Neurogenesis:
Nerve Growth or Regeneration with Herbs and Food Plants

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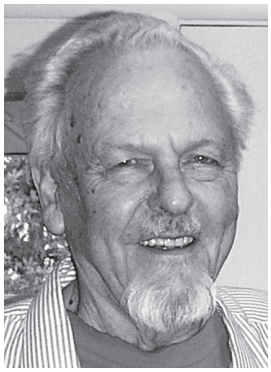
Thanks to Kevin Spelman, PhD, and Alan Tillotson, PhD, for constructive criticisms and suggestions.



In his distinguished career, *James Duke* served the US Department of Agriculture for over 30 years. Before retiring, he developed his ethnobotanical and phytochemical database online at www.ars-grin.gov/duke. It is one of the most frequently consulted areas of the USDA website. Duke grows hundreds of plants on his six-acre Green Farmacy Garden with his wife, Peggy. Since retiring from the USDA, Dr. Duke has served for five years as Senior Science Advisor to Nature's Herbs and with allherb.com. Since 2001, he has been a distinguished herbal lecturer at Tai Sophia Healing Institute (now Maryland University of Integrative Health). He has written over 30 books on medicinal plants.

My reliable *Dorland's Illustrated Medical Dictionary* (25th edition, 1974) defines "neurogenic" first as "forming nervous tissue, or stimulating nervous energy"; but I define it as "stimulating nerve growth or regeneration." Dorland's didn't define the word "neuritogenic" back in 1974, but I define it as "stimulating growth or regeneration of small nerves called axons or neurites." Doctors have prescribed or suggested many medicines and modalities for progressive neuropathy (in Dorland's defined as a "disturbance of the nerves"). In the 83 year-old me, it's catastrophic, causing tingling feet and creaking knees. In other words, I have arthritic and wobbly knees that creak as I climb the stairs. Below the knee, my legs are numb and tingly.

Your reductionistic ranter, senile senior Jim Duke, suffers serious neuropathy, possibly caused by one or more of the following: most likely spinal stenosis and spondylosis; cryptic Lyme disease for nearly a decade; possibly pesticides (many of my USDA colleagues seem to have suffered pesticide poisonings, but not many of them worked with Agent Orange as did I); alcohol (my liver tests have never fingered my generous consumption of alcohol); or diabetes (my tests have never indicated diabetes).

I seek a "food farmacy" approach that might reduce neuropathic suffering, but it may be more expansive than reductive. I base it on some challenging assumptions:

1. All food plants contain thousands of different biologically active phytochemicals familiar to our genes from when our ancestors first ingested plants containing such phytochemicals possibly millions of years ago.

2. When chemically out of balance (diseased), our bodies try to achieve health by getting in balance homeostatically, mostly sequestering needed (phyto)chemicals and voiding unneeded or contraindicated (phyto)chemicals. It is my questionable assumption, after compiling data for 30 years, that probably all edible plants contain both some neurogenic and antineurogenic phytochemicals. Ingesting plants that contain greater quantities of needed chemicals can help bring the body back to health.

3. My public domain USDA database already has identified many of the chemicals in many food plants that might help preserve, protect, or even generate new nerves or neurites. Queried intelligently, the database can identify the most promising food "farmaceuticals" to help the body heal itself. And that is why, in this rant, I list some of the phytochemicals and herbs that offer hope for neuropaths who are too old to go the surgical route (like me). If I do an equally intense review of antineuritogenic

and antineurogenic phytochemicals, we can better identify edible food farmacy "prescriptions" for various neuropathies and related diseases. Some studies refer to the herb itself or the extracts of the herb; in my opinion, better studies refer to both.

Most of the PubMed research on this topic is done on tissue culture (PC12D cells), cultures derived from animal cells, most often rats, and some tissue cultures called astrocytes or stellar cells. In these cultures, nerve growth factor (NGF) increases the proportions of nerve cells called neurites (hence "neuritogenic" or "generating nerves") and increases the length of the nerves. The Japanese studied *Verbena littoralis* (Paraguayan beach verbena), and their extracts barely changed the neurites in the absence of NGF at rather high dosages. But in the presence of very low levels of NGF (2 nanograms per milliliter), the regrowth of nerves was much more dramatic (Li, Matsunaga et al 1999; Li, Ishibashi et al 2003). The human immune system, like acupuncture and meditation, can generate NGF which makes the neuritogenic phytochemicals more active. Thus there is an apparent synergy between our NGF and neuritogenic foods, supplements or phytochemicals.

Cannabis sativa plant. Image by Petr Brož (CC-BY-SA 3.0). Source: http://commons.wikimedia.org/wiki/File:Cannabis_sativa_plant_(4).JPG

Neurogenic Spices

Some spices contain neurogenic compounds: angelica, anise, applemint, basil, bay, caraway, cayenne, celery, citrus, clary sage, clove, coriander, fenugreek, ginger, horseradish, lavender, marjoram, orange peel, onion, oregano, parsley, pennyroyal, rosemary, sage, spearmint, summer savory, tarragon, thyme, turmeric, and wasabi. It is easy to say that these spices contain neurogenic compounds, but I am trying to figure those which have more neurogenic than antineurogenic phytochemicals. Big Pharma is not going to do that; clinical herbalists can.

Cannabis sativa (Marijuana)

We have plenty of marijuana, mostly illegal, but soon to be legally grown, in the nation's capital. There will be political roadblocks to using this medicinal plant; "grass" ain't GRAS (generally regarded as safe by the FDA). We dare not plant it in our Green Farmacy Garden, even though it is very promising in neuropathy. I suspect it is still illegal in Maryland, but in my woodland rambles near the Middle Patuxent River just north of my garden, I have stumbled on three small clandestine plots. Larger plots are often booby-trapped, making wandering through the woods dangerous. Some chronic users anecdotally claim it can expand the mind. German scientists advise that long-time *Cannabis* use may increase innate NGF. On the downside, it may increase risk of schizophrenia (Jockers-Scherübl 2003).

There are hundreds of PubMed citations on cannabinoids and multiple sclerosis (MS), a demyelinating disease of the central nervous system (CNS). Current pharmaceutical treatments are sometimes ineffective and may have noteworthy side effects. Hence, some MS patients may resort to *Cannabis*, anecdotally believed to help some symptoms like bladder dysfunction, pain, spasticity, and tremors. Animal research shows cannabinoids to be

helpful with spasticity and tremor. Phase III clinical trials may rationalize cannabinoids for MS (Croxton & Miller 2004).

Cannabidiol (CBD) is currently used for MS spasticity and pain. (Karmaus, Wagner et al 2012). A 1:1 mix of delta-9-tetrahydrocannabinol plus cannabidiol, oromucosally introduced, has been approved in some countries, reducing traditional psychotropic *Cannabis* actions. No tolerance, abuse or addictive issues were found (Oreja-Guevara 2012). Germany approved a *Cannabis* extract in 2011 to treat refractory spasticity in MS, but it is often used off-label for anorexia, nausea, and neuropathic pain (Grotenhermen & Müller-Vahl 2012).

The endogenous cannabinoids, anandamide and 2-arachidonoyl glycerol, interact with the G-protein coupled cannabinoid (CB) receptors CB(1) and CB(2). The CB system is emerging as a key regulator of neuronal cell fate, conferring neuroprotection. Many poor neurological conditions are associated with excitotoxicity, oxidative stress, and neuroinflammation. Some CB molecules inhibit these events and slow or stop the neurodegeneration. Such may offer hope in Alzheimer's disease, MS, and cerebral ischemia (Gowren, Noonan et al 2011).

Various Familiar and Obscure Herbs

A Finnish study showed that two of 10 policemen who volunteered to be sprayed with crowd-control pepper spray (*Capsicum* or its capsaicins) had increased levels of NGF in their tears (Vesaluoma et al 2000). In 1999 the Japanese added several neuritogenic species: the well known *Equisetum giganteum* (horsetail), *Panax ginseng* (ginseng), and *Ruta gravolens* (rue), and the obscure *Gymmopteris rufa*, *Picrorhiza scrophulariiflora*, *Imperata cylindrica*, and *Gochnatia polymorpha*. *Picrorhiza* induced the longest neurites, but horsetail was best at neurogenesis though the neurites were short (Li, Matsunaga et al 1999). In 2003, Japanese scientists studying the *kampo* medicine *Ninjin-yoei-to* found that it increased NGF secretion in cultured astrocytes. The compound contained several species including roots of *Polygala tenuifolia* and *Panax ginseng* extracts. Onjisaponins A, B, E, F and G, major saponins in *Polygala*, strongly increased NGF level, much more than the *ginsenosides* Rb1 and Rg1 (Yabe et al 2003). Another study found that Asian goldthread (*Coptis*) extracts neuritogenically enhanced the activities of NGF in tissue culture. Weaker activity was demonstrated by berberine and even less by coptisine and palmatine, alkaloids present in goldthread, but also in American barberries, goldenseal, goldthread and yellowroots (Shigeta et al 2002). Syracuse scientists studying the important hepatoprotective *Silybum marianum* (milk thistle) extract found it also to be neuritogenic and NGF-genic (Kittur 2002).

Neurogenic: stimulating nerve growth or regeneration

Neuritogenic: stimulating growth or regeneration of small nerves called axons or neurites

Legumes

Wake Forest scientists found that estradiol was nearly twice as active as soy phytoestrogens at stimulating NGF (Pan, Anthony et al 1999). Notice that the authors specify *soy* phytoestrogens, most of whose phytoestrogens are shared by many other edible legumes much more pleasing to my occidental palate. (I suspect that most soy-sponsored phytoestrogen studies will have "soy" specified in their title, even though genistein is genistein is genistein.) A Japanese study concluded that "genistein enhanced the NGF-induced neurite outgrowth" in PC12 tissue culture cells (Nakajima, Niisato et al 2011). A 2011 Italian study found that soy genistein injected in the paws of diabetic rats relieved painful peripheral neuropathy, and restored NGF in diabetic sciatic nerves (Valsecchi et al 2011). Another study showed that daidzein and genistein found in most edible legumes (but in this case *Pueraria thomsonii*, kudzu) exhibited cytoprotective activity that might even help in Parkinson's disease (Lin et al 2010). As early as 1993, University of North Carolina researchers suggested that not only genistein but other inhibitors of protein tyrosine kinases increased the length of neurites in the presence of NGF (Miller, Lee et al 1993).

Neuritogenic Aphrodisia?

A California study showed that icariin from *Epimedium spp*. (horny goat weed) was both erectogenic and neuritogenic, at least in rats (Schindel et al 2010). Hmm, maybe a little *Ginkgo biloba* added to the horny goat weed might be worth trying for erecto- and neuro-genesis, as ginkgo extracts also may promote peripheral nerve regeneration (Lin, Wang et al 2008). The Amazonian aphrodisiac *Ptychopetalum olacoides* (muira puama) also possesses some neuritogenic phytochemicals (Tang et al 2008). Finally, some ginsenosides from *Panax spp*. seem to be both neuritogenic and aphrodisiac (Rudakewich & Benishin 2001; Ma, Li et al 2010).

Melatonin-Containing Food Plants

N-acetylserotonin, a natural chemical intermediate in the synthesis of melatonin, is a potent neurogenic (Tosini, Ye et al 2012). The following food plants are reported to contain more than 100 picograms melatonin per gram: oats (1,796), corn (1,366), rice (1,006), radish (657), angelica (623), ginger (584) tomato (506), banana (466), chrysanthemum (417), barley (378), mustard greens (112), and cabbage (107). These all contain melatonin and I assume that all melatonin-containing plants might also contain the precursor N-acetylserotonin. Melatonin injection has been shown to increase NGF content (Pongsa-Asawapaiboon et al 1998). A very recent Turkish study with spinally damaged rats showed that melatonin restored NGF levels to normal after the spinal damage (Ersahin et al 2012). My spine, on the other hand, has been slowly damaged over decades of abuse such as sitting too long at the computer, gardening, and even jogging up into my 60s. Can melatonin help me at age 83?

Mushrooms

Several mushrooms exhibit neurogenic activities. *Pleurotus giganteus* (oyster mushroom) "contains bioactive compounds that mimic NGF and are responsible for neurite stimulation" (Phan, Wong et al 2012). My friend Dr. Kevin Spelman, RH (AHG), notes that "CD56 (NCAM) is upregulated by an aqueous extract of *Ganoderma lucidum* (reishi), and is implicated as having a role in several neuronal activities including cell–cell adhesion, neurite outgrowth, synaptic plasticity, and learning and memory" (personal communication on March 2, 2013; Spelman et al 2011).

Worms

I've eaten many wild critters, but I do not remember eating the traditional medicinal *di long* (earthworm) with potential for neural regeneration in China (Chang et al 2011). *Di long* is part of the Traditional Chinese Medicine (TCM) materia medica and has been long used in China to promote nerve function. The extract seems to enhance sciatic nerve regeneration and function recovery following injury, suggesting the clinical potential of *Lumbricus* extract on the treatment of peripheral nerve injury in humans (Wei, Yin et al 2009). TCM specialist Thomas Garran tells me that there are four species listed: *Pheretina aspergillum*, *P. vulgaris*, *P. guillelmi*, and *P. pectinifera*. It is used in decoction at 5-10 g dosages or as a pill or powder at 1-2 g dosages. It is also applied externally. Studies show it is used also for a variety of inflammatory conditions from asthma to herpes zoster to urinary tract infections (personal communication, Mar. 2, 2013). Several abstracts concern silkworm corpses which contain phospholipids and aromatic amines that stimulate production of NGF (Kwon et al 2003). I do not think I will ingest them either.

Antineuritogenic Compounds

Fond of a nightly wine at happy hour, I was disappointed to be reminded that alcohol can cause or aggravate alcoholic neuropathy (which has not yet been my diagnosis). In one study, alcohol decreased NGF (Gottesfeld, Simpson et al 1996). Some neuritogenic compounds occur in plants whose extracts prove to be antineurogenic. Extracts of *Geranium thunbergii*, *Humulus lupulus*, *Rosmarinus officinalis* and *Salvia officinalis* inhibited NGF-induced neuritic outgrowth in tissue culture (Takano, Inokuchi et al 2011). They might be avoided, but note that at least two compounds in rosemary, carnosic acid and rosmarinic acid, are neurotrophic. Excitotoxins and glutamates are also antineuritogenic. An

Table 1: Some Neurogenic Phytochemicals and Their Sources

Phytochemical	Plant Source	PubMed ID
ASIATIC-ACID: Neurogenic	16105244	gotu kola
ASTRAGALOSIDE-IV: Neurogenic	19409437	astragalus
ASTRAGALOSIDES: NGF-Activator	19409437	astragalus
BAICALEIN: Neuritogenic	19327378	Baikal skullcap
BAICALEIN: Neuroprotective	19327378	Baikal skullcap
BERBERINE: Neuritogenic, NGF-Genic	12506995	goldthread, goldenseal, barberry, amur cork tree, prickly poppy
BISDEMETHOXYCURCUMIN: Neuritogenic	22145830	turmeric
BETA-BOSWELLIC-ACID: Neuritogenic	20217445	*Boswellia serrata*
CARNOSOL: NGF-Genic	14600414	rosemary, sage
COPTISINE: Neuritogenic, NGF-Genic	12506995	bloodroot, California poppy, celandine, fumitory, goldthread, great scarlet poppy, opium poppy, plume poppy, prickly poppy
CURCUMIN: Neurogenic	16646663; 17617388; 18299980; 18362141; 19882093; 22145830	turmeric
DOPAMINE: Neurogenic	15128392; 16246330	banana peel, avocado, cacao
ELEUTHEROSIDE-B: Neuritogenic	18612196	eleuthero
ELEUTHEROSIDE-E: Neuritogenic	18612196	eleuthero
ESTRADIOL: NGF-Genic	10352122	pomegranate
(+)-EUDESMIN: Neuritigenic, NGF-Genic	17225460	magnolia
beta-EUDESMOL: Neurogenic	12023507	ginger, celery seed, hops, walnut, angelica, watermint
FALCARINONE: Neuritogenic	16219303	celery, caraway, dang gui, ivy, notoginseng, parsley
FERULIC-ACID: Neuritogenic	21809545	asafetida, chia, pineapple, apple, peanut, lemon, tarragon, grapefruit, wheat, potato, garlic, corn, cabbage etc.
GARCINIA-XANTHONE-E: NGF-genic	14600386	garcinia
GARCINOL: `Neurogenic	21214247	garcinia
GENTISIDE-A: Neuritogeni	20189814	some gentian
GENTISIDE-B: Neuritogeni	20189814	some gentian
GENTISIDES C-K, esp. GENTISIDE C: Neuritogenic	20813533	some gentian
GINKGOLIDE: possibly NGF-Genic	16716609	ginkgo
5-HYDROXY-3,6,7,8,3′,4′-HEXAMETHOXYFLAVONE: Neuritogenic	22140566	citrus, esp. orange peel
ISORHAMNETIN: Neurogenic	22761636	tarragon, dill, ginkgo, grapefruit, yarrow
NEOVIBSANIN-A: Neuritogenic	20233658	*Viburnum*
NEOVIBSANIN-B: Neuritogenic	20233658	*Viburnum*
NEOVIBSANIN-L: Neuritogenic	20233658	*Viburnum*
(8Z)-NEOVIBSANIN-M (4) Neuritogenic	20233658	*Viburnum*
OLEANOLIC-ACID: Neuritogenic	12762811, 15235225	clove, thyme, sage, lavender, marjoram, basil, summer savory
PARTHENOLIDE: Neurogenic	19900365	feverfew, tansy
PEONY-GLYCOSIDES: NGF-Genic	20176057	peony
PROTOCATECHUIC-ACID: `Neurogenic	21946114	onion, coriander, oregano, wheat
QUERCETIN: NGF-Genic	19370542	ubiquitous
ROSMARINIC-ACID: Neurotrophic	20633629	heal-all, oregano, marjoram, spearmint, rosemary, bugle, clary sage, applemint, european pennyroyal
SCHISANDRIN: Neurogenic	21302324; 18547723	schisandra
SCOPARONE: Neuritogenic	218547723	tarragon
SOMINONE: Neurogenic	16553605; 19594760	ashwagandha
WITHANOLIDE-A: Neurogenic	15711595; 18670181	ashwagandha
WITHANOSIDE-IV: Neurogenic	16553605; 19594760	ashwagandha
WITHANOSIDE-VI: Neurogenic	18670181	ashwagandha
WOGONIN: Neuritogenic	20888794	Baical skullcap

Argentinian study suggests that aggregated HDL (high density lipoproteins), like fibrillar beta-amyloid peptides, can be neurodegenerative, if associated with oxidative stress in the central nervous system (Kivatinitz, Grabois et al 1995; Kivatinitz, Pelsman et al 1997).

True to the reductionist title of my column, see Table 1 for a few phytochemicals reported to be neuritogenic, neurogenic or neuroprotective, and some of their better known sources. When I list several herb sources unalphabetically after a particular phytochemical, these are arranged from the richest to the lowest in my evibase. ■

(Dr. Duke provided JAHG with a very extensive list of phytochemicals. We've trimmed it to fit the most common plants as well as ones discussed in other articles of this Lyme disease special issue. For the full list please point your browser to: http://www.americanherbalistsguild.com/journal_samples.)

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