Major component in turmeric enhance effect of chemotherapy drug in head and neck cancer

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Curcumin, the major component in the spice turmeric, when combined with the drug Cisplatin enhances the chemotherapy's suppression of head and neck cancer cell growth, researchers with UCLA's Jonsson Cancer Center have found.

A naturally occurring spice widely used in South Asian and Middle Eastern cooking, Turmeric has long been known to have medicinal properties, attributed to its anti-inflammatory effects. Previous studies have shown it can suppress the growth of certain cancers, said Dr. Marilene Wang, a professor of head and neck surgery, lead author of the study and a Jonsson Cancer Center researcher.

"Head and neck cancers, particularly cases diagnosed in a later stage, are terrible cancers that often require very radical surgeries and chemotherapy and radiation," Wang said. "They often don't present until late, and the structures in the head and neck are so vital that our treatments often cause disfigurement and severe loss of function. So using non-toxic curcumin as a treatment was a very appealing idea."

The study, done in cells in Petri dishes and then in mouse models, appears in the October issue of the journal *Molecular Cancer Therapeutics*.

In India, women for years have been using turmeric for medicinal

purposes, as an anti-aging agent rubbed into their ski, to treat cramps during menstruation, as a poultice on the skin to promote wound healing and as an additive in cosmetics, said scientist Eri Srivatsan, an adjunct professor of surgery and a Jonsson Cancer Center researcher who, along with Wang, has been studying curcumin and its anti-cancer properties for six years.

A 2005 study by Wang and Srivatsan first showed that curcumin suppressed the growth of head and neck cancer cells, first in cells and then in mouse models. In the animal studies, the curcumin was applied directly onto the tumors in paste form because it did not dissolve in saline, which would have allowed it to be injected.

In need of a better way to deliver the curcumin, the team collaborated with Dr. Kapil Mehta of M.D. Anderson Cancer Center and found that encapsulating the tumor in a liposome, an artificially prepared vehicle that enclosed the spice component within its membrane, made the treatment injectable. The curcumin was injected into the tail vein of a mouse, where it circulated into the blood stream, slowing down and eventually stopping the cancer growth, a study in 2008 found.

"This was a very positive finding, developing an efficient way to deliver the treatment," Wang said. "Our study also showed that the curcumin was very well tolerated."

In this study, the team wanted to combine the curcumin with the chemotherapeutic drug Cisplatin, which is very toxic at the doses needed to fight head and neck cancers, damaging kidneys, the ears and the bone marrow. They hoped that if they added curcumin to the mix, they might be able to lower the Cisplatin dose and cause less organ damage. Their finding, that the curcumin made the Cisplatin work better, was very promising, Wang said.

"We knew that both the curcumin and the Cisplatin, when given alone, had an effect against head and neck cancers," Wang said. "This finding that curcumin enhances Cisplatin means that, in the future, we may be able to give this chemotherapy in lower doses."

The study noted that "the mechanisms of the two agents through different growth signaling pathways suggest potential for the clinical use of sub-therapeutic doses of Cisplatin in combination with curcumin, which will allow effective suppression of tumor growth while minimizing the toxic side effects."

The study found that curcumin suppressed head and neck cancer growth by regulating cell cycling, Srivatsan said. It binds to an enzyme and prevents the enzyme IKK, an inhibitor of kappa B kinase, from activating a transcription factor called nuclear factor kappa B (NFκB), which promotes cancer growth. Cisplatin's suppressive action involves a different pathway through the tumor suppressor proteins p16 and p53, both proteins that again inhibit the activity of cancer growth promoter NFκB.

"We needed to know the mechanism to help us translate this from the lab into the clinic," Wang said. "That information will help us make better decisions on how to design therapies."

The next step in the clinical setting is to give patients oral curcumin prior to surgery and, after surgery, study the excised tumors to determine curcumin's effect on tumor markers, specifically whether there is reduced expression of markers such as growth promoting NFκB. They also will be monitoring to determine if the curcumin results in any side effects. After that, the team would give curcumin to patients also getting chemotherapy and radiation to see if the tumor suppression found in the cells lines and mouse models can be replicated in humans.

Although turmeric is used in cooking, the amount of curcumin needed to produce a clinical response is much larger, about 500 milligrams. Expecting a positive effect through eating foods spiced with turmeric is not realistic, the researchers said.

Curcumin also has a suppressive effect on other cancers, Wang said, including breast, colon and pancreatic cancers. However, the mechanism of suppression in those cancers has not yet been uncovered. It also may be effective against Alzheimer's and aging, Wang said.

Provided by University of California Los Angeles

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