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Parkinson's Disease Research, Education & Clinical Center

Nutrition and Parkinson's Disease – What your patients need to know

John E. Duda, MD

Director, Parkinson's Disease Research, Education and Clinical Center Philadelphia VA Medical Center

Associate Professor of Neurology, Perelman School of Medicine at the University of Pennsylvania

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Disclosure Statement

- I have no personal financial conflicts of interest
- I will be discussing numerous off-label indications for the treatment of Parkinson's disease

Objectives

1. Explain how dietary choices can affect symptom control in Parkinson's disease.

2. Discuss the current state of our knowledge regarding the basic mechanisms playing a role in the pathophysiology of Parkinson's disease and how the microbiome may contribute.

3. Discuss how food choices may contribute to these basic mechanisms and the possibility that sound nutritional lifestyle modifications may provide disease modifying effects.

Does diet contribute to risk of PD?

- Analysis of Health Professionals Follow-Up Study and the Nurses' Health Study
- Over 130,000 subjects! Over 500 PD subjects!
- Conclusion: Dietary patterns with a high intake of fruit, vegetables, legumes, whole grains, nuts, fish, and a low intake of saturated fat and a moderate intake of alcohol may protect against PD

Am J Clin Nutr 2007;86:1486 –94.

Dietary Flavonoids may be part of the reason

- Same studies, over 20 years f/u and >800 PD
- Assessed intake of five major sources of flavonoid-rich foods (tea, berry fruits, apples, red wine, and orange/orange juice)
- In men, after adjusting for multiple confounders, participants in the highest quintile of total flavonoids had a 40% lower PD risk than those in the lowest quintile
- Also, intakes of anthocyanins and a rich dietary source, berries, were significantly associated with a lower PD risk (HR 0.76 for anthocyanins and 0.77 for berries).

Neurology (2012)78:1138–1145

Coffee is protective

- One of the most consistently identified nutrients associated with PD protection

- Meta-analysis of over 900,000 subjects
- Found a 28% reduction in risk of developing PD
- Maximum benefit reached at approximately 3 cups of coffee daily.

Geriatr Gerontol Int 2014;14(2):430-9.

Green & Black Tea are also protective

- Consumption of 3+ cups/ day of tea delayed motor symptom onset by 7.7 years.

Parkinsonism Relat Disord 2009;15(1):41-6

Dairy increases risk in multiple studies

- Nurses' Health Study (121000) & Health Professional Follow-up Study (51000)
  - 1.8x risk
- Honolulu Heart Program (7500 men)
  - 2.3x risk
- American Cancer Society's Cancer Prevention Study II Nutrition Cohort (57000 men, 73000 women)
  - Up to 1.8x risk
- EPIC-Greece Cohort (26,173)
  - Strong positive association with milk but not cheese or yogurt.

What about treatment considerations?

Dietary management of motor fluctuations

- Low protein diet and protein redistribution diets have been tried
- Meta-analysis in 2010 included 16 studies
- No support for low protein diet
- However, over two-thirds of studies reported >80 response rates
- All studies reported reductions in motor impairment or improvements in fluctuations

Mov Disord 2010;25:2021-34

Which patients respond best

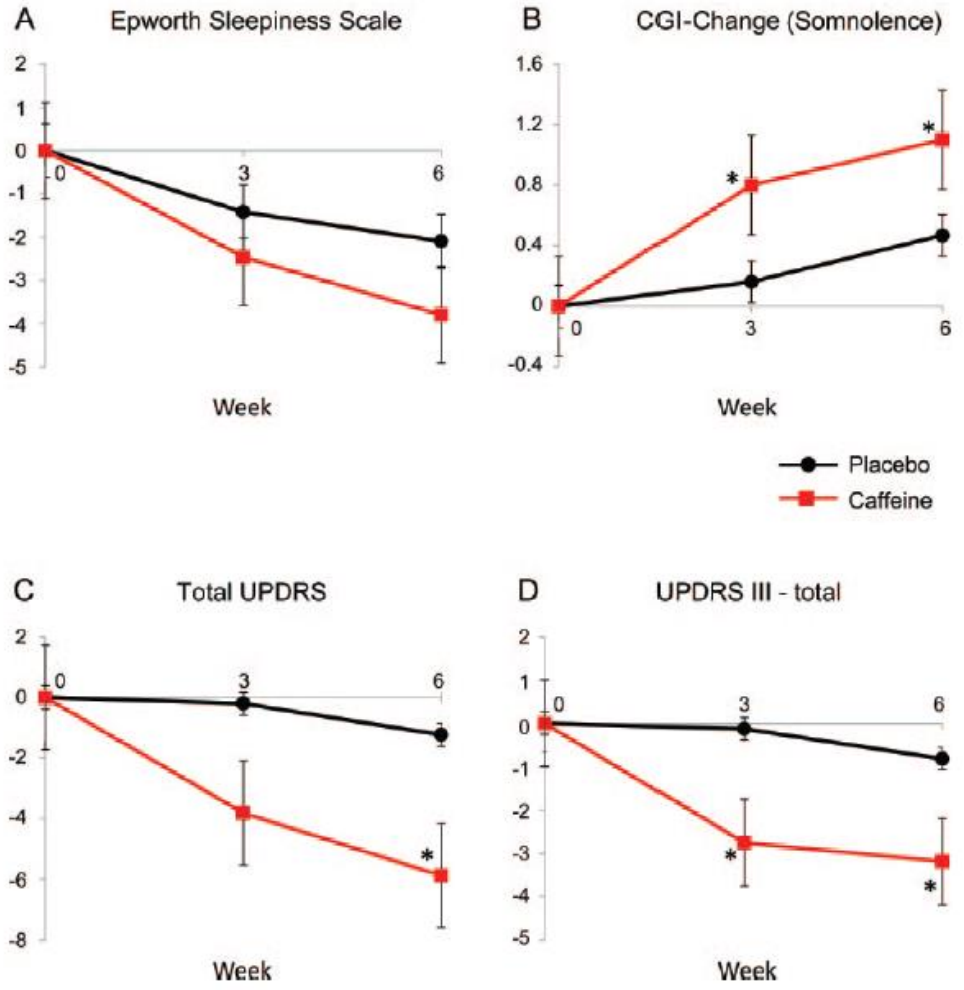
- Three studies addressed this question

Source (year)	Reference	Feature
Riley et al. (1988)	24	Shorter duration of Parkinson's disease Shorter lenght of levodopa treatment
Bracco et al. (1991)	26	Shorter duration of fluctuations
Giménez-Roldán et al. (1991)	28	Older age at onset and shorter duration of fluctuations

- Efficacy and benefits appeared to be higher when started early
- Long term compliance was possible

Caffeine for the treatment of PD

- 6-week randomized controlled trial of 100-200mg of caffeine in PD with daytime somnolence



Neurology 2012;79;651

Randomized unblinded trial of plant-based diet in PD

- Compared the effect of a plant-food menu to an omnivorous menu on motor performance of 25 PD patients, 12 in the intervention group (PDi) and 13 in the control group (PDc).
- After 4 weeks, the PDi group showed a significant reduction in UPDRS total score (47.67 vs. 74.46, P = 0.008) and sub-score III motor performances (25.42 vs. 46.46, P = 0.001), and the modified Hoehn and Yahr Staging Scale (1.96 vs. 3.15, P = 0.005)

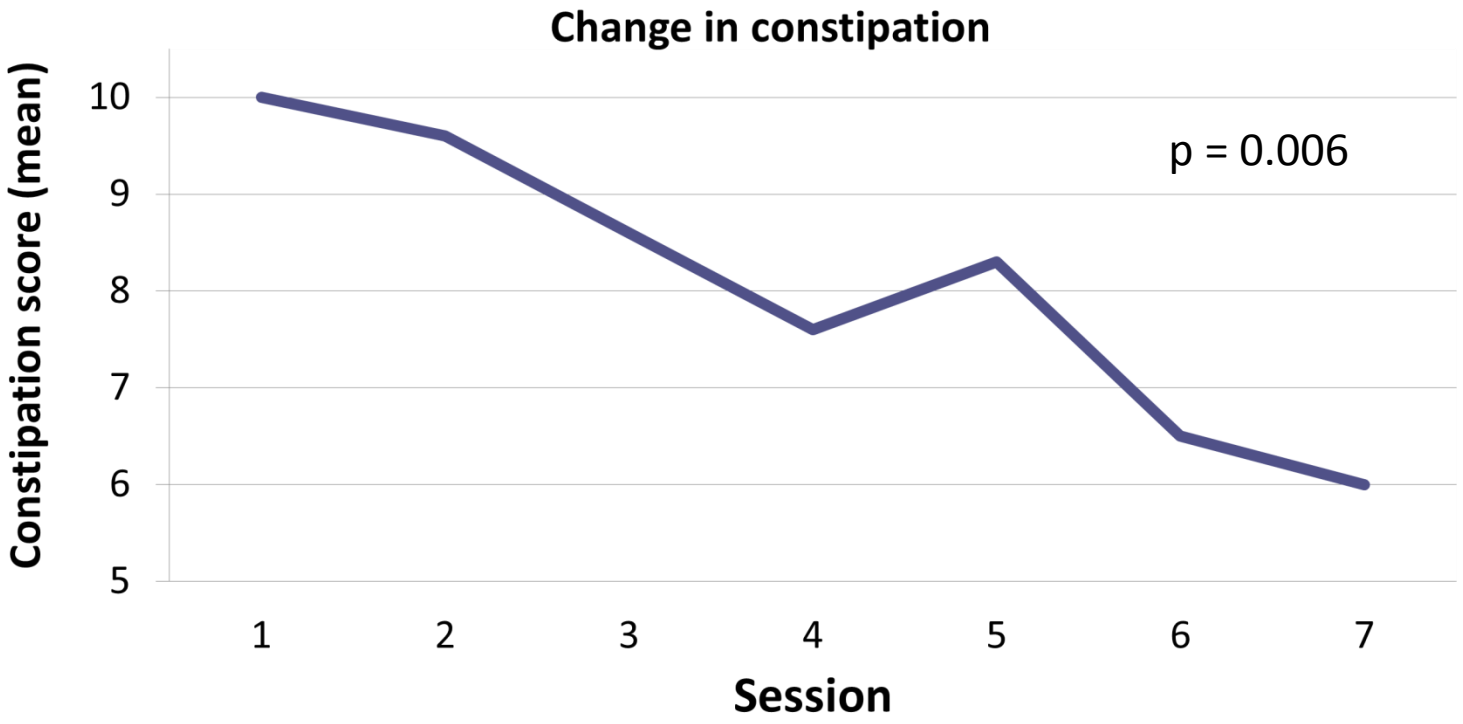
Nutr Neurosci 2011;14:1-9.

Diet modification trial in Veterans with Parkinson's disease

- 13 PD patients enrolled in a 14-week dietary intervention studying the feasibility and effects of a plant-based diet in PD.
- 7 participants completed the study.
- Participants attended 7 bi-weekly educational seminars and food demos
- Primary outcome was Constipation Scale score. Secondary outcomes included motor UPDRS, PDQ-39, and diet changes

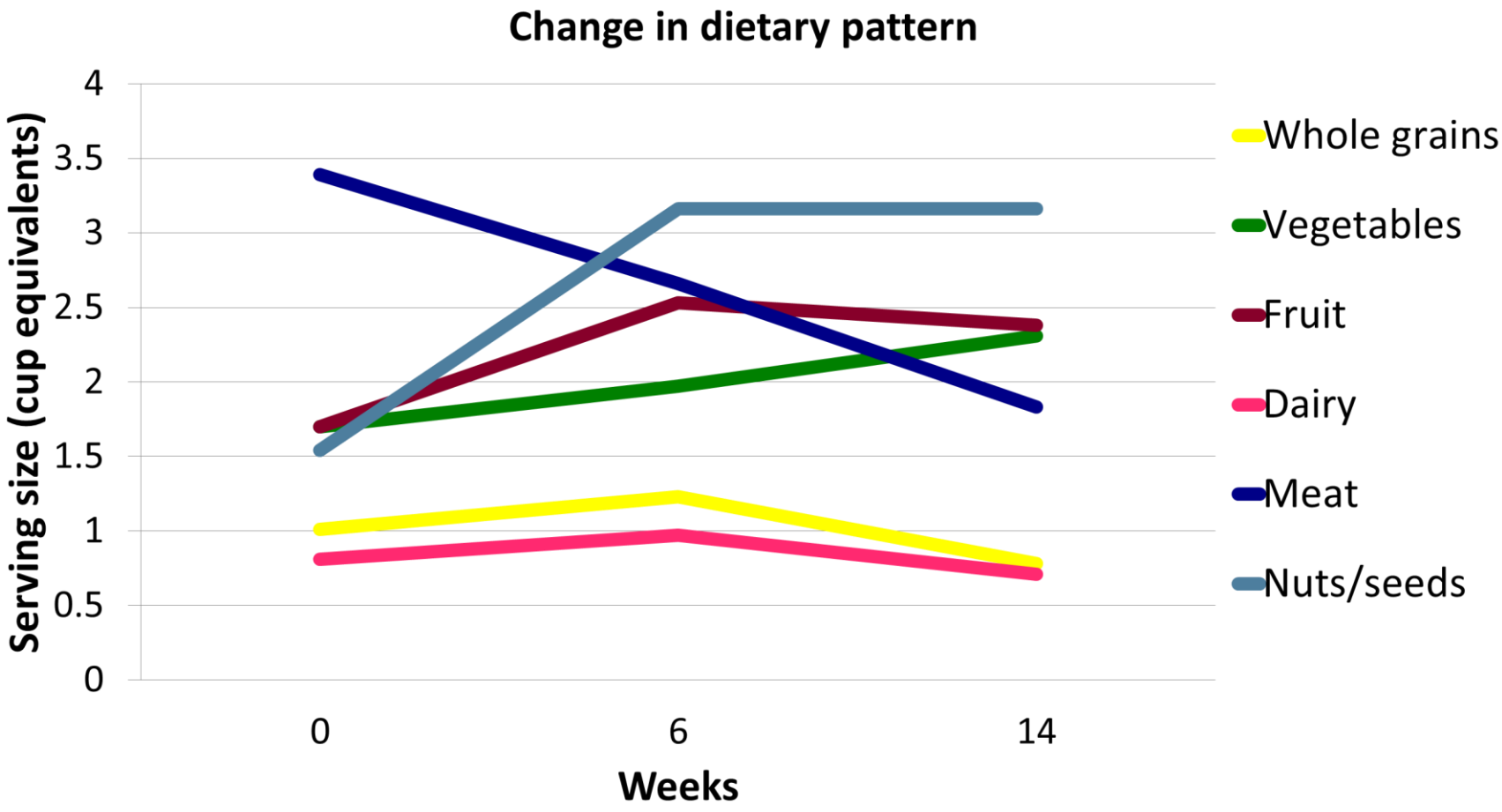
Shital Shah, Heidi Watson, Helen Kane, John Duda in preparation

Constipation Scale scores over time



Constipation was correlated with fiber intake (r = -0.787, p = 0.036)

Less Meat, More Nuts and Greens



Effect on Symptoms

	UPDRS I		UPDRS II		UPDRS III		UPDRS Total		PDQ-39	
	Baseline	Final	Baseline	Final	Baseline	Final	Baseline	Final	Baseline	Final
	11.1	7.9	11.9	11.6	22.7	20.7	45.7	40.1	146.1	118.3
p Value	0.121		0.925		0.447		0.263		0.272	

Obviously under-powered, but change in total UPDRS approaching a clinically meaningful difference

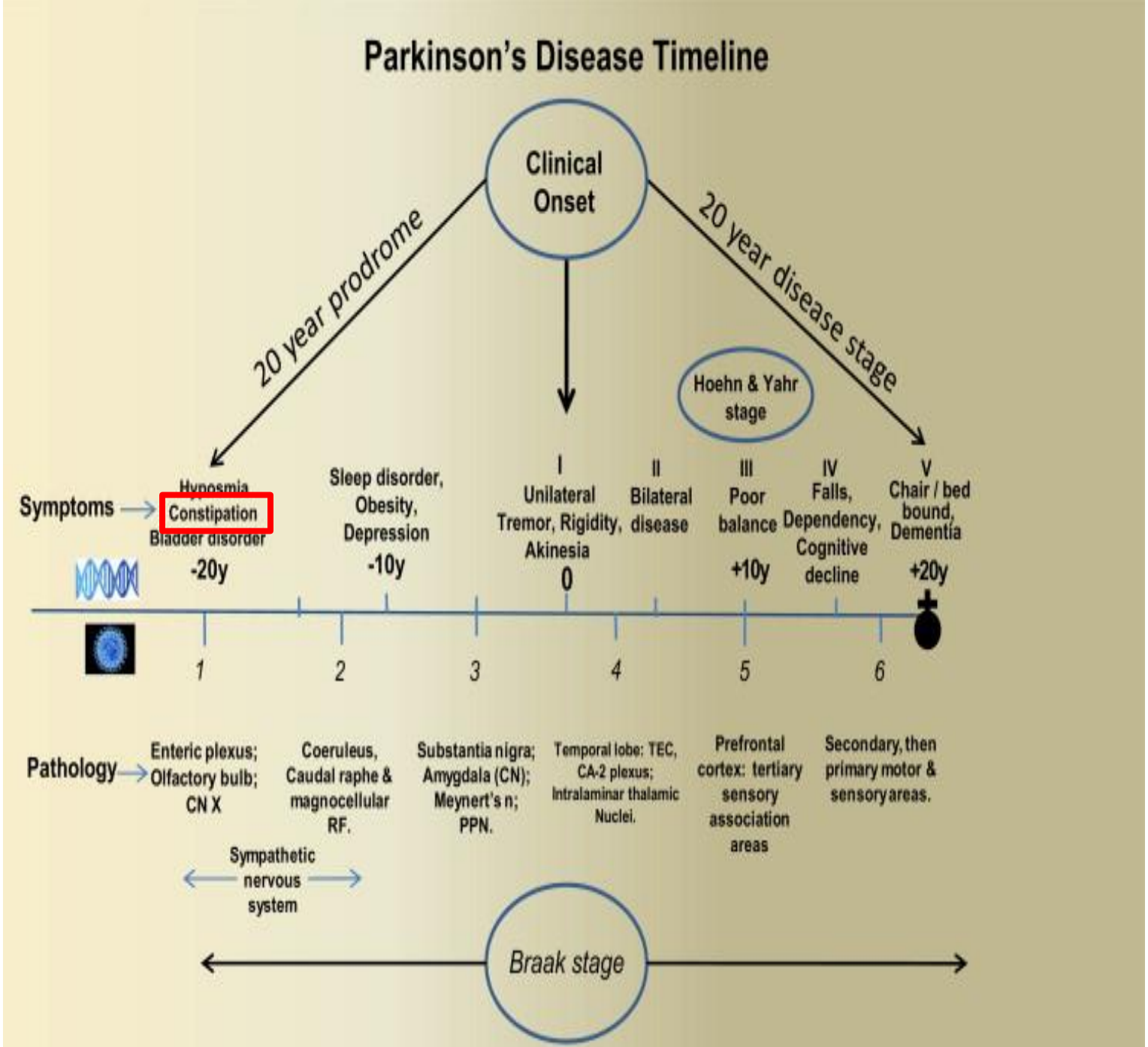
		UPDRS I	UPDRS II	UPDRS III	Total UPDRS	PDQ-39
Meat	**r**	0.458	-0.830	-0.239	-0.484	-0.377
	p	0.302	0.021	0.606	0.271	0.405

no correlations were seen for whole grains, vegetables, fruit or dairy

Conclusions

- A significant improvement was seen in constipation with increased dietary fiber consumption.
- Non-significant improvements were seen in the UPDRS and PDQ-39.
- Non-significant trends were seen in decreased meat, dairy, sugar, and fat intake and increased nut, vegetable and fiber consumption.
- This pilot study supports larger and longer studies of nutritional education and modification in the treatment of Parkinson's disease.
- A sample size of 40 would have allowed us to assess the effects of diet on PD symptoms.

The microbiome and PD



Hawkes, C., Tredici, K and Braak, H. Parkinsonism and related disorders 2010 ■

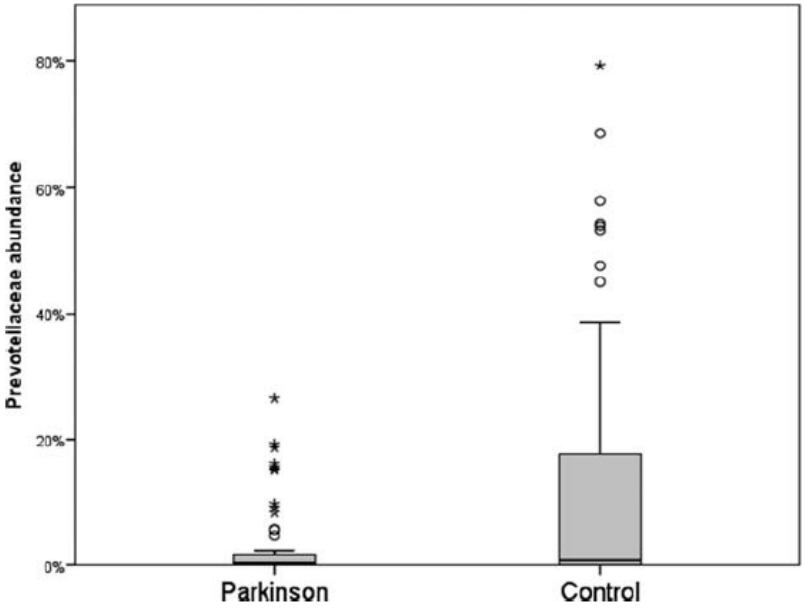
What if constipation was not an early symptom, but a risk factor for PD?

- Mid-life constipation suggests poor nutritional intake of dietary fiber
- The longer feces stays in bowels, the more neurotoxins may be absorbed
- Many pesticides have been shown to be able to cause alpha-synuclein to aggregate
- Intestinal dysbiosis may lead to inflammation and membrane permeability with absorption of bacterial endotoxins

Am J Epidemiol 2011;174:546-51

The gut microbiome is different in PD

- 72 PD and 72 controls
- 16S ribosomal RNA analysis of stool samples
- Abundance of Enterobacteriaceae was related to the severity of postural instability and gait difficulty
- 77.6% reduction in abundance of Prevotella in patients with PD
- Prevotella have been shown to be health-promoting and anti-inflammatory by the production of short chain fatty acid compounds



Mov Dis 2015;30:351-8

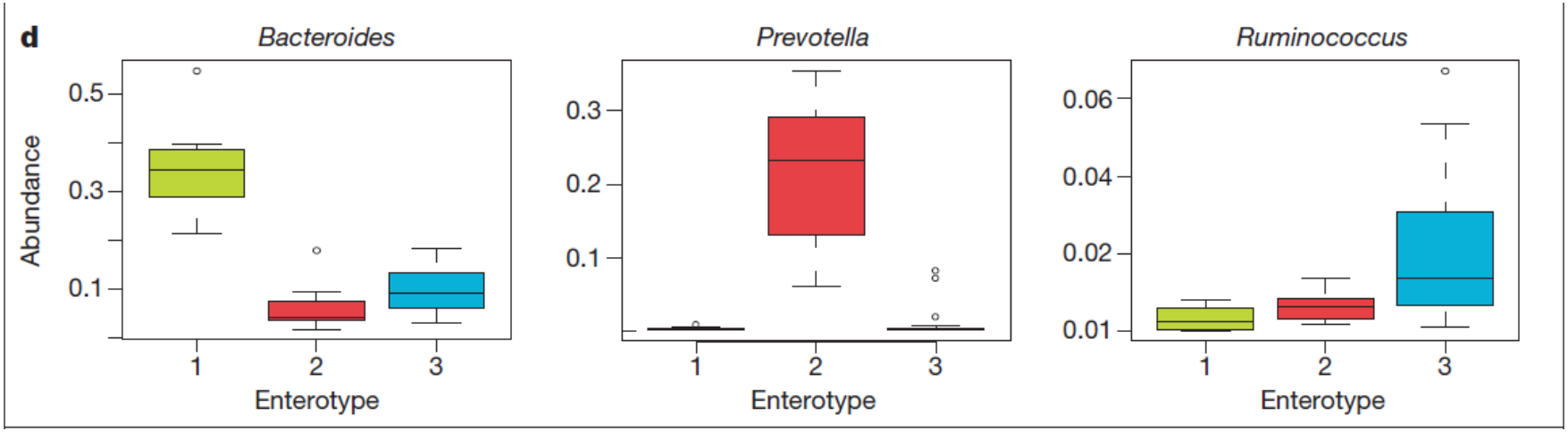
The gut microbiome is different in PD

- Second study with 38 PD samples and 34 controls
- Assessed sigmoid colonic biopsies and stool
- Found a non-significant 50% decrease in Prevotella in biopsies but no difference in stool
- SCFA- producing Blautia, Coprococcus, and Roseburia were significantly more abundant in feces of controls than PD patients
- Bacteria from the genus Faecalibacterium were significantly more abundant in the mucosa of controls than PD.
- Putative, “proinflammatory” Proteobacteria of the genus Ralstonia were significantly more abundant in mucosa of PD than controls

Mov Dis 2015;30:1351-1360

Human gut flora enterotypes

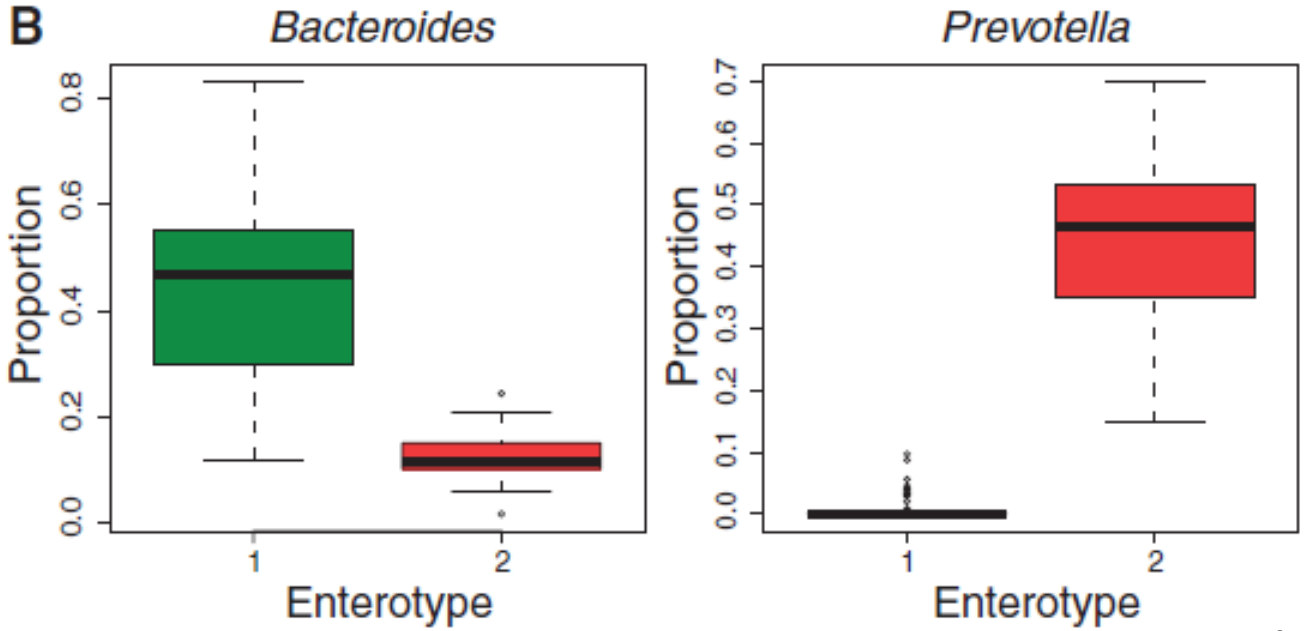
- 3 distinct enterotypes identified
- One of the distinguishing factors is prevalence of Prevotella



Nature 2011;473:174-80

Long term diet patterns are strongly associated with enterotype

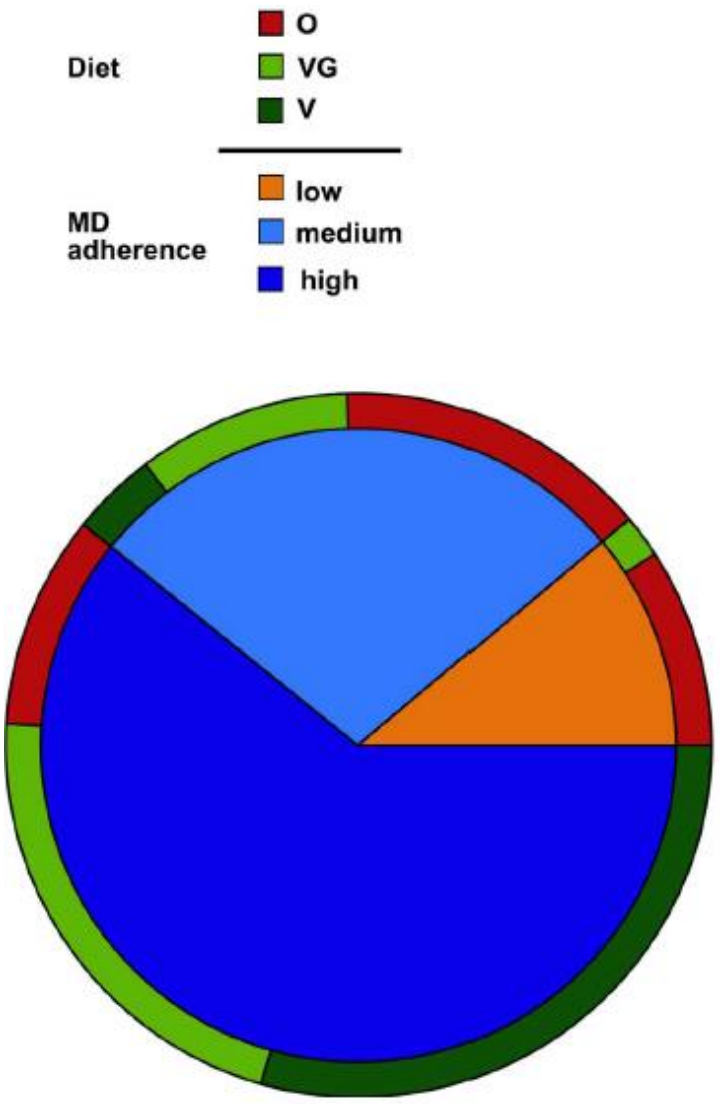
- 100 healthy controls
- Segregated into two enterotypes
- Protein and animal fat consumption – Bacteroides
- Carbohydrate consumption - Prevotella



Science 2011;334:105-8

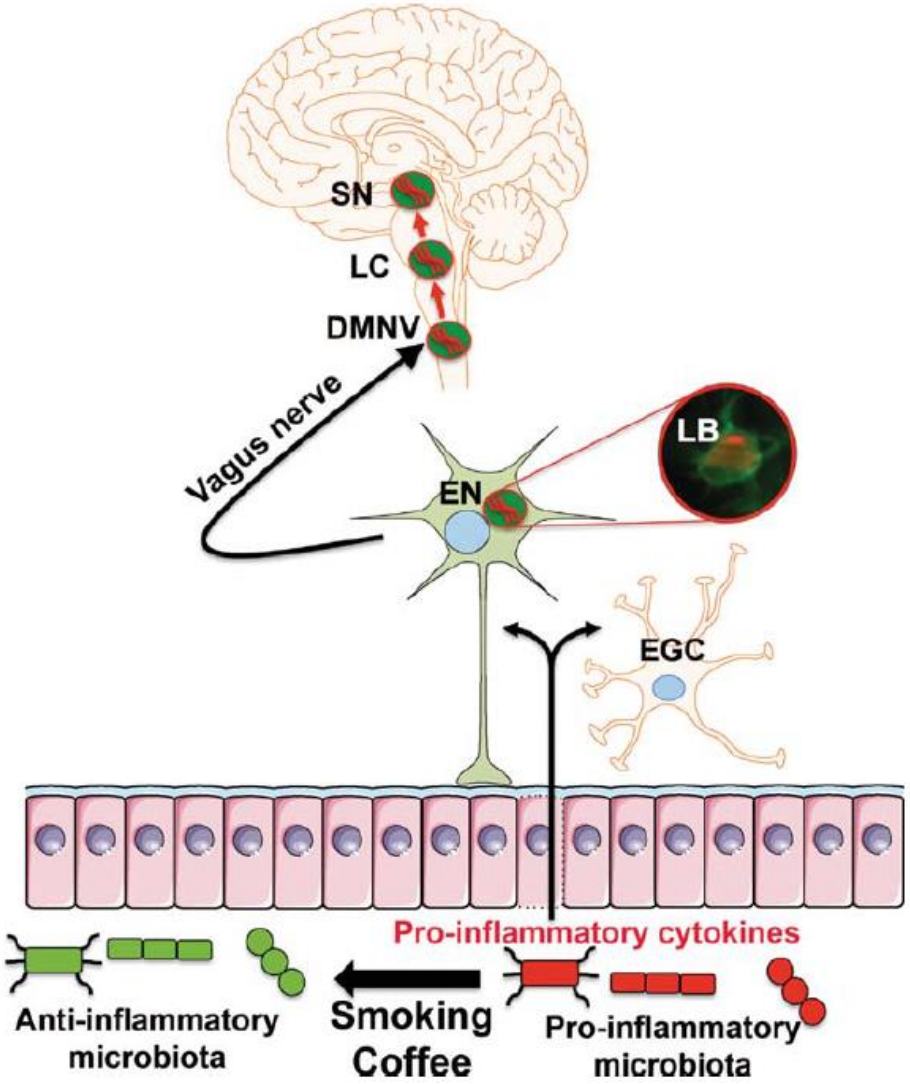
Adherence to Mediterranean diet increases Prevotella and SCFAs

- 153 vegan, vegetarian or omnivore Italians
- The majority of vegans and vegetarians and 30% of omnivores had high Mediterranean diet scores (vegetable-based)
- There were significant associations between consumption of vegetable-based diets and increased levels of fecal short-chain fatty acids, Prevotella and some fiber degrading firmicutes, despite overall diet type



Gut 2015 Sep 28. pii: gutjnl-2015-309957

The protective benefits of coffee and smoking may be mediated by microbes



Mov Dis 2014;29:976-9

Use of probiotics for the treatment of PD constipation

- 40 pts with PD + constipation
- 65 mL fermented milk drink containing 6.5 x 10^9 CFU of *Lactobacillus casei* Shirota daily x 5 weeks
- Probiotic group: Significant improvements in:
  - Stool consistency
  - Days per week patients felt bloated
  - Abdominal pain
  - Sensation of incomplete emptying (all P <0.01)

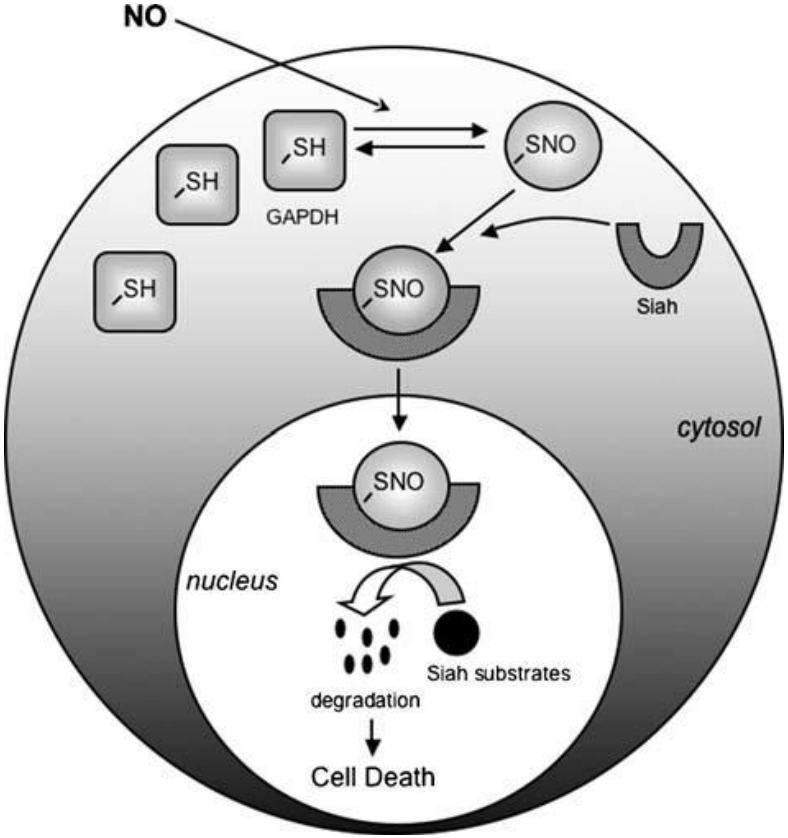
Minerva Gastroenterol Dietol 2011;57:117-21

Could plant phytonutrients be neuroprotective in PD?

Group	Sub-group	Individual compound or phytonutrient	Major food source
1. Flavonoids	1.1 Flavonols	Kaemferol Quercetin Myricetin	Apples, onions, tomatoes, lettuce, celery, tea, red wines
	1.2 Flavones	Apigenin Luteolin	
	1.3 Flavanols	(+)-Catechin (-)-Epicatechin (-)-Epigallocatechin (-)-Epicatechin gallate Proanthocyanidins	Tea
	1.4 Anthocyanidins	Pelargonidin Cyanidin Delphinidin Peonidin Petunidin Malvidin	Cherries, blueberries
	1.5 Flavanones	Hesperdin Neohesperidin Naringin	Citrus fruits
	1.6 Chalcones & dichalcones	Retrochalcone Isosalipurpuring Phloretin	
	1.7 Isoflavones	Genistein Daidzein Coumestrol	Pulses, eg, soy
2. Carotenoids	2.1 Provitamin A hydrocarbon carotenoids	β-carotene α-carotene	Red to orange pigmented fruits and vegetables,

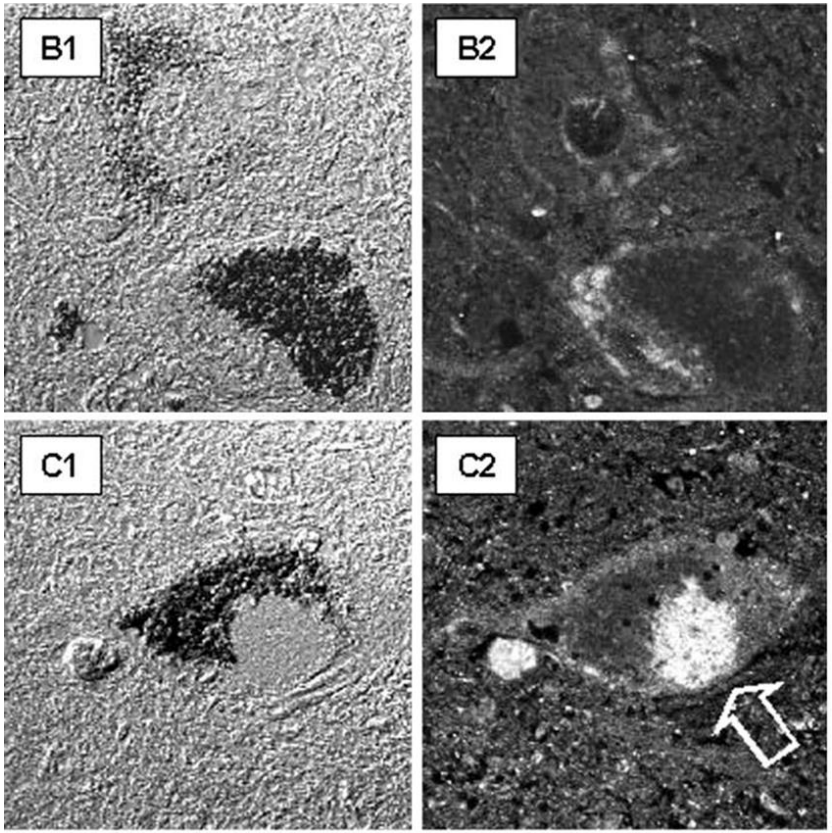
GAPDH may be important in PD neurodegeneration

Oxidative stress leads to translocation of GAPDH and programmed cell death



Cell Mol Neurobiol **26**, 525-536 (2006)

GAPDH accumulates in the nucleus in PD nigra

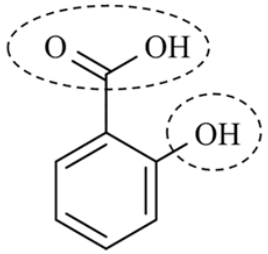


Experimental Neurology **166,** 29–43 (2000)

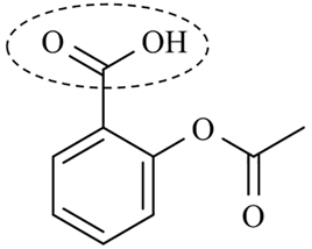
Salicylates may impede GAPDH mediated cell death

- Salicylic acid and its derivatives bind to GAPDH, prevent its translocation to the nucleus and prevent cell death
- Two classes of compounds from the Chinese medicinal herb Glycyrrhiza foetida (licorice), glycyrrhizin and the SA-derivatives amorfrutins, not only appear to bind GAPDH more tightly than SA, but also exhibit a greater ability to suppress translocation of GAPDH to the nucleus and cell death.

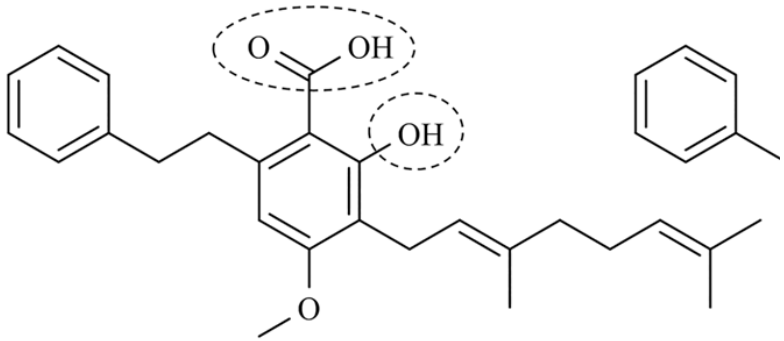
Salicylic acid (SA)



Acetyl SA (Aspirin)



Amorfrutin B1



PLoS ONE 10(11): e0143447 (2015)

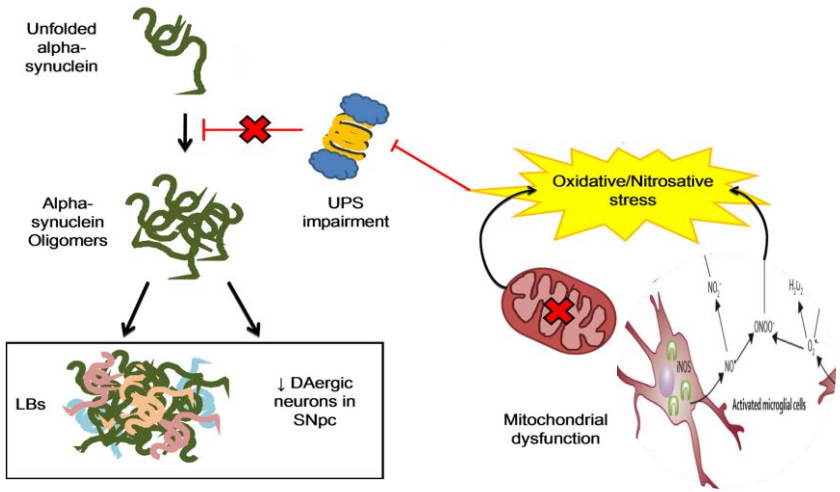
Some vegetarians have as much serum salicylate as those taking baby aspirin

Non-vegetarians	*Vegetarians*	*Patients taking low dose aspirin*
0.07 (0.02–0.20) n = 39	0.11* (0.04–2.47) n = 37	10.03 (0.23–25.40) n = 14

Values are median (range).
*Significantly greater than non-vegetarians, median of the difference 0.05 μmol/litre (95% confidence interval for difference, 0.03 to 0.08; p <0.0001).

J Clin Pathol 2001;54:553–5

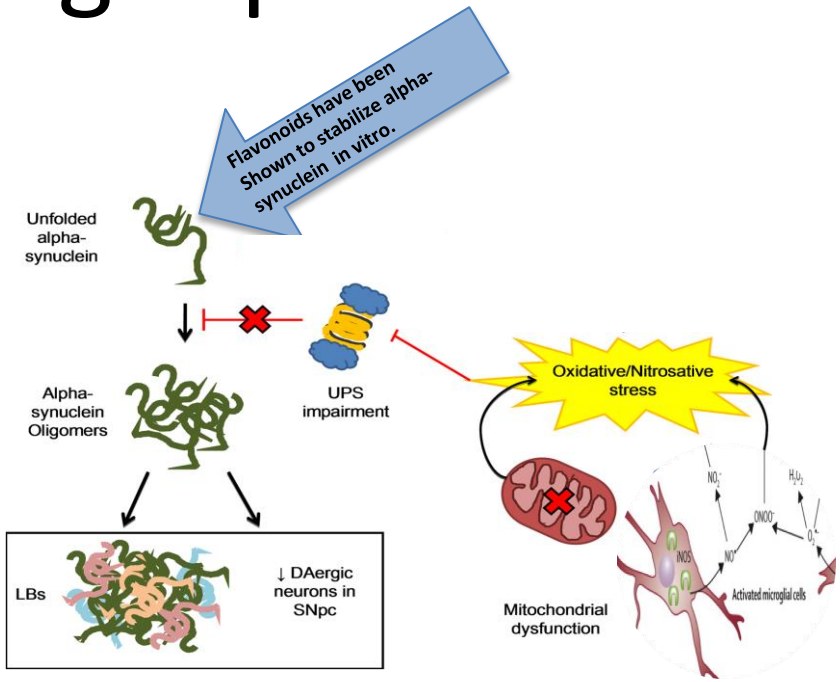
How might plants affect PD?



Images adapted from http://dx.doi.org/10.3389/fnagi.2010.00017 and http://dx.doi.org/10.1016/S1474-4422(09)70062-6

Some of the basic mechanisms thought to be involved in the pathophysiology of PD

How might plants affect PD?



Images adapted from http://dx.doi.org/10.3389/fnagi.2010.00017 and http://dx.doi.org/10.1016/S1474-4422(09)70062-6

Some flavonoids have been shown to stabilize alpha-synuclein in vitro. Biochemistry. 2009;48(34):8206-24.

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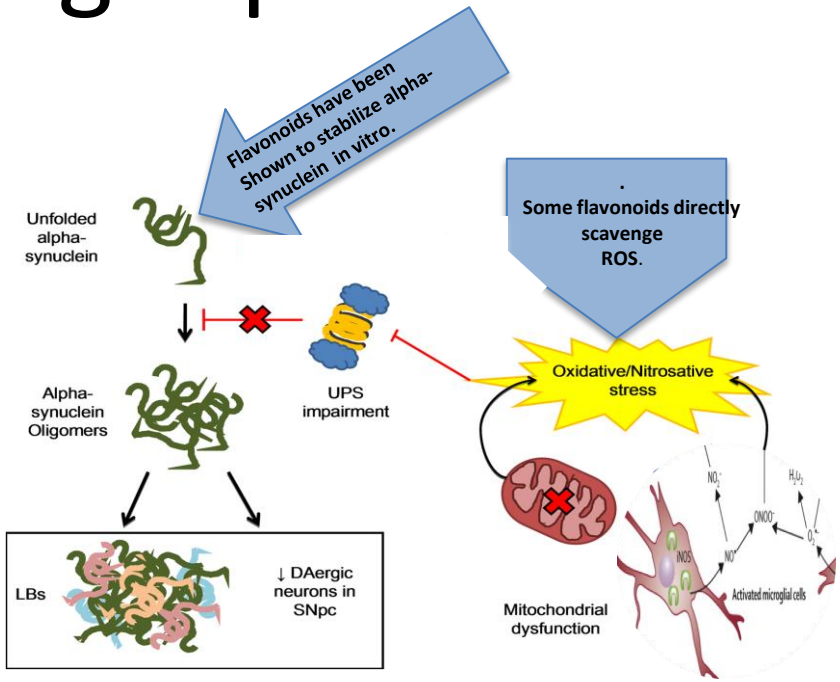

Images adapted from http://dx.doi.org/10.3389/fnagi.2010.00017 and http://dx.doi.org/10.1016/S1474-4422(09)70062-6

Many phytochemicals have antioxidant properties. Flavonoids, the largest group of phytochemicals, directly scavenge reactive oxygen species. Nutr Neurosci. 2012;15(1):1-9.

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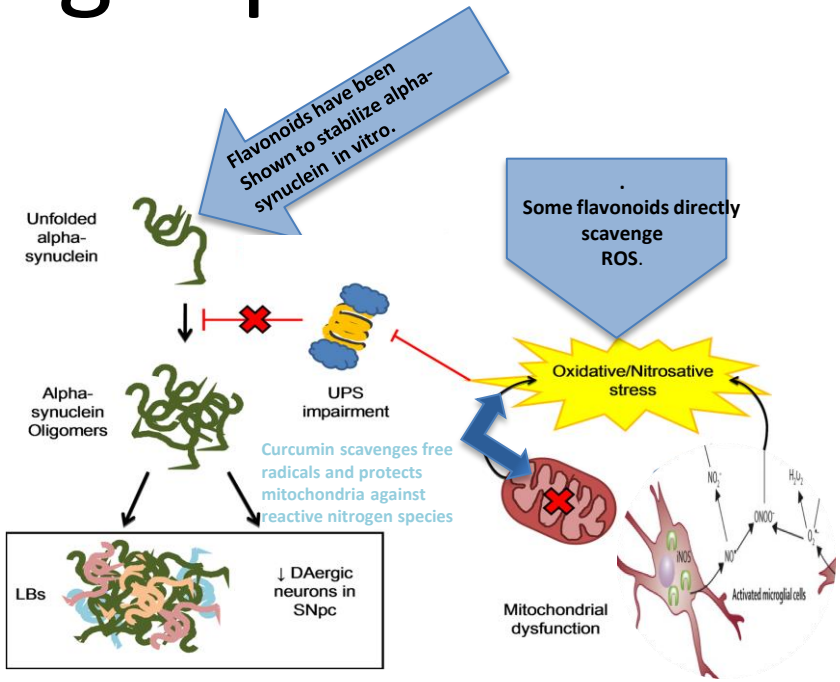
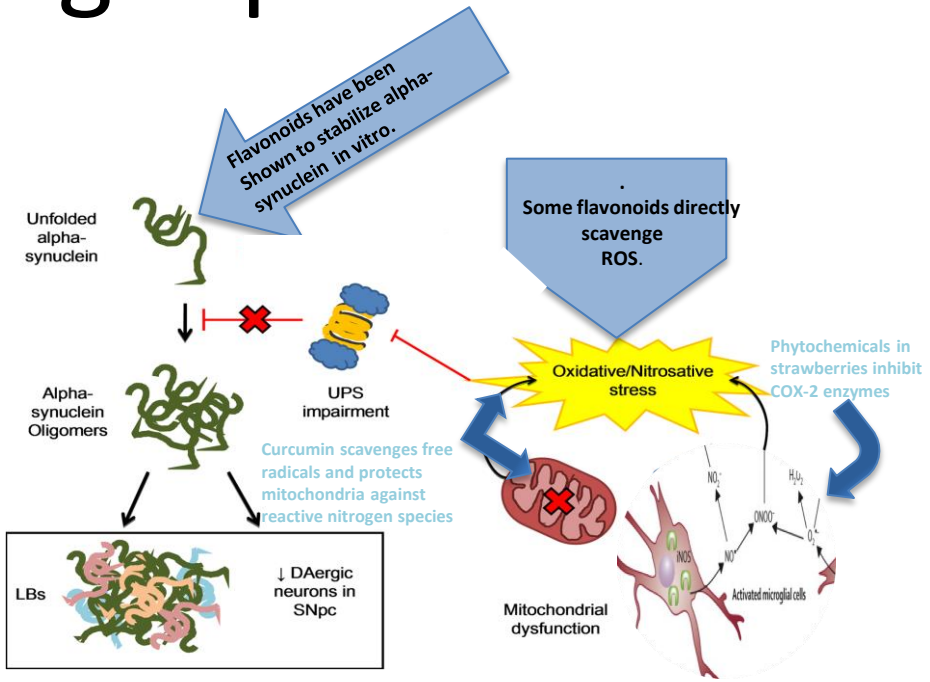


Images adapted from http://dx.doi.org/10.3389/fnagi.2010.00017 and http://dx.doi.org/10.1016/S1474-4422(09)70062-6

Curcumin, a polyphenol found in turmeric, scavenges free radicals and protects mitochondria against reactive nitrogen species. Curr Pharm Des. 2012;18(1):91-9.

How might plants affect PD?



Images adapted from http://dx.doi.org/10.3389/fnagi.2010.00017 and http://dx.doi.org/10.1016/S1474-4422(09)70062-6

Phytochemicals in strawberries inhibit cyclooxygenase (COX) which is a key enzyme that plays an important role in the conversion of arachidonic acid to various eicosanoids involved in inflammation. Neural Regen Res. 2014;9(16):1557-66

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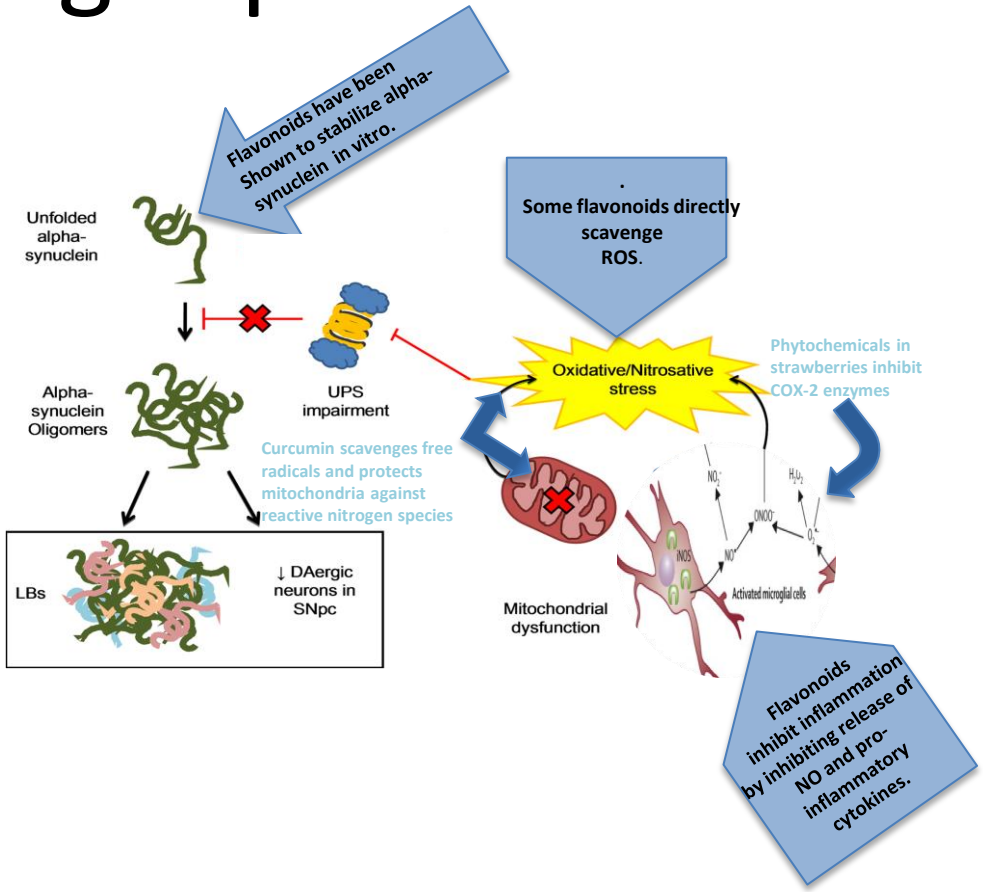

Images adapted from http://dx.doi.org/10.3389/fnagi.2010.00017 and http://dx.doi.org/10.1016/S1474-4422(09)70062-6

Flavonoids inhibit inflammation by inhibiting release of NO and pro-inflammatory cytokines. Br J Nutr. 2008;99 E Suppl 1:ES60-77.

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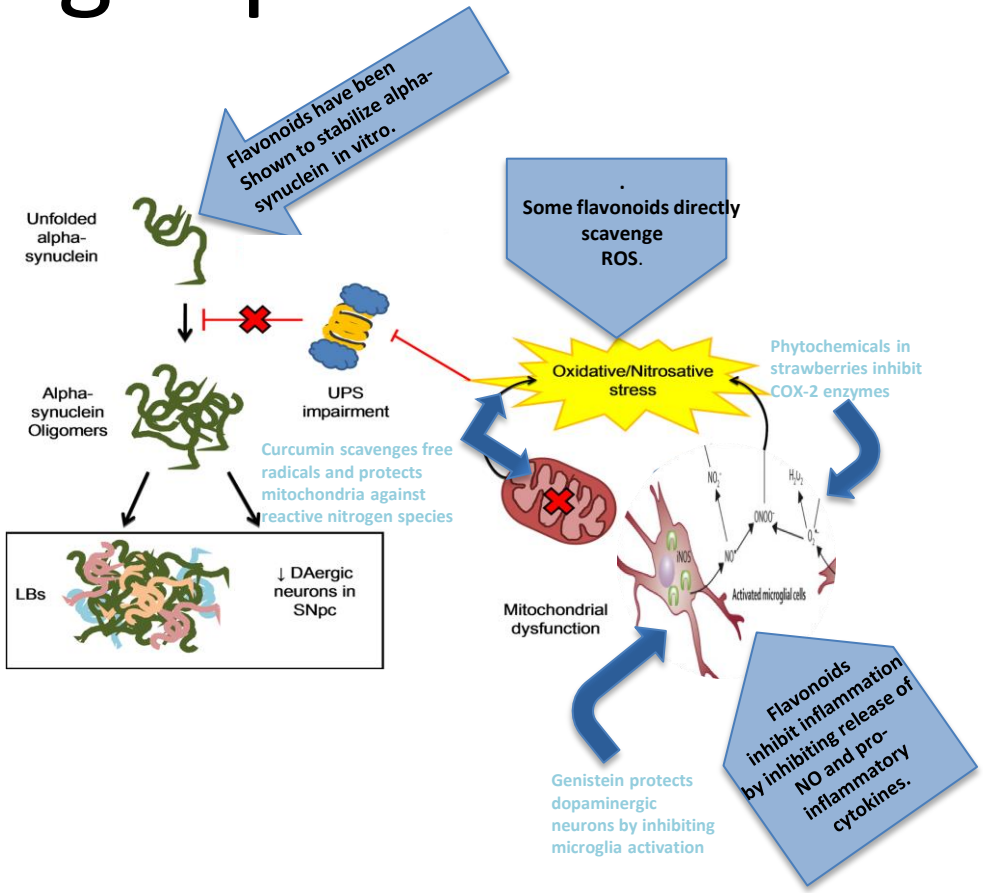

Images adapted from http://dx.doi.org/10.3389/fnagi.2010.00017 and http://dx.doi.org/10.1016/S1474-4422(09)70062-6

Genistein, an isoflavone found in soybeans, protects dopaminergic neurons by inhibiting microglia activation. Food Funct. 2010;1(1):15-31

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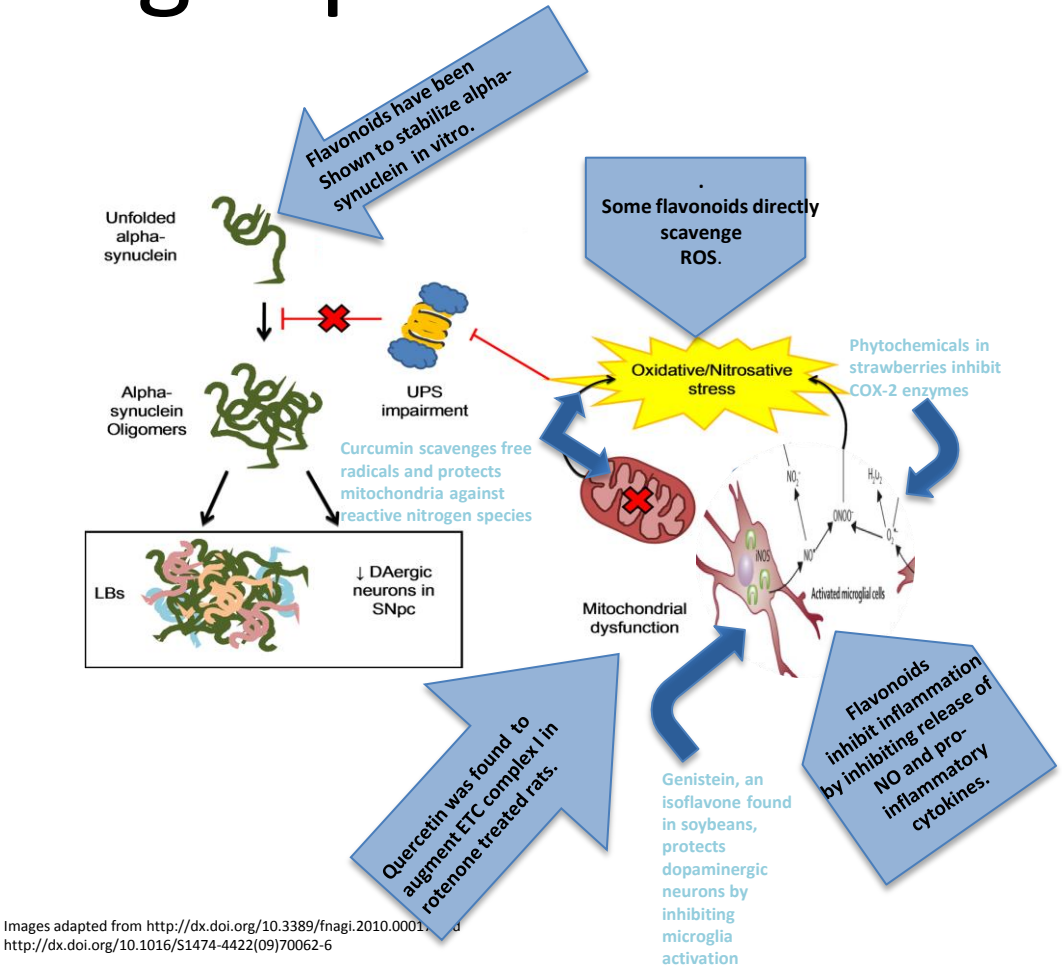

Images adapted from http://dx.doi.org/10.3389/fnagi.2010.0001[illegible]d
http://dx.doi.org/10.1016/S1474-4422(09)70062-6

Quercetin, a flavone found in teas, grapes, onions, apples, tomatoes, and berries was found to augment electron transport complex I in rotenone treated rats. Neuroscience. 2013;236:136-48.

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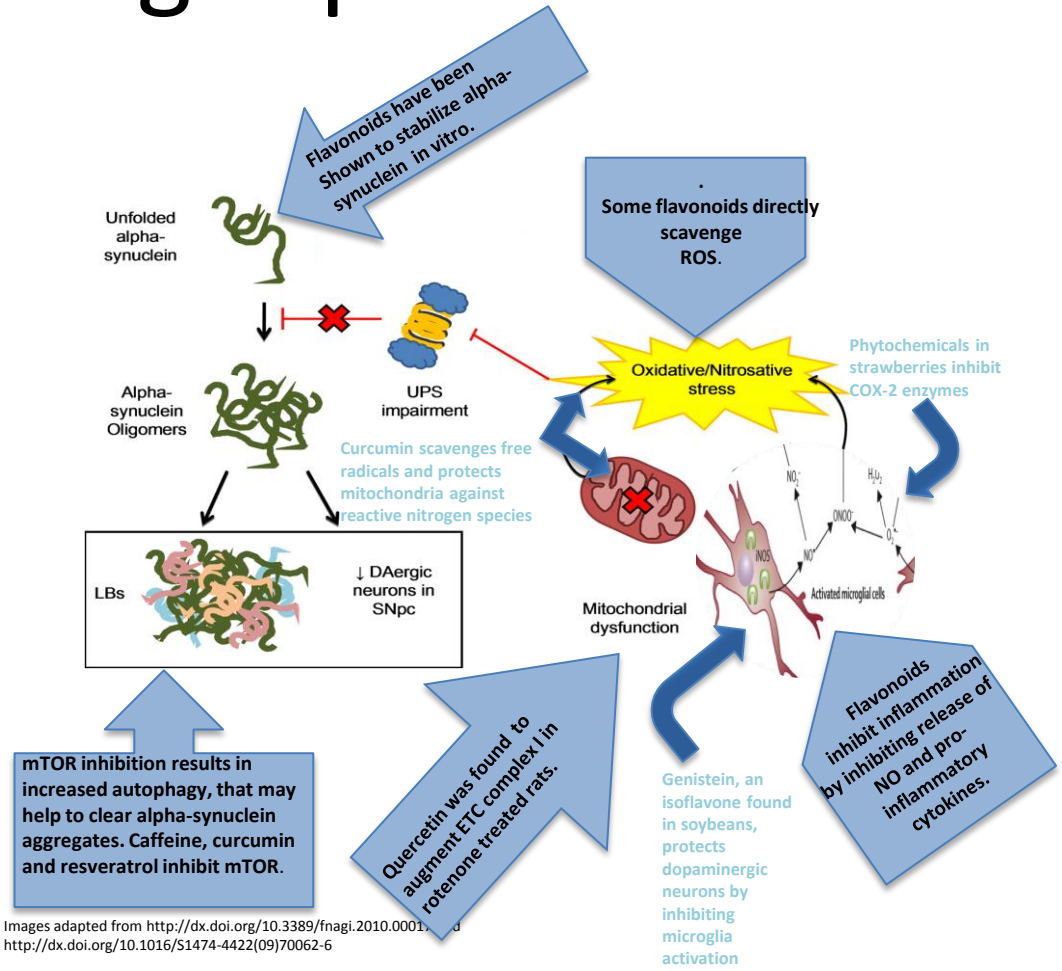

Images adapted from http://dx.doi.org/10.3389/fnagi.2010.0001[illegible]d
http://dx.doi.org/10.1016/S1474-4422(09)70062-6

Some phytochemicals inhibit mTOR and induce autophagy which may clear Lewy bodies. Anticancer Agents Med Chem. 2010;10(7):571-81

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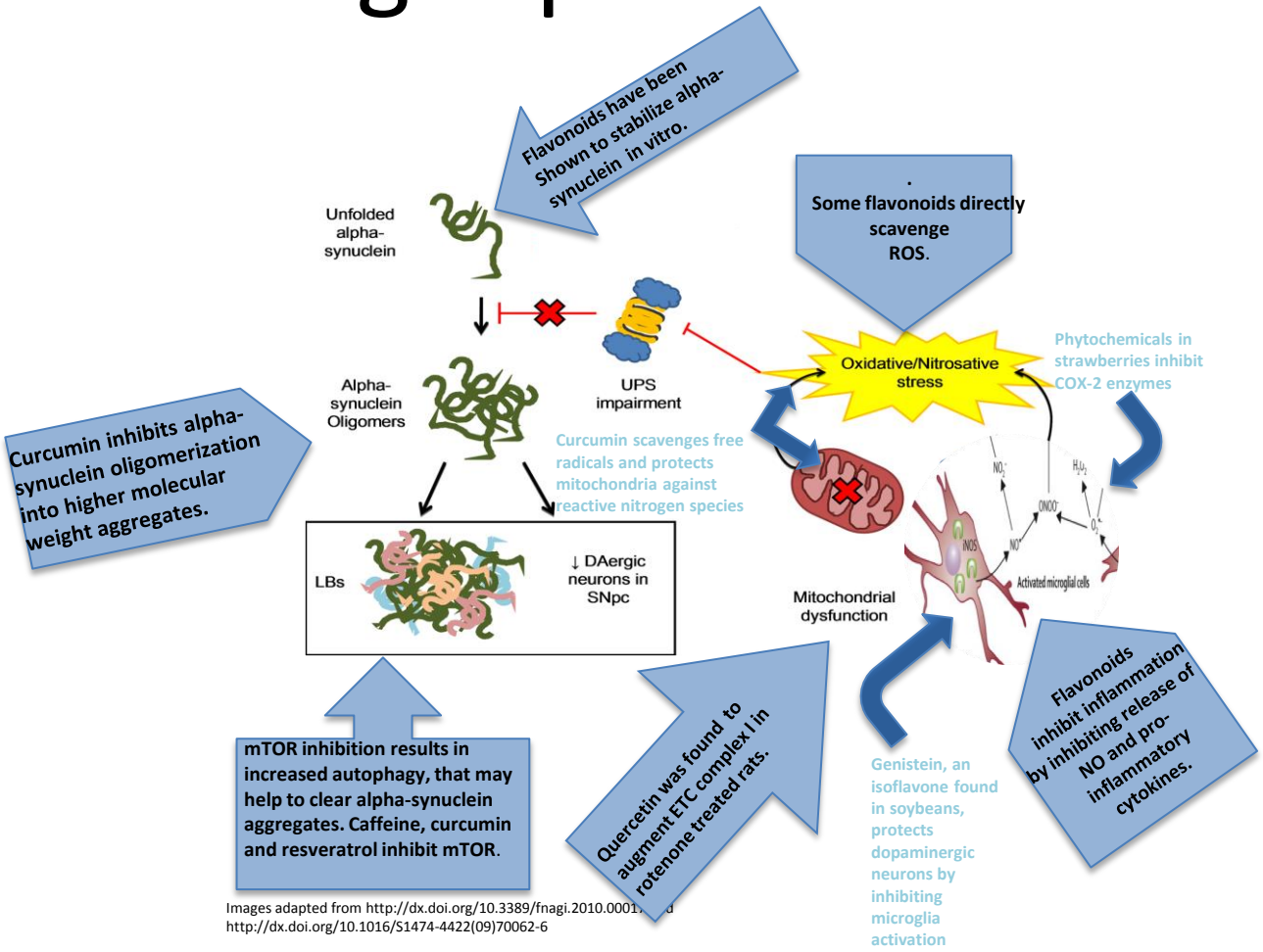

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http://dx.doi.org/10.1016/S1474-4422(09)70062-6

Curcumin has also been shown to inhibit alpha-synuclein oligomerization into higher molecular weight aggregates. Acta Neuropathol 2008;115:479–489

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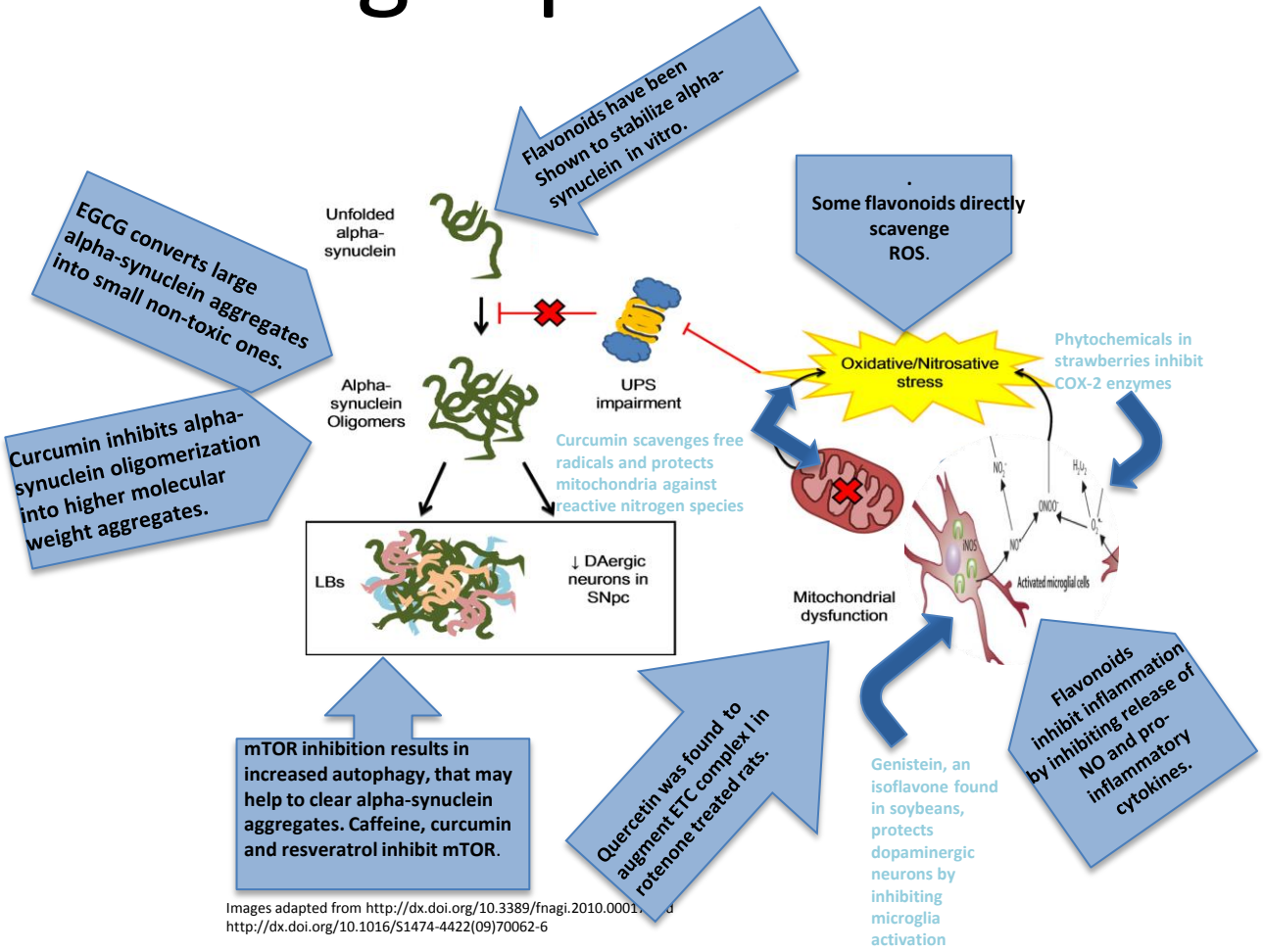

Images adapted from http://dx.doi.org/10.3389/fnagi.2010.0001[illegible]d
http://dx.doi.org/10.1016/S1474-4422(09)70062-6

Epigallocatechin gallate (EGCG), a member of a family of flavanols and most abundant in green tea, inhibits fibril formation of alpha-synuclein, by binding beta-sheet rich aggregates, transforming large alpha-synuclein fibrils into smaller, non-toxic, amorphous protein aggregates that are not toxic to cells. FEBS Lett. 2011, 585, 1113–1120.

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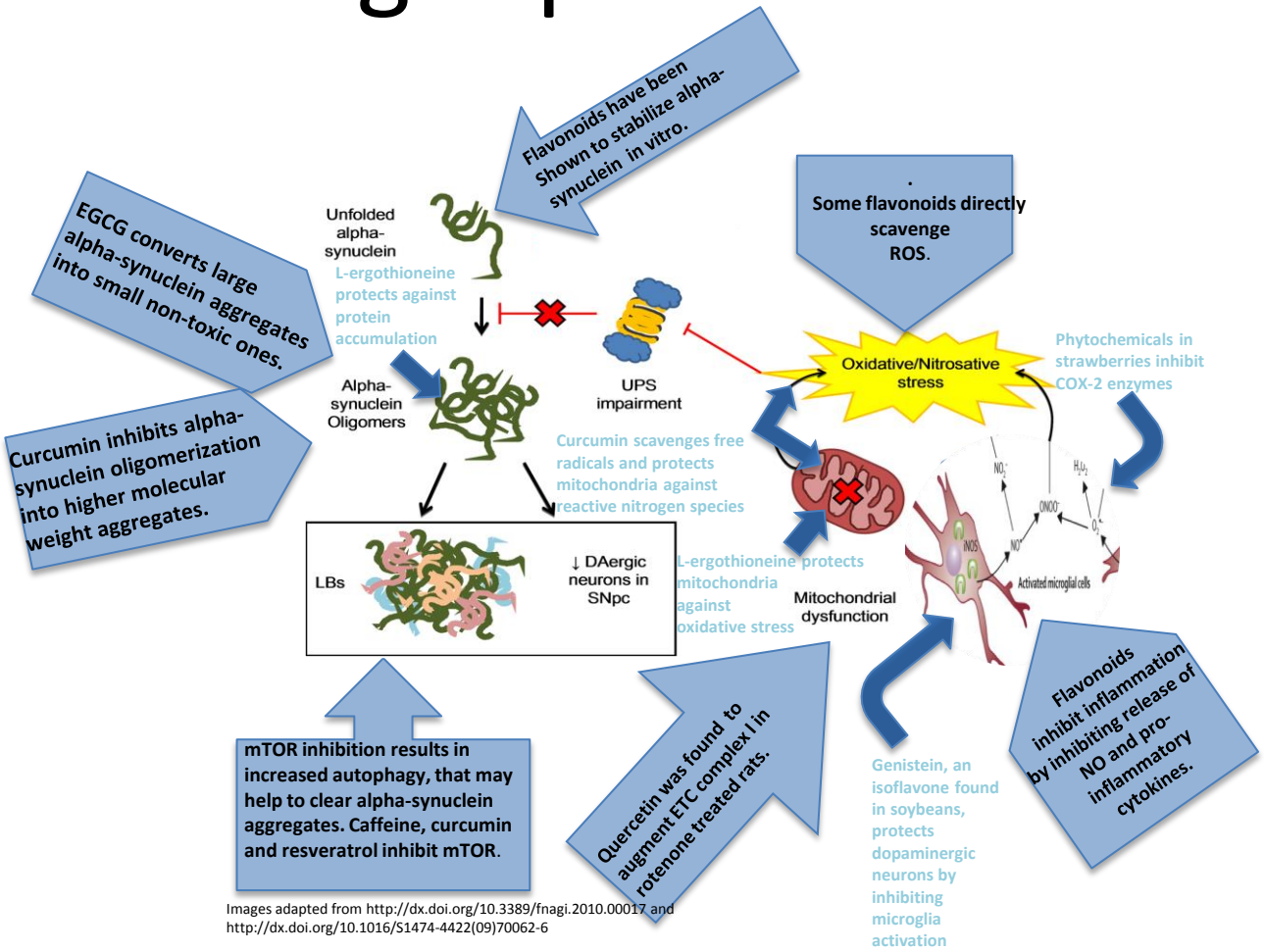

Images adapted from http://dx.doi.org/10.3389/fnagi.2010.00017 and http://dx.doi.org/10.1016/S1474-4422(09)70062-6

L-ergothioneine is an amino-acid, derived from histidine and found in mushrooms. It scavenges ROS, chelates metal cations, and protects against protein aggregation. Recently, it was shown that the metabolomics profiles of PD patients contained lower levels of ergothioneine. Cell Death Differ. 2010;17:1134

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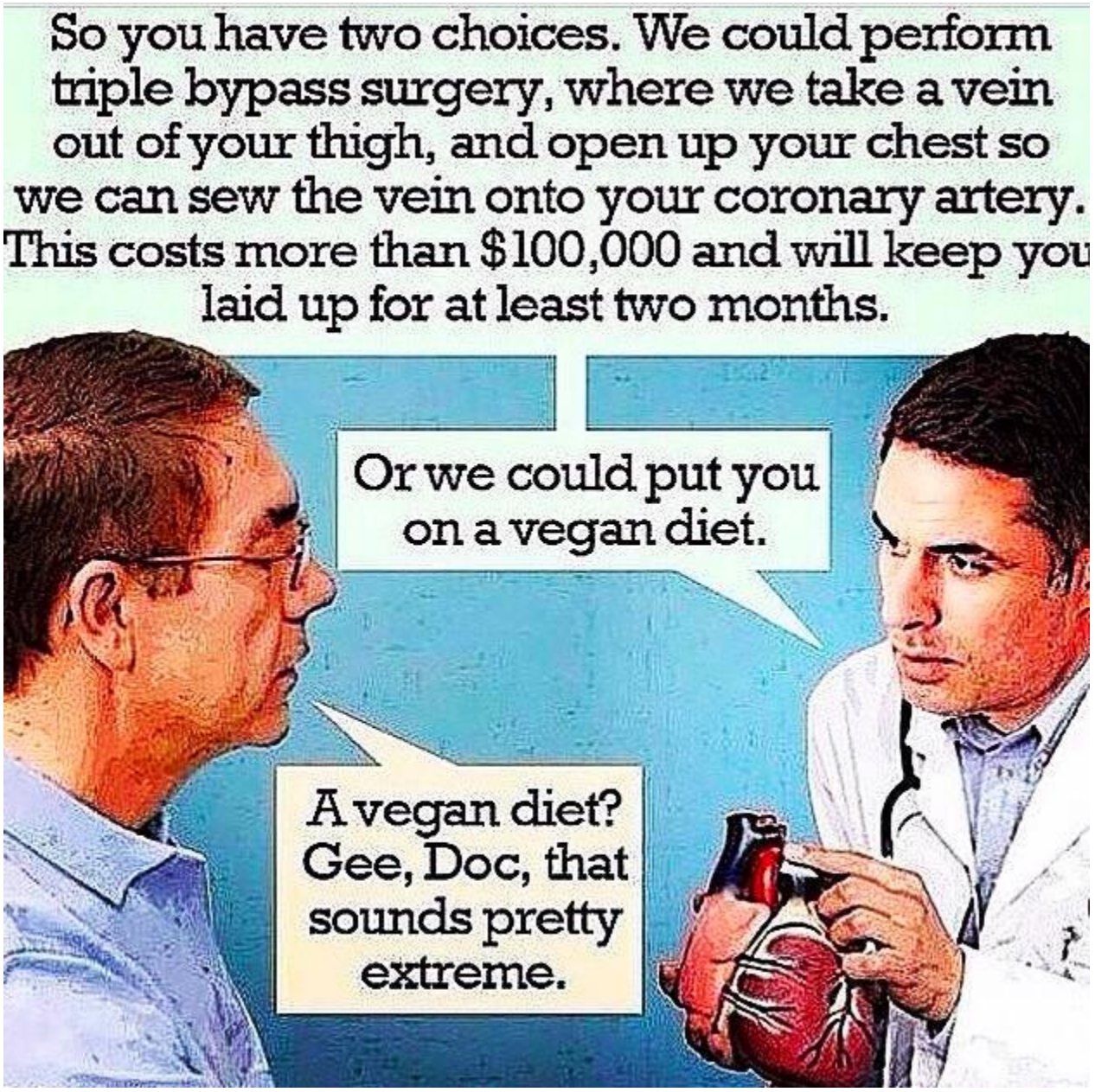
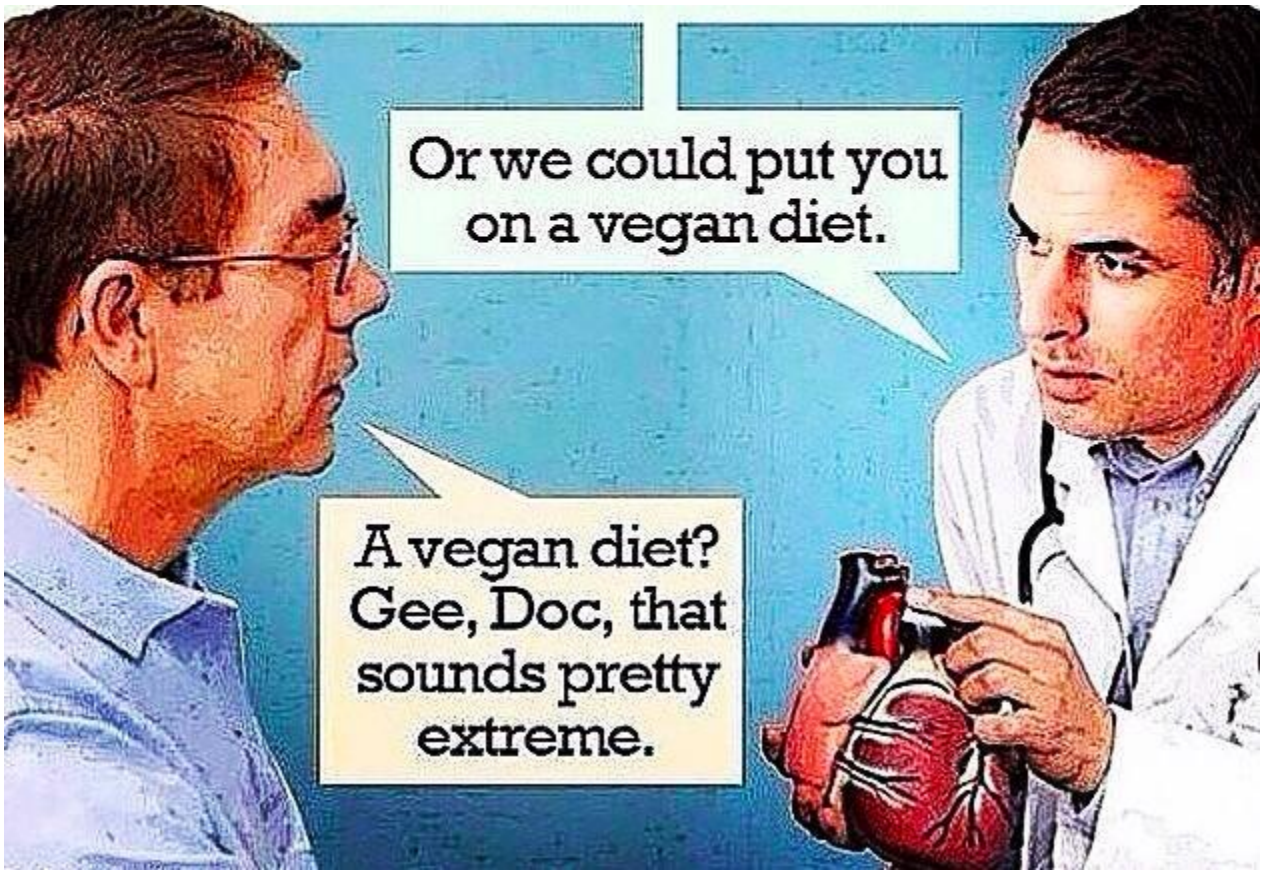
Dietary modifications in Parkinson's disease: A neuroprotective intervention?

Shital P. Shah [a,*], John E. Duda [a,b]


So you have two choices. We could perform triple bypass surgery, where we take a vein out of your thigh, and open up your chest so we can sew the vein onto your coronary artery. This costs more than $100,000 and will keep you laid up for at least two months.
Or we could put you on a vegan diet.
A vegan diet? Gee, Doc, that sounds pretty extreme.

So, you have several choices; we could give you a bunch of medications that could give you lightheadedness, nausea, sleepiness and a propensity to gamble your life savings away; we could surgically implant pacemakers into your brain; we could put a tube into your stomach connected to a pump that you have to refill every day,



Before and after giving up dairy!

Where to go for more info

www.nutritionfacts.org

www.pcrm.org

www.ohsheglows.com

www.forksoverknives.com