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Grape seed extract halts cell cycle, checking growth of colorectal tumors in mice

PHILADELPHIA – Chemicals found in grape seeds significantly inhibited growth of colorectal tumors in both cell cultures and in mice, according to researchers who have already demonstrated the extract's anti-cancer effects in other tumor types.

Their study, published in the October 18 issue of *Clinical Cancer Research*, documented a 44 percent reduction of advanced colorectal tumors in the animals, and also revealed, for the first time, the molecular mechanism by which grape seed extract works to inhibit cancer growth. The authors found that it increases availability of a critical protein, Cip1/p21, in tumors that effectively freezes the cell cycle, and often pushes a cancer cell to self destruct.

"With these results, we are not suggesting that people run out and buy and use grape seed extract. That could be dangerous since so little is known about doses and side effects," said Rajesh Agarwal, Ph.D., professor in the Department of Pharmaceutical Sciences at the University of Colorado Health Sciences Center in Denver.

"The value of this preclinical study is that it shows grape seed extract can attack cancer, and how it works, but much more investigation will be needed before these chemicals can be tested as a human cancer treatment and preventive," he said.

The skin and seeds of grapes are a rich source of proanthocyanidins, a class of antioxidant flavonoids that remove harmful free oxygen radicals from cells. Grape products (juice and red wine) are known for their heart healthy effects, especially in lowering levels of blood cholesterol, Agarwal said, and because grape seeds contain higher concentrations of these chemicals, they are widely marketed as a dietary supplement.

Agarwal and his team of investigators were first to report, in 1999, that grape seed extract also has chemopreventive activity against skin cancer. Their subsequent preclinical work has shown that the extract also retards growth of prostate cancer cells.

In this study, Agarwal tested the extract on colorectal cancer, the second most common malignancy in Americans as well as the second leading cause of cancer deaths in this country. They exposed two different human colon carcinoma cells to the extract, and found a dose- and time-dependent inhibition of cell growth.

"Beneficial effects were correlated with how much extract was used and how long it was used for," Agarwal said. The number of live cells decreased by 92 percent in one cell line when the highest dose was given for the longest time period, which was two days, he said.

The researchers then performed a cell cycle distribution analysis, looking to see specific growth inhibitory effects. They found that the longer the extract was used, the more cells were "arrested" in the G1 phase of the cell cycle, the time when the cell is preparing to duplicate its DNA before dividing, and, correspondingly fewer cells had advanced to the "S" phase, when DNA is being actively duplicated.

They then studied the extract's effect on the molecular regulators that control the cell cycle, and found a strong dose-dependent increase in Cip1/p21 protein. In fact, the amount of Cip1/p21 protein within the cells increased by more than 150 times after 12 hours of treatment, Agarwal said. The researchers also noted a corresponding decrease in a number of different cyclin proteins and associated cyclin-dependent kinases (CDKs).

This all makes sense, according to Agarwal. One of the hallmarks of cancer is rampant cell growth due to loss of control of the cell cycle, and CDKs help push the cycle from a quiet state through to cell division. The Cip1/p21 protein, however, is powerful enough to inhibit the activity of CDKs and can also control apoptosis, or programmed cell death, he said.

"This protein physically interacts with CDKs," Agarwal said. "In normal cells, it attaches to CDKs to inhibit growth, but if a cell wants to grow, as it does in cancer, levels of Cip1/p21 are reduced, or non-functional."

Indeed, further experimentation demonstrated that grape seed extract increased the level of Cip1/p21 protein, allowing it to bind to and shut down the CDKs driving the cell cycle. The investigators also found that the extract can do that even if a cancer cell is missing p53 function (which also helps controls the cell cycle).

"That is good news, because most cancers are missing p53," Agarwal said.

Finally, the researchers tested the extract in mice. They implanted the animals with advanced human colorectal cancer cells and at the same time, gave the mice grape seed extract through a feeding tube. They tested only one dose, which was larger than a human would comparatively use, Agarwal said, and after eight weeks, tumor volume in treated mice were reduced by 44 percent and tumor weight by percent, compared to control animals. No toxic side effects were observed in treated mice, despite the high doses.

Similar to the cell culture studies, Cip1/p21 protein levels increased in tumors in mice treated with grape seed extract, Agarwal said.

As a first step toward translating their findings into the clinic, the research team now plans to determine the lowest effective, as well as the highest non-toxic doses, by which grape seed extract can offer anticancer benefit in mice.

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Editors Note: For a PDF of this study, please e-mail decicco@aacr.org or Ortiz@aacr.org

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