Citrus Shows Promise For Certain Childhood Cancer

ScienceDaily (Dec. 1, 2004) — COLLEGE STATION – Orange juice and cancer don't mix. In fact, the popular citrus drink could become a cocktail to prevent or stop the deadly disease in humans.

Research by Texas Agriculture Experiment Station scientists has shown that citrus compounds called limonoids targeted and stopped neuroblastoma cells in the lab. They now hope to learn the reasons for the stop-action behavior and eventually try the citrus concoction in humans.

Neuroblastomas account for about 10 percent of all cancer in children, Harris said, and is usually a solid tumor in the neck, chest, spinal cord or adrenal gland. The finding in citrus is promising not only for its potential to arrest cancer, but because limonoids induce no side affects, according to Dr. Ed Harris, Experiment Station biochemist who collaborated on the study with Dr. Bhimu Patil, a plant physiologist at the Texas A&M University-Kingsville Citrus Center in Weslaco.

"Limonoids are naturally occurring compounds," Harris said. "Unlike other anti-cancer drugs that are toxic, limonoids apparently do not hurt a person. That's the beautiful potential."

Patil calls citrus fruit "a vast reservoir of anti-carcinogens." As a plant physiologist, he has succeeded in isolating and purifying a number of limonoids from citrus so that the biochemists could evaluate and compare their anti-cancer abilities at the molecular level.

"Limonoids are unique to citrus," Patil said. "They are not present in any other fruits or vegetables. My goal is to find the direct benefits of citrus on human health."

He said a challenging task is to isolate the limonoid compounds, "because some are present in very small concentrations."

In fact, citrus breeders seeking to improve the fruit's tastiness for consumers and yield for producers led researchers to discover limonoids – eight of which have been characterized from extractions at the Weslaco facility, according to the researchers.
"If I ask why one should drink orange juice every day," Harris noted, "almost everyone would say for vitamin C. That's true, but we also need to learn two new words – flavonoids and limonoids."

Harris explained that flavonoids and limonoids – nutrient-packed pigments that give color and taste to fruit – may work against cancer in any of three ways: prevent it from forming, slow the growth of existing cancer, or kill cancer cells.

"The limonoids, which differ structurally from flavonoids, seem to do all three," he said of tests in his lab by one of Patil's graduate students, Shibu Poulose, who also worked in Harris' College Station lab. Their work emphasized the compounds' ability to kill existing the neuroblastoma cells with the rationale that if the method and time limonoids take to obliterate the cancer could be found, perhaps scientists could exploit it to help cure the disease.

What Poulose found with the extracted limonoid was that the neuroblastoma cells died with relatively small amounts of concentrated limonoids and all in 48 hours or less.

They tested this in several ways. First, the limonoids were put through a test to see whether they would quench the oxygen radicals – cancer-causing substances that are destructive to normal cells. The limonoids appeared to be as effective as vitamin C in some of the tests.

Test of cell viability were more impressive, however. The neuroblastoma cells were all dead within two days with just 5, 10 and 50 micromoles of limonoids. A micromole is about the equivalent of a tiny skin flake. Some limonoids were more effective than others, but all had killing potential. These amounts of limonoids could easily be obtained from a glass of orange or grapefruit juice.

Next, cell viability tests aimed at whether the cell death was caused by apoptosis -- a programmed cell death that spirals in an unstoppable fashion unstoppably once the vulnerable spot on the cell is hit.

"Suppose we have cancer and the cancer cell mutates repeatedly until it takes over our organs," he said. "So, a compound comes in and spots those cells with the unusual metabolism and kills them by degrading the cells' protein and fragmenting their DNA until the cells succumb.

"Apoptosis is beneficial. It's the immunity system in the body that causes the white cells to recognize things that are not supposed to be there and attack them," Harris explained. Apoptosis early in life removes those white cells that would attack the body's own protein, for example.

To test this, the researchers applied 1, 5, 10 and 50 micromolar amounts of limonoids to neuroblastoma cells, then put an apoptosis-blocking chemical on an identical comparison set. Neuroblastoma cells with the blocker did not die, indicating that the limonoids trigger apoptosis which in turn results in the cell death. In their tests, the cancer cells treated with limonoids – but not the apoptosis blocker – all died within 36 hours.

The researchers also looked at caspases, destructive enzymes that are activated to cause chain reactions that lead to cell death. "A question was whether limonoids turn on apoptosis which then turn on the caspases and if so, whether that means there is caspases resting in our cells (that could be activated to help fight cancer in us)," he said.

This part of the research revealed that with only 5 micromoles of a limonoid known as LG, the cancer cells were dying in as little as 12 hours.

"The last phase in killing cancer is to make sure the DNA is destroyed because that is the death knell for the cell," Harris said. "It's intriguing that this amount appeared to have no effect on normal cells and only certain types of cancer cells are vulnerable. Fortunately, breast cancer cells are on the list of vulnerable cells. This makes it all the more imperative to learn how the process works."
"We don't have the answer to that yet," he said, "but we have observed that those limonoids with the greatest potency have a closed ring in their chemical structure and that is different from other compounds."

Limonoids with a sugar unit attached, the so-called limonoid glucosides, are water soluble and tasteless; those without the sugar, the aglycons, are responsible for bitterness of some citrus. It was the limonoid glucosides, in this study that had "a dramatic effect" on cancer cell death.

"Now that we have seen the cancer cells die and in such a short time," Harris said, "we need to find out why they are so vulnerable and exploit it. It could be that ultimately we are able to give patients an oral cocktail of limonoids in such concentration as to stop their cancer."

Patil said the researchers also will be studying limonoids to find the limits for adding to food. One of the limonoids, glucoside, is tasteless, he noted, so it might become a food additive for its health benefits, but food engineers would need to know how much to add for human consumption.

His lab also is examining whether the compounds vary among citrus species and at different times of the year.

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