Crit Rev Food Sci Nutr*. 2017;57(14):3154–63. doi:10.1080/10408398.2015.1096763.

39. Umu ÖCO, Rudi K, Diep DB. Modulation of the gut microbiota by prebiotic fibres and bacteriocins. *Microb Ecol Health Dis*. 2017;28(1):1348886. doi:10.1080/16512235.2017.1348886.

40. Clairembault T, Leclair-Visonneau L, Coron E, *et al*. Structural alterations of the intestinal epithelial barrier

in Parkinson's disease. *Acta Neuropathol Commun*. 2015;3:12. doi:10.1186/s40478-015-0196-0.

41. Alpert PT. The role of vitamins and minerals on the immune system. *Home Health Care Manag Pract*. 2017;29(3):199–202. doi:10.1177/1084822317713300.

42. Saeed F, Nadeem M, Ahmed RS, *et al*. Studying the impact of nutritional immunology underlying the modulation of immune responses by nutritional compounds – a review. *Food Agric Immunol*. 2016;27(2):205–29. doi:10.1080/09540105.2015.1079600.

43. Duggan C, Gannon J, Walker WA. Protective nutrients and functional foods for the gastrointestinal tract. *Am J Clin Nutr*. 2002;75(5):789–808. doi:10.1093/ajcn/75.5.789.

44. Singh RK, Chang H-W, Yan D, *et al*. Influence of diet on the gut microbiome and implications for human health. *J Transll Med*. 2017;15(1):73. doi:10.1186/s12967-017-1175-y.

45. Heineman HEO, Jaynes HO, Heflin JL. Pesticides – a dairy industry problem. *J Dairy Sci*. 1966;49(5):509–16. doi:10.3168/jds.S0022-0302(66)87906-7.

46. Chen H, O'Reilly E, McCullough ML, *et al*. Consumption of dairy products and risk of Parkinson's disease. *Am J Epidemiol*. 2007;165(9):998–1006. doi:10.1093/aje/kwk089.

47. Samson K. Pesticide in milk may have caused PD-like damage. *Neurology Today*. 2016;16(2):1. doi:10.1097/01.NT.0000480653.11072.9e.

48. Houser MC, Tansey MG. The gut-brain axis: is intestinal inflammation a silent driver of Parkinson's disease pathogenesis? *NPJ Parkinson's Dis*. 2017;3(1):3. doi:10.1038/s41531-016-0002-0.

49. Gocki J, Bartuzi Z. Role of immunoglobulin G antibodies in diagnosis of food allergy. *Postepy Dermatol Alergol*. 2016;33(4):253–6. doi:10.5114/ada.2016.61600.

50. Ulluwishewa D, Anderson RC, McNabb WC, *et al*. Regulation of tight junction permeability by intestinal bacteria and dietary components. *J Nutr*. 2011;141(5):769–76. doi:10.3945/jn.110.135657.

51. Freeman LR, Haley-Zitlin V, Rosenberger DS, Granholm AC. Damaging effects of a high-fat diet to the brain and cognition: a review of proposed mechanisms. *Nutr Neurosci*. 2014;17(6):241–51. doi:10.1179/1476830513Y.0000000092.

52. Dhaka V, Gulia N, Ahlawat KS, *et al*. Trans fats – sources, health risks and alternative approach – a review. *J Food Sci Technol*. 2011;48(5):534–41. doi:10.1007/s13197-010-0225-8.

53. Morris MC, Tangney CC. Dietary fat composition and dementia risk. *Neurobiol Aging*. 2014;35 Suppl 2:S59–64. doi:10.1016/j.neurobiolaging.2014.03.038.

54. Dufault R, LeBlanc B, Schnoll R, *et al*. Mercury from chlor-alkali plants: measured concentrations in food product sugar. *Environ Health*. 2009;8(1):2. doi:10.1186/1476-069X-8-2.

55. Meng Q, Ying Z, Noble E, *et al*. Systems nutrigenomics reveals brain gene networks linking metabolic and brain disorders. *EBioMedicine*. 2016;7:157–66. doi:10.1016/j.ebiom.2016.04.008.

56. Bray GA. Potential health risks from beverages containing fructose found in sugar or high-fructose corn syrup. *Diabetes Care*. 2013;36(1):11–2. doi:10.2337/dc12-1631.

57. Macdonald IA. A review of recent evidence relating to sugars, insulin resistance and diabetes. *Eur J Nutr*. 2016;55 Suppl 2:17–23. doi:10.1007/s00394-016-1340-8.

58. Aviles-Olmos I, Limousin P, Lees A, Foltynie T. Parkinson's disease, insulin resistance and novel agents of neuroprotection. *Brain*. 2013;136(2):374–84. doi:10.1093/brain/aws009.

59. Yue X, Li H, Yan H, *et al*. Risk of Parkinson disease in diabetes mellitus: an updated meta-analysis of population-based cohort studies. *Medicine (Baltimore)*. 2016;95(18):e3549. doi:10.1097/MD.0000000000003549.

60. Parker K, Salas M, Nwosu VC. High fructose corn syrup: production, uses and public health concerns. *BMBR*. 2010;5(5):71–8.

61. Sharma A, Amarnath S, Thulasimani M, *et al*. Artificial sweeteners as a sugar substitute: are they really safe? *Indian J Pharmacol*. 2016;48(3):237–40. doi:10.4103/0253-7613.182888.

62. Maher TJ, Wurtman RJ. Possible neurologic effects of aspartame, a widely used food additive. *Environ Health Perspect*. 1987;75:53–7.

63. Tandel KR. Sugar substitutes: health controversy over perceived benefits. *J Pharmacol Pharmacother*. 2011;2(4):236–43. doi:10.4103/0976-500X.85936.

64. Choudhary AK, Lee YY. Neurophysiological symptoms and aspartame: what is the connection? *Nutr Neurosci*. 2018;21(5):306–16. doi:10.1080/1028415X.2017.1288340.

65. Nair AT, Ramachandran V, Joghee NM, *et al*. Gut microbiota dysfunction as reliable non-invasive early diagnostic biomarkers in the pathophysiology of Parkinson's disease: a critical review. *J Neurogastroenterol Motil*. 2018;24(1):30–42. doi:10.5056/jnm17105.

66. Ruiz-Ojeda FJ, Plaza-Díaz J, Sáez-Lara MJ, *et al*. Effects of sweeteners on the gut microbiota: a review of experimental studies and clinical trials. *Adv Nutr*. 2019;10 Suppl 1:S31–48. doi:10.1093/advances/nmy037.

67. Lohner S, Toews I, Meerpohl JJ. Health outcomes of non-nutritive sweeteners: analysis of the research landscape. *Nutr J*. 2017;16(1):55. doi:10.1186/s12937-017-0278-x.

68. Shults CW, Haas RH, Passov D, *et al*. Coenzyme Q10 levels correlate with the activities of complexes I and

II/III in mitochondria from Parkinsonian and nonParkinsonian subjects. *Ann Neurol*. 1997;42(2):261–4. doi:10.1002/ana.410420221.

69. Shults CW, Beal MF, Fontaine D, *et al*. Absorption, tolerability, and effects on mitochondrial activity of oral coenzyme Q10 in parkinsonian patients. *Neurology*. 1998;50(3):793–95.

70. Shults CW, Oakes D, Kieburtz K, *et al*. Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline. *Arch Neurol*. 2002;59(10):1541–50.

71. Storch A, Jost WH, Vieregge P, *et al*. Randomized, double-blind, placebo-controlled trial on symptomatic effects of coenzyme Q(10) in Parkinson disease. *Arch Neurol*. 2007;64(7):938–44. doi:10.1001/archneur.64.7.nct60005.

72. Strijks E, Kremer HPH, Horstink MWIM. Q10 therapy in patients with idiopathic Parkinson's disease. *Mol Aspects Med*. 1997;18:237–40. doi:10.1016/S0098-2997(97)00008-3.

73. Holmay MJ, Terpstra M, Coles LD, *et al*. N-acetylcysteine boosts brain and blood glutathione in Gaucher and Parkinson's diseases. *Clin Neuropharmacol*. 2013;36(4):103–6. doi:10.1097/WNF.0b013e31829ae713.

74. Martínez M, Martínez N, Hernández AI, *et al*. Hypothesis: can N-acetylcysteine be beneficial in Parkinson's disease? *Life Sci*. 1999;64(15):1253–7.

75. Schulz JB, Lindenau J, Seyfried J, Dichgans J. Glutathione, oxidative stress and neurodegeneration. *Eur J Biochem*. 2000;267(16):4904–11.

76. Dringen R, Hamprecht B. N-acetylcysteine, but not methionine or 2-oxothiazolidine-4-carboxylate, serves as cysteine donor for the synthesis of glutathione in cultured neurons derived from embryonal rat brain. *Neurosci Lett*. 1999;259(2):79–82.

77. Celik M, Barkut IK, Oncel C, Forta H. Involuntary movements associated with vitamin B12 deficiency. *Parkinsonism Relat Disord*. 2003;10(1):55–7.

78. de Souza A, Moloi MW. Involuntary movements due to vitamin B12 deficiency. *Neurol Res*. 2014;36(12):1121–8. doi:10.1179/1743132814Y.0000000396.

79. Fernandes de Abreu DA, Eyles D, Féron F. Vitamin D, a neuro-immunomodulator: implications for neurodegenerative and autoimmune diseases. *Psychoneuroendocrinology*. 2009;34 Suppl 1:S265–77. doi:10.1016/j.psyneuen.2009.05.023.

80. Knekt P, Kilkkinen A, Rissanen H, *et al*. Serum vitamin D and the risk of Parkinson's disease. *Arch Neurol*. 2010;67(7):808–11. doi:10.1001/archneurol.2010.120.

81. Harish G, Venkateshappa C, Mythri RB, *et al*. Bioconjugates of curcumin display improved protection against glutathione depletion mediated oxidative stress in a dopaminergic neuronal cell line: implications for Parkinson's disease. *Bioorg Med Chem*. 2010;18(7):2631–8. doi:10.1016/j.bmc.2010.02.029.

82. Pandey N, Strider J, Nolan WC, *et al*. Curcumin inhibits aggregation of alpha-synuclein. *Acta Neuropathol*. 2008;115(4):479–89. doi:10.1007/s00401-007-0332-4.

83. Pathak-Gandhi N, Vaidya ADB. Management of Parkinson's disease in Ayurveda: medicinal plants and adjuvant measures. *J Ethnopharmacol*. 2017;197:46–51. doi:10.1016/j.jep.2016.08.020.

84. Manyam BV, Dhanasekaran M, Hare TA. Effect of antiparkinson drug HP-200 (*Mucuna pruriens*) on the central monoaminergic neurotransmitters. *Phytother Res*. 2004;18(2):97–101. doi:10.1002/ptr.1407.

85. Cilia R, Laguna J, Cassani E, *et al*. Mucuna pruriens in Parkinson disease: a double-blind, randomized, controlled, crossover study. *Neurology*. 2017;89(5):432–8. doi:10.1212/WNL.0000000000004175.