Double-Whammy: Food-Drug Interactions

Components in grapefruit and other foods may dramatically affect absorption and metabolism of therapeutic drugs

by Yvonne Lin

A 29-year-old man, who had been taking a prescription allergy medication, twice a day, for over a year, drank two glasses of grapefruit juice with his medication and went out to mow the lawn. Suddenly, he became ill, stumbled into his home and collapsed. The coroner found that the man had died of irregular heartbeats caused by drug toxicity.

Because of the deadly consequences of this allergy medication interacting with grapefruit juice and other drugs, the allergy medication was pulled off pharmacy shelves.

Scientists in industry and in academe are constantly vigilant about drug interactions and now are looking at food-drug interactions with increasing interest.

About ten years ago, scientists accidentally discovered and reported the very first grapefruit juice-drug interaction. Doctors Spence, Bailey, and Arnold were studying the interaction between the consumption of alcohol and a drug to lower blood pressure. The investigators wanted to conduct a "blind" study. By disguising the taste of alcohol, the subjects would not know if they were taking the drug with alcohol. A taste-test of every juice in one of the investigator's refrigerators was conducted on a Saturday evening. Double-strength white grapefruit juice (a single dilution of frozen concentrate) was chosen to mask the taste of alcohol. Patients received the drug either with grapefruit juice alone (control) or grapefruit juice with alcohol. After the study subjects took the drug, they showed drug levels in their blood three times higher than predicted.

The high drug levels puzzled the investigators. They double-checked that the correct dose was given and that they were measuring the right levels. Since previous studies administered the drug with water instead of grapefruit juice, Bailey took the drug with water and then with grapefruit juice. After taking the drug with juice, his blood concentrations were five-fold greater than with water. He experienced dizziness and redness in the face. The higher drug levels were attributed to an interaction with grapefruit juice.

Over the last ten years, at least 40 drugs have been examined for an interaction with grapefruit juice, but scientists are only beginning to understand how grapefruit juice affects the body.

What is the cause of the grapefruit juice-drug interaction? Basic research at institutions including the University of Washington are helping to shed light on the phenomenon.

It appears that grapefruit juice changes how much drug gets into the body. Certain compounds in grapefruit juice act on the small intestine where the bulk of drug absorption occurs. After you swallow a pill, it usually passes through your stomach, then the pill dissolves in the small intestine and the drug is absorbed. The small intestine, however, has developed clever ways to prevent foreign substances from being absorbed.

First, a protein called P-glycoprotein, or "P-gp," for short, acts like a bouncer in front of a nightclub. If P-gp doesn't like the way the drug looks, P-gp just pumps the drug back into the intestine. That way, the drug never gets into the blood circulation.

The second way the body defends itself is through an enzyme called Cytochrome P450 3A. Called CYP3A for short, it is one the most important enzymes in the body. Its main job is to metabolize or transform drugs into forms that are easier to eliminate, and it prevents the unsafe build-up of drugs in the body. There is a large quantity of CYP3A in the liver and in the small intestine.

The intestinal CYP3A is like a fire chief in the nightclub, throwing out people when the club gets too crowded. Grapefruit juice has compounds in it that block P-gp and CYP3A from acting. Imagine the flood of people into the nightclub if the bouncer and the fire chief couldn't do their jobs. The same thing happens in your body: drugs can build to dangerous levels without those protective guards in place.

A surprising aspect of drug interactions is that a single glass of grapefruit juice can block P-gp and CYP3A for up to 24 hours. In general, the interaction between grapefruit juice and a drug would be greatest if you took both of them together. If you drank grapefruit juice for breakfast but didn't take the drug until later that evening, the interaction of the grapefruit juice and the drug would be less. However, if you drank grapefruit juice one morning, and then took the drug the next morning, the effects of grapefruit juice would nevertheless still be seen.

The reason for the long-lasting effects of grapefruit juice is that the body needs to regenerate the protective mechanisms in the small intestine. Grapefruit juice is known as a "suicide inhibitor" of CYP3A. Once CYP3A is inactivated by grapefruit juice, the CYP3A enzymes are broken down. To regenerate CYP3A, the body needs to synthesize new enzyme. Over the course of the day, your body constantly regenerates P-gp and CYP3A, but can't keep up if you start drinking too much grapefruit juice.

Interestingly, the magnitude of the grapefruit juice-drug interaction is different when large amounts of grapefruit juice are consumed compared with a single glass of grapefruit juice. For instance, when a single glass of normal-strength grapefruit juice was given to volunteers taking a popular cholesterol-lowering drug, only a very small increase in blood level of the drug was observed. In another study, volunteers were given double-strength grapefruit juice, three times a day for two days, before taking the drug. Their blood levels of the drug were nearly twelve times higher than normal.

Recently, it was shown that high grapefruit juice consumption not only affects intestinal CYP3A, but also affects CYP3A found in the liver.

Liver CYP3A is responsible for metabolizing the drug circulating in the body. When blocked by grapefruit juice, the drug levels in the body stay much higher for a longer time. For some drugs, higher blood levels can result in side effects, from dizziness to death.

But the news about grapefruit juice is not all bad. For example, the absorption of

cyclosporine, a drug given to organ-transplant patients, can actually be enhanced. Without help, not much cyclosporine is absorbed into the body because P-gp and CYP3A kick it out or destroy it before it gets a chance to do its job. Low blood levels of cyclosporine can lead to organ rejection.

But scientists are trying to isolate the compounds in grapefruit juice that block P-gp and CYP3A from working. Once they identify those compounds, they want to manufacture a "super-pill" of cyclosporine and the grapefruit juice compounds in order to help more of the cyclosporine to be absorbed. This idea could be applied to other medications that are poorly absorbed, such as drugs treating AIDS and epilepsy.

As one of the most studied interactions, the potential seriousness of grapefruit juice-drug interactions has caused a re-evaluation of the "safeness" of food products. Natural herbal remedies such as St. John's Wort, echinecea, and even orange juice have been studied.

In laboratory experiments, orange juice had noticeable effects, but when it comes to real-world situations, the effects are not as great as for grapefruit juice.

In contrast, St. John's Wort can cause a significant drug interaction. Investigators from the UW's pharmacy department and their collaborators in Maryland studied St. John's Wort in 13 subjects. After the subjects took St. John's Wort for two weeks, the CYP3A activity was increased in the body. So, in general, drugs that are metabolized by CYP3A will be processed even faster when taking this herbal supplement. The consequences would vary depending upon the drug, but this may mean that drugs to lower cholesterol, to control seizures, or to prevent organ rejection after a transplant may be less effective when taken with St. John's Wort.

To prevent drug interactions, hospitals have considered excluding grapefruit juice from patients' meals. Pharmacies have even created special labels to warn of grapefruit juice-drug interactions. Although grapefruit juice may not be harmful to everyone, the safest advice—besides, of course, to check with the doctor—may be to avoid taking any medication with grapefruit juice. Meanwhile, in the not-too-distant future, the compounds in grapefruit juice may be used to make certain drugs safer, cheaper, and more effective. ■

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Conservation Genetics: Tracking the Tusks

In what has been termed "trickle-down genomics" for an environmental cause, Northwest researchers seek to halt the decline of the African elephant population using a technique originally developed for the human genome

by Barbara Berg

In his 27 years of fieldwork in the forests and Savannah of southeastern Tanzania, Sam Wasser has amassed quite a collection of animal artifacts. Bone fragments and elephant skulls are of little interest to the procession of four-legged visitors to his camp—except for one. If a family of elephants happens to pay a visit, something extraordinary happens.

"An elephant will ignore everything else and go right up to the elephant skulls, examining and caressing them," Wasser says. "It's as if it knows."

This almost eerie sense of ancestry illustrates the intensely bonded family and social structure that elephants use to survive—ties that are rapidly being frayed, Wasser says, by poachers who slaughter the fascinating giants for their prized ivory tusks.

Wasser, a conservation biologist at the University of Washington who has devoted most of his life to conservation biology efforts, is not a man to sit still as extinction happens before his eyes. In an unusual collaboration with two genetics experts at Fred Hutchinson Cancer Research Center in Seattle, Wasser hopes to halt the decline of the African elephant population using a novel application of technology originally developed to analyze the human genome.

Kenine Comstock, Elaine Ostrander, and Wasser are part of the emerging discipline of conservation genetics, a field comprised of scientists who tackle conservation biology issues with molecular methods. Using DNA microsatellite marker analysis—a method Ostrander's group uses to locate cancer susceptibility genes and to map the canine genome—Comstock is determining the genetic distinctiveness of populations of elephants in regions throughout Africa.

The goal of the project, explains Wasser, is to develop a way to track the geographic origin of ivory as a means of determining whether it was obtained from illegal sources.

A family of elephants in Tarangire National Park in Tanzania.

Kenine Comstock analyzes elephant DNA at the Fred Hutchinson Cancer Research Center in Seattle. Comstock hopes that genome technology can be applied to preventing extinction of African elephants.

The Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES), whose member countries agree to control trade of products originating from animals threatened by extinction, currently does not allow any sale of African ivory. But, says Wasser, "there is rampant poaching despite CITES rules."

In 1998, Botswana, Namibia and Zimbabwe were permitted a one-time sale of ivory to Japan. Conservation biologists including Wasser are convinced that even the slightest relaxation of trade bans leads to dramatic increases in poaching, since no easy methods exist for determining the geographic origin of ivory.

"Our biggest hope is that this project will be able to provide some scientific data about how ivory sales affect poaching and aid in making sound political decisions about the ivory trade," says Comstock, a postdoctoral fellow in Ostrander's lab.

Wasser became concerned about the poaching problem while studying reproductive and stress hormones in elephants. He and collaborators at Princeton University realized that poaching was having a long-term impact on elephants, subjecting them to enormous stress that affects their reproduction and survival.

"Poachers go for the biggest tusks, which typically are found on bulls and matriarchs," explains Wasser. Killing matriarchs destroys the entire social structure, putting the surviving members of a family at great peril.

As a first step toward saving these endangered animals, researchers from Harvard University began experimenting with methods to determine the geographic origin of ivory by attempting to match isotopes in the tusk with chemical compounds in soil from different regions. That approach proved unsuccessful. Wasser reasoned that isolating DNA from tusks, which are very long incisors, or cutting teeth, would be a superior method to analyze the unique genetic fingerprints of regional elephant populations.

Developing a strategy for isolating DNA from tusks required some collaboration, and Wasser obtained help from the British Columbia Bureau of Legal Dentistry, which had experience in DNA isolation from teeth for forensic purposes. The DNA is actually isolated from the dentin-producing cells in the core of the tusk, explains Wasser.

After demonstrating that DNA could be extracted from tusks, Wasser's goal was to isolate DNA from elephants all over Africa, analyze the DNA for distinct patterns, and construct a genetic map that would allow him to visualize differences between elephants from different geographic regions. DNA obtained from a suspect tusk could then be compared to the map to determine its origin.

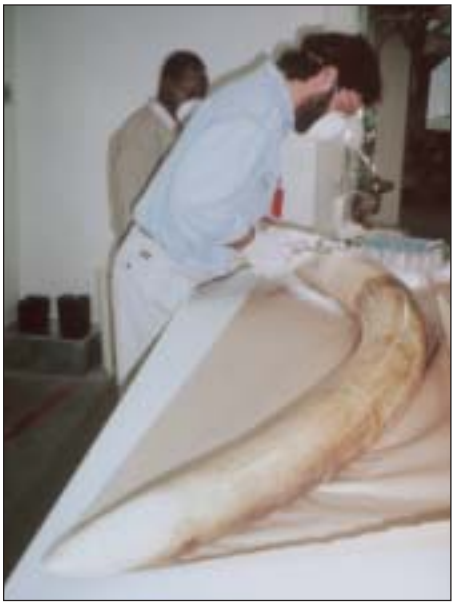
So how does a scientist get access to DNA samples from all those elephants? "One thing you see a lot of in the field is elephant feces," Wasser says, who has successfully isolated hormones from animal waste for years. It's also a perfect source for obtaining DNA.

Wasser knew that rangers regularly patrol grounds of African national parks, and he reasoned that he could involve them in the project by asking them to obtain fecal samples on their rounds. But to embark on a large-scale genetic analysis of elephant DNA, Wasser would need some help back at home.

"It was clear we needed microsatellite analysis," Wasser says. "There were no existing genetic markers for elephants." Microsatellite DNA markers are regions of chromosomes that are highly variable, or polymorphic, among individuals in a population.

A panel of microsatellite DNA markers can be used to generate a so-called "DNA fingerprint," which may be unique to elephants originating in a particular geographic region. Elephants from a common region are more likely to possess the same variations at each of the polymorphic sites.

Comstock, who had heard of Wasser's elephant project, approached him in 1998 to find out whether "I could use my expertise in molecular biology to address a serious conservation issue." She knew that the project would proceed much more quickly in a laboratory that routinely performed this



University of Washington conservation biologist Sam Wasser and collaborator Ben Mutayoba at Sokoine University of Agriculture in Tanzania test whether DNA can be isolated from tusks.

type of DNA analysis, and Ostrander's lab was the obvious choice.

As head of the Hutchinson Center's program in genetics and genomics, Ostrander is an expert in using microsatellite DNA markers to find genes implicated in prostate and other cancers.

"We could not do this project without Elaine," Wasser says. Although Ostrander is best known for her work on cancer genetics and for developing a canine genetic map, she has a long-standing interest in conservation biology and is enthusiastic about the power of genome technology to further environmental causes—what she refers to as "trickle-down genomics."

"This project shows how the technology and ideas developed as part of the human genome project are now trickling down to benefit a myriad of other species," says Ostrander.

Comstock has already identified 20 elephant microsatellite DNA markers, more than enough for a useful a genetic map. In addition to the benefit the map will have for conservation efforts, her preliminary analysis has uncovered an interesting aspect of basic elephant biology. "Some of the really exciting applications are the questions we can answer about migration patterns and speciation," she says. Comstock sees striking genetic differences between forest and savannah elephants, whose relatedness has been questioned among biologists since the 1800s.

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The project's success depends on strong collaborations with scientists in Africa. Ben Mutayoba at Sokoine University of Agriculture in Tanzania performs the DNA isolation from the elephant feces samples and ships the DNA to Comstock in Ostrander's Seattle laboratory. "Because of USDA restrictions, we can't bring elephants feces from Africa into the U.S.," she says. Another collaborator in Kenya, Nick Georgiadis, has 400 elephant tissue samples that he will share with Comstock for DNA analysis.

Back in Seattle, Wasser and Comstock reflect on the urgency of addressing the poaching problem. "At a CITES meeting last April in Nairobi, there wasn't enough information about how legal ivory sales affect poaching to come to any long-term decisions about the ivory trade," Comstock says.

"I believe it is inevitable that the ivory sales ban will be lifted," Wasser predicts. "Before it is, I want to have an accurate way to track poaching." ■

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