

Grapefruit juice lets patients take lower dose of cancer drug

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A glass a day of grapefruit juice lets patients derive the same benefits from an anti-cancer drug as they would get from more than three times as much of the drug by itself, according to a new clinical trial. The combination could help patients avoid side effects associated with high doses of the drug and reduce the cost of the medication.

Researchers at the University of Chicago Medicine study the effects that foods can have on the uptake and elimination of drugs used for [cancer treatment](#). In a study published in August in [Clinical Cancer Research](#), they show that eight ounces a day of [grapefruit juice](#) can slow the body's metabolism of a drug called sirolimus, which has been approved for [transplant patients](#) but may also help many people with cancer.

Patients who drank eight ounces a day of grapefruit juice increased their sirolimus levels by 350 percent. A drug called ketoconazole that also slows [drug metabolism](#) increased sirolimus levels by 500 percent.

"Grapefruit juice, and drugs with a similar mechanism, can significantly increase [blood levels](#) of many drugs," said study director Ezra Cohen, MD, a cancer specialist at the University of Chicago Medicine, "but this has long been considered an overdose hazard. Instead, we wanted to see if grapefruit juice can be used in a controlled fashion to increase the availability and efficacy of sirolimus."

Grapefruit juice's pharmaceutical prowess stems from its ability to inhibit enzymes in the [intestine](#) that break down sirolimus and several

other drugs. The effect begins within a few hours of what the researchers refer to as "grapefruit juice administration." It wears off gradually over a few days.

Cohen and colleagues organized three simultaneous phase-1 trials of sirolimus. Patients received only sirolimus, sirolimus plus ketoconazole, or sirolimus plus grapefruit juice. They enrolled 138 patients with [incurable cancer](#) and no known [effective therapy](#).

The first patients started with very low sirolimus doses, but the amounts increased as the study went on, to see how much of the drug was required in each setting to reach targeted levels, so that patients got the greatest anti-cancer effect with the least side effects.

The optimal cancer-fighting dose for those taking sirolimus was about 90 mg per week. At doses above 45 mg, however, the drug caused serious gastrointestinal problems, such as nausea and diarrhea, so patients taking sirolimus alone switched to 45 mg twice a week.

The optimal doses for the other two groups were much lower. Patients taking sirolimus plus ketoconazole, needed only 16 mg per week to maintain the same levels of drug in the blood. Those taking sirolimus plus grapefruit juice, needed between 25 and 35 mg of sirolimus per week.

"This is the first cancer study to harness this drug-food interaction," the authors note.

No patients in the study had a complete response, but about 30 percent of [patients](#) in the three trials had stable disease, meaning a period when their cancers did not advance. One patient receiving grapefruit juice had a partial response—significant tumor shrinkage—that lasted for more than three years.

Although ketoconazole produced a slightly stronger drug-retention effect, grapefruit juice has the advantage that it is non-toxic, with no risk of overdose. "Therefore," the authors wrote, "we have at our disposal an agent that can markedly increase bioavailability (in this study by approximately 350%) and, critically in the current environment, decrease prescription drug spending on many agents metabolized by P450 enzymes."

Sirolimus was the first of a series of drugs, known as mTOR inhibitors, that were developed to prevent rejection of transplanted organs but that also have anti-cancer effects. As the first of its class, it was also the first to come off patent, making it less costly. "Further cost savings," the authors suggest, could be realized "by combining the [drug](#) with agents that inhibit its metabolism."

Because different people produce varied amounts of the enzymes that break down sirolimus, the effect of grapefruit juice can vary, but tests of enzyme levels may be able to predict how an individual patient will respond.

"The variation in potency of the grapefruit juice itself may be far greater than the variation in the enzymes that break down [sirolimus](#)," Cohen said. An early version of the study used canned grapefruit juice, generously donated by a Chicago-based grocery chain. But tests of the product found it lacked the active ingredients. So the researchers shifted to a frozen concentrate product supplied by the Florida Department of Citrus.

Provided by University of Chicago Medical Center

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