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Genes modulated by *Ginkgo biloba*revealed by DNA microarrays

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URBANA, ILLINOIS Millions of people take herbal remedies for conditions ranging from mild problems such as the common cold to severe disorders, such as Alzheimer's Disease. But even when these types of medicine have proved effective in clinical trials, it often remains unclear how they work in the body. Researchers typically test a hypothesis that is essentially an educated guess as to how, for example, a herbal medicine such as Echinacea might potentially boost the immune system. But, a new approach could help speed such research by removing a lot of the guesswork.

Pete Schultz of The Scripps Research Institute in La Jolla, California, and his colleagues have used DNA microarrays to see how a Ginkgo biloba extract affects brain function on the molecular level (Proc Natl Acad Sci USA 2001, **98**:6577-6580.). Although thousands of consumers buy Ginkgo biloba off the shelf to ease symptoms of aging such as short-term memory loss, hearing loss, and lack of attention, definitive clinical-trial data are lacking. "There's no scientific proof to say that it enhances memory," pointed out Coran Watanabe, a post-doctoral researcher in Schultz's laboratory and lead author of the study.

To see how the remedy affected the brain on the molecular level, Watanabe and her colleagues fed mice diets supplemented with a standard *Ginkgo biloba* extract for four weeks. They then dissected out the cortex and the hippocampus; prepared labelled RNA from both tissues, and tested with microarrays for expression of 12,000 genes. Of these genes, only 10 were activated more than three-fold in the ginkgo-fed animals compared with control animals fed otherwise identical mouse chow.

Most of the genes are already known to carry out reactions that might help protect brain cells. For example, the only gene activated by ginkgo in the hippocampus makes a protein called transthyretin, which is known to block the aggregation of amyloid beta protein in test-tube experiments, and is reduced in the cerebrospinal fluid of patients with Alzheimer's disease. Raising transthyretin, by implication, might block formation of the plaques that 'gum up' brain cells in Alzheimer's patients. In addition, two of the genes activated in the cortex, *tyrosine/threonine phosphatase I* and microtubule-associated *tau*, have been linked to the formation and breakdown of the intracellular tangles that are linked with Alzheimer's disease.

Although the results are consistent with a neuromodulatory role for *Ginkgo biloba*, it is still not clear whether the changes might have therapeutic effects, harmful effects, or none at all, said Schultz. "But at least you know where to begin to look," he suggested.

"What this study showed is that ginkgo hits some targets that made total sense with respect to the possibility of it acting in the brain. It sort of makes you a believer," commented Stephen Barnes, associate director of the Botanical Center for Dietary Supplements Research at the University of Alabama. The method should prove widely useful to help pin down the biological effects of botanicals and other complex mixtures - both helpful and harmful. "You're going to see a ton of this," he said.

Once researchers spot the genes that are activated or depressed by a given extract, they can then go back and carry out more traditional experiments to assess whether activating a particular gene has a therapeutic or harmful effect. "They can also purify the extract to find compounds that have a more selective effect," Schultz explained. "What's more, many of the genes activated by a complex mixture may come as a surprise, and they could reveal unexpected effects of the mixture," Barnes added.

"This allows us to make a quantum leap forward in terms of generating new hypotheses," Barnes concluded. "It changes the rules completely.

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