Putting the squeeze on grapefruit juice

Quaffing a glass of grapefruit juice boosts the potency of a wide variety of drugs, as many studies have shown. Scientists think that one or more compounds in the juice incapacitate an enzyme that breaks down drugs, effectively increasing the amount of medicine available to the body—sometimes with dangerous consequences.

Now, researchers at the University of Michigan and Parke-Davis Pharmaceutical Research, both in Ann Arbor, have identified a compound in grapefruit juice called bergamottin that could be responsible for the effect. In the test tube, bergamottin inactivates cytochrome P450 3A4, a digestive enzyme that metabolizes many drugs, ranging from antihistamines to medications for high blood pressure (SN: 5/24/97, p. 327).

The finding builds on previous research, done in collaboration with scientists at Wayne State University in Detroit, that isolated a derivative of bergamottin and found that it inactivates the enzyme. Using improved separation techniques, the Michigan team discovered that bergamottin was not only more abundant than its derivative but more effective at shutting down the enzyme.

The researchers report their findings in the April CHEMICAL RESEARCH IN TOXICOLOGY.

Many drugs are metabolized in the intestines before they can enter the blood. Therefore, the compounds responsible for the action of grapefruit juice might be harnessed to reduce the effective dosage, says study coauthor Paul F. Hollenberg of Michigan. Moreover, individuals absorb drugs with varying efficiency, depending on the amount of cytochrome P450 3A4 they have. Knocking out the enzyme could make actual dosages more uniform, he suggests.

Bergamottin is "an important lead, but the jury is still out" on whether it causes the grapefruit juice effect, says David G. Bailey of the University of Western Ontario in London. Other compounds that inhibit the enzyme in the laboratory don't reproduce the juice's effect on drugs taken by people.

Bailey and his colleagues first stumbled across the grapefruit juice effect in 1989, while studying how alcohol interacts with a drug called felodipine, used to treat high blood pressure. When they gave grapefruit juice to their volunteers to mask the taste of the alcohol, the researchers found four times the expected amount of felodipine in their blood (SN: 2/9/91, p. 85).

Bailey conducted a pilot study on himself, taking the drug with either grapefruit juice or water and then measuring concentrations of the drug in his blood. "Lo and behold, my levels were five times higher with grapefruit juice," he says. Further studies confirmed his hypothesis. "When we first reported it, no one believed us. It's so off-the-wall."

Knowing the pharmacology of felodipine, Bailey reasoned that cytochrome P450 3A4 was involved. The enzyme metabolizes about 60 percent of all drugs, making them more easily soluble in water so they can be flushed out of the body.

In the new study, the Michigan researchers used ethyl acetate, an organic solvent, to extract some of the chemicals in freshly squeezed grapefruit juice. They found a high concentration of bergamottin in the mix.

In contrast, orange juice extracts didn't contain bergamottin at all—in accordance with the observation that orange juice doesn't cause the same drug effects.

Bergamottin appears to cause irreversible changes in cytochrome P450 3A4 in the region where it binds drugs, says study coauthor Kan He of Michigan. Additional experiments should reveal more details of that inactivation.

The ultimate proof will come from human tests of bergamottin to see if it can reproduce the grapefruit juice effect, says Bailey. —*C. Wu*

Why aren't there more cannibals around?

Nutritionally, eating the neighbors makes a lot of sense. That's why David W. Pfennig has wondered for years why cannibalism is so rare among animals.

Now he and his colleagues have used naturally cannibalistic tiger salamanders to test the idea that the risk of disease limits the evolution of cannibalism. Their results provide the first laboratory demonstration that eating one's own species packs a greater risk of disease than eating a different species.

"Cannibalism is a good way of getting a nutritious meal," says Pfennig, an ecologist at the University of North Carolina at Chapel Hill. A person existing on, say, lettuce would have a much tougher time obtaining all the vital amino acids and other nutrients than someone routinely lunching on coworkers. Earlier research in the laboratory suggested that tadpoles and mosquitofish excel nutritionally when they eat healthy compatriots. "They grow better when they eat their own kind," Pfennig says. Also, "it's a great way to get rid of competitors."

From amoebas to humans, many animals can become cannibalistic under the right circumstances. Still, "it tends to be something that is not normally seen," Pfennig says.

For years, scientists have suspected that the risk of disease could limit the spread of cannibalism because pathogens that target the dinner target the diner, too. The theory seems to play out as predicted, Pfennig's team reports in the May ANIMAL BEHAVIOUR.

He and his coworkers studied the effects of a serious hemorrhagic disease that sweeps through salamander colonies both in nature and in the laboratory. Five of 12 previously healthy tiger salamanders that ate sick salamanders of their own species died before metamorphosing. Other tiger salamanders flagged, but eventually recovered, after eating salamanders of another species suffering from what appeared to be the same disease.

The researchers also checked menu preferences of young tiger salamanders raised in crowded conditions. These youngsters had grown into so-called cannibal morphs, with big bodies and extra-wide mouths. When given a choice in the laboratory, 9 out of 11 ate salamanders of a different species and ignored their own.

The idea that pathogens limit cannibalism makes sense to James P. Collins, who has studied tiger salamanders extensively at Arizona State University in Tempe. He, Pfennig, and their colleagues have documented that salamander eggs are less likely to grow into cannibal morphs if they come from regions where the hemorrhagic disease is endemic.

Ecologist Mark A. Elgar of the Pierre and Marie Curie University in Paris notes that Pfennig is the first researcher to measure cannibalism costs directly in a nonhuman species. Observations of a Papua New Guinea tribe showed that its members caught the deadly disease kuru from eating human brains.

Pfennig's new work is "a nice, convincing, and original study," Elgar says. "I suspect the costs [of cannibalism] will vary between species, but risk of personal injury and pathogens are likely to be high on this list." —*S. Milius*

When crowded, some young tiger salamanders turn into big, wide-mouthed cannibals (left), who easily gulp down smaller salamanders.

Pfennig

Science Service, Inc. is collaborating with JSTOR to digitize, preserve, and extend access to *Science News*. www.jstor.org