

X Marks the Spot: COX-2-I's and XOI's



by Jim Duke, PhD

In my seventies, I seem to have been protected from the agonizing crises of gout (a sexist disease, affecting males about twice as often as females, and elitist, said to be more frequent in geniuses) by celery. According to Murray (1994), over 95 percent of gout sufferers are men over 30 (and 90 percent of cases are big toe cases). Though some 10 to 20 percent of the population may have elevated uric-acid levels, only 0.3 percent are suffering gout. Seems that simple celery works, like allopurinol, preventing the crises.

But I am just a walking anecdote, instead of a limping podagric case. Is it the celery, serendipity, or senility? Are celery stalks or celery seed extracts as efficacious as allopurinol at preventing gout? I think it is time to check this out clinically after my seven gout-free years. Yes, more than seven years ago, I discontinued the gout-preventing pharmaceutical, allopurinol and started celery seed extracts. I hope that through the activities of Citizens for Health, we can get American regulators to force the pharmaceutical industry to include not only their pharmaceutical but the placebo and one of the more promising herbal alternatives in those 800 million dollar trials to prove a new drug safe and efficacious. We will stridently seek three armed clinical trials, the new drug, the old herb, and placebo. In those few clinical trials so far comparing pharmaceutical with herb (e.g. saw palmetto, St. John's wort) the herbs have stood up well. Maybe Hildegard von Bingen's mention of celery seed for gout more than a millenium ago portended celery as THE herbal alternative for gout, comparable with allopurinol.

There are two sets of inhibitors that reductionists like myself view as helpful in gout, both before the crisis and after the crisis: the Xanthine Oxidase Inhibitors (XOI's), and the Cyclooxygenase II-Inhibitors (COX-2-I's). If you go to the USDA database [<http://www.ars-grin.gov/duke>] the first query (asking only for non-ubiquitous chemicals) will reveal three xanthine oxidase inhibitors: caffeic acid, luteolin, and umbelliferone, and two COX-2-I's, apigenin and eugenol. But that was before the new article by Momin and Nair (2002) reporting six more COX-2-I's from celery seed: sedanolide (1); senkyunolide-N (2); senkyunolide-J (3); 3-hydroxymethyl-6-methoxy-2,3-dihydro-1H-indol-2-ol (4); L-tryptophan (5); 7-[3-(3,4-dihydroxy-4-hydroxymethyl-tetrahydro-furan-2-yloxy)-4,5-dihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy]-5-hydroxy-2-(4-hydroxy-3-methoxy-phenyl)-chromen-4-one (6), active at levels as low as 250 pg mL. This brings the total of antiinflammatory compounds in celery to more than two dozen. But the only hypouricemic compound I find reported is fiber itself, hinting that the food farmacy stalks might be even better at preventing gout than the celery seeds or their extracts. The fiber can help lower uric acid levels.

But what about the XOI's? Some authors, e.g. Hatano et al (1991), state that xanthine oxidase causes gout and is also responsible for oxidative damage to living tissues. Hence, some pharmaceutical firms are screening for xanthine oxidase inhibitors. Nakanishi et al (1990) studied the xanthine-oxidase inhibitory (XOI) activity of 77 vegetables, 42 spices and 24 fruits. The ethanolic



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.

extract of *Perilla* (dare I call it “chiso liqueur”) showed marked XO-inhibitory activity. Two caffeic esters were responsible for the activity. (Z,E)-2-(3,4-dihydroxyphenyl)-ethenyl-ester, termed XOI-A on the patent, had an IC₅₀ of 0.021 ug/ml (equal with allopurinol at 0.021 ug/ml) and occurred at levels of 280 ppms in the extract. The other, a (Z,E)-2-(3,4-dihydroxyphenyl)-ethenyl-ester of 3-(3,4-dihydroxyphenyl)-2-propenoic-acid, (termed XOI-B, occurred at 70 ppms in the extract and was not nearly so potent (IC₅₀=0.124 ug/ml). Note that the seeds also contain luteolin (IC₅₀=0.11) (Apigenin and luteolin are the chief flavones in the seeds). Luteolin is also more potent than allopurinol as an XO-inhibitor. I speculate that quercetin (IC₅₀=>0.4 ug/ml) is also present in the leaves. Thus there are at least 4 compounds in chiso with xanthine-oxidase activity, possibly synergic. Wakashiro (personal communication) had not studied whether the activities were antagonistic, additive or synergic. On the European Patent Application, Wakashiro et al (1991) tabulate the data as follows:

COMPOUND	IC ₅₀ (ug/ml)
XOI-A	0.021
XOI-B	0.124
Allopurinol	0.021
Luteolin	0.110
Quercetin	>0.400

Adding licorice to the chiso liqueur might or might not) improve the gout prevention activities; licorice also contains several xanthine-oxidase inhibitors.

Murray (1994) notes that, even more than allopurinol, folic acid inhibits xanthine oxidase, the enzyme which produces uric acid. He suggests that at pharmacological levels (10-40 mg/day) folic acid may be an effective treatment for gout. That would be all but impossible to obtain herbally or dietarily. Highest in my database, and I am rather skeptical, is ginseng with 68 ppms. Leafy vegetables are more promising, the jew's mallow with 32 ppm, spinach 27, endive 25, asparagus 18, and parsley with 17 ppm, on a dry

weight basis. That means I'd have to take a kilo of ginseng to get 68 mg folacin!

Remember that the cartoon character, Popeye, drawn by a gout-sufferer, had uric-acid tophi on his elbows. But popeye's spinach may have hurt more than helped, oxalic acid may possibly aggravate gout. Murray also suggests 200-400 mg quercetin, taken with bromelain, the latter believed to enhance the absorption of quercetin. Quercetin is only 1/20th as potent as allopurinol at inhibiting xanthine-oxidase. But it is both an XOI and a COX-2-I.

Like Henry VIIIth and Sitting Bull, I had high uric acid levels which led to gout crises. Are they a thing of the past? Thanks to Hildegard von Bingen who suggested celery and its XOI's and COX-2-I's, I hope so. Man o man, the crisis of gout is a pain in the foot. Keep serving me celery, as I soar thru my seventies, and help tranquilize that creeping blood pressure of mine.

References

- Hatano T, et al 1991. Inhibitory Effects of Galloylated Flavonoids on Xanthine Oxidase. *Pl. Med.* 57(1): 83-4.
- Momin RA, Nair MG 2002. Antioxidant, cyclooxygenase and topoisomerase inhibitory compounds from *Apium graveolens* Linn. seeds. *Phytotherapy* 2002 May;9(4): 312-8
- Murray MT 1994. *Natural Alternatives to Over-The-Counter and Prescription Drugs*. Wm. Morrow & Co., Inc., New York.
- Nakanishi, T., Nishi, M., Inada, A., Obata, H., Tanabe, N., Abe, S. and Wakashiro, M. 1990. Two New Potent Inhibitors of Xanthine Oxidase from Leaves of *Perilla frutescens* Britton var. *acuta* Kudo. *Chem. Pharm. Bull.* 38(6): 1772-4.
- Okuda T, Yoshida T and Hatano T 1994. Chemistry and Antioxidative Effects of Phenolic Compounds from Licorice, Tea, and Composite and Labiate Herbs. Chap.15. pp. 133-153 In Ho et al, 1994. *Food Phytochemicals for Cancer Prevention II. Teas, Spices and Herbs*. ACS Symp. Series 547.
- Wakashiro M 1990. Two New Potent Inhibitors of Xanthine Oxidase from Leaves of *Perilla frutescens* Britton var. *acuta* Kudo. *Chem. Pharm. Bull.* 38(6): 1772-4.
- Wakashiro M, Abe S, Tanabe N, and Obata H 1991. *Pharmaceuticals Containing Xanthine-Oxidase Inhibitors (from Perilla frutescens) for the Treatment of Gout*. European Patent Application 429.038.1772-4.