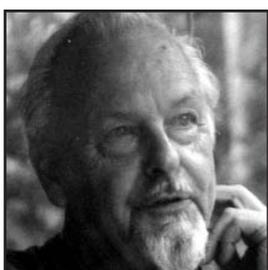


# Reductionist's Rhetoric

## An Inflammatory Investigation of Antiinflammatory Activities

by Jim Duke, PhD



James Duke received his PhD in Botany from the University of North Carolina, moving on to postdoctoral studies at Washington University and the Missouri Botanical Garden where he assumed professor and curator duties, respectively.

Dr. Duke spends a significant amount of his time exploring the ecology and culture of the Amazonian Rain Forest. In addition to a distinguished 30-year career with the United States Department of Agriculture, Dr. Duke sits on the board of directors and advisory councils of numerous organizations involved in plant medicine and the rainforest. He is also an accomplished musician, poet, and songwriter.

Even the allopathic journals are starting to echo the health food periodicals proclaiming that antiinflammatories and antioxidants (and/or a diet including 5 different vegetables and 5 different fruits) can slow the aging process and prevent the big killers: cardiopathy, cancer, diabetes, iatrogenesis. It is so ironic to hear Larry King plugging grape juice and vintners plugging their red wines for their antioxidant value. Many single out resveratrol as a major antiinflammatory and antioxidant phytochemical in the grape. Holists just munch on their apple a day or sip their red wine or grape juice for their antiinflammatory antioxidants while some reductionists (not me!) get out Ockham's razor and dissect them, looking for the most important antiinflammatory compound. Me? I make these dreadfully long list of active phytochemicals to see which of many possible chemicals are contributing to grape's useful activities and indications either antagonistically, or more likely additively or synergistically.

With that rhetorical introduction, I'd like to introduce you to a new query on the phytochemical database online at the USDA. (I'm gonna' walk you thru what I call the Multiple Activity Menu (MAM) query — or what the USDA database terms the “superactivity query.”

I believe the human body, long accustomed to many foods and their phytochemicals, under the direction of our 25,000 genes, selectively and homeostatically mines for long-familiar chemicals needed to keep the body in balance (and successfully excretes those in excess). The body and its genes are simply not familiar with new synthetics (partially explaining why half of them will be recalled in a decade!).

In the USDA database, look down to the last entry under Activity Searches. Click on Search for

“plants/chemicals with a superactivity.” For today's antiinflammatory tirade, select “Cardiopathy/Heart Problems.” That will first show you the activities we believe contribute to the prevention, amelioration, or remediation of heart disease.

### Superactivity cardiopathy/heart problems

There follows a long list of herbs. The grape (*Vitis vinifera*) comes out on top with 35 activities and 126 chemicals. Carrot comes in second with 34 activities and 117 phytochemicals. Now don't jump to conclusions. All herbs contain cardioprotective chemicals. This very superficial query, though useful, too often tells us which herbs have been most studied rather than which is truly best. Stay tuned as we expansionists refine that capacity. Yes, having suffered a minor stroke-like dizzy spell yesterday, I ate some grapes and a carrot and took a baby aspirin.

I will focus my antiinflammatory tirade on one of the compounds in the grape —resveratrol -- since it has several cardioprotective activities that just might save me from a coronary. But by no means do I think resveratrol is the silver bullet. It is just one of over three dozen antiinflammatory compounds contributing, often additively and synergistically, to the antiinflammatory activities of the grape. I could spend a day online and add another dozen or two based on those many new buzzwords for antiinflammatory, like iNOS-Inhibitor, NF-Kappa-beta-Inhibitor, NO-Inhibitor etc., etc., ad nauseum.

There are as many anticancer activities as well. I'll wager more than half of you readers think you have to drink red wine to get resveratrol. I'm ready also to wager, before Sidney Sudberg (AHG professional member and analytical chemist) does the analysis, that there is more



*Vitis spp.*

resveratrol in one edible grape leaf than there is in a liter of wine or grape juice. Stay tuned, but enjoy a few stuffed grape leaves while you wait. And don't worry; though the FDA may withdraw some (or all) of the synthetic COX-2-Inhibitors, the natural versions, like resveratrol, have co-existed with our genes for millions of years and probably will not be removed.

Finally if you want the long litany of details about the coronary phytochemicals in grape, hit the bluelit query "Details" following the *Vitis vinifera* entry. You'll get a 16-page list of the indications and the phytochemicals in grapes reported to have cardioprotective activity (sometimes with quantitative data). I won't bore you with that either. Check it out, if you want to see more.

Each month we learn of some new

antiinflammatory mechanisms, more often invented by researchers with allopathic backgrounds and economic motivations, looking for THE silver bullet. And sooner or later someone like me figures "this might be important." Recently I saw a flurry of abstracts on inducible nitric oxide synthase (iNOS) inhibition and NF-kappaB-Inhibition. Rather than do the 'PubMed crawl', pulling out the few entries that relate to herbs, I asked my right-hand lady Mary Jo Bogenschutz-Godwin to do that for me. Here's her summary of the research ordeal:

"It took me about 12 hours to cover over 100 abstracts, but that's because most of them were useful. The time it takes depends on the number of abstracts and the quantity of information. Sometimes there are only a few abstracts; other times you get the big pile but

### Some heart friendly activities of resveratrol

- ACE-Inhibitor
- Antiaggregant
- Antianginal
- Antiarrhythmic
- Antiartherosclerotic
- Antiatherogenic
- Antiatheromic
- Antiatherosclerotic
- Antiatherotic
- Anticardiac
- Anticardiospasmic
- Anticoagulant
- Anticoronary
- Antiedemic
- Antihemorrhagic
- Antihemorrhoidal
- Antihypercholesterolemic
- Antihypertensive
- Antiinfarctal
- Antiinflammatory
- Antiischemic
- Antioxidant
- Antiplatelet
- Antistress
- Antistroke
- Antitachycardic
- Antithrombic
- Arteriodilator
- Beta-Adrenergic Receptor Blocker
- COX-2-Inhibitor
- Calcium-Antagonist
- Cardioprotective
- Cardiorelaxant
- Cardiosedative
- Cardiotoxic
- Cyclooxygenase-Inhibitor
- Diuretic
- Estrogenic
- Hypocholesterolemic
- Hypotensive
- Myocardiotoxic
- Nervine
- Sedative
- Vasodilator
- Vasoprotective
- Vasorelaxant
- Vasotonic
- Venotonic

with few useful ones or the information is repetitive. It just depends. The hotter topics tend to be more difficult to work through. But as I read through them it's usually easy to see a trend of activities, one activity is usually associated with another or several. So the chemicals work in synergy and so do the activities....Eventually it forms a bigger picture and you start to see the synergy or antagonism between activities and hence different species or a family relation."

This is what I gather from what I've read as to the pathways. Some of this is lifted verbatim, some a pieced puzzle: Inducible nitric oxide synthase generates high amounts of the toxic and inflammatory mediator nitric oxide (NO). NO overproduction by iNOS results in severe hypotension and inflammation. The inhibition of NO production via the down regulation of iNOS expression may modulate the inflammatory responses. Suppression of PGE(2) biosynthesis occurs via downregulation of COX-2/iNOS expression. Down-regulate COX-2 and iNOS expression, and you inhibit production of NO and PGE2 through suppression of NF-kappaB activation. You also inhibit IL-6 and IL-8 mRNA expression via the suppression of NF-kappaB

binding activities. You inhibit lipopolysaccharide (LPS) and PAF to inhibit NF-kappaB. PAF is involved in activation of the NF-kappaB pathway. Nuclear factor-kappaB (NF-kappaB), a transcription factor, is critically involved in the molecular regulation of a number of proinflammatory cytokines such as interleukin-2 (IL-2) and interferon gamma (IFN gamma). NF-kappaB and activator protein-1 (AP-1) are two major transcription factors centrally involved in (proinflammatory) IL-1 beta gene expression. You inhibit NF-kappaB activation by blocking phosphorylation of IkappaBalpha and its degradation. Stabilization of cytoplasmic I-kappaBalpha leads to inhibition of NF-kappaB nuclear translocation and of subsequent IL-8 promoter activation. IkappaB kinase (IKK) complex has been shown to be responsible for cytokine-mediated stimulation of genes involved in inflammation. Inhibition of IKK kinase activity prevents the degradation of IkappaBalpha and IkappaBbeta

It appears to me there are thousands of antiinflammatory processes going on (not to mention proinflammatory), perhaps interacting with many of our ~ 25,000 genes. I may commit harikari with Ockham's razor. If inflammation, like oxidation, is important to the aging process, this assumes greater importance in nutrigenomics. I tabulate as an appendix, expecting the editor not to publish it, just a few of the many chemical compounds that Mary Jo dredged up [*Ed: Correct, please see the AHG website for the list or wait for USDA publication*]. All will soon be available on the USDA database to make for even longer and longer lists of the many phytochemicals interacting with our ~25,000 genes. Is that reductionism or expansionism?

One of these days I expect the phytochemical database to wed with a nutrigenomic database, so that those few who can afford to chart their genetic profile will be better advised about which foods and herbs are better, and which worse, for them personally. Pharmaceuticals are prescribed as though we were all average. I ain't. Are you? Because of our many genetic differences, what works for me, might not work for you or your patient. So even with phytochemical, genetic, and nutrigenomic rationalizations, the experience of the clinical herbalist or nutritionist, carefully counseling the individual patient, not "an average," remains the strongest component of any holistic approach.